RESEARCH PROTOCOL

Measurement and Validation of Fetal Heart and Fetal Movement Signals Detected via Non-adhesive Sensors

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1) RESEARCH TEAM & KEY CONTACTS

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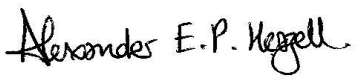
Name: Professor Alexander Heazell Address: Maternal and Fetal Health Research Centre 5th Floor Research, St. Mary's Hospital Oxford Road, Manchester M13 9WL Email: alexander.heazell@manchester.ac.uk Telephone: (0161) 276 6484 Signed:  24/05/2022	Name: Dr Jayawan Wijekoon Address: D31b Sackville Street Building, Sackville Street, Manchester, M1 3BU Email: jayawan.wijekoon@manchester.ac.uk Telephone 0161 306 4736 Fax 0161 306 8946
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2) INTRODUCTION

A multidisciplinary team of a doctor and engineers have developed a new sensor that will be able to detect mothers' and babies' heartbeat and babies movements in late pregnancy. This sensor can be placed in contact with the mothers' skin over the pregnant uterus without having to be stuck down. We anticipate that this sensor would allow us to monitor babies for longer periods of time which might help us to better identify babies who are being deprived of oxygen during pregnancy. We need to test these sensors on women in late pregnancy for two reasons. Firstly, we need to ensure they reliably measure mother and babies heart rates without interference from movement or other electrical equipment. Secondly we need to ensure that the information they provide is accurate (compared to current measurement techniques).

We will carry out a study in two phases. The first phase will include up to 24 women to develop the sensors to ensure that they can obtain consistent signals from mothers' and babies' heartbeats without interference from movement and other electronic devices. We will adjust the electronics in the sensors to ensure they give the best signal. The second phase will include up to 45 women to see whether the information detected by the sensors is comparable to existing technologies. This information will help us to see whether these sensors can be organised into a new device for fetal monitoring which can then be tested.

3) BACKGROUND

Current technologies to objectively assess fetal wellbeing including fetal movement counting using "kick charts" and intermittent cardiotocography have little or no effect on reducing perinatal

mortality, even in high-risk populations.[1-3] Despite this, they are commonly used in clinical practice, particularly for pregnancies at high-risk of adverse pregnancy outcome. One reason for the use of these technologies is that there are no more effective alternatives. There is limited evidence that computerised analysis of the fetal heart rate trace, in high-risk pregnancies, is associated with a reduction in stillbirth.[3] This suggests that computerised analysis can detect abnormalities which are not detected by visual analysis of the heart rate trace.

One suggestion to improve the technologies is to increase the period of monitoring, or even develop an approach which can continuously assess fetal wellbeing.[4] This has led to the development of various devices to objectively measure fetal activity or fetal heart rate. However, none of these devices have been adopted into clinical practice. The plethora of potential devices suggests that the concept is popular but that a practical, reliable and acceptable device has not yet been developed. We have demonstrated that professionals would be willing to use continuous monitoring, especially in mothers at high-risk of complications, although they had concerns about the practicality of the approach and of causing maternal anxiety.[5] Using one device which has been developed to market (MONICA AN24) we demonstrated that women were willing to use a device to monitor the fetal heart rate for extended periods but that some physical aspects of the device, specifically the adhesive electrodes and wires led to concerns from women that they may disconnect or damage the device.[6,7] There was also evidence of significant periods where the fetal heart rate signal was lost amounting to 31% of each trace on average.[7] This suggests that improvements in sensors to detect fetal heart rate are needed.

Working together with researchers in the School of Engineering (Departments of Electronic Engineering and Textiles) we have developed non-adhesive capacitively-coupled sensors which can detect signals of the magnitude of the fetal heart rate which is approximately 100 times weaker than an adult heart rate. It is envisaged that these non-adhesive sensors would be arranged in an array to detect the fetal heart rate irrespective of the position of the fetus. Before we can develop a device we need to ensure that these sensors can consistently and reliably detect the mother's and baby's heart rate.

4) STUDY OBJECTIVES

4.1 Primary Question/Objective:

The primary aim of this project is to conduct initial studies using non-adhesive sensors to determine whether they are able to consistently detect the mother's and baby's heart rate and whether this can be distinguished from background electrical noise.

4.2 Secondary Question/Objective:

This project will determine whether placing these sensors in an array (a group) provides better detection of the mother's and baby's fetal heart rate and movements.

This project will determine whether the electronic signals detected can reliably detect mother's and baby's heart rates when compared to currently established methods.

This project will determine women's experiences of having the sensors applied to their abdomen and the concept of longer-term fetal monitoring.

5) STUDY DESIGN & PROTOCOL

5.1 Participants

We will conduct a cohort study of women with a healthy singleton pregnancy over 28 weeks' gestation.

5.2 Study Intervention and/or Procedures

In the first part of the study we will ask up to 24 pregnant women to wear the device and determine whether the device consistently detects the electronic signals and to reduce recording of background electrical noise e.g. from electrical wires / devices / sockets etc. which are likely to emit electrical activity in the same microvolt range as the fetal heart rate trace.

In the first part of the study participants will be from three separate time periods in late pregnancy (8 women in each time frame) 28weeks +0 days - 31weeks +6 days (usually written as 31+6) , 32+0-35+6 weeks and finally from 36+0 until 40+0 weeks. Women will be recruited from the Tommy's research clinics and the antenatal clinics at St Mary's Hospital, Manchester. All participants will have an ultrasound scan prior to participation to measure baby's size, the liquor volume and umbilical artery Doppler (if not already performed in the preceding 7 days). This will ensure that baby is well before the sensors are used. We will measure the electrical activity of the participants skin and soft tissues using an electrodermal activity meter which uses two adhesive electrodes attached to the maternal abdomen. If needed, we will make adaptations to the electronics to optimise the detection of the mother's and baby's heart rate. All participants will give written informed consent before any experimental activities commence.

Participants will be asked to lie on an examination couch for up to 60 minutes at 45 degrees while the electronic sensor(s) are held in contact with the maternal abdomen by an elastic garment (A typical array of sensors is shown in Appendix A) with or without conductive gel applied. If participants are uncomfortable they will be able to sit or stand to relieve their discomfort. Basic information including body mass index, stage of pregnancy and estimated fetal weight will be recorded on a proforma. Participant comfort or discomfort during the period of monitoring will be assessed by non-participant observation during the monitoring session. These observations will be undertaken by a MSc student who is a registered midwife.

If consistent signals can be obtained we will assess whether the sensors can accurately display maternal heart rate and fetal heart rate at different stages of late pregnancy. To assess whether the recording is accurate we will compare the output from the sensors with current methods to assess

maternal heart rate (ECG), fetal heart rate (traditional CTG and MONICA24). We will use ultrasound scan to assess whether fetal movements are associated with expected changes in fetal heart activity.

In the second phase of the study, to assess sensor reliability we will recruit up to 15 women from each gestational age group from 28+0-31+6 weeks, 32+0-35+6 weeks and finally from 36+0 until 40+0 weeks. Women will be approached if they have healthy singleton pregnancies and have a pre-pregnancy BMI from 20-35. As previously, women will be recruited from the Tommy's research clinics and the antenatal clinics at St Mary's Hospital, Manchester. All participants will have an ultrasound scan prior to participation to measure baby's size, the liquor volume and umbilical artery Doppler (if not already performed in the preceding 7 days). This will ensure that baby is well before the sensors are used. We will measure the electrical activity of the participants skin and soft tissues using an electrodermal activity meter which uses two adhesive electrodes attached to the maternal abdomen. The correlation between the maternal and fetal heart rates obtained using established techniques and the new sensors will be calculated.

Participants will be asked to complete a short baseline questionnaire before commencing the monitoring process, a saliva sample will then be collected for cortisol analysis. Participants will be asked to lie on an examination couch for up to 60 minutes at 45 degrees while the electronic sensor(s) are gently held in contact with the maternal abdomen by an elastic belt. In addition to the new sensors the fetal and maternal heart rate will be recorded using the MONICA AN24 device and fetal movements will be recorded with ultrasound (for 20 minutes of the 60). If participants are uncomfortable they will be able to sit or stand to relieve their discomfort. Participant comfort or discomfort during the period of monitoring will be assessed by non-participant observation during the monitoring session. These observations will be undertaken by a MSc student who is a registered midwife. Basic information including body mass index, stage of pregnancy and estimated fetal weight will be recorded on a proforma (see Appendix B). In addition, participants will be asked to complete a questionnaire about anxiety and wearing the device after the monitoring process (see Appendix C). At this point, a further saliva sample will be collected for a comparative cortisol measurement.

Participants who agree to have an interview about their experience of wearing the sensor to monitor their baby's heart rate pattern will be interviewed by the Lydia Hughes (Masters student / midwife). This interview will follow a semi-structured interview guide (see Appendix B). The interview will be conducted prior to the participant leaving the hospital. The interview will be audio-recorded and transcribed verbatim. Once the transcription has been checked against the audio recording for validity the audio recording will be deleted; data will be stored on a password protected hard drive to prevent the risk of third-party access. Data will only be utilised for the purpose of the study and will be disposed of upon completion. To ensure the wellbeing of the participants, a distress protocol has been devised and will be activated where necessary (Appendix C).

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6) STUDY PARTICIPANTS

6.1 Inclusion Criteria:

Participants will be included if they have a non-anomalous singleton pregnancy after 28 weeks' gestation with an estimated fetal weight >10th centile < 90th centile. Participants will be 16 years or over in order that they can give independent consent.

6.2 Exclusion Criteria:

Participants will be excluded if there are fetal anomalies (as defined by the NHS Fetal Anomaly Screening Programme - https://www.gov.uk/guidance/fetal-anomaly-screening-programme-overview), it is a multiple pregnancy, there is evidence of Fetal Growth Restriction (Estimated Fetal Weight <10th centile) or if participants cannot speak or do not understand fluent English. Participants will not be able to participate if they are unable to give informed consent. Participants <16 years of age will be excluded from this study.

6.3 Recruitment:

Eligible pregnant women will be identified in the research and antenatal clinics through the routine work of the clinical staff. Only members of the clinical care team will have access to any identifiable data prior to consent. In addition, we will display recruitment posters so that potential participants will know that the study is being undertaken in the clinical area.

If potential participants agree, a research midwife or CI will discuss the study with them and provide a participant information sheet and will be asked to complete a consent to contact form. Participants will have at least 24 hours to decide whether or not to participate in the research. If they agree to participate, then an appointment will be made for them to attend the Maternal and Fetal Health Research Centre to undertake the study. Written consent will be taken prior to participating in the study recorded on the specified form.

6.5 Participants who withdraw consent [or lose capacity to consent]:

Participants can withdraw consent at any time without giving any reason, as participation in the research is voluntary, without their care or legal rights being affected. For participants who voluntarily withdraw from the study who have previously consented to the study data up to the time of withdrawal will be included in the study unless the participants specifically request for all of their data be removed.

As participation in the study is limited to a single window during which participants will have a period of monitoring capacity to consent will be continuously monitored. After this period of contact ongoing capacity will not be assessed and participants' data will be included in the study unless participants specifically request for their data to be removed.

7) OUTCOME MEASURES

At this stage this study is primarily of academic interest. These studies will determine whether the non-adhesive electrodes can detect signals from the fetal heart rate and fetal movements and distinguish this from background noise and the maternal heart rate.

These studies will demonstrate whether the sensors are comfortable and what women's experiences are of the monitoring procedure.

Upon completion of the study we will know if these sensors can reliably detect maternal and fetal heart rate and changes associated with fetal movement. We will also know whether an array of sensors performs better than a single sensor alone. We will know whether women find the monitoring process comfortable and acceptable.

8) DATA COLLECTION, SOURCE DATA AND CONFIDENTIALITY

Data will be obtained from the medical case records by the research staff. The data will initially be recorded on a paper case report form. These data will then be transferred to a secure electronic database held on the University of Manchester online storage. The only personal data to be collected is the hospital unit number and participant initials to allow traceability of medical records. These will be stored in a separate password protected computer file from the study data linked only by a participant number. Non-identifiable data will be stored on University Computers. All computers will be password protected and encrypted according to University of Manchester policy. We will not store personal identifiable information with study data. Information will be coded by participant study number. Participants will not be identifiable from the stored data set itself.

If they agree to participate in the interview after the monitoring period this will be audio-recorded and transcribed. Once the transcription has been checked against the audio recording for accuracy the original recording will be deleted. The transcription will be identified by their study number.

Each participant will be assigned a study number, this will be linked to the consent form only. Personal identifiable data, including consent forms, will be stored in a locked filing cabinet in the Maternal Fetal Health Research Centre.

Storage of personal identifying data will only be accessible to research staff directly involved in this project in line with GCP guidelines and will only be stored on NHS computers. Electronic data will be linked using the study number; no personal identifiable data will be stored on the electronic research database. Any laptops used will be password protected and will contain no identifiable participant data.

To maintain confidentiality computer records specific to the research outcomes will use the participant's study number to identify them (this study number will be listed on the consent form, allowing linkage back to the individual). Personal data will remain confidential within the research team. Confidentiality procedures in line with University of Manchester Research Governance guidelines and NHS Code of Confidentiality will be adhered to at all times. If direct quotations are published from questionnaires the confidentiality of all participants will be maintained with the use of pseudonyms.

The research team will have access to personal data. Study data and material may be looked at by individuals from the University of Manchester, from regulatory authorities or from the NHS Trust, for monitoring and auditing purposes, and this may well include access to personal information.

Consent forms will be retained as essential study documents. Personal data from the pseudo-anonymised database will be deleted as soon as the study dataset is complete (anticipated to be 18 months from commencing the study) and no further validation is required from clinical records. The anonymised data will be stored for 10 years in line with regulatory requirements.

The data generated by the study will be analysed by the study team comprising Lydia Hughes (Masters Student), Lisen Zhu (PhD student), Prof Alexander Heazell, Dr Jayawan Wijekoon and Dr Anura Fernando. The Chief Investigator will be the custodian of the data for the study.

9) STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis

All data collection and analysis will take place simultaneously and will be analysed by the research team. In the first phase of the study we will be recording the presence of maternal and fetal electrocardiogram recordings and any interference from movement / other electrical sources. In the second phase of the study we will analyse the agreement between signals obtained via the novel sensors and information obtained from established methods (ultrasound, MONICA AN24 device) using correlation.

9.2 Qualitative Analysis

Thematic analysis will be used Braun & Clarke's six-step thematic analysis framework will be used (Appendix D) to analyse the interview data as it is appropriate for this form of qualitative data by providing a flexible yet structured framework to explore participants' experiences, uncovering themes and patterns. It will highlight diverse perspectives to ensure that all voices are represented, which is integral in health-care research. Initial themes will be derived by the Masters student and discussed with the wider research team.

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9.3 Sample Size:

A sample size calculation could not be performed. We have consulted with other researchers with expertise in medical devices who suggested that up to 24 women would be sufficient to ensure that signals could be consistently obtained and allow changes to the device. To test reliability greater numbers are required as the stage of pregnancy and other factors (mother/baby size) may have an effect. We plan to continuously analyse our data, if we achieve our objectives before the planned number of participants are recruited we will not continue to recruit.

The proposed sample size for the qualitative data is 15. During interviews and observations, the researcher wishes to reach a point of data saturation whereby no new themes are emerging, a typical sample size for qualitative data is 5-30 depending on the nature and complexity; 12 participants is suggested as sufficient to understand the lived experiences of individuals in depth.

10) DATA MONITORING AND QUALITY ASSURANCE

The study will be subject to the audit and monitoring regime of the University of Manchester. The investigators / institutions will facilitate study-related monitoring, audits, review by independent ethics committee and regulatory inspections providing direct access to source data / documents to authorised study or regulatory personnel.

11) SAFETY CONSIDERATIONS AND ADVERSE EVENTS

As this is a preliminary study to assess whether sensors can detect maternal and fetal heart rate there are likely no safety implications for participants. However, if examination of the maternal or fetal heart rate identified a problem during the experimental protocol the procedure would be stopped and the mother transferred to a left-lateral position to allow a period for the abnormal observations to resolve. The mother would be clinically assessed by the research midwife, if the abnormal observations do not resolve the mother would be transferred to the maternity department at St Mary's Hospital for further management. A handover would be given to the clinical staff by the research midwife looking after the participant. The need to terminate the protocol would be recorded in the study and reported in the final analysis.

We will stop the study earlier if we achieve our outcomes before completing our recruitment targets.

12) PEER REVIEW

This study has been peer-reviewed as part of the Maternal and Fetal Health Research Centre annual peer review from Tommy's. The funding for the project has been continued following a favourable peer review although we have not been given specific comments. Additional independent external review has been obtained from Prof Fiona Dennison from the University of Edinburgh.

13) ETHICAL and REGULATORY CONSIDERATIONS

13.1 Approvals

Health Research Authority approval will be obtained before commencing research processes. The Medicines and Health Regulatory Agency (MHRA) have confirmed that as this study is for academic interest only, approval from the MHRA is not required. The study will be conducted in full conformance with all relevant legal requirements and the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) and the UK Policy Framework for Health and Social Care Research 2017.

13.2 Risks

As with any study maintaining confidentiality is an important consideration and measures will be put in place to ensure this. For example, all paper confidential information will be stored securely in a locked filing drawer in the Maternal & Fetal Health Research Centre and will only be accessible to members of the research team. All electronic information will use trial identification numbers and will be stored on a secure computer.

Participants may also be concerned that the views they express during the study may affect their rapport with their care givers. All pregnant participants will be reassured that this will not happen as the questionnaires will be administered by a research midwife who is not involved in delivering patient care, nor will divulge participants' views to staff members. Potential participants may feel under pressure to participate. Participants will be assured that participation / non-participation will not affect their care.

There is a risk that women receiving monitoring with new sensors may believe that they are receiving additional monitoring of their baby and therefore do not need to be aware of normal signs of pregnancy compromise. Due to this risk all women would be made aware that the purpose of the study is to assess the ability of these new sensors to detect mother and baby's heart rates. This information will be available in the participant information sheet, the consent form and will be subsequently reiterated prior to written consent and use of the sensors.

If any participant discloses something which raises serious concerns about the safety of themselves or others, it may be necessary to break confidentiality and inform relevant parties. If the issue was regarding the safety of a child or vulnerable adult the Manchester University Foundation NHS Trust's child protection and adult safeguarding policies would be followed.

There are no risks to the researchers.

14) STATEMENT OF INDEMNITY

The University has insurance available in respect of research involving human subjects that provides cover for legal liabilities arising from its actions or those of its staff or supervised students. The University also has insurance available that provides compensation for non-negligent harm to research subjects occasioned in circumstances that are under the control of the University.

15) FUNDING and RESOURCES

This study is funded by Tommy's and internal funding from the University of Manchester from the Engineering and Physical Sciences Research Council (EPSRC).

16) PUBLICATION POLICY

The investigators will disseminate the results of this study at appropriate national and international scientific meetings such as the British Maternal Fetal Medicine Society. The findings will be included in a Masters Thesis submitted by Ewa Matthews and a PhD thesis submitted by Mr Mhd Anas Alsakkel. No personal identifiable information will be included in the dissemination of study findings.

Primary responsibility for preparing publications will lie with the Chief Investigator, Prof Alexander Heazell. To safeguard the integrity of the study, data from the study will not be presented in public before the main results are published without the prior consent of the co-investigators. Acknowledgements will include the trial staff at the study site.

Participants will not be informed of the results directly as this would require storing personal information (address/email address) for an extended period. We will publish a summary on our new departmental website (currently under development) and will signpost participants to that.

17) REFERENCES

1. Alfirevic Z, Stampalija T, Gyte GM. Fetal and umbilical Doppler ultrasound in normal pregnancy. *Cochrane Database Syst Rev* 2010; (8): CD001450.
2. Alfirevic Z, Stampalija T, Gyte GM. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. *Cochrane Database Syst Rev* 2010; (1): CD007529.
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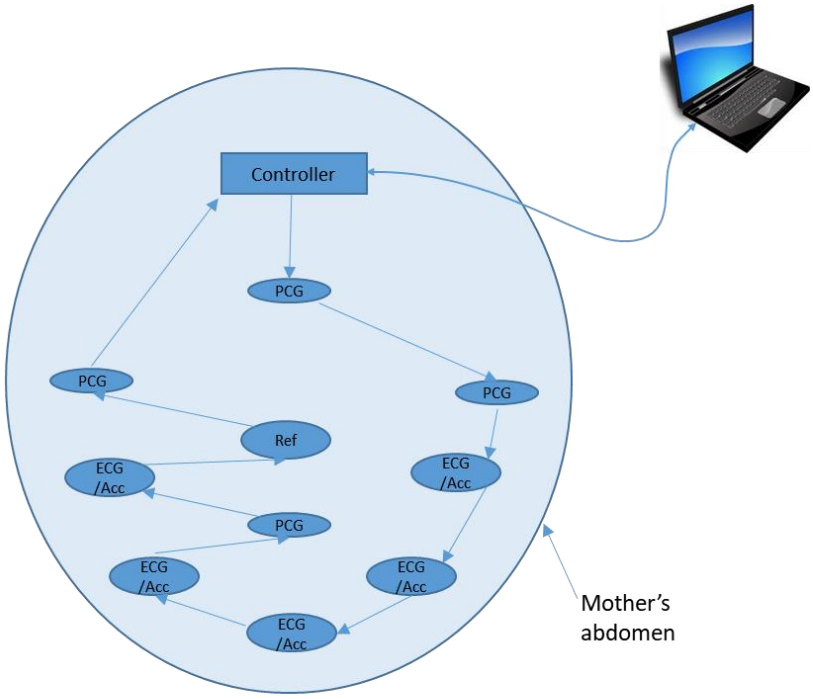
4. Brown R, Wijekoon JH, Fernando A, Johnstone ED, Heazell AE. Continuous objective recording of fetal heart rate and fetal movements could reliably identify fetal compromise, which could reduce stillbirth rates by facilitating timely management. *Medical hypotheses* 2014; **83**(3): 410-7.
5. Brown R, Johnstone ED, Heazell AE. Professionals' views of fetal-monitoring support the development of devices to provide objective longer-term assessment of fetal wellbeing. *J Matern Fetal Neonatal Med* 2016; **29**(10): 1680-6.
6. Crawford A, Hayes D, Johnstone ED, Heazell AEP. Women's experiences of continuous fetal monitoring - a mixed-methods systematic review. *Acta Obstet Gynecol Scand* 2017; **96**(12): 1404-13.
7. Crawford A, Anyadi P, Stephens L, et al. A mixed-methods evaluation of continuous electronic fetal monitoring for an extended period. *Acta Obstet Gynecol Scand* 2018; **97**(12): 1515-23.

Appendix A

The diagram in Figure 1 shows illustration of a typical planned sensor array design.



PCG: phonocardiographic sensor
ECG: electrocardiogram
Ref: driven reference electrode for ECG array
Acc: accelerometer

Figure 1. Sketch of potential sensor array configuration for fetal heart monitoring

An array of sensors similar to the one presented in Figure 1 will be held onto a pregnant woman's abdomen by means of an elasticated vest such as the one shown in Figure 2:

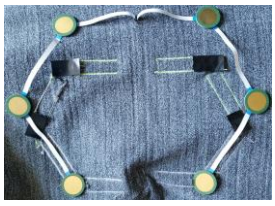


Figure 2. Demonstration 0f an ECG sensor arrangement.

Electrical safety

The only intended active element of the array is the reference electrode commonly known as the "right leg driver". The body, acting as an antenna, picks up electrical environmental noise (primarily at 50Hz) that interferes with electropotentials picked up at the skins surface. The driven right leg actively cancels this interference. This driver is connected to a patient via a 100 kΩ resistor. The other electrodes are capacitively coupled to their respective amplifiers, the d.c. current flowing under no-fault will be much lower than the "right leg driver" electrode.

For the "right leg driver", with the op-amp power supply voltage set at 5V, in the no-fault condition, the limit is 10 μA (American Standard). The maximum current that could flow from the amplifier into the body in a single fault condition is less than the regulatory limit of 50μA [1] (for example, a fault might constitute the grounding of another electrode). [This limit increases to 5mA at 100kHz]. These current limit conditions require that the equipment is isolated from the patient.

Driven right leg circuits [2] have been in common usage within ECG equipment for a number of years.

Electrical Isolation

All testing on pregnant women will be carried out with the monitoring laptop **PC using battery power**, so as to ensure that any equipment fault will not result in electric shock at mains voltage. We will attached the laptop computer to a monitor that will be mains powered. **Additional signal and power line isolation is provided between laptop and the patient mount ECG equipment** – It avoids excessive electrical *noise* coupling, but also adds another layer to patient safety.

References for Appendix A

1. "Safe current limits for electromedical apparatus". ANSI/AAMI ES1-1993. See Table 1.
2. "Driven-right-leg circuit design". Winter, B.B. and Webster, J.G., 1983. IEEE Transactions on Biomedical Engineering, (1), pp.62-66.