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# Vaginal hysterectomy versus vaginal Assisted NOTES Hysterectomy (VANH): a randomised controlled trial VANH-trial

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Vaginal hysterectomy versus vaginal Assisted NOTES Hysterectomy (VANH): a randomised controlled trial

VANH-trial

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Abstract

Introduction: Natural orifice transluminal endoscopic surgery (NOTES) is a minimal invasive technique using natural body orifices like the vagina. Benefits of a vaginal assisted NOTES hysterectomy (VANH) are no visible scars, less blood loss, shorter surgery time and it allows more women to undergo a hysterectomy in a day-care setting compared with the total laparoscopic hysterectomy. Trials comparing vaginal hysterectomy (VH) and VANH are lacking. The aim of this study is to compare hysterectomy by VANH versus VH for same-day
discharge, complications, surgical outcomes, post-operative recovery, quality of life, costs and cost-effectiveness.

**Methods and analysis:** The study is a single-blinded, multicentre, randomised controlled trial.

Eligible women with benign indication for hysterectomy will be randomly allocated to the VH (control) group or the VANH (intervention) group. The primary outcome is same-day discharge. We calculated a sample size of 124 women assuming 27% SDD difference with an alpha of 0.05 and power of 0.8. A total of 83 patients will be included in the VANH-group and 41 patients in the VH-group, using an enrolment ratio of 2:1. Secondary outcomes are; surgery related complications, surgical outcomes, post-operative recovery, quality of life, costs and cost-effectiveness.

**Ethics and dissemination:**
The study was approved on 27 May 2021 by the Ethics Committee of the Zuyderland Medical Centre Heerlen. The first patient was randomized on 8 July 2021. The last participant randomized should be treated before 31 December 2022. The results will be presented in peer-reviewed journals and at scientific meetings within 4 years after starting recruitment.
Clinical Trial registration: ClinicalTrials.gov register = NCT04886791; registered 24 May 2021; https://clinicaltrials.gov/ct2/show/NCT04886791

Word count: 2584 words (without references)

Article Summary

Strengths and limitations of this study:

- Randomised controlled trial
- Multicentre study
- Blinding of participants
- Limited generalisability

Keywords: hysterectomy, vNOTES, vaginal assisted NOTES hysterectomy, vaginal hysterectomy, same-day discharge, protocol
Introduction:

Hysterectomy is one of the most performed gynaecological surgeries worldwide [1, 2]. In the Netherlands they yearly perform about 8,000 hysterectomies [3]. The most common benign indications to perform a hysterectomy are uterine leiomyomas (51.4%), abnormal uterine bleeding (41.7%), endometriosis (30%) and prolapse (18.2%) [2, 4-6].

The four approaches to perform a hysterectomy for a benign disease are abdominal hysterectomy (AH), vaginal hysterectomy (VH), (total) laparoscopic hysterectomy ((T)LH) and robotic-assisted hysterectomy (RH) [7, 8].
The VH is the approach of preference for a benign indication because of quicker recovery and
the least amount of complications [4]. Compared to a LH, it is more difficult during a VH to
perform an opportunistic salpingectomy and to inspect the abdominal cavity [9].

The rate of VH and AH has decreased since the introduction of laparoscopy and the number of
LH has significantly increased between 2002 and 2012 [10].

In 2004, a novel approach of endoscopic surgery was described, ‘Natural Orifice Transluminal
Endoscopic Surgery’ (NOTES) by researchers at the John Hopkins University [11]. It is a
surgical technique using natural orifices of the body (e.g. mouth, anus, urethra, vagina) to
perform scarless surgery [12]. The first vaginal assisted NOTES hysterectomy (VANH) was
performed in 2012 [13].

The Vaginal NOTES (vNOTES) has been described for multiple indications, for example
hysterectomy, adnexectomy, cystectomy, salpingectomy in case of an ectopic pregnancy,
myomectomy and sacrocolpopexy [14-16]. The HALON trial was the first randomised
controlled trial (RCT) which compared LH with VANH [17]. This trial showed VANH was
non-inferior to LH. VANH had a significantly shorter surgery time, allowed more women to
undergo a hysterectomy as a day-care procedure and less postoperative complications compared
with LH [17]. A recent published review of Housmans supports this data [16].

No studies have been performed comparing the VH with VANH. Because the VH is the
preferred method to perform a hysterectomy for a benign indication [18], there is a need to
compare VH with VANH. The aim of this RCT is to compare VH with VANH performed as a
same day discharge (SDD) procedure.

**Methods and analysis:**

**Aims and Outcome Measures**

The aim of this study is to compare VH with VANH.

The primary outcome is the proportion of SDD. Secondary outcomes are complications scored
by Clavien Dindo classification [20], surgical outcomes (conversion rate, surgery time, blood
loss, number of performed opportunistic salpingectomies per group), post-operative recovery
(using the EQ-5D-5L questionnaire and Recovery Index-10 (RI-10) respectively), pain first 7
days post-operative (measured using the Numeric Rating Scale (NRS)), quality of life, costs
(for example intervention and hospital costs, using an adapted version of the iMCQ questionnaire [21]) and cost-effectiveness.

We hypothesize that women who underwent a VANH procedure are more often able to be treated in a SDD setting.

**Patient and public involvement**

No patient involved.

**Study Design, Participants**

The design of this study is a single-blind, multicentre, RCT. The participating centres (Zuyderland Medical Centre Heerlen and Catharina Hospital Eindhoven) are both non-university teaching hospitals. Patients of 18 years and older of age, Dutch speaking, with a benign indication for a VH and who have given written and oral informed consent are eligible to participate in this study. Exclusion criteria are any contraindication for VH such as, history of more than one caesarean section, endometriosis, rectal surgery or pelvic radiation, suspected rectovaginal endometriosis, history of pelvic inflammatory disease (PID), virginity, pregnancy,
need for concomitant prolapse or incontinence surgery or a contraindication for general
anaesthesia [19]. The recruitment has started July 2021 and is ongoing.

Procedures, Recruitment, Randomization and Collection of data

Patients scheduled for a VH for a benign indication will be informed about the study during
their visit at the outpatient clinic. Eligible patients who fulfil the inclusion criteria will be
identified and counselled by the research coordinator or staff of the participating centres.

Eligible patients will also be counselled about an elective salpingectomy during surgery. They
will be informed, that when participating in this study, it is only possible to undergo the surgery
under general anaesthesia. To secure blinding of the participants, general anaesthesia is
necessary because a VANH can only be performed using general anaesthesia. Unblinding of
the patients is only permissible when a patients life is in danger due to the surgery.

Patients will be informed about the aims, methods, reasonably anticipated benefits, and
potential hazards of the study. They will be assured that their participation is voluntary and that
they are free to discontinue participation at any time. They will be notified that refusal to
participate or decision to withdraw will not affect their care. When a patient does not want to
participate in the RCT, they are asked to participate in a prospective cohort.
After receiving informed consent, the randomisation procedure with permuted block randomisation will be conducted by the Data Management program of Zuyderland Medical Centre. This program is only accessible for the principal-investigator. This principal-investigator will inform the attending physician via central telephone about the randomisation. Only ‘group A’ or ‘group B’ will be noted in the patient file, without specifying the planned type of surgery. Randomisation will be 1:2 for VH group and the VANH group with a block length of six. Patients are randomly divided in both study groups, using allocation concealment. The study will be single blind with the participants blinded to their treatment allocation.

Figure 1 = Study flowchart (attachment)

Figure 1 shows the study flowchart. With exception of the baseline questionnaires and the NRS pain score, all questionnaires will be sent by e-mail and the patients will be reminded twice if not completed within 1 day (the first 7 days postoperative) and 1 week (other questionnaires).

When a patient decides to discontinue, all the data that is collected until that specific moment can be used. The following baseline characteristics will be collected pre-operatively: age, body mass index (BMI), ethnicity, education level, vaginal parity, medication use, intoxications,
comorbidities, surgical history, indication of surgery, chronic pain defined as pain > 6 months not related to indication of surgery and numeric rating scale for pain before surgery.

Health-related quality of life (HRQoL) is measured with the EQ-5D-5L, which examines the patient’s HRQoL on the day of the interview [22, 23]. It comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each with five response levels (no problems to extreme problems) and a Visual Analogue Scale (VAS) [24]. The EQ-VAS records the patient’s self-rated health with endpoints labelled ‘the best health you can imagine’ at the top and ‘the worst health you can imagine’ at the bottom. Responses to the EQ-5D dimensions can be converted into an index score representing HRQoL.

The RI-10 questionnaire is a standardized questionnaire to measure 5 levels of recovery. This includes for example feelings, pain, mobility, and self-care.

Costs will be calculated by estimating individual resource use by means of a questionnaire based on the iMTA Medical Consumption Questionnaire [21], completed by patients. The questionnaire has a recall period of 6 weeks. Questions focus on resource use outside the hospital (e.g. general practitioner visits, medication, etcetera), and the use of informal care and productivity losses. Costs within the hospital will be collected using hospital records.
**Interventions**

All participants will be counselled for SDD. The surgery will be scheduled in the morning before 12 pm.

**VANH-group:**

Participants will be admitted to the day-care ward. Preoperative cefazolin 2 gram and 500 mg metronidazole will be administered intravenously. Elective salpingectomy will be performed on patients’ request. During surgery, the surgeon will estimate surgical feasibility and safety of performing elective salpingectomy. The participants receive the standard pain medication according to the local pain protocol. When a patient reports a NRS-score of 4 or higher, additional pain medication will be proposed.

**VH group:**

Participants will be admitted to the day-care ward. Preoperative cefazolin 2 gram and 500 mg metronidazole is administered intravenously. Elective salpingectomy will be performed on patients’ request. During surgery, the surgeon will estimate surgical feasibility and safety of performing elective salpingectomy. The participants receive the standard pain medication
according to the local pain protocol. When a patient reports a NRS-score of 4 or higher, additional pain medication will be proposed.

**Statistical Issues**

**Sample Size:**

We are arranging a study of independent cases with an enrolment ratio of 1:2 in favour of the VANH-group (1 VH versus 2 VANH).

According to literature, the mean postoperative hospital stay after a VH is 1.13 days to 2.2 days [25-29]. A recently performed pilot study showed the feasibility of SDD after a VH with a SDD percentage of 63% [30]. The HALON trial reported SDD in 77% of the patients undergoing a VANH procedure [17]. We hypothesize 50% SDD is feasible in the control group and 77% SDD in the intervention group. With an alpha of 0.05 and a power of 0.8 and an enrolment ratio of 1:2, this will result in a total of 36 patients in the control group and 72 patients in the intervention group. Taking 15% lost to follow up in account, we have to include 124 patients of which 41 patients randomised in the control group and 83 patients in the intervention group.

**Data Analysis:**
The data will be analysed using SPSS (version 26), based on an intention to treat principle a per protocol analysis will be performed, the data will be stratified for centre. If the treatment effect is homogenous across centres we will also perform an un-stratified analysis.

Differences in baseline/patient characteristics between the VANH and VH group will be will be analysed by an independent sample t-tests or a Mann-Whitney U-tests in case of non-normal distribution for numeric variables. For categorical variables, the chi-square tests or the Fisher exact tests will be used. Depending on the number of missing values, the missing values will be excluded or imputed. Imputation of the results will be executed according to the guidelines of Jakobsen et al [31]. The primary outcome, i.e. proportion of SDD between both groups, will be analyzed by univariable and multivariable logistic regression analyses.

For numeric secondary outcomes, the independent sample t-test will be used. The categorical secondary outcomes will be analyzed using univariable and multivariable logistic regression analyses.

An economic evaluation will be performed alongside the clinical trial to determine the cost-effectiveness of VANH compared to VH. The evaluation adopts a societal perspective and has a time horizon of 3 months and adheres to the Dutch guideline for economic evaluations in health care and the Dutch manual for costing research [32, 33]. Societal costs over the study
period will be calculated by multiplying individual resource use (as collected with the adapted
iMCQ and using hospital records) with the costs per unit. The quality-adjusted life year
(QALY) is the health outcome of choice in the economic evaluation and is calculated using the
EQ-5D-5L index scores at baseline, 6 and 12 weeks, by means of the area under the curve
method. Cost-effectiveness is then expressed in the incremental cost effectiveness ratio (ICER):
the difference in costs between the two treatments divided by the difference in
QALYs. Bootstrapping techniques will be used to summarise the uncertainty in estimates of
incremental costs, effects and the ICER. In addition, the probability of VANH being more cost-
effective compared to VH, for a range of maximum monetary values that a decision-maker
might be willing to pay for a QALY gained, is presented in a cost-effectiveness acceptability
curve (CEAC). Several one-way sensitivity analyses and scenario analyses will be performed
to assess the robustness of results.

**Discussion:**

Since vNOTES is an upcoming minimally invasive surgical technique, valuable research is
needed to define the indications for VANH.
Recent evidence shows VANH to be an effective and safe technique with potential benefits like shorter surgery time, a higher percentage of surgery in a day-care setting and less postoperative complications compared with LH [16, 17, 34, 35].

To our knowledge, the VANH trial is the first multicentre RCT to compare VH with VANH as SDD procedure and investigates complication rates, treatment related outcomes, post-operative recovery and quality of life and cost-effectiveness.

It is important to compare the VANH with the VH for benign indications. This research contributes to gain insight in the safety and feasibility of this new emerging technique. It contributes to a safe implementation and further development of this method.

**Ethics and dissemination:**

The VANH trial protocol and the informed consent documents have been approved on 27th of May 2021 by the Ethics Committee of the Zuyderland Medical Centre Heerlen. The protocol of the VANH trial is registered at the ClinicalTrials.gov register, with the number NCT04886791; at 24 May 2021.

All eligible women will receive a patient information folder with details about the design of the study, the aim and background of the study and the pros and cons of participating in this study.
Written informed consent will be obtained from all participants. This will be obtained by the principal investigator (IB), the project leader (MW) or the sub-investigator (NS).

In case of important modifications of the protocol or the informed consent documents, the Ethics Committee of Zuyderland Medical Centre Heerlen, all trial participants and Clinicaltrials.gov will be informed.

The VANH trial is non-commercial and investigator driven. All authors declare that there are no competing interests.

An encrypted Excel key file has been made. In this file, the participants number will be linked to the concerning study number. Only the (head)investigators have access to this file. The obtained data will be saved in an eCRF in the program ‘Research Manager’, for which a password is necessary. Here as well only the (head)investigators have access. All paper documents, like the informed consent, baseline questionnaires and CRF papers, will be stored in a chart. This chart will be stored in a locked closet. On the informed consent forms no study number will be mentioned, thus the study number can not be tracked back to the participant.

Author affiliations

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Author contributions

IPWB and MMLHW were responsible for the development of the trial protocol. IPWB was responsible for the logistical aspects of the trial. MMLHW, HAAMV, AD, NS managed the trial in the different hospitals and commented on the protocol and the paper. LH and IPWB were responsible for the trial coordination.

All authors read and approved the final paper.

Competing interests
All authors declare that there are no competing interests.

**Patient consent**

Obtained

**Ethical approval**

This study has been approved by the ethics committee of the Zuyderland Medical Centre (METC. NL76240.096.21). The study is registered at the ClinicalTrials.gov register, with the number NCT04886791; registered 24 May 2021.

**Declarations**

**Ethics approval and consent to participate**

The VANH study was approved by the Medical Ethical Committee of the Zuyderland Medical Centre Heerlen at 27th of May 2021 (METCZ20210035). Written informed consent to participate in the study will be obtained from all participants.

**Consent for publication**
Not applicable.

Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

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**Figure 1 = Study flowchart**

**Enrollment**

Inclusion criteria VANH study:
- ≥ 18 years
- Dutch speakers
- Benign indication hysterectomy
- Possible to perform a VH based on gynecological examination
- Written + oral informed consent

- Informed consent

- Baseline gynecological

- Baseline questionnaire, IMCQ, EQ-5D-5L

- Randomization (n=124) 1:2
  - VH N = 41
  - VANH N = 83

- Follow-up

  Until 12 weeks after surgery

**Exclusion criteria:**
- Contra-indication for VH
- History of ≥ 1 caesarean section
- Endometriosis
- Rectal surgery/pelvic radiation
- Suspected rectovaginal endometriosis
- History of PID
- Virginity
- Pregnancy
- Indication for concomitant prolapse and/or incontinence surgery
- Contra-indication for general

- Registration/ informed consent: Cohort group

  - No
    - No

  - Yes
    - Inclusion cohort study

  NRS + use of analgesics.
  2, 7 days and 4 weeks PO*: RI-10
  6 and 12 weeks PO: RI-10, IMCQ, EQ-
Dear editors of BMJ Open,

We wish to submit an original study protocol ‘Vaginal hysterectomy versus vaginal Assisted NOTES Hysterectomy (VANH): a randomised controlled trial’ for consideration by BMJ Open.

We confirm that this work is original and has not been published elsewhere, nor is it currently under consideration for publication elsewhere.

This randomised controlled trial will investigate the differences between the vaginal hysterectomy with the VANH, with primary outcome same day discharge.

NOTES is an emerging technique within endoscopic minimally invasive surgery, using the natural orifices of the body to enter the abdominal cavity. The vaginal route is called vNOTES. Possible advantages of this technique are less post-operative pain, no visible abdominal scars and shorter hospital admittance. Literature reports quicker discharge when patients underwent a vaginal assisted NOTES hysterectomy (VANH) compared to a laparoscopic hysterectomy and less postoperative pain.

The VANH-trial is an innovative project, using the newest techniques to improve care for our patients.

We have no conflicts of interest to disclose.

Thank you for your consideration of this manuscript.

Sincerely,

Drs. Ilse Bekkers
Resident in training in Gynaecology and Obstetrics and PhD student
Zuyderland Medical Centre
Verzekeringscertificaat

Polisnummer: 624.455.607
Soort verzekering: Aansprakelijkheidsverzekering
Verzekeringnemer: Stichting Zuyderland Medisch Centrum
Verzekerde rubrieken:
- Rubriek A: Algemene en medische aansprakelijkheid
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Onderlinge Waarborgmaatschappij Centramed B.A.

Zoetermeer, januari 2021

drs. L. van Dijk RC
directievoorzitter
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| Administrative information | Title | 1 Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | Page 1, title |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | Page 3, Clinical trial registration |
| | 2b | All items from the World Health Organization Trial Registration Data Set | Page 3, Clinical trial registration |
| Protocol version | 3 | Date and version identifier | All the pages in the bottom |
| Funding | 4 | Sources and types of financial, material, and other support | Page 1 |
| Role and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | Page 1 |
| | 5b | Name and contact information for the trial sponsor | N/A |
| | 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 | N/A |
| | 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) | N/A |
| 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 | Page 5, Introduction, paragraph 5 |
| | | 6b | Explanation for choice of comparators | Page 5, Introduction, paragraph 5 |
| Objectives | 7 | Specific objectives or hypotheses | Page 5, Methods & analyses, aims and outcome measures |
| 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) | Page 6, Methods and analyses, study design, participants |
Study setting

Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

Eligibility criteria

Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)

Interventions

11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial

Outcomes

12 Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended

Participant timeline

Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)

Sample size

Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations

Recruitment

Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:
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.

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.

Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions.

Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how.

If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial.

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.
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

Page 6, Methods and analyses, collection of data and study protocol

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

Page 6, Availability of data and materials and study protocol

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

Page 9, Statistical issues, data analysis

20b Methods for any additional analyses (eg, subgroup and adjusted analyses)

Page 9, Statistical issues, data analysis

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)

Page 9, Statistical issues, data analysis

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

Study protocol, page 20

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

Study protocol, page 19

Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Study protocol, page 15

Ethics and dissemination

Research ethics 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

N/A
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)

Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

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

Financial and other competing interests for principal investigators for the overall trial and each study site

Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

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

Authorship eligibility guidelines and any intended use of professional writers

Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Study protocol, page 23

Study protocol, page 23

Study protocol, page 23

Study protocol, page 23

Study protocol, page 23
SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

*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.
# Vaginal hysterectomy versus vaginal Assisted NOTES Hysterectomy (VANH): a protocol for a randomised controlled trial

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Vaginal hysterectomy versus vaginal Assisted
NOTES Hysterectomy (VANH): a protocol for a
randomised controlled trial

VANH-trial

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Abstract

Introduction: Natural orifice transluminal endoscopic surgery (NOTES) is a minimal invasive technique using natural body orifices like the vagina. Benefits of a vaginal assisted NOTES hysterectomy (VANH) are no visible scars, less blood loss, shorter surgery time and it allows more women to undergo a hysterectomy in a day-care setting compared with the total laparoscopic hysterectomy. Trials comparing vaginal hysterectomy (VH) and VANH are lacking. The aim of this study is to compare hysterectomy by VANH versus VH for same-day
discharge, complications, surgical outcomes, post-operative recovery, quality of life, costs and
cost-effectiveness.

Methods and analysis: The study is a single-blinded, multicentre, randomised controlled trial.

Eligible women with benign indication for hysterectomy will be randomly allocated to the VH
(control) group or the VANH (intervention) group. The primary outcome is same-day
discharge. We calculated a sample size of 124 women assuming 27% same day discharge
(SDD) difference with an alpha of 0.05 and power of 0.8. A total of 83 patients will be included
in the VANH-group and 41 patients in the VH-group, using an enrolment ratio of 2:1.

Secondary outcomes are; surgery related complications, surgical outcomes, post-operative
recovery, quality of life, costs and cost-effectiveness.

Ethics and dissemination:
The study was approved on 27 May 2021 by the Ethics Committee of the Zuyderland Medical
Centre Heerlen. The first patient was randomized on 8 July 2021. The last participant
randomized should be treated before 31 December 2022. The results will be presented in peer-
reviewed journals and at scientific meetings within 4 years after starting recruitment.
Clinical Trial registration: ClinicalTrials.gov register = NCT04886791; registered 24 May 2021; https://clinicaltrials.gov/ct2/show/NCT04886791

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Article Summary

Strengths and limitations of this study:

- Randomised controlled trial
- Multicentre study
- Blinding of participants
- Limited generalisability

Keywords: hysterectomy, vNOTES, vaginal assisted NOTES hysterectomy, vaginal hysterectomy, same-day discharge, protocol
Introduction:

Hysterectomy is one of the most performed gynaecological surgeries worldwide [1, 2]. In the Netherlands they yearly perform about 8,000 hysterectomies [3]. The most common benign indications to perform a hysterectomy are uterine leiomyomas (51.4%), abnormal uterine bleeding (41.7%), endometriosis (30%) and prolapse (18.2%) [2, 4-6].

The four approaches to perform a hysterectomy for a benign disease are abdominal hysterectomy (AH), vaginal hysterectomy (VH), (total) laparoscopic hysterectomy ((T)LH) and robotic-assisted hysterectomy (RH) [7, 8].
The VH is the approach of preference for a benign indication because of quicker recovery and the least amount of complications [4]. Compared to a LH, it is more difficult during a VH to perform an opportunistic salpingectomy and to inspect the abdominal cavity [9].

The rate of VH and AH has decreased since the introduction of laparoscopy and the number of LH has significantly increased between 2002 and 2012 [10].

In 2004, a novel approach of endoscopic surgery was described, ‘Natural Orifice Transluminal Endoscopic Surgery’ (NOTES) by researchers at the John Hopkins University [11]. It is a surgical technique using natural orifices of the body (e.g. mouth, anus, urethra, vagina) to perform scarless surgery [12]. The first vaginal assisted NOTES hysterectomy (VANH) was performed in 2012 [13].

The Vaginal NOTES (vNOTES) has been described for multiple indications, for example hysterectomy, adnexectomy, cystectomy, salpingectomy in case of an ectopic pregnancy, myomectomy and sacrocolpopexy [14-16]. The HALON trial was the first randomised controlled trial (RCT) which compared LH with VANH [17]. This trial showed VANH was non-inferior to LH. VANH had a significantly shorter surgery time, allowed more women to
undergo a hysterectomy as a day-care procedure and less postoperative complications compared
with LH [17]. A recent published review of Housmans supports this data [16].

No studies have been performed comparing the VH with VANH. Because the VH is the
preferred method to perform a hysterectomy for a benign indication [18], there is a need to
compare VH with VANH. The aim of this RCT is to compare VH with VANH performed as a
same day discharge (SDD) procedure.

**Methods and analysis:**

**Aims and Outcome Measures**

The aim of this study is to compare VH with VANH.

The primary outcome is the proportion of SDD. Secondary outcomes are complications
scored by Clavien Dindo classification [19], surgical outcomes (conversion rate, surgery time,
blood loss, number of performed opportunistic salpingectomies per group), post-operative
recovery (using the EQ-5D-5L questionnaire and Recovery Index-10 (RI-10) respectively),
pain first 7 days post-operative (measured using the Numeric Rating Scale (NRS)), quality of
life, costs (for example intervention and hospital costs, using an adapted version of the iMCQ
questionnaire [20]) and cost-effectiveness. Generally, the ovaries will not be removed, unless explicitly requested by the patient. This will be noted and taken into account.

We hypothesize that women who underwent a VANH procedure are more often able to be treated in a SDD setting.

**Patient and public involvement**

No patient involved.

**Study Design, Participants**

The design of this study is a single-blind, multicentre, RCT. The participating centres (Zuyderland Medical Centre Heerlen and Catharina Hospital Eindhoven) are both non-university teaching hospitals. Patients of 18 years and older of age, Dutch speaking, with a benign indication for a VH and who have given written and oral informed consent are eligible to participate in this study. Exclusion criteria are history of more than one caesarean section, endometriosis, rectal surgery or pelvic radiation, suspected rectovaginal endometriosis, history of pelvic inflammatory disease (PID), virginity, pregnancy, need for concomitant prolapse or
incontinence surgery or a contraindication for general anaesthesia [21]. The recruitment has
started July 2021 and is ongoing.

Procedures, Recruitment, Randomization and Collection of data

Patients scheduled for a VH for a benign indication will be informed about the study during
their visit at the outpatient clinic. Eligible patients who fulfil the inclusion criteria will be
identified and counselled by the research coordinator or staff of the participating centres.

Eligible patients will also be counselled about an elective salpingectomy during surgery. They
will be informed, that when participating in this study, it is only possible to undergo the surgery
under general anaesthesia. To secure blinding of the participants, general anaesthesia is
necessary because a VANH can only be performed using general anaesthesia. Unblinding of
the patients is only permissible when a patient's life is in danger due to the surgery.

Patients will be informed about the aims, methods, reasonably anticipated benefits, and
potential hazards of the study. They will be assured that their participation is voluntary and that
they are free to discontinue participation at any time. They will be notified that refusal to
participate or decision to withdraw will not affect their care. When a patient does not want to
participate in the RCT, they are asked to participate in a prospective cohort.
After receiving informed consent, the randomisation procedure with permuted block randomisation will be conducted by the Data Management program of Zuyderland Medical Centre. This program is only accessible for the principal-investigator. This principal-investigator will inform the attending physician via central telephone about the randomisation. Only ‘group A’ or ‘group B’ will be noted in the patient file, without specifying the planned type of surgery. Randomisation will be 1:2 for VH group and the VANH group with a block length of six. Patients are randomly divided in both study groups, using allocation concealment.

The study will be single blind with the participants blinded to their treatment allocation.

Figure 1 = Study flowchart (see supplementary 1)

Figure 1 shows the study flowchart. With exception of the baseline questionnaires and the NRS pain score, all questionnaires will be sent by e-mail and the patients will be reminded twice if not completed within 1 day (the first 7 days postoperative) and 1 week (other questionnaires).

When a patient decides to discontinue, all the data that is collected until that specific moment can be used. The following baseline characteristics will be collected pre-operatively: age, body mass index (BMI), ethnicity, education level, vaginal parity, medication use, intoxications,
comorbidities, surgical history, indication of surgery, chronic pain defined as pain > 6 months not related to indication of surgery and numeric rating scale for pain before surgery.

Health-related quality of life (HRQoL) is measured with the EQ-5D-5L, which examines the patient’s HRQoL on the day of the interview [22, 23]. It comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each with five response levels (no problems to extreme problems) and a Visual Analogue Scale (VAS) [24]. The EQ-VAS records the patient’s self-rated health with endpoints labelled ‘the best health you can imagine’ at the top and ‘the worst health you can imagine’ at the bottom. Responses to the EQ-5D dimensions can be converted into an index score representing HRQoL.

The RI-10 questionnaire is a standardized questionnaire to measure 5 levels of recovery. This includes for example feelings, pain, mobility, and self-care.

Costs will be calculated by estimating individual resource use by means of a questionnaire based on the iMTA Medical Consumption Questionnaire [20], completed by patients. The questionnaire has a recall period of 6 weeks. Questions focus on resource use outside the hospital (e.g. general practitioner visits, medication, etcetera), and the use of informal care and productivity losses. Costs within the hospital will be collected using hospital records.
Interventions

All participants will be counselled for SDD. The surgery will be scheduled in the morning before 12 pm.

VANH-group:

Participants will be admitted to the day-care ward. Preoperative cefazolin 2 gram and 500 mg metronidazole will be administered intravenously. Elective salpingectomy will be performed on patients’ request. During surgery, the surgeon will estimate surgical feasibility and safety of performing elective salpingectomy. The participants receive the standard pain medication according to the local pain protocol. When a patient reports a NRS-score of 4 or higher, additional pain medication will be proposed.

VH group:

Participants will be admitted to the day-care ward. Preoperative cefazolin 2 gram and 500 mg metronidazole is administered intravenously. Elective salpingectomy will be performed on patients’ request. During surgery, the surgeon will estimate surgical feasibility and safety of performing elective salpingectomy. The participants receive the standard pain medication
according to the local pain protocol. When a patient reports a NRS-score of 4 or higher, additional pain medication will be proposed.

**Statistical Issues**

**Sample Size:**

We are arranging a study of independent cases with an enrolment ratio of 1:2 in favour of the VANH-group (1 VH versus 2 VANH).

According to literature, the mean postoperative hospital stay after a VH is 1.13 days to 2.2 days [25-29]. A recently performed pilot study showed the feasibility of SDD after a VH with a SDD percentage of 63% [30]. The HALON trial reported SDD in 77% of the patients undergoing a VANH procedure [17]. We hypothesize 50% SDD is feasible in the control group and 77% SDD in the intervention group. With an alpha of 0.05 and a power of 0.8 and an enrolment ratio of 1:2, this will result in a total of 36 patients in the control group and 72 patients in the intervention group. Taking 15% lost to follow up in account, we have to include 124 patients of which 41 patients randomised in the control group and 83 patients in the intervention group.

**Data Analysis:**
The data will be analysed using SPSS (version 26), based on an intention to treat principle a per protocol analysis will be performed, the data will be stratified for centre. If the treatment effect is homogenous across centres we will also perform an un-stratified analysis.

Differences in baseline/patient characteristics between the VANH and VH group will be will be analysed by an independent sample t-tests or a Mann-Whitney U-tests in case of non-normal distribution for numeric variables. For categorical variables, the chi-square tests or the Fisher exact tests will be used. Depending on the number of missing values, the missing values will be excluded or imputed. Imputation of the results will be executed according to the guidelines of Jakobsen et al [31]. The primary outcome, i.e. proportion of SDD between both groups, will be analyzed by univariable and multivariable logistic regression analyses.

For numeric secondary outcomes, the independent sample t-test will be used. The categorical secondary outcomes will be analyzed using univariable and multivariable logistic regression analyses.

An economic evaluation will be performed alongside the clinical trial to determine the cost-effectiveness of VANH compared to VH. The evaluation adopts a societal perspective and has a time horizon of 3 months and adheres to the Dutch guideline for economic evaluations in health care and the Dutch manual for costing research [32, 33]. Societal costs over the study
period will be calculated by multiplying individual resource use (as collected with the adapted iMCQ and using hospital records) with the costs per unit. The quality-adjusted life year (QALY) is the health outcome of choice in the economic evaluation and is calculated using the EQ-5D-5L index scores at baseline, 6 and 12 weeks, by means of the area under the curve method. Cost-effectiveness is then expressed in the incremental cost effectiveness ratio (ICER): the difference in costs between the two treatments divided by the difference in QALYs. Bootstrapping techniques will be used to summarise the uncertainty in estimates of incremental costs, effects and the ICER. In addition, the probability of VANH being more cost-effective compared to VH, for a range of maximum monetary values that a decision-maker might be willing to pay for a QALY gained, is presented in a cost-effectiveness acceptability curve (CEAC). Several one-way sensitivity analyses and scenario analyses will be performed to assess the robustness of results.

Discussion:

Since vNOTES is an upcoming minimally invasive surgical technique, valuable research is needed to define the indications for VANH.
Recent evidence shows VANH to be an effective and safe technique with potential benefits like shorter surgery time, a higher percentage of surgery in a day-care setting and less postoperative complications compared with LH [16, 17, 34, 35].

To our knowledge, the VANH trial is the first multicentre RCT to compare VH with VANH as SDD procedure and investigates complication rates, treatment related outcomes, post-operative recovery and quality of life and cost-effectiveness.

It is important to compare the VANH with the VH for benign indications. This research contributes to gain insight in the safety and feasibility of this new emerging technique. It contributes to a safe implementation and further development of this method.

**Ethics and dissemination:**

The VANH trial protocol and the informed consent documents have been approved on 27th of May 2021 by the Ethics Committee of the Zuyderland Medical Centre Heerlen. The protocol of the VANH trial is registered at the ClinicalTrials.gov register, with the number NCT04886791; at 24 May 2021.

All eligible women will receive a patient information folder with details about the design of the study, the aim and background of the study and the pros and cons of participating in this study.
Written informed consent will be obtained from all participants. This will be obtained by the principal investigator (IB), the project leader (MW) or the sub-investigator (NS). There is also an insurance for the participants (see supplementary 2).

In case of important modifications of the protocol or the informed consent documents, the Ethics Committee of Zuyderland Medical Centre Heerlen, all trial participants and Clinicaltrials.gov will be informed.

The VANH trial is non-commercial and investigator driven. All authors declare that there are no competing interests.

An encrypted Excel key file has been made. In this file, the participants number will be linked to the concerning study number. Only the (head)investigators have access to this file. The obtained data will be saved in an eCRF in the program ‘Research Manager’, for which a password is necessary. Here as well only the (head)investigators have access. All paper documents, like the informed consent, baseline questionnaires and CRF papers, will be stored in a chart. This chart will be stored in a locked closet. On the informed consent forms no study number will be mentioned, thus the study number can not be tracked back to the participant.

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Author contributions

IPWB and MMLHW were responsible for the development of the trial protocol. IPWB was responsible for the logistical aspects of the trial. MMLHW, HAAMV, AD, NS managed the trial in the different hospitals and commented on the protocol and the paper. LH and IPWB were responsible for the trial coordination.

All authors read and approved the final paper.
Competing interests

All authors declare that there are no competing interests.

Patient consent

Obtained

Ethical approval

This study has been approved by the ethics committee of the Zuyderland Medical Centre (METC. NL76240.096.21).

The study is registered at the ClinicalTrials.gov register, with the number NCT04886791; registered 24 May 2021.

Declarations

Ethics approval and consent to participate

The VANH study was approved by the Medical Ethical Committee of the Zuyderland Medical Centre Heerlen at 27th of May 2021 (METCZ20210035). Written informed consent to participate in the study will be obtained from all participants.
Consent for publication

Not applicable.

Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

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Enrollment

Inclusion criteria VANH study:
- ≥ 18 years
- Dutch speakers
- Benign indication hysterectomy
- Possible to perform a VH based on gynecological examination
- Written + oral informed consent

Informed consent

Registration/informed consent: Cohort group

No

Baseline gynecological

Baseline questionnaire, IMCQ, EQ-5D-5L

Randomization (n=124) 1:2

VH
N = 41

VANH
N = 83

Follow-up

Until 12 weeks after surgery

Exclusion criteria:
- Contra-indication for VH
- History of >1 caesarean section
- Endometriosis
- Rectal surgery/pelvic radiation
- Suspected rectovaginal endometriosis
- History of PID
- Virginity
- Pregnancy
- Indication for concomitant prolapse and/or incontinence surgery
- Contra-indication for general

NRS + use of analgesics.
2, 7 days and 4 weeks PO*: RI-10
6 and 12 weeks PO: RI-10, IMCQ, EQ-
Verzekeringscertificaat

Polisnummer 624.455.607

Soort verzekering Aansprakelijkheidsverzekering

Verzekeringnemer Stichting Zuyderland Medisch Centrum

Verzekerde rubrieken Rubriek A: Algemene en medische aansprakelijkheid
Rubriek B: Werkgeversaansprakelijkheid
Rubriek C: Productaansprakelijkheid
Rubriek D: Milieuaansprakelijkheid
Rubriek E: Particuliere aansprakelijkheid

Verzekerde bedragen Rubriek A t/m E
€ 5.000.000 als maximum per aanspraak, met een
maximum van € 10.000.000 per jaar

Voorwaarden Polisvoorwaarden Centramed 2020

Ingangsdatum 1 januari 2002

Verzekerstermijn De verzekering is aangegaan tot 1 januari 2024 met
voortzetting voor termijnen van drie jaar.

Onderlinge Waarborgmaatschappij Centramed B.A.

Zoetermeer, januari 2021

drs. L. van Dijk RC
directievoorzitter
### Administrative information

| Item No | Description | Page |
|---------|-------------|------|
| 1       | Title       | Page 1, title |
| 2a      | Trial registration | Page 3, Clinical trial registration |
| 2b      | All items from the World Health Organization Trial Registration Data Set | Page 3, Clinical trial registration |
| 3       | Protocol version | All the pages in the bottom |
| 4       | Funding     | Page 1 |
| 5a      | Roles and responsibilities | Page 1 |
| 5b      | Name and contact information for the trial sponsor | N/A |
| 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 | N/A |
| 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) | N/A |

### Introduction

| Item No | Description | Page |
|---------|-------------|------|
| 6a      | Background and rationale | Page 5, Introduction, paragraph 5 |
| 6b      | Explanation for choice of comparators | Page 5, Introduction, paragraph 5 |

### Objectives

| Item No | Description |
|---------|-------------|
| 7       | Specific objectives or hypotheses | Page 5, Methods & analyses, aims and outcome measures |

### Trial design

| Item No | Description |
|---------|-------------|
| 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) | Page 6, Methods and analyses, study design, participants |
Study setting

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

Eligibility criteria

Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

Interventions

Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

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)

Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

Relevant concomitant care and interventions that are permitted or prohibited during the trial

Outcomes

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

Participant timeline

Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)

Sample size

Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations

Recruitment

Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:
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.

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.

Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions.

Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how.

If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial.

Methods: Data collection, management, and analysis

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.
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

Page 6, Methods and analyses, collection of data and study protocol

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

Page 6, Availability of data and materials and study protocol

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

Page 9, Statistical issues, data analysis

20b Methods for any additional analyses (eg, subgroup and adjusted analyses)

Page 9, Statistical issues, data analysis

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)

Page 9, Statistical issues, data analysis

Methods: 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

Study protocol, page 20

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

Study protocol, page 19

Auditing

23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Study protocol, page 15

Ethics and dissemination

24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

N/A
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) N/A

Consent or assent

26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Page 6, Methods and analyses, Procedures, Recruitment, Randomization and Collection of data

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 Study protocol, page 23

Declaration of interests

28 Financial and other competing interests for principal investigators for the overall trial and each study site Page 6, Title page

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 Study protocol, page 23

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 Insurance certificate

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 N/A

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 N/A

Appendices

Inform consent materials

32 Model consent form and other related documentation given to participants and authorised surrogates Informed consent form
SPIRIT Checklist: Recommended items to address in a clinical trial protocol and related documents*

*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.