

BMJ Open Ambulatory antenatal fetal electrocardiography in high-risk pregnancies (AMBER): protocol for a pilot prospective cohort study

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To cite: Liu B, Marler E, Thilaganathan B, *et al.* Ambulatory antenatal fetal electrocardiography in high-risk pregnancies (AMBER): protocol for a pilot prospective cohort study. *BMJ Open* 2023;**13**:e062448. doi:10.1136/bmjopen-2022-062448

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-062448>).

Received 16 March 2022
Accepted 12 September 2022



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ABSTRACT

Introduction Fetal heart rate (FHR) monitoring is a vital aspect of fetal well-being assessment, and the current method of computerised cardiotocography (cCTG) is limited to the hospital setting. Non-invasive fetal ECG (NIFEKG) has the ability to produce FHR patterns through R wave detection while eliminating confusion with maternal heart rate, but is presently limited to research use. Femom is a novel wireless NIFEKG device that is designed to be placed without professional assistance, while connecting to mobile applications. It has the ability to achieve home FHR monitoring thereby allowing more frequent monitoring, earlier detection of deterioration, while reducing hospital attendances. This study aims to assess the feasibility, reliability, and accuracy of femom (NIFEKG) by comparing its outputs to cCTG monitoring.

Methods and analysis This is a single-centred, prospective pilot study, taking place in a tertiary maternity unit. Women with a singleton pregnancy over 28⁺⁰ weeks' gestation who require antenatal cCTG monitoring for any clinical indication are eligible for recruitment. Concurrent NIFEKG and cCTG monitoring will take place for up to 60 min. NIFEKG signals will be postprocessed to produce FHR outputs such as baseline FHR and short-term variation (STV). Signal acceptance criteria is set as <50% of signal loss for the trace duration. Correlation, precision and accuracy studies will be performed to compare the STV and baseline FHR values produced by both devices. The impact of maternal and fetal characteristics on the effectiveness of both devices will be investigated. Other non-invasive electrophysiological assessment parameters will be assessed for its correlation with the STV, ultrasound assessments and maternal and fetal risk factors.

Ethics and dissemination Approval has been obtained from South-East Scotland Research Ethics Committee 02 and MHRA. The results of this study will be published in peer-reviewed journals, and presented at international conferences.

Trial registration number NCT04941534.

INTRODUCTION

Fetal heart rate (FHR) monitoring in the form of cardiotocography (CTG) constitutes one of the main methods of antenatal fetal surveillance. Through the visual analysis of FHR patterns derived from Doppler

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This will be a prospective and comprehensive assessment of fetal heart rate (FHR) tracing assessed by computerised cardiotocography compared with ambulatory non-invasive fetal ECG monitoring.
- ⇒ The primary aim of the study is to establish the feasibility of ambulatory FHR monitoring to allow women-led home or remote fetal surveillance.
- ⇒ While a secondary aim of the study is to assess the reliability of ambulatory FHR monitoring for clinical use, it is a pilot study, and as such it is not possible to know if it will be sufficiently powered to do so.
- ⇒ Another secondary aim is to evaluate the accuracy of non-invasive fetal ECG, but as very few adverse pregnancy outcomes are likely to be included, the accuracy of the device in detecting poor fetal outcome will require further study.

ultrasound technology, clinicians have hoped to identify fetal compromise to prevent stillbirth and other adverse perinatal outcomes. This method is limited by a lack of stringent guidance for interpretation, a high rate of inter and intra-observer variation, and according to a Cochrane review, does not reduce the rate of perinatal mortality when compared with pregnancies that had not undergone CTG monitoring.¹⁻³ Subsequent development of the computerised CTG (cCTG) analysis has allowed a standardised algorithm to produce numerical values for vital FHR parameters, such as short-term variation (STV).⁴⁻⁶ STV is defined as averaged FHR differences between successive 3.75-second epochs (epoch-to-epoch variation), and low STV values are a strong predictor of poor fetal outcome such as fetal acidemia and intrauterine demise.^{4 7 8} The use of cCTG has led to a reduction in inter and intra-observer variation and consequently fewer perinatal deaths compared with traditional CTG use.^{3 9} However, cCTG requires application by healthcare professionals in a

hospital setting, thereby inherently limited by availability of hospital appointments and clinical expertise.

Non-invasive fetal ECG (NIFECCG) is one of the earliest reported methods of FHR monitoring.¹⁰ Using an abdominal ECG, both fetal and maternal heart rate (MHR) patterns can be produced through detection of the QRS complexes and derivation of the RR intervals.^{10 11} Due to the complexity of the technology and data processing, low fetal signal to noise ratio, and high levels of electrical interference, NIFECCG has mostly been limited to research purposes.¹² Despite these potential limitations, it bears several advantages over the CTG technology. These include a more precise FHR extraction through signal processing of RR intervals, minimisation of confusion with MHR, and reduced signal loss in women with a higher body mass index (BMI).^{13 14} Furthermore, fetal ECG can provide more insight into cardiac morphology such as arrhythmias and cardiac time intervals, which may be of use in assessing fetal well-being.^{13 15} Additionally, existing literature on NIFECCG has not established a consensus on standardised criteria for signal acceptance or the optimal monitoring schedules to demonstrate fetal well-being.

Telemedicine is a rapidly developing field, aiming to provide patients with immediate test results in the comfort of their own home or away from the clinic/ward. This may in turn provide earlier alerts to seek medical attention, while reducing hospital admissions and healthcare burden.^{16 17} Femom is a novel NIFECCG device developed by Biorhythm Pte Ltd, a bioengineering company in Singapore (figure 1). It is composed of five built-in wireless electrodes embedded in a flexible polymer spreader, with attachable single use adhesive gel electrodes that clip into the base of each device electrode. The pod, or the main body of the device contains the built-in electronics, is used for data acquisition, digitalisation and transmission. It provides the function of FECCG, maternal ECG and uterine activity detection, which will be transferred via Bluetooth to a tablet or mobile phone for



Figure 1 Photograph demonstrating femom placed on the maternal abdomen.

postmonitoring algorithm analysis and storage. Previous commercial NIFECCG devices comprised of ECG electrodes that required fitting by trained professionals. The use of the polymer spreader allows standardised placement of the femom device with ease by women without clinical assistance. The femom device has the potential to allow home or remote FHR monitoring using NIFECCG technology and to provide maternal reassurance while enabling earlier detection of fetal deterioration.

The objectives of our study are to establish the feasibility, reliability and accuracy of femom as an ambulatory FHR NIFECCG monitor. Our primary objective is to assess the level of agreement of FHR indices obtained by NIFECCG and cCTG. A secondary objective is to examine the impact of fetal and maternal characteristics on signal loss/acquisition from NIFECCG. These data will be used to develop evidence-based signal acceptance criteria and monitoring regimes. We will also assess the relationship of other non-invasive electrophysiological assessment (NIEA) parameters such as phase-rectified signal averaging (PRSA) and cardiac time intervals (CTIs) to STV.

METHODS

Recruitment and sampling

This is a single-centred pilot study taking place at St George's Hospital NHS Foundation Trust, a tertiary level maternity unit in London. Study process and procedures are shown in figure 2. Pregnant women attending the maternity Day Assessment Unit who require cCTG monitoring for a clinical reason will be approached and recruited for concurrent NIFECCG monitoring after informed, written consent. No follow-up assessments are required, unless the participant returns for another clinically indicated cCTG monitoring and wishes to undergo repeat NIFECCG monitoring. Delivery and neonatal outcome data will be collected after birth from their medical records. Study recruitment will take place from June 2021 to December 2022.

Sample size

There is no previous research on the agreement between cCTG and NIFECCG FHR parameters derived from femom. In this pilot study, we aim to collect 100 interpretable NIFECCG traces to establish the level of agreement and generate pilot data, as a sample size calculation is not possible. Interpretable traces are defined as FHR traces with <50% signal loss, as described by Seliger *et al* for signal acceptance criteria of clinically interpretable antenatal NIFECCG.¹⁸ Existing literature on a similar NIFECCG device (Monica AN24, Monica Healthcare, Nottingham, UK) using the same signal acceptance criteria have reported a success rate as low as 49% of the collected traces meeting this criteria.^{19–21} Moreover, we estimate an additional 30% trace exclusion due to technical issues arising from using a novel device.²² Therefore, we anticipate that we will need to recruit 200 participants to obtain 100 participants with interpretable and informative traces.

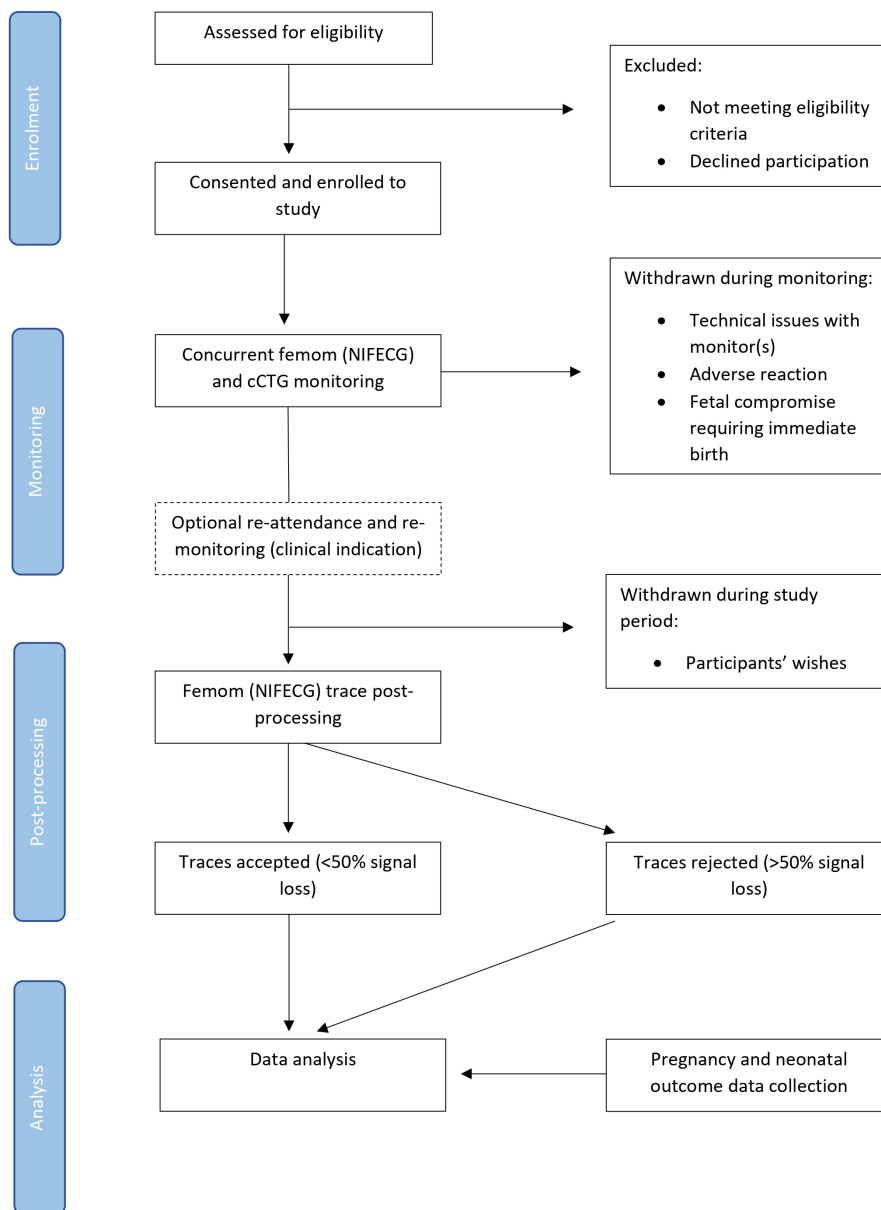


Figure 2 Study flow chart outlining the enrolment, monitoring, postprocessing and analysis steps of the study. cCTG, computerised cardiotocography; NIFEKG, non-invasive fetal ECG.

Inclusion and exclusion criteria

All women with a singleton pregnancy over 28⁺⁰ weeks' gestation, with a clinical indication for antenatal cCTG monitoring and can provide informed consent (has capacity, are able to speak English or has access to an interpreter) will be eligible to participate. Women with a pacemaker or ECG gel electrode allergy, and those with a fetus with known major cardiac anomalies and/or arrhythmia will be excluded. Women who are distressed or in labour will not be approached. If a cCTG demonstrates an abnormal or suspicious FHR pattern requiring immediate medical assessment, the participant will be withdrawn from the study.

Study procedures and data collection

Eligible participants consented to taking part in the study will be fitted with the NIFEKG by the researcher, with

the cCTG secured around the device. NIFEKG will be connected via Bluetooth to the research tablet, with its outputs displayed in real time and stored on a PC-based software (figure 3). The cCTG outputs will be displayed and the Dawes Redman criteria analysed through the Sonicaid FetalCare3 (Huntleigh Healthcare, Cardiff, UK). This is installed on both the trust computer and the research tablet, and signals from the cCTG machine will be split to allow data transfer to both computers. Recordings from both NIFEKG and cCTG will be commenced simultaneously, and continued for up to 60 min.

Both traces will be terminated at the same time at the end of the monitoring. The anonymised data comprising NIFEKG trace, raw cCTG comma separated values (CSV) data file, and the cCTG Dawes Redman analysis derived from the aforementioned softwares are assigned

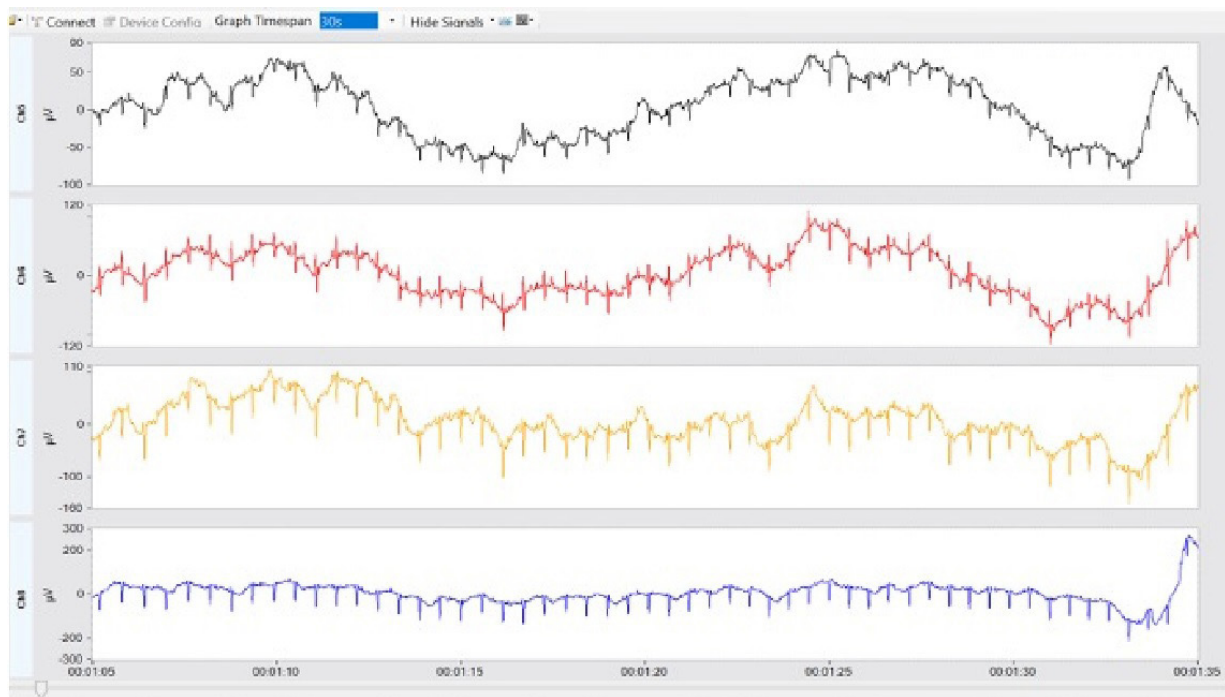


Figure 3 PC-based software displaying the abdominal ECG signals from femom (non-invasive fetal ECG) combining both maternal and fetal QRS complexes at the time of monitoring, captured across four channels. Maternal R waves are clearly seen as the high amplitude peaks, while fetal R waves are imbedded within the maternal QRS complexes.

with a participant ID number, and uploaded to a secure shared OneDrive folder. The NIFECG trace at the time of collection offers no clinically interpretable information, therefore any clinical decisions are made according to the cCTG trace, as per local clinical guidelines. Post-processing includes noise filtering, removal of maternal QRS complexes, amplification of fetal QRS complexes, and FHR derivation from calculation of the RR intervals. **Figures 4 and 5** demonstrate clean ECG traces following

noise filtering, and the final NIFECG FHR trace produced after postprocessing, respectively. The FHR parameters in each 2 min epoch as well as the overall values for each trace will be compared with those produced by the cCTG. The overall signal loss of the trace, and hence trace acceptance, will be determined following post-processing.

Participants who have not had, or are not scheduled to have a fetal well-being scan in 2 weeks will be offered an ultrasound assessment of fetal growth and Dopplers.

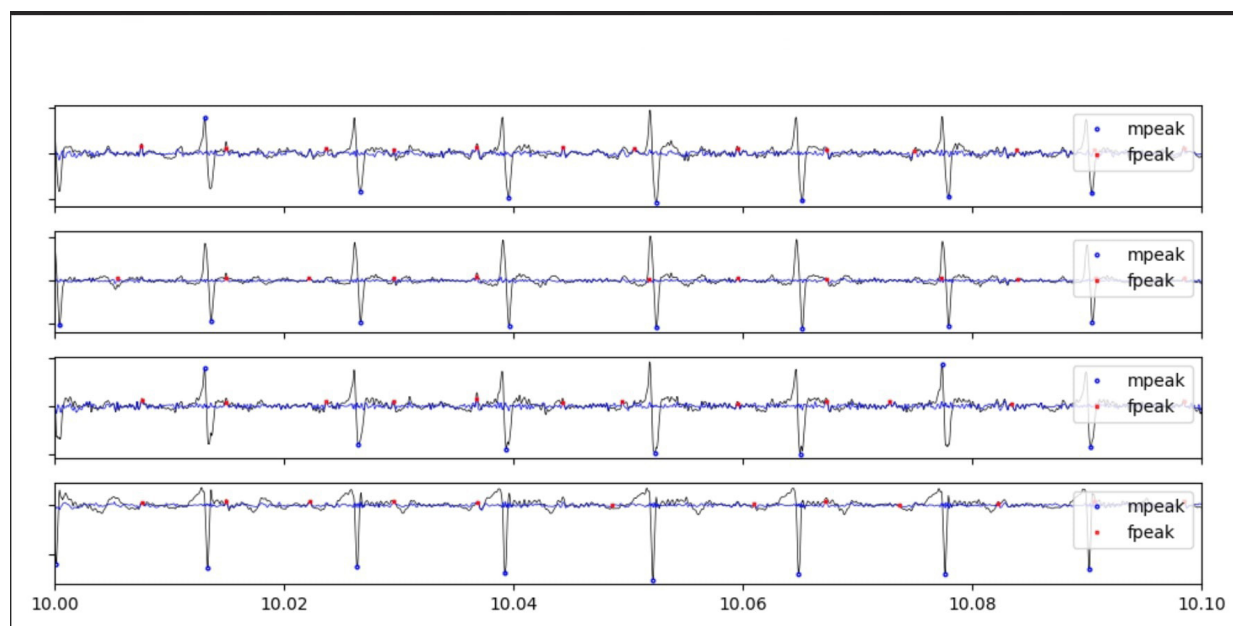


Figure 4 Raw ECG trace after noise filtering and processing, displayed on the four channels as derived from PC-based software. Maternal (mpeak) and fetal (fpeak) R waves are marked by the blue and red dots, respectively.

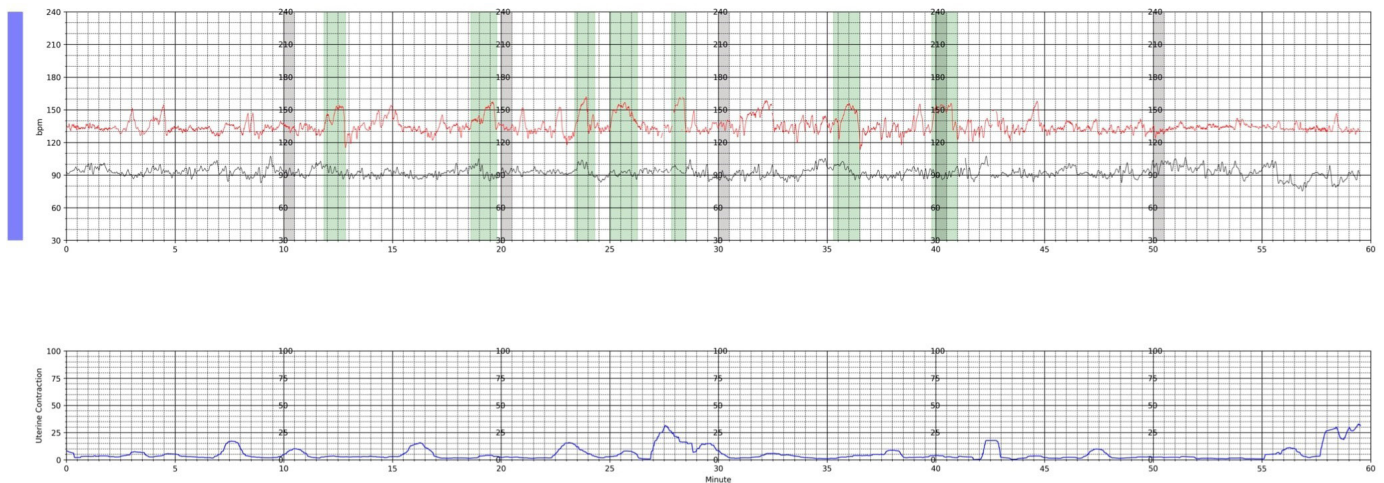


Figure 5 Final fetal heart rate (FHR) trace produced postprocessing of the femom (non-invasive fetal ECG) trace. FHR is shown in red and the maternal heart rate (MHR) in black. The bottom channel shows uterine activity in blue in arbitrary units, captured through electromyography.

Doppler assessment will include umbilical, fetal middle cerebral artery and maternal uterine artery pulsatility index (PI). Abnormal Dopplers are defined as umbilical artery PI above the 95th centile, middle cerebral artery PI below the 5th centile and a summative uterine artery PI over 2.5. Clinical management of these findings will be in accordance with local guidelines. These measurements will be used to assess placental function/reserve, assess the correlation between fetal growth velocity and Doppler indices against both the cCTG and NIFECG outputs such as baseline FHR and STV, as well as the NIFECG specific NIEA parameters—PRSA and CTIs. As our participant sample will largely include a low-risk population, we anticipate a low incidence of adverse events. Therefore, statistical analysis comparing fetuses with abnormal versus those with normal ultrasound findings will not be feasible.

Data analysis

Objective 1: to assess the agreement of key FHR parameters derived from NIFECG compared with cCTG

STV values from each cCTG trace will be extracted from the Dawes Redman analysis. STV values from the concurrently derived NIFECG traces will be produced following postprocessing of the fetal RR intervals, using the same definition of STV as formulated by Street *et al.*⁴ Linearity of the values from the two devices will be compared using Spearman's or Pearson's correlation coefficients, following assessment of normality using the Shapiro-Wilk test. Bland-Altman plots will be constructed using data produced from accuracy and precision analysis, which will include bias, precision, 95% limits of agreement and mean percentage difference. The same analysis will be performed with baseline FHR from both devices. We will also explore whether the difference between the two devices is correlated with the magnitude of signal loss, so that standardised signal acceptance criteria may be formulated for future research and clinical use.

Objective 2: to examine the impact of fetal and maternal characteristics on effectiveness of NIFECG monitoring (signal loss)

Signal loss is reported as a percentage of the entire trace, forms a component of the Dawes Redman analysis. These values will be extracted from each cCTG trace, and calculated from the concurrent postprocessed NIFECG traces. Fetal characteristics such as gestational age, estimated fetal weight and placental localisation will be collected from each participant at the time of monitoring. Maternal characteristics consisting of age, ethnicity, height, weight, hair coverage, pregnancy/medical comorbidities will also be recorded. Multivariate logistic regression analysis will be performed to assess the impact of these characteristics on the success of the NIFECG trace in meeting signal acceptance criteria. Multiple regression analysis will also be performed to examine the predictive value of these characteristics on signal loss from both devices. We will also aim to establish whether the NIFECG has any advantages over the cCTG in certain patient groups with known difficulties in signal acquisition using cCTG (eg, high BMI).

Objective 3: to assess the relationship between NIEA parameters and STV

CTIs and PRSA will be derived from NIFECG traces that achieve signal acceptance criteria. Correlations will be assessed between CTIs acquired from NIFECG (PR interval, QRS duration, QT and QTc intervals) and STV values derived from NIFECG and cCTG. Multiple regression analysis will be performed to determine the predictive value of the CTI values on the STV. The same analysis will be undertaken with PRSA. Further regression analyses can be used to study the impact of fetal/maternal characteristics and complications, ultrasound and Doppler findings on the NIEA parameters as well as the STV.



Patient and public involvement and satisfaction questionnaires

No patient and public involvement (PPI) was sought during the set up or design of this pilot validation study. However, all participants recruited to this pilot study will be asked to complete a satisfaction questionnaire using a Likert scale following their monitoring, which will be used to gauge the opinions of users and suggest any areas for improving femom. This will contribute to future involvement of PPI, optimisation of design and development of the final femom model.

Ethics and dissemination

This study has received ethical approval from South-East Scotland Research Ethics Committee 02 (REC reference 19/SS/0109, IRAS ID 260032), and MHRA (CI/2020/0028) as well as HRA approvals. All participants will be given time to read the patient information sheet (PIS), and sign the informed consent form. Monitoring will take place in the hospital setting, and any adverse events at the time of monitoring will be identified and reported. Participants will be provided with contact details in the PIS to seek advice regarding concerns following monitoring or to withdraw their participation if necessary.

The results of this study will be published in peer-reviewed journals, and presented at national and international conferences. The commercial sponsor (Biorhythm Pte) will proceed with regulatory clearance of various geographies following dissemination of the results. Further studies will be set up and conducted based on our findings, prior to the approvals for clinical use.

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Contributors BL is the lead author of the protocol and doctoral student of this study. EM is the lead research midwife and have assisted in the study set up and conduct. BT and AB are consultants in Obstetrics and Fetal Medicine, principal investigators of the study, and form the supervisory team for the doctoral student. They have both contributed to the conceptualisation, study design, statistical analysis and protocol review. All authors have reviewed and approved the final version of the protocol.

Funding This work is funded by its commercial sponsors—Biorhythm Pte Ltd (award/grant number: N/A). The funder had no role in the preparation of this manuscript, and will not be involved in the conduct, analysis or reporting of the results. The authors have full access to the data.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer-reviewed.

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