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# HOspital care versus TELemonitoring in high-risk pregnancy (HOTEL); study protocol for a multicentre non-inferiority randomised controlled trial

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|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2019-031700 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 15-May-2019 |
| Complete List of Authors: | van den Heuvel, Josephus; UMC Utrecht<br>Ganzevoort, Wessel; Amsterdam Universitair Medische Centra<br>De Haan-Jebbink, Jiska; OLVG<br>van der Ham, D.P.; Martini Ziekenhuis<br>Deurloo, Koen; Diakonessenhuis Utrecht Zeist Doorn Locatie Utrecht<br>Seeber, Laura; Sint Antonius Hospital<br>Franx, Arie; UMC Utrecht<br>Bekker, Mireille; UMC Utrecht |
| Keywords: | Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, OBSTETRICS, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Maternal medicine < OBSTETRICS, Fetal medicine < OBSTETRICS |
| | |

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**Protocol**

# HOspital care versus TELemonitoring in high-risk pregnancy (HOTEL); study protocol for a multicentre non-inferiority randomised controlled trial

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Word count: max 4000, nu 2649

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## Abstract

### Introduction

Pregnant women faced with complications of pregnancy often require long-term hospital admission for maternal and/or fetal monitoring. Antenatal admissions cause a burden to patients as well as hospital resources and costs. A telemonitoring platform connected to wireless cardiotocography (CTG) and automated blood pressure devices can be used for telemonitoring in pregnancy. Home telemonitoring might improve autonomy and reduce admissions and thus costs. The aim of this study is to compare the effects on patient safety, satisfaction and cost-effectiveness of hospital care versus telemonitoring (HOTEL) as an obstetric care strategy in high-risk pregnancies requiring daily monitoring.

### Methods and analysis

The HOTEL trial is a multicentre randomized controlled clinical trial with a non-inferiority design. Eligible pregnant women are >26+0 weeks of singleton gestation requiring monitoring because of preeclampsia (hypertension with proteinuria), fetal growth restriction, preterm rupture of membranes without contractions, recurrent reduced fetal movements, or a fetal demise in obstetric history.

Randomisation takes place between traditional hospitalization versus telemonitoring until delivery. During telemonitoring pregnant women at home will use the Sense4Baby CTG device and Microlife blood pressure monitor and they will have daily telephone calls with an obstetric health care professional as well as weekly visits to the hospital.

Primary outcome is a composite of adverse perinatal outcome, defined as perinatal mortality, 5-minute Apgar < 7 or arterial cord blood pH < 7.05, maternal morbidity (eclampsia, HELLP syndrome, thromboembolic event), neonatal intensive care admission and caesarean section rate. Patient satisfaction and preference of care will be assessed using validated




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questionnaires. We will perform an economic analysis. Outcomes will be analysed according to the intention to treat principle.

## Ethics and dissemination

The study protocol was approved by the Ethics Committee of the Utrecht University Medical Center and the boards of all six participating centres. Trial results will be submitted to peer-reviewed journals.

**Trial registration** NTR6076, registered September 2016

**Keywords**

Telemonitoring, preeclampsia, preterm birth, fetal growth restriction, high-risk pregnancy, telemedicine, fetal monitoring, home-based care, eHealth

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**Strengths and limitations of this study**

- An estimated 11% of all pregnant women require daily monitoring at some point during pregnancy because of complications, leading to hospital admission.
- This is the first randomised trial to evaluate a digital health innovation for telemonitoring of both fetal and maternal parameters, self- recorded by the pregnant patient at home.
- To minimise bias by patient selection, the randomised multicentre design increases generalizability of the study results comparing hospital admission versus telemonitoring during high-risk pregnancy.
- Alongside safety reporting of perinatal outcomes, analysis of patient preferences and cost-effectiveness of both strategies will be performed.
- Digital innovations need multi-faceted evaluation before widespread implementation.

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## Introduction

For pregnant women diagnosed with complications, increased monitoring and observation of maternal and fetal parameters is recommended.[1] The aim of daily monitoring in high-risk pregnancies is to assess fetal and maternal condition using tests such as blood pressure (BP), urinary and blood analysis and cardiotocography (CTG). This increased surveillance essentially leads to antenatal hospitalisation in up to 11% of pregnancies, mostly for preterm rupture of membranes (PROM), fetal growth restriction (FGR), (gestational) diabetes mellitus, imminent preterm birth, fetal anomalies, and hypertensive disorders including preeclampsia (PE).[2,3,4] These admissions, often until delivery, result in dissatisfaction with the in-hospital stay, family burden and significant costs.[5,6]

Recent technological advancements in health care (*eHealth*) have resulted in remote monitoring platforms, mobile device-supported care, telemedicine and teleconsultation.[7] eHealth has the potential to increase patient engagement and empowerment and create better access to health care while reducing the necessity for hospital visits or admittance.[8] Pregnant women are frequent users of smartphones and internet, and therefore already equipped with the hardware to take self-measurements at home and the mind-set to communicate these digitally with their prenatal care professional.[9] Telemonitoring of pregnancy is perceived to be one of the most promising answers to the possibilities of e-health in antenatal care.

Using a validated automated blood pressure monitoring device (Microlife WatchBP) and a wireless, portable CTG system (Sense4Baby), a telemonitoring strategy could replace hospital admission that require these types of monitoring.[10,11] Measurements, self-recorded by the pregnant women at home, are saved on the included tablet in a personal profile. Using a secured Internet portal, the data are integrated in the electronic patient record system enabling access for health care professionals. A pilot study using the Sense4Baby system was



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performed in UMC Utrecht to examine the accuracy of the tracings, the system's usability and participants' experiences and acceptability. Feedback and experiences from participants were positive about the used technology and no clinical relevant adverse events occurred (unpublished data, see also Patient involvement under Methods).

Currently, no clinical trials have evaluated this novel strategy with telemonitoring of self-recorded data in high-risk pregnancy before. While the patient at home will take care of measurements of CTG and blood pressure, a considerable amount of time could be saved on hospital ward or outpatient clinic for health care providers. Telemonitoring might therefore reduce costs and might offer a more acceptable form of pregnancy care.[12] However, risks of unevaluated implementation of digital innovations include usability problems, issues regarding safety and reimbursement, and adverse effects, resulting in disappointing adoption by the end-users. Therefore, patient safety and effectiveness of telemonitoring compared to antenatal admission have yet to be examined in a prospective trial.

In the HOTEL trial, a multicentre randomised controlled trial, we aim to compare hospital care to telemonitoring in high-risk pregnancy requiring daily monitoring. We will evaluate patient safety and clinical effectiveness as well as patient satisfaction and cost effectiveness of both strategies.

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## Methods

### Design and setting

This multicentre randomised controlled trial will be performed in 6 Dutch perinatal care units, including 2 university hospitals.

### Patient and public involvement

Prior to the start of the trial, pregnant women were involved in study set up. A pilot study was performed to check feasibility and acceptance of telemonitoring in pregnancy (see under Introduction) In focus groups, women with either antenatal admission or participation in the telemonitoring pilot joined our focus group studies (total n = 22) to report on satisfaction of antenatal care.[submitted data]

Hospitalized patients recalled anxiety, boredom and concerns about privacy on ward. Their family life was disturbed because of frequent travelling of partners and worries over their other child(s). The patients in the home telemonitoring group reported that use of the monitoring devices was uncomplicated after instruction. They reported relief about sleeping at home, better food, seeing partners and first child(s) more often and good feeling of security with at home monitoring and weekly face-to-face visits. With use of these focus group interviews, the telemonitoring strategy and study communications were improved and we developed the questionnaire that is used at the end of the study period.

### Eligibility criteria

Definitions of the inclusion criteria are fully described in Table 1. Eligible women must be ≥ 18 years old with a singleton pregnancy ≥ 26+0 weeks gestational age requiring hospital admittance for maternal or fetal surveillance for one (or multiple) of the following reasons: (1) preeclampsia; (2) preterm prelabour rupture of membranes (PPROM) without contractions; (3)



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fetal growth restriction (FGR); (4) recurrent reduced fetal movements; (5) fetal anomaly requiring daily monitoring (e.g. fetal gastroschisis); (6) intrauterine fetal death in previous pregnancy.

Exclusion criteria for participation in the study are (1) pregnancy complications requiring intravenous therapeutics or expected obstetric intervention within 48 hours; (2) current blood pressure >160/110 mmHg; (3) active antepartum haemorrhage or signs of placental abruption; (4) CTG registration with abnormalities indicating fetal distress or hypoxia; (5) place of residence > 30 minutes travel distance from a hospital; (6) multiple pregnancy; (7) insufficient knowledge of Dutch or English language or impossibility to understand training or instructions of telemonitoring devices.

| | **Inclusion criteria** | **Additional definitions or criteria (other than exclusion criteria)** |
|---|---|---|
| 1 | Preeclampsia | Defined as:<br>- hypertension (diastolic blood pressure > 90 mmHg and/or systolic blood pressure > 140 mmHg with proteinuria<br>- no restriction on use of oral antihypertensive medication |
| 2 | Preterm rupture of membranes | - No present contractions<br>- cephalic or breech position, with engaged fetal head or breech |
| 3 | Fetal growth restriction | Defined as:<br>- fetal abdominal circumference (fAC) or estimated fetal weight (EFW) <10th percentile and abnormal Doppler sonography assessment defined as pulsatility index (PI) of umbilical artery >p95 and/or absence or reversed end diastolic flow velocity flow of umbilical artery<br>- fAC or EFW <p3 with or without abnormal umbilical artery Doppler flow |
| 4 | Recurrent reduced fetal movements | |
| 5 | Fetal anomaly requiring daily monitoring | |
| 6 | Intrauterine fetal death in previous pregnancy | |

**Table** 1 Additional information on inclusion criteria.



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**Recruitment and randomisation**

Eligible women will be approached and informed by obstetric care professionals i.e. physicians, (research) midwives or research nurses. Following counselling and sufficient time for questions, written informed consent is obtained and participants will be randomly allocated to either hospital admission or telemonitoring. Randomisation will be performed through a secured web-based domain (Research Online, Julius Research Support, UMC Utrecht) and will be stratified for diagnosis for inclusion and centre of inclusion. Block randomisation with variable block sizes of 4 and 6 is used.

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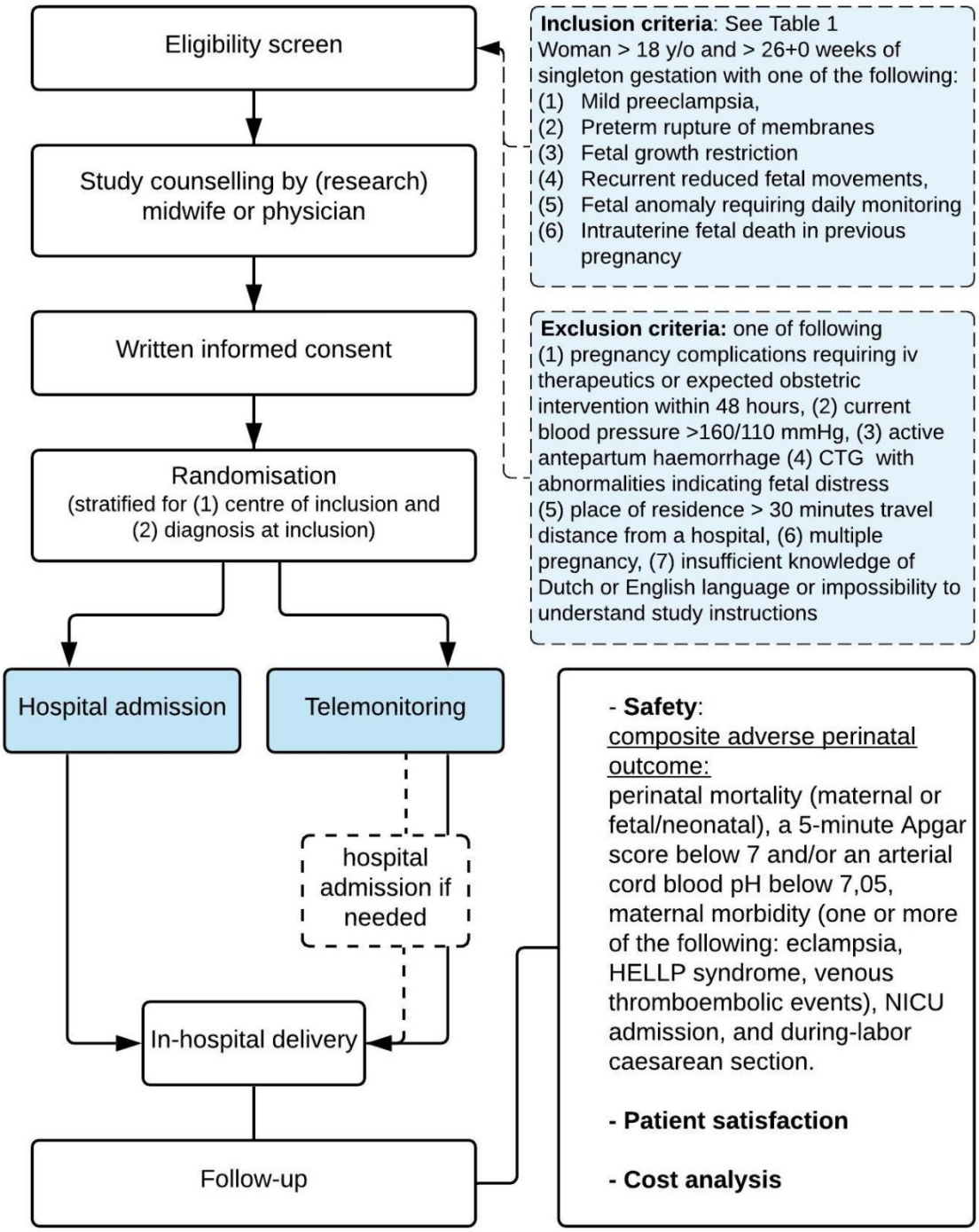


**Figure 1 :** Flowchart of study procedures



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**Intervention group: telemonitoring**

Prior to the start of the study we will provide support and training of the telemonitoring strategy in each participating hospital to ensure local reliance on the technological aspects as well as task definition for the different roles. A telemonitoring team in each centre will be trained how to register, train and technically enrol new participants on the novel platform after randomisation for telemonitoring. As set in each local research protocol, responsibilities of health care providers are assigned to each task within the strategy: training new participants, daily monitoring of uploaded parameters, antenatal management after reviewing new results, and daily telephone contact with the pregnant women at home.

After randomisation for telemonitoring, the participant will be trained in using the medical devices involved in the system (Sense4Baby CTG system and the Microlife Watch BP, both CE marked). The training will be conducted using standardized instructions of use. The instructions include a contact sheet with telephone numbers for technical or health related questions, accessible 24/7. Each participant will receive an individual treatment plan according to national and/or local guidelines, including fetal CTG monitoring and blood pressure measurement, both once daily. Participants at home are contacted by phone every day by the telemonitoring team, to discuss present symptoms or questions regarding the pregnancy. Possible protocolled steps in the management, after the uploaded test results are checked, are: 1) expectant management, 2) same-day clinical assessment (e.g. in case of CTG abnormalities, rise in BP or symptoms) or 3) if necessary clinical admission. The participant will visit the outpatient clinic at least once a week for real-time contact and when needed ultrasound assessment, blood or urinary analysis. Should hospital admission be necessary in case of change in clinical presentation or deterioration (e.g. non-reassuring CTG, hypertension, contractions, antepartum haemorrhage, signs of infection, maternal distress or technical difficulties), the patient will be monitored in the hospital as per local protocol and all data of interest during the admission will be collected. In



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the case this same participant can be discharged from ward again (e.g. after treatment optimisation for hypertension), she may go home with telemonitoring - as per randomisation- until delivery. All consultations in the outpatient department and possible ward admissions during pregnancy will be recorded for the study.

**Control group: hospital admission**

Pregnant women allocated to hospital admittance will receive standard obstetric care according to national and local guidelines and current state of the art, including daily fetal monitoring and blood pressure measurements. All participating centres committed to following guidelines for different diagnoses and management as set by the Dutch Society of Obstetrics and Gynecology. Blood and/or urine sampling and fetal ultrasound will be performed when indicated and according to local protocol. In case the necessity of hospital admission is no longer present, the patient may be discharged and if necessary admitted to ward again, as per randomisation, not allowing cross-over to telemonitoring.

**Outcome measures**

The primary outcome is maternal and fetal/neonatal safety during perinatal care from study inclusion by recording incidence of perinatal mortality and maternal and neonatal morbidity. The composite of adverse perinatal outcome is defined as: 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 and caesarean section rate.

Secondary outcome will consist of patient satisfaction, quality of life and cost effectiveness.

The satisfaction, experience and quality of life of every participating pregnant woman will be surveyed with help of the EuroQol 5D (EQ-5D), State Trait Anxiety Inventory (STAI) and Edinburgh Postnatal Depression Score (EPDS) questionnaires.[13,14,15] Surveys are sent by



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e-mail at study start, and 1, 3, 5 weeks after randomisation and 4 weeks after delivery. With the help of focus group discussion (see under Patient involvement), we created a questionnaire which will be filled out 4 weeks after delivery.

The cost effectiveness and budget impact analyses (CEA and BIA) will be assessed from different perspectives, i.e. hospitals, health insurance companies and from the societal perspective. The budget impact analysis will follow ISPOR guidelines for budget impact analyses to calculate the differences in budgetary impact of telemonitoring and hospital admittance in high-risk pregnancies. For the CEA and the BIA, we will record duration of telemonitoring and duration of admittance (number of days), number of consultations and health care provider involved, number and length of CTG registration, number of maternal blood analyses and ultrasound assessments, emergency transport to the hospital and emergency caesarean sections. Besides this maternal use of health services, all health service use of the newborn during the follow-up period (until discharge to home) will be recorded.

**Sample size**

The sample size calculation is based on the assumption that the composite of adverse perinatal outcome will be equal in the telemonitoring and the hospital admittance patient groups: a non-inferiority trial. To estimate this risk for adverse perinatal outcome in our inclusion criteria, we made use of the results of three large Dutch randomised controlled trials for patients with PPROM, FGR and preeclampsia.[16,17,18] The incidence of this composite primary outcome in the high-risk pregnancy group is estimated at 20%.

In the sample size calculation an increase of no more than 10% in the adverse perinatal outcome is accepted. If alpha = 0.05 and power is 80%, the sample size per arm is 200 pregnant women. The sample size was calculated for non-inferiority testing using PASS software.



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**Data handling, analysis and result reporting**

At study entry, baseline data like patient demographics, medical and obstetric history and current pregnancy details are collected. At delivery relevant data will be collected for the assessment of perinatal outcomes such as gestational age at birth, birth weight, condition at birth (Apgar scores, umbilical cord blood gas analysis), neonatal admission (type of ward and number of days). Neonatal mortality and morbidity will be specified. For the mother, data will be collected on treatment for pain relief, mode of delivery and adverse outcomes (eclampsia, thromboembolic events and HELLP syndrome). Standardized online case record forms developed by Julius Centre for Research Support (UMC Utrecht) are used, including source data verification options.

Data analyses will primarily be carried out according to the intention-to-treat principle, i.e. the participants will be analysed according to their randomized allocation, regardless of the actual interventions received by the patient. Results will be reported according to CONSORT guidelines, using the extension for non-inferiority trials. Supplementary, we will perform analyses per protocol. If necessary, skewed continuous variables will be transformed to normality prior to the analyses.

The primary outcome, the composite (dichotomous) endpoint of perinatal mortality will be analysed with logistic regression analysis with correction of predefined confounders as parity, taken into account that randomisation has already taken place with stratification for centre of inclusion and diagnosis of pregnancy complication.

Secondary outcomes, patient satisfaction and health related quality of life, will be analysed with a general linear model for continuous outcomes. Assumptions for general linear model (i.e. normality, homoscedasticity) will be checked with residual analyses. In case of heteroscedasticity, the analyses will be repeated with robust (Hubert-White) estimators for standard errors. If distributional assumptions are violated, first a log transformation of the



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outcome will be analysed. If this transformation does not result in a valid regression analysis, intervention effects will be evaluated with a Mann-Whitney test without any corrections.

Time to delivery will be evaluated by Kaplan-Meier estimates, with account for different durations of gestation at entry, and will be tested with the log rank test.

For the cost-effectiveness analysis, all health care resources use will be transformed into cost estimates, by multiplying number of units of health care use, i.e. number of days in hospital, number of laboratory tests and other diagnostic tests with standard unit prices as provided by the Dutch guideline for costing research in health economic evaluation studies (National Health Care Institute, Zorginstituut Nederland, 2016). For medical costs, the process of care is divided into three cost stages (antenatal stage, delivery/childbirth, postnatal stage). Cost differences between the two treatment arms will be related to effect differences (primary outcome) between the treatment arms (if any). If non-inferiority of telemonitoring is confirmed, the analysis will be restricted to analysis of cost differences between the two treatment arms (cost-minimization analysis). The cost effectiveness analysis will be performed from both the healthcare perspective and the societal perspective.

**Study monitoring and safety**

To monitor the conduct of the trial and safeguard the interest of participants, an independent Data Safety Monitoring Board (DSMB) will be established. A study monitor will periodically visit participating centres, assessing quality of data and auditing trial conduct. All serious adverse events, reported by either participant or local clinician, will be recorded, and reported to the accredited ethics committee and the DSMB following international GCP guidelines.

**Ethics and dissemination**

This trial has been approved by the Medical Research Ethics Committee (MREC) of the UMC Utrecht. Trial reference number: 16-516. The MREC of the UMC Utrecht is accredited by the



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Central Committee on Research Involving Human Subjects (CCMO) since November 1999. For all participating study sites approval by the boards of management is obtained. Changes to the study protocol are documented in amendments and submitted for approval to the MREC. After completion of the trial the principal investigator will report on the results of the main study and submit a manuscript to a peer-reviewed medical journal. Supplementary analyses will be reported separately.

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**Trial Sponsor:**

Institution: University Medical Center Utrecht Utrecht University

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**Data availability statement:**



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The datasets used and/or analyzed during the current study will be made available from the corresponding author on reasonable request.

**Authors' contributions**

Study concept, trial design and study protocol: JFH, AF, MB

Acquisition of data: JFH, AF, MB, WG, JdHJ, KD, DH, LS

Drafting of the manuscript: JFH, AF, MB

Critical revision of the manuscript for important intellectual content: all authors

Study supervision: AF, MB

All authors edited the manuscript and read and approved the final draft.

**Funding statement**

This work was supported by Stichting Achmea Gezondheidszorg grant number Z659 and BMA-Telenatal BV. Neither the sponsor, nor Stichting Achmea Gezondheidszorg nor BMA-Telenatal is involved in the study design, interpretation of data or planned result reporting.

**Competing interests statement.**

The authors declare that they have no competing interest.



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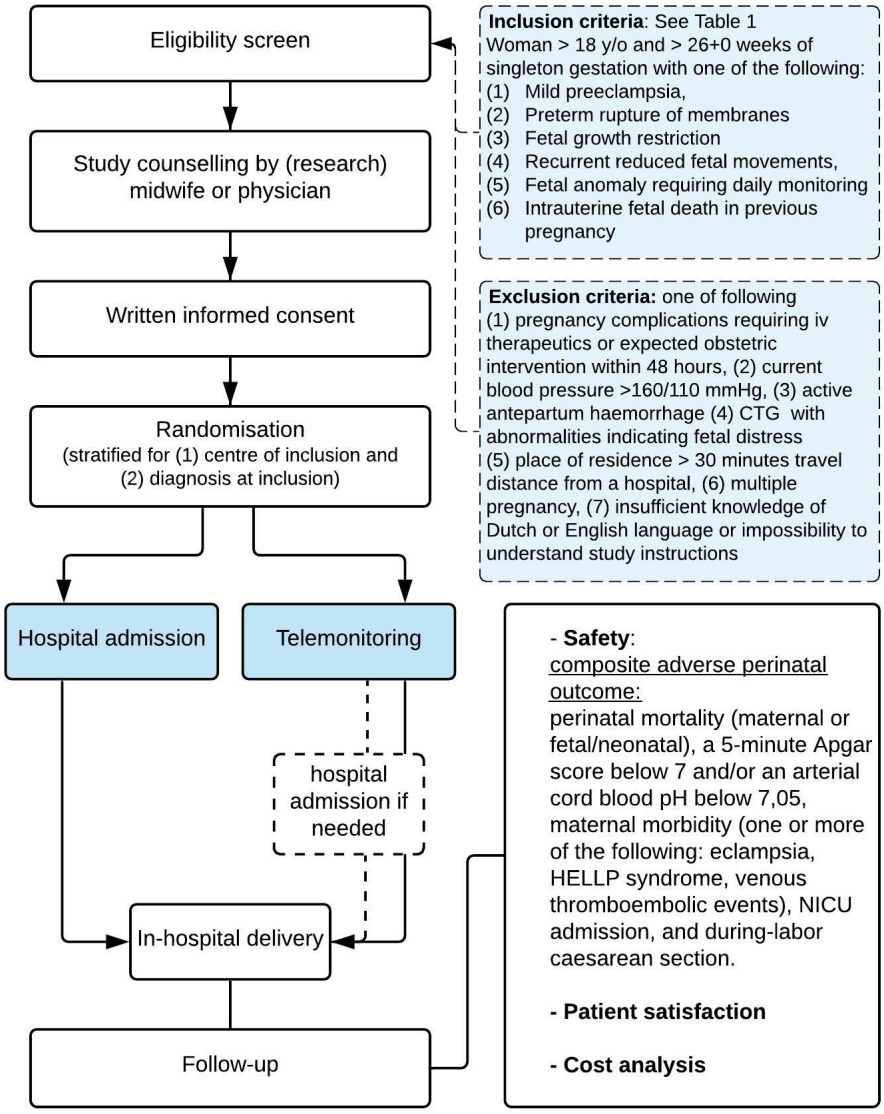


Figure 1 : Flowchart of study procedures

123x152mm (300 x 300 DPI)

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addresed on manuscript page |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 3, 14 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | 3, 14 |
| Protocol version | 3 | Date and version identifier | |
| Funding | 4 | Sources and types of financial, material, and other support | 18 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 18 |
| | 5b | Name and contact information for the trial sponsor | 17-18 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 18 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 14 |
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5,6 |
| | 6b | Explanation for choice of comparators | 5,6 |
| Objectives | 7 | Specific objectives or hypotheses | 6 |

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|---|---|---|---|---|
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 13 | |
| **Methods: Participants, interventions, and outcomes** | | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 7 | |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 7,8 | |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 10,11 | |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 10,11 | |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | n/a | |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 10,11 | |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 12 | |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | Fig 1 | |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 13 | |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 8,13 | |
| **Methods: Assignment of interventions (for controlled trials)** | | | | |
| Allocation: | | | | |



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| | | | |
|---|---|---|---|
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 8 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 8 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 8 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | n/a |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | n/a |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 13,14 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 13,14 |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 13,14 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 14 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 14,15 |



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|---|---|---|---|---|
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 14 | |
| **Methods: Monitoring** | | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 15 | |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | n/a | |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 15 | |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 15 | |
| **Ethics and dissemination** | | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 15 | |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 15 | |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 8 | |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n/a | |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 13,15 | |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 19 | |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 18 | |

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|---|---|---|---|---|
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | | |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 15 | |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | n/a | |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 18 | |
| **Appendices** | | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | appendix | |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a | |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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# HOspital care versus TELemonitoring in high-risk pregnancy (HOTEL); study protocol for a multicentre non-inferiority randomised controlled trial

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| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2019-031700.R1 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 08-Aug-2019 |
| Complete List of Authors: | van den Heuvel, Josephus; UMC Utrecht<br>Ganzevoort, Wessel; Amsterdam Universitair Medische Centra<br>De Haan-Jebbink, Jiska; OLVG<br>van der Ham, D.P.; Martini Ziekenhuis<br>Deurloo, Koen; Diakonessenhuis Utrecht Zeist Doorn Locatie Utrecht<br>Seeber, Laura; Sint Antonius Hospital<br>Franx, Arie; UMC Utrecht<br>Bekker, Mireille; UMC Utrecht |
| Primary Subject Heading: | Obstetrics and gynaecology |
| Secondary Subject Heading: | Patient-centred medicine |
| Keywords: | Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, OBSTETRICS, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Maternal medicine < OBSTETRICS, Fetal medicine < OBSTETRICS |
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**Protocol**

# HOspital care versus TELemonitoring in high-risk pregnancy (HOTEL); study protocol for a multicentre non-inferiority randomised controlled trial

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## Abstract

### Introduction

Pregnant women faced with complications of pregnancy often require long-term hospital admission for maternal and/or fetal monitoring. Antenatal admissions cause a burden to patients as well as hospital resources and costs. A telemonitoring platform connected to wireless cardiotocography (CTG) and automated blood pressure devices can be used for telemonitoring in pregnancy. Home telemonitoring might improve autonomy and reduce admissions and thus costs. The aim of this study is to compare the effects on patient safety, satisfaction and cost-effectiveness of hospital care versus telemonitoring (HOTEL) as an obstetric care strategy in high-risk pregnancies requiring daily monitoring.

### Methods and analysis

The HOTEL trial is an ongoing multicentre randomized controlled clinical trial with a non-inferiority design. Eligible pregnant women are >26+0 weeks of singleton gestation requiring monitoring because of preeclampsia (hypertension with proteinuria), fetal growth restriction, preterm rupture of membranes without contractions, recurrent reduced fetal movements, or an intrauterine fetal death in a previous pregnancy.

Randomisation takes place between traditional hospitalization versus telemonitoring until delivery. During telemonitoring pregnant women at home will use the Sense4Baby CTG device and Microlife blood pressure monitor and they will have daily telephone calls with an obstetric health care professional as well as weekly visits to the hospital.

Primary outcome is a composite of adverse perinatal outcome, defined as perinatal mortality, 5-minute Apgar < 7 or arterial cord blood pH < 7.05, maternal morbidity (eclampsia, HELLP syndrome, thromboembolic event), neonatal intensive care admission and caesarean section rate. Patient satisfaction and preference of care will be assessed using validated




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questionnaires. We will perform an economic analysis. Outcomes will be analysed according to the intention to treat principle.

**Ethics and dissemination**

The study protocol was approved by the Ethics Committee of the Utrecht University Medical Center and the boards of all six participating centres. Trial results will be submitted to peer-reviewed journals.

**Trial registration** NTR6076, (September 2016)

**Keywords**

Telemonitoring, preeclampsia, preterm birth, fetal growth restriction, high-risk pregnancy, telemedicine, fetal monitoring, home-based care, eHealth

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**Strengths and limitations of this study**

- An estimated 11% of all pregnant women require daily monitoring at some point during pregnancy because of complications, leading to hospital admission.
- This is the first randomised trial to evaluate a digital health innovation for telemonitoring of both fetal and maternal parameters, self- recorded by the pregnant patient at home.
- To minimise bias by patient selection, the randomised multicentre design increases generalizability of the study results comparing hospital admission versus telemonitoring during high-risk pregnancy.
- Alongside safety reporting of perinatal outcomes, analysis of patient preferences and cost-effectiveness of both strategies will be performed.
- Digital innovations need multi-faceted evaluation before widespread implementation.

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## Introduction

For pregnant women diagnosed with complications, increased monitoring and observation of maternal and fetal parameters is recommended.[1] The aim of daily monitoring in high-risk pregnancies is to assess fetal and maternal condition using tests such as blood pressure (BP), urinary and blood analysis and cardiotocography (CTG). This increased surveillance essentially leads to antenatal hospitalisation in up to 11% of pregnancies, mostly for preterm rupture of membranes (PROM), fetal growth restriction (FGR), (gestational) diabetes mellitus, imminent preterm birth, fetal anomalies, and hypertensive disorders including preeclampsia (PE).[2,3,4] These admissions, often until delivery, result in dissatisfaction with the in-hospital stay, family burden and significant costs.[5,6]

Recent technological advancements in health care (*eHealth*) have resulted in remote monitoring platforms, mobile device-supported care, telemedicine and teleconsultation.[7] eHealth has the potential to increase patient engagement and empowerment and create better access to health care while reducing the necessity for hospital visits or admittance.[8] Pregnant women are frequent users of smartphones and internet, and therefore already equipped with the hardware to take self-measurements at home and the mind-set to communicate these digitally with their prenatal care professional.[9] Telemonitoring of pregnancy is perceived to be one of the most promising answers to the possibilities of e-health in antenatal care.

Using a validated automated blood pressure monitoring device (Microlife WatchBP) and a wireless, portable CTG system (Sense4Baby), a telemonitoring strategy could replace hospital admission that require these types of monitoring.[10,11] Measurements, self-recorded by the pregnant women at home, are saved on the included tablet in a personal profile. Using a secured Internet portal, the data are integrated in the electronic patient record system enabling access for health care professionals. A pilot study (*n*=76) using the Sense4Baby system was



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performed in UMC Utrecht to examine the accuracy of the tracings, the system's usability and participants' experiences and acceptability. Feedback and experiences from participants were positive about the used technology and no clinical relevant adverse events occurred (unpublished data, see also Patient involvement under Methods).

Currently, no clinical trials have evaluated this novel strategy with telemonitoring of self-recorded data in high-risk pregnancy before. While the patient at home will take care of measurements of CTG and blood pressure, a considerable amount of time could be saved on hospital ward or outpatient clinic for health care providers. Telemonitoring might therefore reduce costs and might offer a more acceptable form of pregnancy care.[12] However, risks of unevaluated implementation of digital innovations include usability problems, issues regarding safety and reimbursement, and adverse effects, resulting in disappointing adoption by the end-users. Therefore, patient safety and effectiveness of telemonitoring compared to antenatal admission have yet to be examined in a prospective trial.

In the HOTEL trial, a multicentre randomised controlled trial, we aim to compare hospital care to telemonitoring in high-risk pregnancy requiring daily monitoring. We will evaluate patient safety and clinical effectiveness as well as patient satisfaction and cost effectiveness of both strategies.



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## Methods

### Design and setting

This ongoing multicentre randomised controlled trial will be performed in 6 Dutch perinatal care units, including 2 university hospitals. The study will be open label. The trial protocol was registered in September 2016 (NTR6076) and first inclusion took place in December 2016.

### Patient and public involvement

Prior to the start of the trial, pregnant women were involved in study set up. A pilot study was performed to check feasibility and acceptance of telemonitoring in pregnancy (see under Introduction) In focus groups, women with either antenatal admission or participation in the telemonitoring pilot joined our focus group studies (total n = 22) to report on satisfaction of antenatal care.[submitted data]

Hospitalized patients recalled anxiety, boredom and concerns about privacy on ward. Their family life was disturbed because of frequent travelling of partners and worries over their other child(s). The patients in the home telemonitoring group reported that use of the monitoring devices was uncomplicated after instruction. They reported relief about sleeping at home, better food, seeing partners and first child(s) more often and good feeling of security with at home monitoring and weekly face-to-face visits. With use of these focus group interviews, the telemonitoring strategy and study communications were improved and we developed the questionnaire that is used at the end of the study period.

### Eligibility criteria

Definitions of the inclusion criteria are fully described in Table 1. Eligible women must be ≥ 18 years old with a singleton pregnancy ≥ 26+0 weeks gestational age requiring hospital admittance for maternal or fetal surveillance for one (or multiple) of the following reasons: (1)



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preeclampsia; (2) preterm prelabour rupture of membranes (PPROM) without contractions; (3) fetal growth restriction (FGR); (4) recurrent reduced fetal movements; (5) fetal anomaly requiring daily monitoring (e.g. fetal gastroschisis); (6) intrauterine fetal death in previous pregnancy.

Exclusion criteria for participation in the study are (1) pregnancy complications requiring intravenous therapeutics or expected obstetric intervention within 48 hours; (2) current blood pressure >160/110 mmHg; (3) active antepartum haemorrhage or signs of placental abruption; (4) CTG registration with abnormalities indicating fetal distress or hypoxia; (5) place of residence > 30 minutes travel distance from a hospital; (6) multiple pregnancy; (7) insufficient knowledge of Dutch or English language or impossibility to understand training or instructions of telemonitoring devices.

| | **Inclusion criteria** | **Additional definitions or criteria (other than exclusion criteria)** |
|---|---|---|
| 1 | Preeclampsia | Defined as:<br>- hypertension (diastolic blood pressure > 90 mmHg and/or systolic blood pressure > 140 mmHg with proteinuria following ISSHP criteria at the time of study design (FGR is defined below[13]<br>- no restriction on use of oral antihypertensive medication |
| 2 | Preterm rupture of membranes | - No present contractions<br>- cephalic or breech position, with engaged fetal head or breech |



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| | | |
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| 3 | Fetal growth restriction | Defined as:<br>- fetal abdominal circumference (fAC) or estimated fetal weight (EFW) <10th percentile and abnormal Doppler sonography assessment defined as pulsatility index (PI) of umbilical artery >p95 and/or absence or reversed end diastolic flow velocity flow of umbilical artery<br>- fAC or EFW <p3 with or without abnormal umbilical artery Doppler flow |
| 4 | Recurrent reduced fetal movements | |
| 5 | Fetal anomaly requiring daily monitoring | |
| 6 | Intrauterine fetal death in previous pregnancy | |

**Table** 1 Additional information on inclusion criteria.

**Recruitment and randomisation**

Eligible women will be approached and informed by obstetric care professionals i.e. physicians, (research) midwives or research nurses. Following counselling and sufficient time for questions, written informed consent is obtained and participants will be randomly allocated in a 50:50 ratio to either hospital admission or telemonitoring. Randomisation will be performed through a secured web-based domain (Research Online, Julius Research Support, UMC Utrecht) and will be stratified for 6 diagnoses for inclusion and 6 centres of inclusion. Block randomisation with



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variable block sizes is used. Cross over of trial arm is not permitted and will be considered a protocol violation. An overview of the study procedures is shown in Figure 1.

**Intervention group: telemonitoring**

Prior to the start of the study we will provide support and training of the telemonitoring strategy in each participating hospital to ensure local reliance on the technological aspects as well as task definition for the different roles. A telemonitoring team in each centre will be trained how to register, train and technically enrol new participants on the novel platform after randomisation for telemonitoring. As set in each local research protocol, responsibilities of health care providers are assigned to each task within the strategy: training new participants, daily monitoring of uploaded parameters, antenatal management after reviewing new results, and daily telephone contact with the pregnant women at home.

After randomisation for telemonitoring, the participant will be trained in using the medical devices involved in the system (Sense4Baby CTG system and the Microlife Watch BP, both CE marked). The training will be conducted using standardized instructions of use. The instructions include a contact sheet with telephone numbers for technical or health related questions, accessible 24/7. Each participant will receive an individual treatment plan according to national and/or local guidelines, including fetal CTG monitoring and blood pressure measurement, both once daily. Participants at home are contacted by phone every day by the telemonitoring team, to discuss present symptoms or questions regarding the pregnancy. Possible protocolled steps in the management, after the uploaded test results are checked, are: 1) expectant management, 2) same-day clinical assessment (e.g. in case of CTG abnormalities, rise in BP or symptoms) or 3) if necessary clinical admission. The participant will visit the outpatient clinic at least once a week for real-time contact and when needed ultrasound assessment, blood or urinary analysis. Should hospital admission be necessary in case of change in clinical presentation or



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deterioration (e.g. non-reassuring CTG, hypertension, contractions, antepartum haemorrhage, signs of infection, maternal distress or technical difficulties), the patient will be monitored in the hospital as per local protocol and all data of interest during the admission will be collected. In the case this same participant can be discharged from ward again (e.g. after treatment optimisation for hypertension), she may go home with telemonitoring - as per randomisation- until delivery. All consultations in the outpatient department and possible ward admissions during pregnancy will be recorded for the study.

**Control group: hospital admission**

Pregnant women allocated to hospital admittance will receive standard obstetric care according to national and local guidelines and current state of the art, including daily fetal monitoring and blood pressure measurements. All participating centres committed to following guidelines for different diagnoses and management as set by the Dutch Society of Obstetrics and Gynaecology. A typical regime on ward includes vital parameter check (blood pressure, temperature on indication) by obstetric nurses, daily cardiotocography and daily rotations by a resident in obstetrics and gynaecology, supervised by an obstetrician, for interpretation of results and further management. Blood and/or urine sampling and fetal ultrasound will be performed when indicated and according to local protocol. In case the necessity of hospital admission is no longer present, the patient may be discharged and if necessary admitted to ward again, as per randomisation, not allowing cross-over to telemonitoring.

**Outcome measures**

The primary outcome is maternal and fetal/neonatal safety during perinatal care from study inclusion onwards by recording incidence of perinatal mortality and maternal and neonatal morbidity. The composite of adverse perinatal outcome is defined as: perinatal mortality (maternal or fetal or neonatal), a 5-minute Apgar score below 7 and/or an arterial pH below



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7,05, maternal morbidity (one or more of the following: eclampsia, HELLP syndrome, thromboembolic events), NICU admission of the new-born and caesarean section rate. The components of the composite outcome are both chosen for either (or both) the possibility to be affected by the new intervention as well as the severity as a stand-alone adverse outcome. All components will be reported separately as a secondary outcome for interpretation of study results.

Secondary outcome will consist of patient satisfaction, quality of life and cost effectiveness.

The satisfaction, experience and quality of life of every participating pregnant woman will be surveyed with help of the EuroQol 5D (EQ-5D), State Trait Anxiety Inventory (STAI) and Edinburgh Postnatal Depression Score (EPDS) questionnaires.[14,15,16] Surveys are sent by e-mail at study start, and 1, 3, 5 weeks after randomisation and 4 weeks after delivery. With the help of focus group discussion (see under Patient involvement), we created a questionnaire which will be filled out 4 weeks after delivery.

The cost effectiveness and budget impact analyses (CEA and BIA) will be assessed from different perspectives, i.e. hospitals, health insurance companies and from the societal perspective. The budget impact analysis will follow ISPOR guidelines for budget impact analyses to calculate the differences in budgetary impact of telemonitoring and hospital admittance in high-risk pregnancies. For the CEA and the BIA, we will record duration of telemonitoring and duration of admittance (number of days), number of consultations and health care provider involved, number and length of CTG registration, number of maternal blood analyses and ultrasound assessments, emergency transport to the hospital and emergency caesarean sections. Besides this maternal use of health services, all health service use of the newborn during the follow-up period (until discharge to home) will be recorded.

**Sample size**



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Before the start of the trial, we formed an expert panel, consisting of gynaecologists, and paediatricians, methodologists, and statisticians to conceive the design, content, and execution of the trial. The sample size calculation is based on the assumption that the composite of adverse perinatal outcome will be equal in the telemonitoring and the hospital admittance patient groups: a non-inferiority trial.To estimate this risk for each individual component of adverse perinatal outcome in our inclusion criteria, we made use of the results of three large Dutch randomised controlled trials for patients with PPROM, FGR and preeclampsia.[17,18,19] No data on perinatal outcome of telemonitoring in high risk pregnancy are available to use in our sample size calculation. The incidence of this composite primary outcome in the high-risk pregnancy group is assumed to be 20% in either group. The panel made a reasoned choice about the acceptable difference in adverse perinatal outcome and feasibility of the trial, since this is the first ongoing trial of telemonitoring in complicated pregnancies. As a result, the non-inferiority margin (Δ) was defined as a 10% absolute increase or less in the telemonitoring group. With a one sided α of 0.05, the study will achieve a power (β) of more than 0.80 if 200 women will be included in each trial arm (400 women in total).

The sample size was calculated for non-inferiority testing with the one-sided Score test (Farrington & Manning) using PASS software.

**Data handling, analysis and result reporting**

At study entry, baseline data like patient demographics, medical and obstetric history and current pregnancy details are collected. At delivery relevant data will be collected for the assessment of perinatal outcomes such as gestational age at birth, birth weight, condition at birth (Apgar scores, umbilical cord blood gas analysis), neonatal admission (type of ward and number of days). Neonatal mortality and morbidity will be specified. For the mother, data will be collected on treatment for pain relief, mode of delivery and adverse outcomes (eclampsia, thromboembolic events and HELLP syndrome). Standardized online case record forms



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developed by Julius Centre for Research Support (UMC Utrecht) are used, including source data verification options. Missing data will be handled according to the complete-case analysis principle, based on the availability of the components needed to determine the primary endpoint.

## Primary outcome

Data analyses will primarily be carried out according to the intention-to-treat principle, i.e. the participants will be analysed according to their randomized allocation, regardless of the actual interventions received by the patient. Results will be reported according to CONSORT guidelines, using the extension for non-inferiority trials. If necessary, skewed continuous variables will be transformed to normality prior to the analyses. Supplementary, we will perform per protocol analyses excluding participants in whom there is a clear deviation or suboptimal execution of the intended care as prescribed by the protocol in either the admission group or the telemonitoring group. Examples include technical difficulties at home or non-compliance of study agreements, cross-over, or participants in the telemonitoring arm with (multiple) hospital admissions accounting for over half of the study period.

The primary outcome, the composite (dichotomous) endpoint of perinatal mortality and morbidity will be analysed with logistic regression analysis with the stratification factors (centre of inclusion and diagnosis of pregnancy complication) and parity as pre-defined covariates in the regression model. No pre-specified subgroup analyses are planned.

## Secondary outcomes

Each individual component outcome within the composite outcome will be reported as a single (secondary) outcome to provide further insight as the incidence and the relative importance between components of the composite outcome differ. Point estimates with confidence intervals for the comparison of groups will be reported for these components of the composite outcome.



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Patient satisfaction and health related quality of life will be analysed with a general linear model for continuous outcomes. Comparison of questionnaires will be made for each time point, with the survey at 4 weeks post delivery being the most important. Assumptions for general linear model (i.e. normality, homoscedasticity) will be checked with residual analyses. In case of heteroscedasticity, the analyses will be repeated with robust (Hubert-White) estimators for standard errors. If distributional assumptions are violated, first a log transformation of the outcome will be analysed. If this transformation does not result in a valid regression analysis, intervention effects will be evaluated with a Mann-Whitney test without any corrections.

Time to delivery with account for different durations of gestation at study entry, will be evaluated with Cox regression with control of the stratification factors and parity as a predifned covariate.

For the cost-effectiveness analysis, all health care resources use will be transformed into cost estimates, by multiplying number of units of health care use, i.e. number of days in hospital, number of laboratory tests and other diagnostic tests with standard unit prices as provided by the Dutch guideline for costing research in health economic evaluation studies (National Health Care Institute, Zorginstituut Nederland, 2016). For medical costs, the process of care is divided into three cost stages (antenatal stage, delivery/childbirth, postnatal stage). Cost differences between the two treatment arms will be related to effect differences (primary outcome) between the treatment arms (if any). If non-inferiority of telemonitoring is confirmed, cost differences between the two treatment arms will be analysed (cost-minimization analysis). The cost effectiveness analysis will be performed from both the healthcare perspective and the societal perspective.

**Study monitoring and safety**

To monitor the conduct of the trial and safeguard the interest of participants, an independent Data Safety Monitoring Board (DSMB) will be established, including a professor of biostatistics,



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an obstetrician and a neonatologist.. A study monitor will periodically visit participating centres, assessing quality of data and auditing trial conduct. All serious adverse events, reported by either participant or local clinician, will be recorded, and reported to the accredited ethics committee and the DSMB following international GCP guidelines. Trial data will be analysed and stored in the UMC Utrecht (study sponsor). No formal interim analysis of efficacy outcome is planned.

**Ethics and dissemination**

This trial has been approved by the Medical Research Ethics Committee (MREC) of the UMC Utrecht. Trial reference number: 16-516. The MREC of the UMC Utrecht is accredited by the Central Committee on Research Involving Human Subjects (CCMO) since November 1999. Approval by the boards of management of Amsterdam University Medical Center, Diakonessenhuis Utrecht, OLVG Amsterdam, Martini Ziekenhuis Groningen and St. Antonius Ziekenhuis Nieuwegein is obtained prior to study start in each centre. Changes to the study protocol are documented in amendments and submitted for approval to the MREC. After completion of the trial the principal investigator will report on the results of the main study and submit a manuscript to a peer-reviewed medical journal. Supplementary analyses will be reported separately.

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**Trial Sponsor:**

Institution: University Medical Center Utrecht Utrecht University

Principal investigator: Prof. Dr. A. Franx

Address: Lundlaan 6, 3584 EA, Utrecht, the Netherlands

**Data availability statement:**

The datasets used and/or analyzed during the current study will be made available from the corresponding author on reasonable request.

**Authors' contributions**

Study concept, trial design and study protocol: JFH, AF, MB

Acquisition of data: JFH, AF, MB, WG, JdHJ, KD, DH, LS

Drafting of the manuscript: JFH, AF, MB

Critical revision of the manuscript for important intellectual content: all authors

Study supervision: AF, MB

All authors edited the manuscript and read and approved the final draft.

**Funding statement**

This work was supported by Stichting Achmea Gezondheidszorg grant number Z659 and BMA-Telenatal BV. Neither the sponsor, nor Stichting Achmea Gezondheidszorg nor BMA-Telenatal is involved in the study design, interpretation of data or planned result reporting.

**Competing interests statement.**



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The authors declare that they have no competing interest.

**Figure legends**

**Figure 1 :** Flowchart of study procedures

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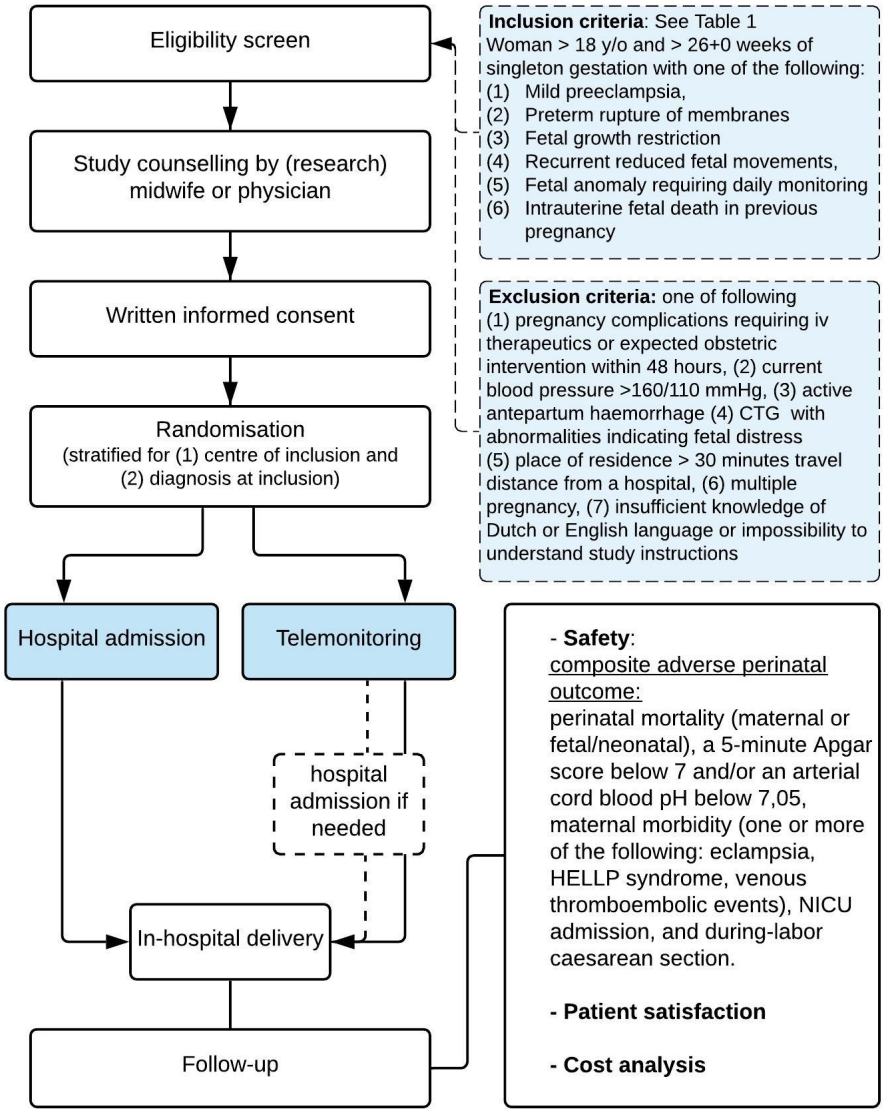


Figure 1 : Flowchart of study procedures

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addresed on manuscript page | |
|---|---|---|---|---|
| **Administrative information** | | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 | |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 3, 14 | |
| | 2b | All items from the World Health Organization Trial Registration Data Set | 3, 14 | |
| Protocol version | 3 | Date and version identifier | | |
| Funding | 4 | Sources and types of financial, material, and other support | 18 | |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 18 | |
| | 5b | Name and contact information for the trial sponsor | 17-18 | |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 18 | |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 14 | |
| **Introduction** | | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5,6 | |
| | 6b | Explanation for choice of comparators | 5,6 | |
| Objectives | 7 | Specific objectives or hypotheses | 6 | |

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|---|---|---|---|---|
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 13 | |
| **Methods: Participants, interventions, and outcomes** | | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 7 | |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 7,8 | |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 10,11 | |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 10,11 | |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | n/a | |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 10,11 | |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 12 | |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | Fig 1 | |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 13 | |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 8,13 | |
| **Methods: Assignment of interventions (for controlled trials)** | | | | |
| Allocation: | | | | |



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| | | | |
|---|---|---|---|
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 8 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 8 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 8 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 8 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | n/a |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 13,14 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 13,14 |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 13,14 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 14 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 14,15 |



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|---|---|---|---|---|
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 14 | |
| **Methods: Monitoring** | | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 15 | |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | n/a | |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 15 | |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 15 | |
| **Ethics and dissemination** | | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 15 | |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 15 | |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 8 | |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n/a | |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 13,15 | |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 19 | |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 18 | |

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|---|---|---|---|---|
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | | |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 15 | |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | n/a | |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 18 | |
| **Appendices** | | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | appendix | |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a | |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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# HOspital care versus TELemonitoring in high-risk pregnancy (HOTEL); study protocol for a multicentre non-inferiority randomised controlled trial

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| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2019-031700.R2 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 05-Sep-2019 |
| Complete List of Authors: | van den Heuvel, Josephus; UMC Utrecht<br>Ganzevoort, Wessel; Amsterdam Universitair Medische Centra<br>De Haan-Jebbink, Jiska; OLVG<br>van der Ham, D.P.; Martini Ziekenhuis<br>Deurloo, Koen; Diakonessenhuis Utrecht Zeist Doorn Locatie Utrecht<br>Seeber, Laura; Sint Antonius Hospital<br>Franx, Arie; UMC Utrecht<br>Bekker, Mireille; UMC Utrecht |
| Primary Subject Heading: | Obstetrics and gynaecology |
| Secondary Subject Heading: | Patient-centred medicine |
| Keywords: | Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, OBSTETRICS, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Maternal medicine < OBSTETRICS, Fetal medicine < OBSTETRICS |
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**Protocol**

# HOspital care versus TELemonitoring in high-risk pregnancy (HOTEL); study protocol for a multicentre non-inferiority randomised controlled trial

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## Abstract

### Introduction

Pregnant women faced with complications of pregnancy often require long-term hospital admission for maternal and/or fetal monitoring. Antenatal admissions cause a burden to patients as well as hospital resources and costs. A telemonitoring platform connected to wireless cardiotocography (CTG) and automated blood pressure devices can be used for telemonitoring in pregnancy. Home telemonitoring might improve autonomy and reduce admissions and thus costs. The aim of this study is to compare the effects on patient safety, satisfaction and cost-effectiveness of hospital care versus telemonitoring (HOTEL) as an obstetric care strategy in high-risk pregnancies requiring daily monitoring.

### Methods and analysis

The HOTEL trial is an ongoing multicentre randomized controlled clinical trial with a non-inferiority design. Eligible pregnant women are >26+0 weeks of singleton gestation requiring monitoring because of preeclampsia (hypertension with proteinuria), fetal growth restriction, preterm rupture of membranes without contractions, recurrent reduced fetal movements, or an intrauterine fetal death in a previous pregnancy.

Randomisation takes place between traditional hospitalization (planned n=208) versus telemonitoring (planned n=208) until delivery. Telemonitoring at home is facilitated with Sense4Baby cardiotocography devices, Microlife blood pressure monitor, and daily telephone calls with an obstetric healthcare professional as well as weekly hospital visits.

Primary outcome is a composite of adverse perinatal outcome, defined as perinatal mortality, 5-minute Apgar <7 or arterial cord blood pH <7.05, maternal morbidity (eclampsia, HELLP syndrome, thromboembolic event), neonatal intensive care admission and caesarean section rate. Patient satisfaction and preference of care will be assessed using validated




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questionnaires. We will perform an economic analysis. Outcomes will be analysed according to the intention to treat principle.

**Ethics and dissemination**

The study protocol was approved by the Ethics Committee of the Utrecht University Medical Center and the boards of all six participating centres. Trial results will be submitted to peer-reviewed journals.

**Trial registration** NTR6076 (September 2016)

**Keywords**

Telemonitoring, preeclampsia, preterm birth, fetal growth restriction, high-risk pregnancy, telemedicine, fetal monitoring, home-based care, eHealth

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**Strengths and limitations of this study**

- An estimated 11% of all pregnant women require daily monitoring at some point during pregnancy because of complications, leading to hospital admission.
- This is the first randomised trial to evaluate a digital health innovation for telemonitoring of both fetal and maternal parameters, self- recorded by the pregnant patient at home.
- To minimise bias by patient selection, the randomised multicentre design increases generalizability of the study results comparing hospital admission versus telemonitoring during high-risk pregnancy.
- Alongside safety reporting of perinatal outcomes, analysis of patient preferences and cost-effectiveness of both strategies will be performed.
- Digital innovations need multi-faceted evaluation before widespread implementation.

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## Introduction

For pregnant women diagnosed with complications, increased monitoring and observation of maternal and fetal parameters is recommended.[1] The aim of daily monitoring in high-risk pregnancies is to assess fetal and maternal condition using tests such as blood pressure (BP), urinary and blood analysis and cardiotocography (CTG). This increased surveillance essentially leads to antenatal hospitalisation in up to 11% of pregnancies, mostly for preterm rupture of membranes (PROM), fetal growth restriction (FGR), (gestational) diabetes mellitus, imminent preterm birth, fetal anomalies, and hypertensive disorders including preeclampsia (PE).[2,3,4] These admissions, often until delivery, result in dissatisfaction with the in-hospital stay, family burden and significant costs.[5,6]

Recent technological advancements in health care (*eHealth*) have resulted in remote monitoring platforms, mobile device-supported care, telemedicine and teleconsultation.[7] eHealth has the potential to increase patient engagement and empowerment and create better access to health care while reducing the necessity for hospital visits or admittance.[8] Pregnant women are frequent users of smartphones and internet, and therefore already equipped with the hardware to take self-measurements at home and the mind-set to communicate these digitally with their prenatal care professional.[9] Telemonitoring of pregnancy is perceived to be one of the most promising answers to the possibilities of e-health in antenatal care.

Using a validated automated blood pressure monitoring device (Microlife WatchBP) and a wireless, portable CTG system (Sense4Baby), a telemonitoring strategy could replace hospital admission that require these types of monitoring.[10,11] Measurements, self-recorded by the pregnant women at home, are saved on the included tablet in a personal profile. Using a secured Internet portal, the data are integrated in the electronic patient record system enabling access for health care professionals. A pilot study (*n*=76) using the Sense4Baby system was



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performed in UMC Utrecht to examine the accuracy of the tracings, the system's usability and participants' experiences and acceptability. Feedback and experiences from participants were positive about the used technology and no clinical relevant adverse events occurred (unpublished data, see also Patient involvement under Methods).

Currently, no clinical trials have evaluated this novel strategy with telemonitoring of self-recorded data in high-risk pregnancy before. While the patient at home will take care of measurements of CTG and blood pressure, a considerable amount of time could be saved on hospital ward or outpatient clinic for health care providers. Telemonitoring might therefore reduce costs and might offer a more acceptable form of pregnancy care.[12] However, risks of unevaluated implementation of digital innovations include usability problems, issues regarding safety and reimbursement, and adverse effects, resulting in disappointing adoption by the end-users. Therefore, patient safety and effectiveness of telemonitoring compared to antenatal admission have yet to be examined in a prospective trial.

In the HOTEL trial, a multicentre randomised controlled trial, we aim to compare hospital care to telemonitoring in high-risk pregnancy requiring daily monitoring. We will evaluate patient safety and clinical effectiveness as well as patient satisfaction and cost effectiveness of both strategies.



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## Methods

### Design and setting

This ongoing multicentre randomised controlled trial will be performed in 6 Dutch perinatal care units, including 2 university hospitals. The study will be open label. The trial protocol was registered in September 2016 (NTR6076) and first inclusion took place in December 2016.

### Patient and public involvement

Prior to the start of the trial, pregnant women were involved in study set up. A pilot study was performed to check feasibility and acceptance of telemonitoring in pregnancy (see under Introduction) In focus groups, women with either antenatal admission or participation in the telemonitoring pilot joined our focus group studies (total n = 22) to report on satisfaction of antenatal care.[submitted data]

Hospitalized patients recalled anxiety, boredom and concerns about privacy on ward. Their family life was disturbed because of frequent travelling of partners and worries over their other child(s). The patients in the home telemonitoring group reported that use of the monitoring devices was uncomplicated after instruction. They reported relief about sleeping at home, better food, seeing partners and first child(s) more often and good feeling of security with at home monitoring and weekly face-to-face visits. With use of these focus group interviews, the telemonitoring strategy and study communications were improved and we developed the questionnaire that is used at the end of the study period.

### Eligibility criteria

Definitions of the inclusion criteria are fully described in Table 1. Eligible women must be ≥ 18 years old with a singleton pregnancy ≥ 26+0 weeks gestational age requiring hospital admittance for maternal or fetal surveillance for one (or multiple) of the following reasons: (1)



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preeclampsia; (2) preterm prelabour rupture of membranes (PPROM) without contractions; (3) fetal growth restriction (FGR); (4) recurrent reduced fetal movements; (5) fetal anomaly requiring daily monitoring (e.g. fetal gastroschisis); (6) intrauterine fetal death in previous pregnancy.

Exclusion criteria for participation in the study are (1) pregnancy complications requiring intravenous therapeutics or expected obstetric intervention within 48 hours; (2) current blood pressure >160/110 mmHg; (3) active antepartum haemorrhage or signs of placental abruption; (4) CTG registration with abnormalities indicating fetal distress or hypoxia; (5) place of residence > 30 minutes travel distance from a hospital; (6) multiple pregnancy; (7) insufficient knowledge of Dutch or English language or impossibility to understand training or instructions of telemonitoring devices.

| | **Inclusion criteria** | **Additional definitions or criteria (other than exclusion criteria)** |
|---|---|---|
| 1 | Preeclampsia | Defined as:<br>- hypertension (diastolic blood pressure > 90 mmHg and/or systolic blood pressure > 140 mmHg with proteinuria following ISSHP criteria at the time of study design (FGR is defined below[13]<br>- no restriction on use of oral antihypertensive medication |
| 2 | Preterm rupture of membranes | - No present contractions<br>- cephalic or breech position, with engaged fetal head or breech |



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|---|---|---|
| 3 | Fetal growth restriction | Defined as:<br>- fetal abdominal circumference (fAC) or estimated fetal weight (EFW) <10th percentile and abnormal Doppler sonography assessment defined as pulsatility index (PI) of umbilical artery >p95 and/or absence or reversed end diastolic flow velocity flow of umbilical artery<br>- fAC or EFW <p3 with or without abnormal umbilical artery Doppler flow |
| 4 | Recurrent reduced fetal movements | |
| 5 | Fetal anomaly requiring daily monitoring | |
| 6 | Intrauterine fetal death in previous pregnancy | |

**Table** 1 Additional information on inclusion criteria.

**Recruitment and randomisation**

Eligible women will be approached and informed by obstetric care professionals i.e. physicians, (research) midwives or research nurses. Following counselling and sufficient time for questions, written informed consent is obtained and participants will be randomly allocated in a 50:50 ratio to either hospital admission or telemonitoring. Randomisation will be performed through a secured web-based domain (Research Online, Julius Research Support, UMC Utrecht) and will be stratified for 6 diagnoses for inclusion and 6 centres of inclusion. Block randomisation with



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variable block sizes is used. Cross over of trial arm is not permitted and will be considered a protocol violation. An overview of the study procedures is shown in Figure 1.

**Intervention group: telemonitoring**

Prior to the start of the study we will provide support and training of the telemonitoring strategy in each participating hospital to ensure local reliance on the technological aspects as well as task definition for the different roles. A telemonitoring team in each centre will be trained how to register, train and technically enrol new participants on the novel platform after randomisation for telemonitoring. As set in each local research protocol, responsibilities of health care providers are assigned to each task within the strategy: training new participants, daily monitoring of uploaded parameters, antenatal management after reviewing new results, and daily telephone contact with the pregnant women at home.

After randomisation for telemonitoring, the participant will be trained in using the medical devices involved in the system (Sense4Baby CTG system and the Microlife Watch BP, both CE marked). The training will be conducted using standardized instructions of use. The instructions include a contact sheet with telephone numbers for technical or health related questions, accessible 24/7. Each participant will receive an individual treatment plan according to national and/or local guidelines, including fetal CTG monitoring and blood pressure measurement, both once daily. Participants at home are contacted by phone every day by the telemonitoring team, to discuss present symptoms or questions regarding the pregnancy. Possible protocolled steps in the management, after the uploaded test results are checked, are: 1) expectant management, 2) same-day clinical assessment (e.g. in case of CTG abnormalities, rise in BP or symptoms) or 3) if necessary clinical admission. The participant will visit the outpatient clinic at least once a week for real-time contact and when needed ultrasound assessment, blood or urinary analysis. Should hospital admission be necessary in case of change in clinical presentation or



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deterioration (e.g. non-reassuring CTG, hypertension, contractions, antepartum haemorrhage, signs of infection, maternal distress or technical difficulties), the patient will be monitored in the hospital as per local protocol and all data of interest during the admission will be collected. In the case this same participant can be discharged from ward again (e.g. after treatment optimisation for hypertension), she may go home with telemonitoring - as per randomisation- until delivery. All consultations in the outpatient department and possible ward admissions during pregnancy will be recorded for the study.

**Control group: hospital admission**

Pregnant women allocated to hospital admittance will receive standard obstetric care according to national and local guidelines and current state of the art, including daily fetal monitoring and blood pressure measurements. All participating centres committed to following guidelines for different diagnoses and management as set by the Dutch Society of Obstetrics and Gynaecology. A typical regime on ward includes vital parameter check (blood pressure, temperature on indication) by obstetric nurses, daily cardiotocography and daily rotations by a resident in obstetrics and gynaecology, supervised by an obstetrician, for interpretation of results and further management. Blood and/or urine sampling and fetal ultrasound will be performed when indicated and according to local protocol. In case the necessity of hospital admission is no longer present, the patient may be discharged and if necessary admitted to ward again, as per randomisation, not allowing cross-over to telemonitoring.

**Outcome measures**

The primary outcome is maternal and fetal/neonatal safety during perinatal care from study inclusion onwards by recording incidence of perinatal mortality and maternal and neonatal morbidity. The composite of adverse perinatal outcome is defined as: perinatal mortality (maternal or fetal or neonatal), a 5-minute Apgar score below 7 and/or an arterial pH below



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7,05, maternal morbidity (one or more of the following: eclampsia, HELLP syndrome, thromboembolic events), NICU admission of the new-born and caesarean section rate. The components of the composite outcome are both chosen for either (or both) the possibility to be affected by the new intervention as well as the severity as a stand-alone adverse outcome. All components will be reported separately as a secondary outcome for interpretation of study results.

Secondary outcome will consist of patient satisfaction, quality of life and cost effectiveness.

The satisfaction, experience and quality of life of every participating pregnant woman will be surveyed with help of the EuroQol 5D (EQ-5D), State Trait Anxiety Inventory (STAI) and Edinburgh Postnatal Depression Score (EPDS) questionnaires.[14,15,16] Surveys are sent by e-mail at study start, and 1, 3, 5 weeks after randomisation and 4 weeks after delivery. With the help of focus group discussion (see under Patient involvement), we created a questionnaire which will be filled out 4 weeks after delivery.

The cost effectiveness and budget impact analyses (CEA and BIA) will be assessed from different perspectives, i.e. hospitals, health insurance companies and from the societal perspective. The budget impact analysis will follow ISPOR guidelines for budget impact analyses to calculate the differences in budgetary impact of telemonitoring and hospital admittance in high-risk pregnancies. For the CEA and the BIA, we will record duration of telemonitoring and duration of admittance (number of days), number of consultations and health care provider involved, number and length of CTG registration, number of maternal blood analyses and ultrasound assessments, emergency transport to the hospital and emergency caesarean sections. Besides this maternal use of health services, all health service use of the newborn during the follow-up period (until discharge to home) will be recorded.

**Sample size**



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Before the start of the trial, we formed an expert panel, consisting of gynaecologists, and paediatricians, methodologists, and statisticians to conceive the design, content, and execution of the trial. The sample size calculation is based on the assumption that the composite of adverse perinatal outcome will be equal in the telemonitoring and the hospital admittance patient groups: a non-inferiority trial. To estimate this risk for each individual component of adverse perinatal outcome in our inclusion criteria, we made use of the results of three large Dutch randomised controlled trials for patients with PPROM, FGR and preeclampsia.[17,18,19] No data on perinatal outcome of telemonitoring in high risk pregnancy are available to use in our sample size calculation. The incidence of this composite primary outcome in the high-risk pregnancy group is assumed to be 20% in either group. The panel made a reasoned choice about the acceptable difference in adverse perinatal outcome and feasibility of the trial, since this is the first ongoing trial of telemonitoring in complicated pregnancies. As a result, the non-inferiority margin (Δ) was defined as a 10% absolute increase or less in the telemonitoring group. With a one sided α of 0.05, the study will achieve a power (β) of more than 0.80 if 200 women will be included in each trial arm. Accounting for a loss to follow-up of 4%, a total of 416 patients are needed, 208 in each arm.

The sample size was calculated for non-inferiority testing with the one-sided Score test (Farrington & Manning) using PASS software.

**Data handling, analysis and result reporting**

At study entry, baseline data like patient demographics, medical and obstetric history and current pregnancy details are collected. At delivery relevant data will be collected for the assessment of perinatal outcomes such as gestational age at birth, birth weight, condition at birth (Apgar scores, umbilical cord blood gas analysis), neonatal admission (type of ward and number of days). Neonatal mortality and morbidity will be specified. For the mother, data will be collected on treatment for pain relief, mode of delivery and adverse outcomes (eclampsia,



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thromboembolic events and HELLP syndrome). Standardized online case record forms developed by Julius Centre for Research Support (UMC Utrecht) are used, including source data verification options. Missing data will be handled according to the complete-case analysis principle, based on the availability of the components needed to determine the primary endpoint.

Primary outcome

Data analyses will primarily be carried out according to the intention-to-treat principle, i.e. the participants will be analysed according to their randomized allocation, regardless of the actual interventions received by the patient. Results will be reported according to CONSORT guidelines, using the extension for non-inferiority trials. If necessary, skewed continuous variables will be transformed to normality prior to the analyses. Supplementary, we will perform per protocol analyses excluding participants in whom there is a clear deviation or suboptimal execution of the intended care as prescribed by the protocol in either the admission group or the telemonitoring group. Examples include technical difficulties at home or non-compliance of study agreements, cross-over, or participants in the telemonitoring arm with (multiple) hospital admissions accounting for over half of the study period.

The primary outcome, the composite (dichotomous) endpoint of perinatal mortality and morbidity will be analysed with logistic regression analysis with the stratification factors (centre of inclusion and diagnosis of pregnancy complication) and parity as pre-defined covariates in the regression model. No pre-specified subgroup analyses are planned.

Secondary outcomes

Each individual component outcome within the composite outcome will be reported as a single (secondary) outcome to provide further insight as the incidence and the relative importance



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between components of the composite outcome differ. Point estimates with confidence intervals for the comparison of groups will be reported for these components of the composite outcome.

Patient satisfaction and health related quality of life will be analysed with a general linear model for continuous outcomes. Comparison of questionnaires will be made for each time point, with the survey at 4 weeks post delivery being the most important. Assumptions for general linear model (i.e. normality, homoscedasticity) will be checked with residual analyses. In case of heteroscedasticity, the analyses will be repeated with robust (Hubert-White) estimators for standard errors. If distributional assumptions are violated, first a log transformation of the outcome will be analysed. If this transformation does not result in a valid regression analysis, intervention effects will be evaluated with a Mann-Whitney test without any corrections.

Time to delivery with account for different durations of gestation at study entry, will be evaluated with Cox regression with control of the stratification factors and parity as a predifned covariate.

For the cost-effectiveness analysis, all health care resources use will be transformed into cost estimates, by multiplying number of units of health care use, i.e. number of days in hospital, number of laboratory tests and other diagnostic tests with standard unit prices as provided by the Dutch guideline for costing research in health economic evaluation studies (National Health Care Institute, Zorginstituut Nederland, 2016). For medical costs, the process of care is divided into three cost stages (antenatal stage, delivery/childbirth, postnatal stage). Cost differences between the two treatment arms will be related to effect differences (primary outcome) between the treatment arms (if any). If non-inferiority of telemonitoring is confirmed, cost differences between the two treatment arms will be analysed (cost-minimization analysis). The cost effectiveness analysis will be performed from both the healthcare perspective and the societal perspective.

**Study monitoring and safety**



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To monitor the conduct of the trial and safeguard the interest of participants, an independent Data Safety Monitoring Board (DSMB) will be established, including a professor of biostatistics, an obstetrician and a neonatologist.. A study monitor will periodically visit participating centres, assessing quality of data and auditing trial conduct. All serious adverse events, reported by either participant or local clinician, will be recorded, and reported to the accredited ethics committee and the DSMB following international GCP guidelines. Trial data will be analysed and stored in the UMC Utrecht (study sponsor). No formal interim analysis of efficacy outcome is planned.

**Ethics and dissemination**

This trial has been approved by the Medical Research Ethics Committee (MREC) of the UMC Utrecht. Trial reference number: 16-516. The MREC of the UMC Utrecht is accredited by the Central Committee on Research Involving Human Subjects (CCMO) since November 1999. Approval by the boards of management of University Medical Center Utrecht, Amsterdam University Medical Center, Diakonessenhuis Utrecht, OLVG Amsterdam, Martini Ziekenhuis Groningen and St. Antonius Ziekenhuis Nieuwegein is obtained prior to study start in each centre. Changes to the study protocol are documented in amendments and submitted for approval to the MREC. After completion of the trial the principal investigator will report on the results of the main study and submit a manuscript to a peer-reviewed medical journal. Supplementary analyses will be reported separately.

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expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): An open-label, randomised controlled trial. Lancet. 2015;385(9986):2492-2501.

**Trial Sponsor:**

Institution: University Medical Center Utrecht Utrecht University

Principal investigator: Prof. Dr. A. Franx

Address: Lundlaan 6, 3584 EA, Utrecht, the Netherlands

**Data availability statement:**

The datasets used and/or analyzed during the current study will be made available from the corresponding author on reasonable request.

**Authors' contributions**

Study concept, trial design and study protocol: JFH, AF, MB

Acquisition of data: JFH, AF, MB, WG, JdHJ, KD, DH, LS

Drafting of the manuscript: JFH, AF, MB

Critical revision of the manuscript for important intellectual content: all authors

Study supervision: AF, MB

All authors edited the manuscript and read and approved the final draft.

**Funding statement**

This work was supported by Stichting Achmea Gezondheidszorg grant number Z659 and BMA-Telenatal BV. Neither the sponsor, nor Stichting Achmea Gezondheidszorg nor BMA-Telenatal is involved in the study design, interpretation of data or planned result reporting.



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**Competing interests statement.**

The authors declare that they have no competing interest.

**Figure legends**

**Figure 1 :** Flowchart of study procedures

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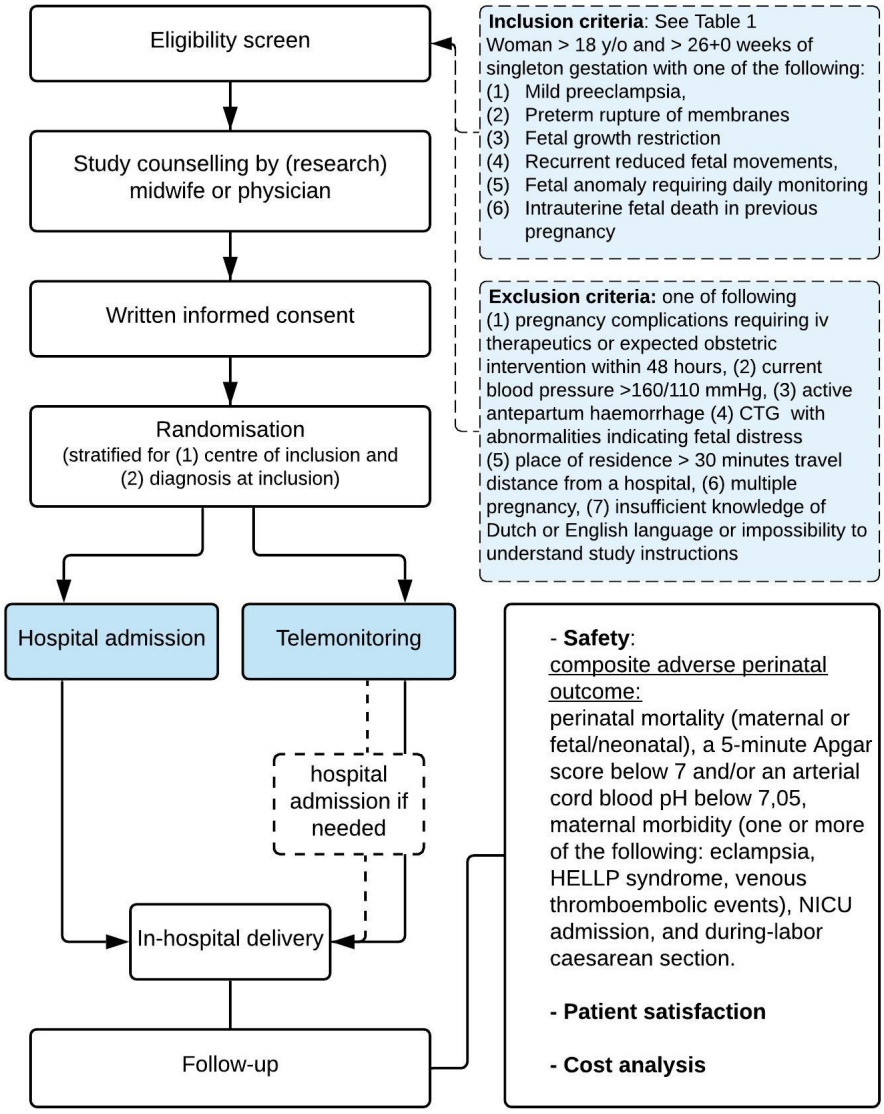


Figure 1 : Flowchart of study procedures

123x152mm (300 x 300 DPI)



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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addresed on manuscript page | |
|---|---|---|---|---|
| **Administrative information** | | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 | |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 3, 14 | |
| | 2b | All items from the World Health Organization Trial Registration Data Set | 3, 14 | |
| Protocol version | 3 | Date and version identifier | | |
| Funding | 4 | Sources and types of financial, material, and other support | 18 | |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 18 | |
| | 5b | Name and contact information for the trial sponsor | 17-18 | |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 18 | |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 14 | |
| **Introduction** | | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5,6 | |
| | 6b | Explanation for choice of comparators | 5,6 | |
| Objectives | 7 | Specific objectives or hypotheses | 6 | |

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|---|---|---|---|---|
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 13 | |
| **Methods: Participants, interventions, and outcomes** | | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 7 | |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 7,8 | |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 10,11 | |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 10,11 | |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | n/a | |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 10,11 | |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 12 | |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | Fig 1 | |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 13 | |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 8,13 | |
| **Methods: Assignment of interventions (for controlled trials)** | | | | |
| Allocation: | | | | |



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|---|---|---|---|
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 8 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 8 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 8 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 8 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | n/a |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 13,14 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 13,14 |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 13,14 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 14 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 14,15 |



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| | | | | |
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| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 14 | |
| **Methods: Monitoring** | | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 15 | |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | n/a | |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 15 | |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 15 | |
| **Ethics and dissemination** | | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 15 | |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 15 | |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 8 | |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n/a | |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 13,15 | |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 19 | |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 18 | |

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| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | | |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 15 | |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | n/a | |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 18 | |
| **Appendices** | | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | appendix | |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a | |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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# HOspital care versus TELemonitoring in high-risk pregnancy (HOTEL); study protocol for a multicentre non-inferiority randomised controlled trial

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| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2019-031700.R3 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 25-Sep-2019 |
| Complete List of Authors: | van den Heuvel, Josephus; UMC Utrecht<br>Ganzevoort, Wessel; Amsterdam Universitair Medische Centra<br>De Haan-Jebbink, Jiska; OLVG<br>van der Ham, D.P.; Martini Ziekenhuis<br>Deurloo, Koen; Diakonessenhuis Utrecht Zeist Doorn Locatie Utrecht<br>Seeber, Laura; Sint Antonius Hospital<br>Franx, Arie; UMC Utrecht<br>Bekker, Mireille; UMC Utrecht |
| Primary Subject Heading: | Obstetrics and gynaecology |
| Secondary Subject Heading: | Patient-centred medicine |
| Keywords: | Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, OBSTETRICS, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Maternal medicine < OBSTETRICS, Fetal medicine < OBSTETRICS |
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**Protocol**

# HOspital care versus TELemonitoring in high-risk pregnancy (HOTEL); study protocol for a multicentre non-inferiority randomised controlled trial

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## Abstract

### Introduction

Pregnant women faced with complications of pregnancy often require long-term hospital admission for maternal and/or fetal monitoring. Antenatal admissions cause a burden to patients as well as hospital resources and costs. A telemonitoring platform connected to wireless cardiotocography (CTG) and automated blood pressure devices can be used for telemonitoring in pregnancy. Home telemonitoring might improve autonomy and reduce admissions and thus costs. The aim of this study is to compare the effects on patient safety, satisfaction and cost-effectiveness of hospital care versus telemonitoring (HOTEL) as an obstetric care strategy in high-risk pregnancies requiring daily monitoring.

### Methods and analysis

The HOTEL trial is an ongoing multicentre randomized controlled clinical trial with a non-inferiority design. Eligible pregnant women are >26+0 weeks of singleton gestation requiring monitoring because of preeclampsia (hypertension with proteinuria), fetal growth restriction, preterm rupture of membranes without contractions, recurrent reduced fetal movements, or an intrauterine fetal death in a previous pregnancy.

Randomisation takes place between traditional hospitalization (planned n=208) versus telemonitoring (planned n=208) until delivery. Telemonitoring at home is facilitated with Sense4Baby cardiotocography devices, Microlife blood pressure monitor, and daily telephone calls with an obstetric healthcare professional as well as weekly hospital visits.

Primary outcome is a composite of adverse perinatal outcome, defined as perinatal mortality, 5-minute Apgar <7 or arterial cord blood pH <7.05, maternal morbidity (eclampsia, HELLP syndrome, thromboembolic event), neonatal intensive care admission and caesarean section rate. Patient satisfaction and preference of care will be assessed using validated




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questionnaires. We will perform an economic analysis. Outcomes will be analysed according to the intention to treat principle.

## Ethics and dissemination

The study protocol was approved by the Ethics Committee of the Utrecht University Medical Center and the boards of all six participating centres. Trial results will be submitted to peer-reviewed journals.

**Trial registration** NTR6076 (September 2016)

**Keywords**

Telemonitoring, preeclampsia, preterm birth, fetal growth restriction, high-risk pregnancy, telemedicine, fetal monitoring, home-based care, eHealth

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**Strengths and limitations of this study**

- An estimated 11% of all pregnant women require daily monitoring at some point during pregnancy because of complications, leading to hospital admission.
- This is the first randomised trial to evaluate a digital health innovation for telemonitoring of both fetal and maternal parameters, self- recorded by the pregnant patient at home.
- To minimise bias by patient selection, the randomised multicentre design increases generalizability of the study results comparing hospital admission versus telemonitoring during high-risk pregnancy.
- Alongside safety reporting of perinatal outcomes, analysis of patient preferences and cost-effectiveness of both strategies will be performed.
- Digital innovations need multi-faceted evaluation before widespread implementation.

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## Introduction

For pregnant women diagnosed with complications, increased monitoring and observation of maternal and fetal parameters is recommended.[1] The aim of daily monitoring in high-risk pregnancies is to assess fetal and maternal condition using tests such as blood pressure (BP), urinary and blood analysis and cardiotocography (CTG). This increased surveillance essentially leads to antenatal hospitalisation in up to 11% of pregnancies, mostly for preterm rupture of membranes (PROM), fetal growth restriction (FGR), (gestational) diabetes mellitus, imminent preterm birth, fetal anomalies, and hypertensive disorders including preeclampsia (PE).[2,3,4] These admissions, often until delivery, result in dissatisfaction with the in-hospital stay, family burden and significant costs.[5,6]

Recent technological advancements in health care (*eHealth*) have resulted in remote monitoring platforms, mobile device-supported care, telemedicine and teleconsultation.[7] eHealth has the potential to increase patient engagement and empowerment and create better access to health care while reducing the necessity for hospital visits or admittance.[8] Pregnant women are frequent users of smartphones and internet, and therefore already equipped with the hardware to take self-measurements at home and the mind-set to communicate these digitally with their prenatal care professional.[9] Telemonitoring of pregnancy is perceived to be one of the most promising answers to the possibilities of e-health in antenatal care.

Using a validated automated blood pressure monitoring device (Microlife WatchBP) and a wireless, portable CTG system (Sense4Baby), a telemonitoring strategy could replace hospital admission that require these types of monitoring.[10,11] Measurements, self-recorded by the pregnant women at home, are saved on the included tablet in a personal profile. Using a secured Internet portal, the data are integrated in the electronic patient record system enabling access for health care professionals. A pilot study (*n*=76) using the Sense4Baby system was



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performed in UMC Utrecht to examine the accuracy of the tracings, the system's usability and participants' experiences and acceptability. Feedback and experiences from participants were positive about the used technology and no clinical relevant adverse events occurred (unpublished data, see also Patient involvement under Methods).

Currently, no clinical trials have evaluated this novel strategy with telemonitoring of self-recorded data in high-risk pregnancy before. While the patient at home will take care of measurements of CTG and blood pressure, a considerable amount of time could be saved on hospital ward or outpatient clinic for health care providers. Telemonitoring might therefore reduce costs and might offer a more acceptable form of pregnancy care.[12] However, risks of unevaluated implementation of digital innovations include usability problems, issues regarding safety and reimbursement, and adverse effects, resulting in disappointing adoption by the end-users. Therefore, patient safety and effectiveness of telemonitoring compared to antenatal admission have yet to be examined in a prospective trial.

In the HOTEL trial, a multicentre randomised controlled trial, we aim to compare hospital care to telemonitoring in high-risk pregnancy requiring daily monitoring. We will evaluate patient safety and clinical effectiveness as well as patient satisfaction and cost effectiveness of both strategies.



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## Methods

### Design and setting

This ongoing multicentre randomised controlled trial will be performed in 6 Dutch perinatal care units, including 2 university hospitals. The study will be open label. The trial protocol was registered in September 2016 (NTR6076) and first inclusion took place in December 2016. Planned end date of the trial is September 1st , 2020.

### Patient and public involvement

Prior to the start of the trial, pregnant women were involved in study set up. A pilot study was performed to check feasibility and acceptance of telemonitoring in pregnancy (see under Introduction) In focus groups, women with either antenatal admission or participation in the telemonitoring pilot joined our focus group studies (total n = 22) to report on satisfaction of antenatal care.[submitted data]

Hospitalized patients recalled anxiety, boredom and concerns about privacy on ward. Their family life was disturbed because of frequent travelling of partners and worries over their other child(s). The patients in the home telemonitoring group reported that use of the monitoring devices was uncomplicated after instruction. They reported relief about sleeping at home, better food, seeing partners and first child(s) more often and good feeling of security with at home monitoring and weekly face-to-face visits. With use of these focus group interviews, the telemonitoring strategy and study communications were improved and we developed the questionnaire that is used at the end of the study period.

### Eligibility criteria

Definitions of the inclusion criteria are fully described in Table 1. Eligible women must be ≥ 18 years old with a singleton pregnancy ≥ 26+0 weeks gestational age requiring hospital



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admittance for maternal or fetal surveillance for one (or multiple) of the following reasons: (1) preeclampsia; (2) preterm prelabour rupture of membranes (PPROM) without contractions; (3) fetal growth restriction (FGR); (4) recurrent reduced fetal movements; (5) fetal anomaly requiring daily monitoring (e.g. fetal gastroschisis); (6) intrauterine fetal death in previous pregnancy.

Exclusion criteria for participation in the study are (1) pregnancy complications requiring intravenous therapeutics or expected obstetric intervention within 48 hours; (2) current blood pressure >160/110 mmHg; (3) active antepartum haemorrhage or signs of placental abruption; (4) CTG registration with abnormalities indicating fetal distress or hypoxia; (5) place of residence > 30 minutes travel distance from a hospital; (6) multiple pregnancy; (7) insufficient knowledge of Dutch or English language or impossibility to understand training or instructions of telemonitoring devices.

| | **Inclusion criteria** | **Additional definitions or criteria (other than exclusion criteria)** |
|---|---|---|
| 1 | Preeclampsia | Defined as:<br>- hypertension (diastolic blood pressure > 90 mmHg and/or systolic blood pressure > 140 mmHg with proteinuria following ISSHP criteria at the time of study design (FGR is defined below[13]<br>- no restriction on use of oral antihypertensive medication |
| 2 | Preterm rupture of membranes | - No present contractions<br>- cephalic or breech position, with engaged fetal head |



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| | | or breech |
| 3 | Fetal growth restriction | Defined as:<br>- fetal abdominal circumference (fAC) or estimated fetal weight (EFW) <10th percentile and abnormal Doppler sonography assessment defined as pulsatility index (PI) of umbilical artery >p95 and/or absence or reversed end diastolic flow velocity flow of umbilical artery<br>- fAC or EFW <p3 with or without abnormal umbilical artery Doppler flow |
| 4 | Recurrent reduced fetal movements | |
| 5 | Fetal anomaly requiring daily monitoring | |
| 6 | Intrauterine fetal death in previous pregnancy | |

**Table** 1 Additional information on inclusion criteria.

**Recruitment and randomisation**

Eligible women will be approached and informed by obstetric care professionals i.e. physicians, (research) midwives or research nurses. Following counselling and sufficient time for questions, written informed consent is obtained and participants will be randomly allocated in a 50:50 ratio to either hospital admission or telemonitoring. Randomisation will be performed through a secured web-based domain (Research Online, Julius Research Support, UMC Utrecht) and will



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be stratified for 6 diagnoses for inclusion and 6 centres of inclusion. Block randomisation with variable block sizes is used. Cross over of trial arm is not permitted and will be considered a protocol violation. An overview of the study procedures is shown in Figure 1.

**Intervention group: telemonitoring**

Prior to the start of the study we will provide support and training of the telemonitoring strategy in each participating hospital to ensure local reliance on the technological aspects as well as task definition for the different roles. A telemonitoring team in each centre will be trained how to register, train and technically enrol new participants on the novel platform after randomisation for telemonitoring. As set in each local research protocol, responsibilities of health care providers are assigned to each task within the strategy: training new participants, daily monitoring of uploaded parameters, antenatal management after reviewing new results, and daily telephone contact with the pregnant women at home.

After randomisation for telemonitoring, the participant will be trained in using the medical devices involved in the system (Sense4Baby CTG system and the Microlife Watch BP, both CE marked). The training will be conducted using standardized instructions of use. The instructions include a contact sheet with telephone numbers for technical or health related questions, accessible 24/7. Each participant will receive an individual treatment plan according to national and/or local guidelines, including fetal CTG monitoring and blood pressure measurement, both once daily. Participants at home are contacted by phone every day by the telemonitoring team, to discuss present symptoms or questions regarding the pregnancy. Possible protocolled steps in the management, after the uploaded test results are checked, are: 1) expectant management, 2) same-day clinical assessment (e.g. in case of CTG abnormalities, rise in BP or symptoms) or 3) if necessary clinical admission. The participant will visit the outpatient clinic at least once a week for real-time contact and when needed ultrasound assessment, blood or urinary analysis.



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Should hospital admission be necessary in case of change in clinical presentation or deterioration (e.g. non-reassuring CTG, hypertension, contractions, antepartum haemorrhage, signs of infection, maternal distress or technical difficulties), the patient will be monitored in the hospital as per local protocol and all data of interest during the admission will be collected. In the case this same participant can be discharged from ward again (e.g. after treatment optimisation for hypertension), she may go home with telemonitoring - as per randomisation- until delivery. All consultations in the outpatient department and possible ward admissions during pregnancy will be recorded for the study.

**Control group: hospital admission**

Pregnant women allocated to hospital admittance will receive standard obstetric care according to national and local guidelines and current state of the art, including daily fetal monitoring and blood pressure measurements. All participating centres committed to following guidelines for different diagnoses and management as set by the Dutch Society of Obstetrics and Gynaecology. A typical regime on ward includes vital parameter check (blood pressure, temperature on indication) by obstetric nurses, daily cardiotocography and daily rotations by a resident in obstetrics and gynaecology, supervised by an obstetrician, for interpretation of results and further management. Blood and/or urine sampling and fetal ultrasound will be performed when indicated and according to local protocol. In case the necessity of hospital admission is no longer present, the patient may be discharged and if necessary admitted to ward again, as per randomisation, not allowing cross-over to telemonitoring.

**Outcome measures**

The primary outcome is maternal and fetal/neonatal safety during perinatal care from study inclusion onwards by recording incidence of perinatal mortality and maternal and neonatal morbidity. The composite of adverse perinatal outcome is defined as: perinatal mortality



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(maternal or fetal or neonatal), a 5-minute Apgar score below 7 and/or an arterial pH below 7,05, maternal morbidity (one or more of the following: eclampsia, HELLP syndrome, thromboembolic events), NICU admission of the new-born and caesarean section rate. The components of the composite outcome are both chosen for either (or both) the possibility to be affected by the new intervention as well as the severity as a stand-alone adverse outcome. All components will be reported separately as a secondary outcome for interpretation of study results.

Secondary outcome will consist of patient satisfaction, quality of life and cost effectiveness.

The satisfaction, experience and quality of life of every participating pregnant woman will be surveyed with help of the EuroQol 5D (EQ-5D), State Trait Anxiety Inventory (STAI) and Edinburgh Postnatal Depression Score (EPDS) questionnaires.[14,15,16] Surveys are sent by e-mail at study start, and 1, 3, 5 weeks after randomisation and 4 weeks after delivery. With the help of focus group discussion (see under Patient involvement), we created a questionnaire which will be filled out 4 weeks after delivery.

The cost effectiveness and budget impact analyses (CEA and BIA) will be assessed from different perspectives, i.e. hospitals, health insurance companies and from the societal perspective. The budget impact analysis will follow ISPOR guidelines for budget impact analyses to calculate the differences in budgetary impact of telemonitoring and hospital admittance in high-risk pregnancies. For the CEA and the BIA, we will record duration of telemonitoring and duration of admittance (number of days), number of consultations and health care provider involved, number and length of CTG registration, number of maternal blood analyses and ultrasound assessments, emergency transport to the hospital and emergency caesarean sections. Besides this maternal use of health services, all health service use of the newborn during the follow-up period (until discharge to home) will be recorded.



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**Sample size**

Before the start of the trial, we formed an expert panel, consisting of gynaecologists, and paediatricians, methodologists, and statisticians to conceive the design, content, and execution of the trial. The sample size calculation is based on the assumption that the composite of adverse perinatal outcome will be equal in the telemonitoring and the hospital admittance patient groups: a non-inferiority trial. To estimate this risk for each individual component of adverse perinatal outcome in our inclusion criteria, we made use of the results of three large Dutch randomised controlled trials for patients with PPROM, FGR and preeclampsia.[17,18,19] No data on perinatal outcome of telemonitoring in high risk pregnancy are available to use in our sample size calculation. The incidence of this composite primary outcome in the high-risk pregnancy group is assumed to be 20% in either group. The panel made a reasoned choice about the acceptable difference in adverse perinatal outcome and feasibility of the trial, since this is the first ongoing trial of telemonitoring in complicated pregnancies. As a result, the non-inferiority margin (Δ) was defined as a 10% absolute increase or less in the telemonitoring group. With a one sided α of 0.05, the study will achieve a power (β) of 0.80 if 200 women will be included in each trial arm. Accounting for a loss to follow-up of 4%, a total of 416 patients are needed, 208 in each arm.

The sample size was calculated for non-inferiority testing with the one-sided Score test (Farrington & Manning) using PASS software.

**Data handling, analysis and result reporting**

At study entry, baseline data like patient demographics, medical and obstetric history and current pregnancy details are collected. At delivery relevant data will be collected for the assessment of perinatal outcomes such as gestational age at birth, birth weight, condition at birth (Apgar scores, umbilical cord blood gas analysis), neonatal admission (type of ward and number of days). Neonatal mortality and morbidity will be specified. For the mother, data will be



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collected on treatment for pain relief, mode of delivery and adverse outcomes (eclampsia, thromboembolic events and HELLP syndrome). Standardized online case record forms developed by Julius Centre for Research Support (UMC Utrecht) are used, including source data verification options. Missing data will be handled according to the complete-case analysis principle, based on the availability of the components needed to determine the primary endpoint.

Primary outcome

Data analyses will primarily be carried out according to the intention-to-treat principle, i.e. the participants will be analysed according to their randomized allocation, regardless of the actual interventions received by the patient. Results will be reported according to CONSORT guidelines, using the extension for non-inferiority trials. If necessary, skewed continuous variables will be transformed to normality prior to the analyses. Supplementary, we will perform per protocol analyses excluding participants in whom there is a clear deviation or suboptimal execution of the intended care as prescribed by the protocol in either the admission group or the telemonitoring group. Examples include technical difficulties at home or non-compliance of study agreements, cross-over, or participants in the telemonitoring arm with (multiple) hospital admissions accounting for over half of the study period.

The primary outcome, the composite (dichotomous) endpoint of perinatal mortality and morbidity will be analysed with logistic regression analysis with the stratification factors (centre of inclusion and diagnosis of pregnancy complication) and parity as pre-defined covariates in the regression model. No pre-specified subgroup analyses are planned.

Secondary outcomes

Each individual component outcome within the composite outcome will be reported as a single (secondary) outcome to provide further insight as the incidence and the relative importance



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between components of the composite outcome differ. Point estimates with confidence intervals for the comparison of groups will be reported for these components of the composite outcome.

Patient satisfaction and health related quality of life will be analysed with a general linear model for continuous outcomes. Comparison of questionnaires will be made for each time point, with the survey at 4 weeks post delivery being the most important. Assumptions for general linear model (i.e. normality, homoscedasticity) will be checked with residual analyses. In case of heteroscedasticity, the analyses will be repeated with robust (Hubert-White) estimators for standard errors. If distributional assumptions are violated, first a log transformation of the outcome will be analysed. If this transformation does not result in a valid regression analysis, intervention effects will be evaluated with a Mann-Whitney test without any corrections.

Time to delivery with account for different durations of gestation at study entry, will be evaluated with Cox regression with control of the stratification factors and parity as a predifned covariate.

For the cost-effectiveness analysis, all health care resources use will be transformed into cost estimates, by multiplying number of units of health care use, i.e. number of days in hospital, number of laboratory tests and other diagnostic tests with standard unit prices as provided by the Dutch guideline for costing research in health economic evaluation studies (National Health Care Institute, Zorginstituut Nederland, 2016). For medical costs, the process of care is divided into three cost stages (antenatal stage, delivery/childbirth, postnatal stage). Cost differences between the two treatment arms will be related to effect differences (primary outcome) between the treatment arms (if any). If non-inferiority of telemonitoring is confirmed, cost differences between the two treatment arms will be analysed (cost-minimization analysis). The cost effectiveness analysis will be performed from both the healthcare perspective and the societal perspective.

**Study monitoring and safety**



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To monitor the conduct of the trial and safeguard the interest of participants, an independent Data Safety Monitoring Board (DSMB) will be established, including a professor of biostatistics, an obstetrician and a neonatologist.. A study monitor will periodically visit participating centres, assessing quality of data and auditing trial conduct. All serious adverse events, reported by either participant or local clinician, will be recorded, and reported to the accredited ethics committee and the DSMB following international GCP guidelines. Trial data will be analysed and stored in the UMC Utrecht (study sponsor). No formal interim analysis of efficacy outcome is planned.

**Ethics and dissemination**

This trial has been approved by the Medical Research Ethics Committee (MREC) of the UMC Utrecht. Trial reference number: 16-516. The MREC of the UMC Utrecht is accredited by the Central Committee on Research Involving Human Subjects (CCMO) since November 1999. Approval by the boards of management of University Medical Center Utrecht, Amsterdam University Medical Center, Diakonessenhuis Utrecht, OLVG Amsterdam, Martini Ziekenhuis Groningen and St. Antonius Ziekenhuis Nieuwegein is obtained prior to study start in each centre. Changes to the study protocol are documented in amendments and submitted for approval to the MREC. After completion of the trial the principal investigator will report on the results of the main study and submit a manuscript to a peer-reviewed medical journal. Supplementary analyses will be reported separately.

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expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): An open-label, randomised controlled trial. Lancet. 2015;385(9986):2492-2501.

**Trial Sponsor:**

Institution: University Medical Center Utrecht Utrecht University

Principal investigator: Prof. Dr. A. Franx

Address: Lundlaan 6, 3584 EA, Utrecht, the Netherlands

**Data availability statement:**

The datasets used and/or analyzed during the current study will be made available from the corresponding author on reasonable request.

**Authors' contributions**

Study concept, trial design and study protocol: JFH, AF, MB

Acquisition of data: JFH, AF, MB, WG, JdHJ, KD, DH, LS

Drafting of the manuscript: JFH, AF, MB

Critical revision of the manuscript for important intellectual content: all authors

Study supervision: AF, MB

All authors edited the manuscript and read and approved the final draft.

**Funding statement**

This work was supported by Stichting Achmea Gezondheidszorg grant number Z659 and BMA-Telenatal BV. Neither the sponsor, nor Stichting Achmea Gezondheidszorg nor BMA-Telenatal is involved in the study design, interpretation of data or planned result reporting.



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**Competing interests statement.**

The authors declare that they have no competing interest.

**Figure legends**

**Figure 1 :** Flowchart of study procedures

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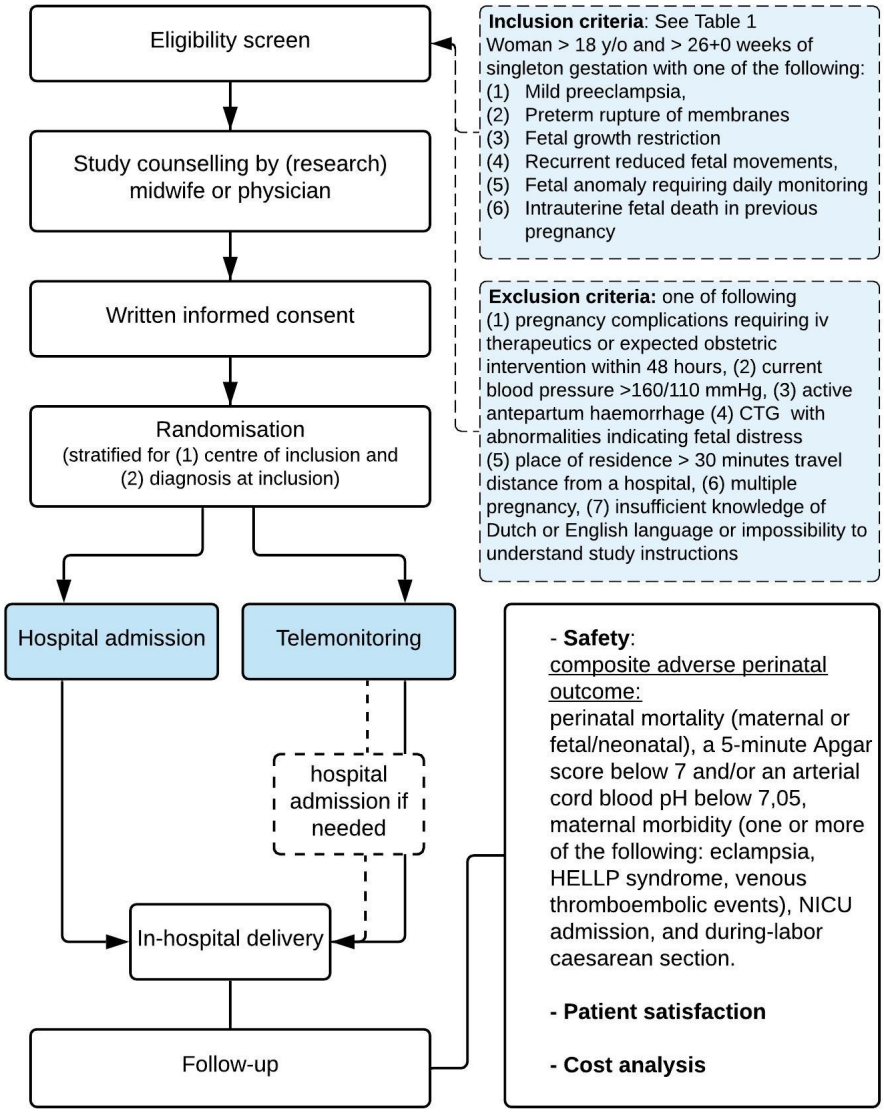


Figure 1 : Flowchart of study procedures

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addresed on manuscript page | |
|---|---|---|---|---|
| **Administrative information** | | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 | |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 3, 14 | |
| | 2b | All items from the World Health Organization Trial Registration Data Set | 3, 14 | |
| Protocol version | 3 | Date and version identifier | | |
| Funding | 4 | Sources and types of financial, material, and other support | 18 | |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 18 | |
| | 5b | Name and contact information for the trial sponsor | 17-18 | |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 18 | |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 14 | |
| **Introduction** | | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5,6 | |
| | 6b | Explanation for choice of comparators | 5,6 | |
| Objectives | 7 | Specific objectives or hypotheses | 6 | |

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|---|---|---|---|---|
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 13 | |
| **Methods: Participants, interventions, and outcomes** | | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 7 | |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 7,8 | |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 10,11 | |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 10,11 | |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | n/a | |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 10,11 | |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 12 | |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | Fig 1 | |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 13 | |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 8,13 | |
| **Methods: Assignment of interventions (for controlled trials)** | | | | |
| Allocation: | | | | |



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| | | | |
|---|---|---|---|
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 8 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 8 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 8 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 8 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | n/a |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 13,14 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 13,14 |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 13,14 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 14 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 14,15 |



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|---|---|---|---|---|
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 14 | |
| **Methods: Monitoring** | | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 15 | |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | n/a | |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 15 | |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 15 | |
| **Ethics and dissemination** | | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 15 | |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 15 | |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 8 | |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n/a | |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 13,15 | |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 19 | |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 18 | |

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|---|---|---|---|---|
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | | |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 15 | |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | n/a | |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 18 | |
| **Appendices** | | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | appendix | |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a | |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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