Effectiveness of laparoscopic niche resection versus expectant management in patients with unexplained infertility and a large uterine caesarean scar defect (uterine niche): protocol for a randomised controlled trial (the LAPRES study)

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ABSTRACT

Introduction A uterine niche is a defect at the site of the uterine caesarean scar that is associated with gynaecological symptoms and infertility. Promising results are reported in cohort studies after a laparoscopic niche resection concerning reduction of gynaecological symptoms in relation to baseline and concerning pregnancy outcomes. However, randomised controlled trials to study the effect of a laparoscopic niche resection on reproductive outcomes in infertile women are lacking. This study will answer the question if laparoscopic niche resection in comparison to expectant management improves reproductive outcomes in infertile women with a large uterine niche.

Methods and analysis The LAPRES study is a randomised, non-blinded, controlled trial, including 200 infertile women with a total follow-up of 2 years. Women with the presence of a large niche in the uterine caesarean scar and unexplained infertility of at least 1 year or failed IVF will be randomly allocated to a laparoscopic niche resection within 6 weeks or to expectant management for at least 9 months. A niche is defined as a niche with a depth of >50% of the myometrial thickness and a residual myometrium of ≤3mm on transvaginal ultrasound. Those receiving expectant management will be allowed to receive fertility therapies, including assisted reproductive techniques, if indicated. The primary outcome is time to ongoing pregnancy, defined as a viable intrauterine pregnancy at 12 weeks’ gestation. Secondary outcome measures are time to conception leading to a live birth, other pregnancy outcomes, received fertility therapies after randomisation, menstruation characteristics, patient satisfaction, quality of life, additional interventions, and surgical and ultrasound outcomes (intervention group). Questionnaires will be filled out at baseline, 6, 12 and 24 months after randomisation. Ultrasound evaluation will be performed at baseline and at 3 months after surgery.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is a randomised controlled trial to evaluate the effect of laparoscopic resection in comparison to expectant management on reproductive outcomes in infertile women with a large uterine niche.
⇒ In line with the idea, Development, Exploration, Assessment and Long-term study framework, was the trial designed after optimisation of the surgical procedure and completion of the learning curve.
⇒ The trial is large and powered to assess time to ongoing pregnancy.
⇒ Laparoscopic niche resection is in the Netherlands currently not offered as a part of usual care, which reduces the risk of selection bias.
⇒ It is an open-label trial, which may affect the outcomes reported by the patients.

Ethics and dissemination The study protocol was approved by the medical ethics committee of the Amsterdam University Medical Centre. (Ref. No. 2017.030). Participants will sign a written informed consent before participation. The results of this study will be submitted to a peer-reviewed journal for publication. Trial registration number: Dutch Trial Register (ref. no. NL6350 http://www.trialregister.nl).

INTRODUCTION

Caesarean sections are rising worldwide.1 The increasing caesarean section rate has raised an interest in the potential long-term sequelae of caesarean scarring. A uterine niche is a defect in the myometrium at the uterine caesarean scar site; the phenomenon has been described frequently in recent


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years. A uterine niche is formally defined by the international Niche Taskforce as ‘an indentation at the site of the caesarean scar with a depth of at least 2 mm’, visible by means of transvaginal ultrasound (TVUS). Previous studies have shown that, in approximately 50%-60% of women with a history of a caesarean section, a niche can be visualised during sonohysterography. Uterine niches are associated with gynaecological symptoms such as postmenstrual spotting, dysmenorrhoea and chronic pelvic pain.

A uterine niche may also reduce fertility. A meta-analysis reported that a caesarean section on average reduced the probability of a subsequent pregnancy by 10% (relative risk, RR 0.91; 95% CI 0.87 to 0.95), relative to a vaginal delivery. None of the studies included in this meta-analysis evaluated the relationship between subsequent fertility and the presence of a uterine niche. Theoretically, the accumulation of blood, mucus and fluid in the niche and uterus may impair the penetration of sperm cells and the implantation of embryos. Sometimes, when combined with an extremely retroverted uterus, a (large) niche may hamper the insertion of an insemination or embryo transfer catheter. A recent study including 1307 women undergoing their first IVF cycle reported significantly lower live birth rate in women with a previous CS compared with women with a previous vaginal delivery (OR 0.63, 95% CI 0.45 to 0.87). Also, in this study, the presence of a niche was not always reported. A recent large prospective cohort study (n=4879) that evaluated the effect of the presence of a niche on reproductive outcomes after single embryo transfer and that corrected for potential confounders such as age, body mass index, fresh or frozen-thawed cycle, the stage of embryo at transfer and endometrial thickness, showed a significant lower live birth rate and higher miscarriage rate in women with a niche compared with women without a niche (aOR 0.61, 95% CI 0.47 to 0.78 and aOR 1.41, 95% CI 1.03 to 1.9). The differences in live birth rate were even larger if the presence of a large niche was compared with the presence of a small niche (aOR 0.42, 95% CI 0.20 to 0.90). These study results indicate an intermediate role of a niche in the lower pregnancy and live birth rates after a CS compared with a vaginal delivery.

In the past 15 years, several innovative surgical procedures have been developed to treat niche-related symptoms. A laparoscopic treatment was first described in 2003. A hysteroscopic niche resection is effective in reducing spotting symptoms in women with small niches, but does not restore the anatomy. A laparoscopic or vaginal niche resection aims to reduce symptoms, restore the anatomy and increase the thickness of the residual myometrium (see figure 1A,B). The latter procedures are suitable for women with large niches with thin residual myometrium.

Studies that evaluated the effect of various surgical interventions have limited sample size and are all single armed without a comparator. Recently, we reported a large prospective cohort study, in which promising fertility and obstetric outcomes were observed in 133 women with a wish to conceive and who underwent laparoscopic resections of large and symptomatic uterine niches. Among these women 88 (66.2%) had infertility of whom 58 (43.6%) had previous failed ART and 45 (33.8%) had an active wish to conceive but without proven infertility yet. The majority of women (62%) conceived following laparoscopic niche resection with a median interval of 3 months after contraception withdrawal (Vissers et al 2023, submitted). Despite the promising results, it is too early to implement laparoscopic niche resection in daily practice as a means to improve reproductive outcomes. According to the principles of the IDEAL (Idea, Development, Exploration, Assessment and Long-term study) framework, a randomised controlled trial (RCT) the next step after optimising outcomes and studying the effect of a new technique in previous cohort studies.

In the current study, we aim to compare the effect of a laparoscopic uterine niche resection with expectant management, for time to ongoing pregnancy and other reproductive outcomes in women with large niches in combination with (1) unexplained infertility for at least 1 year or (2) failed IVF or (3) problems during fertility therapy, such as intrauterine accumulation of fluid and/or technical problems to insert a catheter.

**MATERIALS AND ANALYSIS**

**Design**
The LAPRES study is a single-centre non-blinded RCT, performed in a tertiary referral centre in Amsterdam, the Netherlands, with a total follow-up of 2 years.

**Participants and eligibility criteria**
Women are eligible if a large uterine niche (defined as niche with a depth of ≥50% of the myometrial thickness and a residual myometrial thickness (RMT) ≤3 mm) is observed and if they have at least one of the following problems: (1) unexplained infertility for at least 1 year, (2) failed IVF or (3) problems during fertility therapy, such as intrauterine accumulation of fluid and/or technical problems to insert an intrauterine or embryo transfer catheter. Unexplained infertility was defined as: at least

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**Figure 1** Image of a niche in midsagittal plane using transvaginal ultrasound before (A) and after (B) laparoscopic niche resection in the same women. (A) Extremely retroverted uterus and large niche with intrauterine fluid accumulation in niche and uterine cavity; (image after laparoscopic niche resection. Thickness of the residual myometrium increased and the position of the uterus changed from retroverted (A) to antverted (B).
12 months unprotected intercourse or self-insemination without contraception, regular ovulatory cycle at least one-sided tubal patency (established according to local protocol) and no male factor. Exclusion criteria are pregnancy, age <18 years, insufficient understanding of the Dutch or English language, contraindications for general anaesthesia, a (suspected) malignancy, uterine or cervical polyps, submucosal fibroids, atypical endometrial cells, cervical dysplasia, cervical or pelvic infection or an hydrosalpinx.

Recruitment and randomisation

Before study entry, the uterus and the uterine niche will be evaluated by means of transvaginal sonography. We will use a standardised protocol for the sonographic uterine and niche evaluation. Additionally, a pap smear will be evaluated by means of transvaginal sonography. Before study entry, the uterus and the uterine niche will be evaluated using transvaginal sonography. Eligible patients will be informed by one of the gynaecologists about the aims, methods, design, benefits and possible disadvantages of the laparoscopic niche resection, as a basis for informed consent (online supplemental appendix A). The informed consent form must be signed before involvement in any study-related activity. After written informed consent has been obtained, eligible women will be randomly assigned to the laparoscopic niche resection group or the expectant management group for at least 9 months. Randomisation will be blinded and managed using the research web-based application, which assigns a computer-generated random number to each participant. We will use a permuted block design. All women that decline to participate will be registered anonymously in order to record the number and reason for refusal. Subjects will be able to leave the study at any time and for any reason without any consequences. If women decline to participate, they are offered usual care, which does not include a laparoscopic niche resection.

Intervention (laparoscopic niche resection)

The patients assigned to the laparoscopic niche resection group will undergo a procedure under general anaesthesia in lithotomy position. Full details of the surgical procedure were published previously in our paper on short-term outcomes and in a step-by-step tutorial. In short: the laparoscopic niche resection is continuously guided by hysteroscopy. Adhesions between the uterus and bladder or between the uterus and the abdominal wall will be lysed and the bladder will be dissected from the anterior wall of the uterus and cervix. Due to the thin myometrium overlying the niche, the niche can be transilluminated with the hysteroscopic light to be visualised laparoscopically. The thin part of the niche and all fibrotic tissue will be resected. The uterotomy will be closed using at least four full-thickness single sutures (1.0 multifilament) with sliding knots that include the entire uterine wall and the endometrium. One double inverted matrass suture will be placed across the closed wound to strengthen the wound and ease the tension on the first layer of sutures. If the uterus is (extremely) retroverted even after uterine repair, the round ligaments will additionally be shortened (Baldi anterior) using two continuous running sutures (2.0 multifilament) (see figure 2). An adhesion barrier (Hyalobarrier, Nordic Pharma) will be applied after uterine closure. The anatomical result of niche closure will be evaluated by hysteroscopy at the end of the procedure. To illustrate the procedure, we included a video. Women were advised to use contraception in the first 6 months following niche resection to allow uterine healing prior to subsequent pregnancy.

Control group

The control group will receive usual care according to the local protocol of the referring centre for at least 9 months which means no additional surgical intervention during this period. However, patients are allowed to become pregnant and to receive fertility therapies if indicated, this includes IUI or IVF dependent on their previous received fertility therapies at inclusion. In the intervention group, patients are also allowed to receive fertility therapies if indicated after the intervention from 6 months onwards. All additional therapies received, both by intervention group members and by control group members, will be registered. Any member of the control group who has not become pregnant after 9 months will be given the opportunity to undergo a laparoscopic niche resection.

Evaluation

Patients who are referred to our tertiary referral centre because of a niche and/or related symptoms will be evaluated at our outpatient clinic by trained niche experts as a part of the standard care provision. All such patients will receive a standardised TVUS evaluation of the pelvis, ovaries and uterus. Uterine pathology will be evaluated according to the MUSA guidelines and double endometrial thickness, position of the uterus and presence of sliding sign between bladder and bowels will be documented. In case of suspected adhesions, we will measure the total length of the non-sliding area between the uterus and bladder. The presence of deep endometriosis will also be evaluated.
Niches will be evaluated at baseline in all groups and at 3 months after surgery, in accordance with the international expert recommendations on the evaluation and reporting of niches. The position of the uterus (anteversion, straight, retroversion or extreme retroversion (broken uterus) and presence of a niche (defined as an indentation of at least 2 mm) and fluid accumulation in the niche or uterine cavity will be documented. Gel will be introduced if intrauterine fluid is not present in line with the recommendations of international experts. The length, depth, width and volume of the niche, RMT and adjacent myometrium thickness (AMT), branches of the niche visible in the sagittal and/or transversal plane and distance between the niche and the vesicovaginal fold will be measured. In addition, the presence of any large niches (RMT<50% of AMT, RMT<3 mm) will be documented. All sonographic examiners will undertake the online tutorial (www.nichelearning.online). This learning module is based on the results of a Delphi procedure involving an international group of niche experts.

**Study procedures**

The study will be performed in accordance with Good Clinical Practice (GCP) guidelines. Evaluation of eligibility, niche evaluation and counselling will be performed by physicians with extensive experience in those activities. The surgical interventions will be performed in our centre by at least one of the two experienced gynaecologists (JH and WJKH), each of whom has previously performed more than a hundred laparoscopic niche resections.

**Patient and public involvement**

In 2017, two focus group discussions (N=8 and 5) were conducted. Participants were Dutch patients with a large niche, who were scheduled for surgical treatment for their symptoms. Abnormal uterine bleeding, subfertility, sexual functioning, abdominal pain and self-esteem were themes prioritised by participants, and therefore, taken into account in our study protocol and also outcome parameters were based on input of these focus group discussions.

**Outcome measures**

**Primary outcome measure**

The primary outcome measure is time to ongoing pregnancy, defined as a viable intrauterine pregnancy at twelve weeks gestation.

**Secondary outcome measures**

The key secondary outcome is time to pregnancy leading to a live birth.

Other secondary outcome measures are

- Fertility and pregnancy outcomes: live birth, pregnancy rate, clinical pregnancy rate, ongoing pregnancy rate, miscarriage rate, ectopic pregnancy, pregnancy outcomes including gestational age at delivery, percentage of patients with term delivery, mode of delivery, adverse events during pregnancy and delivery.
- Received fertility therapies after randomisation
- Menstruation characteristics: cycle length, number of days during menstruation, postmenstrual spotting (yes or no) and number of spotting days, pain during menstruation (Verbal Rating Score: VRS), abdominal pain on non-menstruating days (VRS), urinary symptoms (shortlist of SFFI), quality of life based on Short-Form-36 (Aaronson et al, 1998), EQ-5D-5L (The EuroQol Group (1990) (€ : ‘EuroQol—a new facility for the measurement of health-related quality of life’, 1990) and patients self-reported satisfaction (Likert scale)
- Perioperative outcomes (intervention group): surgery time, blood loss during surgery, perioperative and postoperative complications (Clavien-Dindo classification), hysteroscopic result immediately after laparoscopic niche resection, extent of adhesions, subjective characteristics such as surgeon satisfaction and difficulty of the procedure.
- Additional interventions: applied medical and/or surgical interventions because of gynaecological symptoms will be assessed at 6 and 12 months and 2 years follow-up.
- TVUS evaluation will be performed 3 months after a laparoscopic niche resection: presence of a niche, length, depth and with of the niche, RMT, AMT, accumulation of intrauterine fluid, presence of sliding sign or suspected adhesions between the bladder and uterus will be reported in the same way as at baseline.

**Data collection and management**

**Collection of baseline characteristics and patient-reported outcomes**

Baseline characteristics will be collected by means of a digital questionnaire including SF-36 domain scores, EuroQol scores and FSFI scores sent to participants’ email addresses. At 6, 12 and 24 months follow-up, further digital questionnaires will be sent to participants to assess the primary and secondary outcomes (figure 3, flow chart). Reminders for all questionnaires will be sent every 2 weeks; up to three reminders will be sent in each instance. If a participant does not respond to the reminders, a research nurse will call the participant. The gynaecologist, the research nurse or the researcher will also fill out a baseline eCRF (electronic case report form).

**Intraoperative data**

Immediately after the niche resection, the surgeon will be asked to register relevant items regarding the procedure in an eCRF. These items include: surgery time, blood loss during surgery, major and minor perioperative complications, hysteroscopic result immediately after laparoscopic niche resection, extent of adhesions and distance, subjective characteristics such as surgeon satisfaction and difficulty of the procedure.

**Niche evaluation**

All patients in the intervention group will undergo TVUS 3 months after the laparoscopic niche resection to register all uterine and niche features.
Serious adverse events
All serious adverse events (SAEs) will be reported to the medical ethics committee (MEC) by line listing yearly. Life-threatening SAEs or an event that leads to death will be reported to the MEC immediately. All SAEs will be followed until they have abated, until a stable situation has been reached or the patient was discharged.

Confidentiality and data security
All participating researchers receive a login name and password to gain access to researchsurvey.nl, a web-secured randomisation database. Randomisation is performed pseudoanonymously with only the initials and year of birth of the participants. Linking personal data to the study number can only be performed by the trial coordinator. Written informed consent forms are stored in a lockable room. All forms and data will be archived for 15 years in the participating centres.

Statistical analysis
Data will be analysed in accordance with the intention-to-treat principle with a sensitivity analysis according to the per-protocol principle. Baseline characteristics will be presented using percentages, means with SD and 95% CI or medians with IQRs, as appropriate. We will calculate RRs and 95% CIs for all pregnancy outcomes. To study time to ongoing pregnancy, we will construct Kaplan-Meier curves and use the log rank test to compare the treatment groups. In addition, we will estimate the marginal HR with 95% CI using a Cox proportional hazards model. The difference between the two groups in terms of all continuous variables will be analysed using the Mann-Whitney U test for non-parametric data (total number of postmenstrual spotting days during one menstrual cycle, days of spotting at the end of the menstruation, days of intermenstrual spotting, dysmenorrhoea, experienced discomfort due to spotting, niche depth and RMT). Quality of life measures over time will be analysed using linear mixed models using random intercepts for individual women and time point. Fisher’s exact test will be used for the rare binary data, such as the presence of (midcycle) intrauterine fluid and the presence of pain during micturition. Satisfaction with the randomised treatment will be recoded into a binary outcome using ‘dissatisfied’ (combining dissatisfied, very dissatisfied and neutral) or ‘satisfied’ (combining satisfied and very satisfied) and will be analysed using the $\chi^2$ test.

Predefined subgroup analyses
We aim to investigate effect modification of the intervention by the prognosis of individual women, as this avoids looking at many different characteristics separately. To conduct this, we first will develop a prognostic model on the data regressing pregnancy on the following list of a priori selected predictors in a Cox model: (1) age, (2) one versus more previous caesarean sections, (3) postmenstrual spotting complaints (yes or no), (4) presence of midcycle intrauterine fluid accumulation, (5) suspected presence of concomitant adenomyosis and/or endometriosis, (6) duration of infertility, (7) infertile before last CS and (8) previous failed IUI or IVF. Next, we will use the model to estimate the individual probability of pregnancy after 1 year (which represents their characteristics summarised in a prognosis 'score'). Finally, we will fit a new Cox model regressing pregnancy on treatment allocation, score and the interaction between the two.

For the second sensitivity analysis, we will opt for the ‘cloning’ methodological approach for a treatment that is started later in time: the principle is that if the treatment decision is made at some point after diagnosis, we are comparing ‘strategies’ to eventually treat or not rather than assigning treatment at a fixed time point as in an RCT. We start with using the data from all patients for both strategies, then will follow women over time and censored, that is, remove them from analysis when they do not adhere to their assigned strategy, which here involves receiving treatment in the expectant management ‘strategy’ group. For example, a woman who received laparoscopic niche resection at 9 months after randomisation provided data on expectant management for both strategy groups during the first 9 months, was followed after laparoscopic niche resection in the treatment strategy group but censored at the time of laparoscopic niche resection in the expectant management group. Finally, we will fit adjusted (weighted) Kaplan-Meier curves for both groups and conduct a log-rank test to compare the curves. What we obtain is the absolute chance of a live birth over time for both strategies.

Figure 3 LAPRES study flow chart.

Laparoscopic niche resection within 6 weeks + eCRF
Expectant management
TVU (3 months) eCRF
6-month follow-up eCRF
3 months
6-month follow-up eCRF
6 months
Possibility for surgery after 9 months + eCRF
9 months
12-month follow-up eCRF
12 months
24-month follow-up eCRF
24 months
Baseline, eCRF, TVU eCRF
Randomisation
Eligible patients (Woman with a large niche)
Control of inclusion and exclusion criteria
LAPRES study flow chart.
Additional analyses
We plan an additional analysis of effect on the primary outcome, where we exclude women who have decided for other reasons that they do not want to become pregnant for at least a year or who had another surgical intervention including but not limited to a hysteroscopic niche resection or a laparoscopic niche resection or hysterectomy (in other centres) during the first 9 months in the expectant management group. Interim analysis will not be performed because of the long-term follow-up. Total follow-up will extend to 2 years after randomisation.

Sample size calculation
When designing this study, there were no data available on the ongoing pregnancy rates in women with a large niche. However, we did have ongoing pregnancy rates in women undergoing their first IVF cycle who had one previous CS, this was 20.1% in our centre. We assumed that ongoing pregnancy rates will even be lower in women with a large niche. In order to justify a new invasive surgical procedure, we defined that it should at least result in a doubling of the ongoing pregnancies rate. As such, we powered our study on the assumption that the ongoing PR increased from 20% to 40%. Assuming 40% pregnancies in the intervention group, 20% pregnancies in the control group, a (two sided) significance level of 0.05 and a power of 0.80, we need 82 women in each group. Because we expect a drop-out rate of 15%, we intend to include 200 patients.

Ethics and dissemination
The study protocol has been approved by the medical ethics committee (MEC) of the Amsterdam University Medical Centre. (Ref. No. 2017.030). Protocol amendments will be communicated after approval by the central MEC of Amsterdam UMC. The trial has been registered in the International Clinical Trial Registry Platform (ICTRP) (Ref. No. NTR6534; https://trialsearch.who.int/). Eligible women will be counselled in accordance with the GCP guidelines for doctors certified according to the Basic Course on Regulations and Organisation for Clinical Researchers (BROK). Participants will sign a written informed consent before participation (online supplemental appendix A). All recommended items on the SPIRIT 2013 checklist have been addressed in this clinical trial protocol (online supplemental appendix B). The results will be communicated after final inclusion and follow-up, by means of publication in a peer-reviewed international journal and at an international conference.

Patient enrolment began in 2017. We expected completion of follow-up in 2025.

DISCUSSION
In recent years, several innovative surgical therapies have been developed to treat niche-related symptoms or to improve reproductive outcomes. Previous smaller cohort studies reported positive effects on symptoms and reproductive outcomes after laparoscopic niche resection. However, given the lack of RCTs comparing the intervention with expectant management, we do not know exactly how the beneficial effect of laparoscopic niche resection compares with expectant management. The effect of laparoscopic niche resection on reproductive outcomes should be evaluated in RCTs before it is implemented in guidelines and daily practice. We hypothesise that laparoscopic niche resection will lead to better reproductive outcomes compared with expectant management in patients with a large niche and unexplained infertility or failed IVF.

Strengths and limitations
To our knowledge, this is the first RCT that evaluates the effect of laparoscopic niche resection in comparison to expectant management on reproductive outcomes in infertile women with a large uterine niche. The study was designed after the execution of a large cohort study in our centre where we optimised the procedure and completed our learning curve. (Vissers et al 2023, submitted). This is in line with the proposed IDEAL framework for introduction and evaluation of new surgical techniques. Additionally, this risk on selection bias is limited due to the fact that a laparoscopic niche resection in the Netherlands is currently not offered as a part of usual care. To reduce the chance of bias, randomisation will involve allocation concealment by means of a web-based randomisation programme. Given the nature of the procedure, the study cannot be blinded for the patient, which may possibly affect the outcomes reported by the patient. We expect the study to have some limitations as well. We will not be able to study the safety (maternal and/or neonatal outcome) of vaginal delivery after a laparoscopic niche resection, because we advise the included patients as a part of our protocol to undergo an elective caesarean section at term. However, this advice can be debated. Although the thickness of the residual myometrium after a caesarean section and its change during the subsequent pregnancy is associated with the likelihood of a successful labour it is not clear what the optimal cut-off value is for a safe and successful trial of labour. In addition, the chance of uterine rupture during labour is associated with a smaller RMT. There is no evidence that, even with a thick residual myometrium after laparoscopic niche resection, it is safe to deliver vaginally.

Potential impact and implications
So far, given the absence of comparative studies, there is no clear evidence that proves the additional value of a laparoscopic niche resection in order to improve fertility or pregnancy outcomes. However, an increasing number of physicians offer this innovative therapy to their patients with a niche, which may potentially lead to overtreatment. The proposed study is therefore intended to provide more conclusive evidence on the additional value of a laparoscopic niche resection compared with expectant management in women with a large niche.
and unexplained infertility or failed IVF. It will provide insight on reproductive outcomes in potential side effects or complications and on its effect on required fertility therapies and quality of life. These results will guide professionals on the need for uptake of this intervention in guidelines and can be used for counselling of patients with a large niche and infertility on the effect and risks of a laparoscopic niche resection.

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Supplemental material
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REFERENCES


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Information for test subjects on participation in scientific-medical research

LAPRESS study
Women with a large niche and subfertility

Research into the effectiveness of laparoscopic niche resection, in comparison with conservative policy, on pregnancy outcomes in patients with a large niche and unexplained subfertility or an unsuccessful IVF treatment.

Dear Madam,

We are asking you to participate in a medical scientific study. Participation is voluntary. In order to participate, we will need your written permission. You have received this letter because the gynaecologist of the out-patients gynaecology department has established that you have a large niche and you have not yet succeeded in getting pregnant again.

Before you decide whether you want to participate in this study, you will receive an explanation of what the study involves. Take your time to read this information and put any questions you may have to the researcher. You can also ask the independent expert who is named at the end of this letter for additional information. Please feel free to engage your partner - if any - or family members in your considerations.

Further information about participating in such a study can be found on the website of the government: https://www.rijksoverheid.nl/onderwerpen/medisch-wetenschappelijk-onderzoek.

1. General information
This study was set up by the VU University Medical Center and will be performed by gynaecologists in various hospitals.

The Medical Ethical Committee has approved this study. General information about assessing research can be found on the website of the government.

2. Purpose of the study
We want to find out whether the chance of pregnancy increases after a laparoscopic niche resection in comparison with non-resection. We will study this in women with a large niche, and who have not yet succeeded in becoming pregnant again.

In addition, we want to study the effect of the treatment on the chance of pregnancy, possible IUI, IVF or ICSI treatments, gynaecological complaints and costs. We will study this by comparing two groups with one another. Patients who
are eligible for inclusion in this study will be randomly assigned to the following groups:

1. The **expectant group**. This group will not undergo any surgery during 9 months. The patient is allowed, where applicable, to continue fertility treatment such as IUI, IVF or ICSI.

2. The **intervention group**. This group will undergo a laparoscopic niche resection and may not become pregnant during the next six months.

   A total of 200 women will participate in the study, 100 in each group.

### 3. Background to the study

Research shows that women who underwent a Caesarean section may have a defect in the uterus at the location of the scar of the former Caesarean section. The defect is called a niche. This defect can be revealed the use of a water or gel contrast ultrasound scan. You have such a niche. Currently, a laparoscopic niche resection is an international used treatment to women with a large niche and who have gynaecological complaints, because this surgery has been shown to reduce the symptoms of haemorrhaging and pain. Although the effect on fertility is unclear.

During a **laparoscopic niche resection** the recess is removed and the uterus is repaired by a laparoscopic surgery. This has proven to be a safe method.

There are also indications that a niche hampers the realization of a subsequent pregnancy, e.g., if fluid collects in the niche or the uterus, which might make it difficult for an embryo to lodge itself properly, thus preventing a pregnancy. In addition a niche could also influence the vaginal flora which maybe could influence the changes to get pregnant.

Whether a niche really does have a negative effect has been insufficiently researched to date, which is why no standard treatment is offered to women with a large niche who have not yet managed to get pregnant. We have noticed that more than half of the women who have undergone a **laparoscopic niche resection** became pregnant after surgery, the majority of them spontaneously. However, it is not known whether the chance of pregnancy really does improve after a **laparoscopic niche resection** in comparison with no surgery. This is because some women with a niche also achieve spontaneous pregnancy. After a **laparoscopic niche resection** the scar needs 6 months to recover and advice is not to get pregnant during this period. In other words, this surgery may delay the reproductive process.

In some of the women participating in this study, we see that fluid is present in the uterus or in the niche. We would like to gain more insight into the effect of this fluid on the endometrium. For this we would like to carry out additional research on a small group of women. More information about this can you find in this letter.

### 4. What does participation entail?

**Before participation:**
Patient information letter

The defect (niche) in the uterus scar will be assessed in both groups using an internal water or gel contrast ultrasound scan. Measuring this is part of standard gynaecological procedures and takes place before randomisation because these data are needed in order to assess whether you can be considered eligible for this study. Before a laparoscopic niche resection a vaginal swab will be taken, if you give permission for this.

If you are undergoing surgery, we will repeat this ultrasound scan 3 months after the surgery. During this visit a vaginal swab will be taken again, if you give permission for this.

During participation:
If you are randomly selected for the **expecant group**, you will not receive surgery during the first 9 months after randomisation. You are allowed to get pregnant. If so desired, after 9 months you can undergo surgery. If you do become pregnant, in general, caesarean section is advised after a pregnancy lasting 39 weeks.

If you are randomly selected for the **intervention group**, a laparoscopic niche resection will be performed, whereby the recess in your uterus will be removed. The aim is to operate within 6 week after randomisation. In order to ensure that the scar heals properly, you may not become pregnant during the first 6 months. This means that during these 6 months you may not start or continue fertility treatment such as IUI, IVF or ICSI. This is permitted after 6 months. If you become pregnant after surgery, in general, caesarean section is advised after a pregnancy lasting 39 weeks.

If you get pregnant again, we would like to follow the pregnancy of all patients who participated in this study. This will involve making three external ultrasound scans during your routine checks at the outpatients department, to measure the thickness of the uterus wall at the location of the scar, at approximately 12, 20 and 30 weeks of your pregnancy. This means only the ultrasound scan when you are 30 weeks pregnant will be extra; the other two ultrasound scans can be made during routine ultrasound scans. We would also like to ask you a few questions after the pregnancy about the course of the pregnancy and your delivery.

Both groups will receive questionnaires at the start of the study, after 6 months, after 1 year and after 2 years. The questionnaires contain questions about your general heath, menstrual pain, a menstruation calendar, your experience in relation to sex, any fertility treatments and the outcomes of pregnancy. In addition, we ask you to keep a diary of your medication consumption, visits to doctors and hospitals and your sick leave.

In addition to the existing research, we would like to do some additional examination to gain more insight into the influence of a niche and intra-uterine fluid on the endometrium. The extra examinations consist of:
Patient information letter

- Sampling of the endometrium
- Aspiration of fluid from the uterus (if present)

These examinations will take 15 minutes and are prior to any surgery and 3 months after the (possible) surgery. These examinations should be performed on a special period of your menstrual cycle. You must not be pregnant during the extra examinations, so we ask you to use condoms during intercourse form menstruation until the extra examinations. You may have to come to the hospital one extra time for the extra examinations prior to any surgery, but we do our best to combine the extra examinations with other appointments that have already been scheduled. We will combine the extra examinations 3 months after the procedure with the regular follow-up.

Your participation in the additional studies is independent of your participation in the Lapress study. The extra examinations are not compulsory. You can choose whether you want this on the consent form. If you do not consent to the additional examinations, you can simply participate in the rest of the study.

5. What is expected of you

In order to ensure that this study takes place efficiently and for your own safety, it is important that you comply with the following agreements.

The agreements are that you:
- do not participate in another medical scientific study.
- keep your appointments for visits.
- bring the study participation card with you. This states that you are participating in this study. It also states who should be contacted in an emergency. You should also show your card when you visit another doctor.

It is important that you contact the researcher:
- before you start to take other medicines. Even if these are homeopathic medicines, natural medicines, vitamins and/or OTC medicines.
- if you are admitted to hospital or treated in hospital.
- if you suddenly develop health problems.
- if you no longer want to participate in the study.
- if your contact details change.

6. Possible complications

Participating in this scientific study means that, if you are selected for the surgery group, you will undergo keyhole surgery.

7. Possible pros and cons
If you are to undergo a laparoscopic niche resection, you may encounter the following risks and/or nuisance:
- The standard risks of a laparoscopic operation are haemorrhage, a bladder infection or a pelvic infection, a perforation of the uterus which could result in damage to the bladder or a minor risk of intestinal perforation. There is also a small risk that the defect will not disappear completely.
- In addition, you must take into account a recovery period lasting about 4 to 6 weeks before you feel your usual self again. For 2 weeks you should not lift anything heavy (no more than 5 kg).
- Pregnancy is not advised during the first 6 months because the scar has to heal first.
- In addition, an extra ultrasound scan will be made 3 months after the surgery.
- If you get pregnant after a laparoscopic niche resection our advice will be a planned caesarean section to give birth.

Possible advantages of the laparoscopic niche resection
We expect that you will be able to become pregnant faster after surgery, though this is not certain.

Participation in the study also means:
- that you will be asked to complete a number of questionnaires;
- that you will have appointments that you must keep;

All these matters were described above under points 4, 5 and 6.

Sampling of the endometrium and fluid are examinations is a procedure that is more often performed in gynaecology. Some women can have some cramping pain or irregular blood loss. In very rare cases an infection can develop. We advise you to contact a doctor in case of blood loss, abdominal pain or fever.

8. If you do not want to participate, or you want to stop participating in the study
You decide for yourself whether you want to participate in the study. Participation is voluntary. If you do not want to participate, you will receive the usual treatment, and expectant policy will apply. We will not store any details about you for study purpose. The researcher can tell you more about the treatments that exist and their advantages and disadvantages.

If you do participate, you can always change your mind and stop, even during the study. You do not have to say why you want to stop. The data that have been collected up to that moment will be used for the study. We will delete your contact details. The researcher will let you know if new information about the study is available that is important for you. In that case you will be asked whether you want to continue participating.

9. End of the study
Patient information letter

Your participation in the study will end when
- all visits have taken place [according to schedule/as described under point 4]
- you choose to stop
- you become pregnant
- the entire study has come to an end
- the researcher feels it is better for you to stop
- Your doctor, the government or the Medical Ethical Committee responsible for assessment decides to end the study.

The entire study ends when all participants have finished.
The researcher will inform you of all important outcomes of the study after all data have been processed.

10. Use and storage of your details

Your details

All your details will remain confidential. Only the researcher will know which is your code. The researcher retains the key to the code. Reports on the study also use only this code.

Some people are allowed to access your medical and personal details. This is in order to check whether the study was carried out properly and reliably. General information in this respect can be found on the website of the government.

People who can access your details are the research team and the Healthcare Inspectorate.

They will maintain secrecy regarding your details. By signing the Informed Consent form, you are granting permission for the collection and storage of and access to your medical and personal details.

The researcher stores your details during 15 years.

Consent follow up research

We would like your consent to approach you in writing or by phone for any follow up research. If you agree now, you can always withdraw this consent later. To approach you in the future we would like save your contact details (name, address, phone number and email). These contact details will be stored on save location at your hospital and send to the coordinating hospital. These data will not be used for different purposes.

The bodily material

If you give permission for taking endometrium and fluid form the uterus, this bodily material will be stored with a code in the hospital. Only the researcher knows which is your code. The bodily material will only be used to answer the questions of this research and for publication. After the examination the body material will be destroyed.
11. Insurance for test subjects
Insurance has been taken out for everyone who participates in this study. The insurance covers damage caused by the study. Not all damage is covered. More information about the insurance can be found in appendix B. It also states to whom damage should be reported.

12. Informing your GP
We always send a letter to your GP to inform him/her that you are participating in the study. We do this for your own safety. If you do not agree to this, then you cannot participate in this study. You cannot participate in the study if you do not have a GP.

13. No reimbursement for participation
You will not be charged for the costs of the treatment for the study. You will not receive payment for participating in this study.
If you participate in the extra examinations and we can’t schedule sampling of the tissue together with a regular appointment, you will receive a travel and parking fee for the extra visits.

14. Do you have any questions?
If you have any questions, you can contact Prof. Dr. J.A.F. Huirne, gynaecologist or Drs. S. Klein Meuleman, coordinating researcher.

You can contact the independent doctor for independent advice on participating in this study. She knows a lot about the study, but is not involved in this study; this is Dr. M.C. Haak, gynaecologist.

If you have complaints, you should contact the complaints commission of your hospital. All details can be found in appendix A: Contact details.

15. Signing the Informed Consent Form
Once you have had sufficient time to consider (at least 1 week), you will be asked to decide on participation in this study. If you give your permission, we will ask you to confirm this in writing using the enclosed informed consent form. By giving us your written permission, you are indicating that you have understood the information and that you agree to participate in the study.
The researcher will retain the page bearing the signature. You will receive a copy or a second copy of this informed consent form. All details can be found in appendix C: informed consent form.

Thank you for your attention.

Appendices with this information
A. Contact details:
   a. Prof. Dr. J.A.F. Huirne (020-5663754).
Patient information letter

b. Drs. S. Klein Meuleman, coordinating doctor/researcher (020-5663754)

c. Dr. M.C. Haak, independent researcher (071-5262896)

B. Information on the insurance: appendix

C. Informed consent form
Appendix A: contact details of the VU University Medical Center

Local Investigator: Prof. Dr. J.A.F. Huirne
Drs. S. Klein Meuleman, coordinating doctor/researcher.
They can be reached through the Women’s Clinic secretary office of the Amsterdam UMC location AMC. Telephone 020-5663754 during office hours or email address lapresstudie@amsterdamumc.nl

Independent expert: dr. Monique C. Haak, gynecologist LUMC
Email: m.c.haak@lumc.nl (071-5262896)

Complaints:
If you are not satisfied with the study or your treatment, you can report this to your treating physician. In case you do not want to do this, you can also contact Patiëntenvoorlichting en Klachtenopvang (Patient Advice and Liaison Service) at the Amsterdam UMC.
klachten@amsterdamumc.nl,
- On location AMC: 020-5663355
- On location VUMc: 020-4440700/020-4443555

For general information on your rights with respect to the processing of your data you can consult the website of the Dutch Data Protection Law at:https://autoriteitpersoonsgegevens.nl For questions or complaints about the use of your personal data, you can contact the research team or principal investigator in your hospital. You can also contact the privacy officer:
- On location AMC: FG@amc.nl
- On location VUMc: privacy@vumc.nl
Appendix B: information on the insurance

Insurance has been taken out for everyone who participates in this study. The insurance covers damage caused by participation in the study. This applies to damage that occurs during the study or within four years after your participation in the study has ended. Damage must have been reported to the insurer within those four years.

The insurance does not cover all damages. At the end of this text, is a brief summary of damage that is not covered.

These provisions are laid down in the (Dutch) Decree on mandatory insurance for medical scientific research involving human subjects. This decree appears on www.ccmo.nl, the website of the Central Committee on Research involving Human Subjects (see ‘Bibliotheek’ and then ‘Wet- en regelgeving’).

In the event of damage, you can contact directly the insurer [or intermediary].

<table>
<thead>
<tr>
<th>The insurer of the study is:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name: Onderlinge Waarborgmaatschappij Centramed</td>
</tr>
<tr>
<td>Address: P.O. Box 7374. 2701 AJ. Zoetermeer</td>
</tr>
<tr>
<td>Telephone number: +31(0)70-3017070</td>
</tr>
<tr>
<td>E-mail: <a href="mailto:info@centramed.nl">info@centramed.nl</a></td>
</tr>
<tr>
<td>Policy number: 624.529.204</td>
</tr>
</tbody>
</table>

The insurance offers cover amounting to €650,000 per test subject and €5,000,000 for the entire study and €7,500,000 per year for all studies of the same client.

The insurance does not cover the following damage:

- damage due to a risk about which you were informed in the written information. This does not apply if the risk manifests in a more severe form than was foreseen or if the risk was completely improbable;
- the damage would have occurred to your health even if you have not participated in the study;
- damage due to failing to comply (in full) with directions or instructions;
- damage to your offspring, as a consequence of a negative effect of the study on you or your offspring;
- damage due to an existing method of treatment during research into existing methods of treatment.
Appendix C: test subject informed consent form

**LAPRESS study:** Research into the effectiveness of a laparoscopic niche resection in comparison with expectant policy on the pregnancy outcomes of patients with a large niche and unexplained subfertility or an unsuccessful IVF treatment.

I have read the information letter. I was also able to ask questions. I received sufficient answers to my questions. I had ample time to decide whether to participate in the study.

- I know that participation is voluntary. I also know that I can decide at any time not to participate in the study or to end my participation. This does not oblige me to state my reasons.
- I give my permission to inform my GP that I am participating in this study.
- I am aware that some persons can access my details. These persons are mentioned in the information letter.
- I give my permission to collect and use my details as stated, and for the purposes mentioned in the information letter.
- I give my permission to store my details on the study location for 15 years after this study.
- I agree that my data for this study being forwarded to the main investigator of the coordinating hospital, so that I can be contacted by phone, post or email with questionnaires as mentioned in the information sheet.
- I □ do □ do not give my permission to approach me again for a follow-up study subsequent to this study and to forward my contact details to the coordinating hospital for these purposes.
- I □ do □ do not give my permission to take a vaginal swab before and after a laparoscopic niche resection.
- I □ do □ do not give my permission to take endometrium samples, uterine fluid of the uterus before and after a laparoscopic niche resection.
- I want to participate in this study.

Name of the test subject:
Email address:

Signature: __________________________ Date: __/__/__

I declare that I informed this test subject in full about the said study.

If during the study information becomes known that could influence the permission of the test subject, then I will inform him/her in good time.
Patient information letter

Name of the researcher (or his/her representative):

Signature:       Date: __ / __ / __

The test subject will receive a full information letter, together with a copy of the signed informed consent form.
<table>
<thead>
<tr>
<th>Section/item</th>
<th>Item No</th>
<th>Description</th>
<th>Addressed on page number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>1</td>
<td>Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym</td>
<td>1</td>
</tr>
<tr>
<td>Trial registration</td>
<td>2a</td>
<td>Trial identifier and registry name. If not yet registered, name of intended registry</td>
<td>2, 10</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>All items from the World Health Organization Trial Registration Data Set</td>
<td></td>
</tr>
<tr>
<td>Protocol version</td>
<td>3</td>
<td>Date and version identifier</td>
<td>Patient consent form added to document</td>
</tr>
<tr>
<td>Funding</td>
<td>4</td>
<td>Sources and types of financial, material, and other support</td>
<td>12</td>
</tr>
<tr>
<td>Roles and responsibilities</td>
<td>5a</td>
<td>Names, affiliations, and roles of protocol contributors</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>5b</td>
<td>Name and contact information for the trial sponsor</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>5c</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5d</td>
<td>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)</td>
<td></td>
</tr>
</tbody>
</table>
## 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  

3, 4

6b Explanation for choice of comparators  

4

### Objectives

7 Specific objectives or hypotheses  

4

### 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)  

4, 5

## 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  

4, 5

### 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)  

5

### Interventions

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

5, 6

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)  

9

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

8

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

6

### 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  

7, 8

### 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)  

8
### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

<table>
<thead>
<tr>
<th>Method</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence generation</td>
<td>16a</td>
</tr>
<tr>
<td>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.</td>
<td>5</td>
</tr>
<tr>
<td>Allocation concealment mechanism</td>
<td>16b</td>
</tr>
<tr>
<td>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.</td>
<td>5</td>
</tr>
<tr>
<td>Implementation</td>
<td>16c</td>
</tr>
<tr>
<td>Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions.</td>
<td>5</td>
</tr>
</tbody>
</table>

#### Blinding (masking)

<table>
<thead>
<tr>
<th>Method</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how.</td>
<td>N.A.</td>
</tr>
<tr>
<td>If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial.</td>
<td>N.A.</td>
</tr>
</tbody>
</table>

### Methods: Data collection, management, and analysis

<table>
<thead>
<tr>
<th>Method</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data collection methods</td>
<td>18a</td>
</tr>
<tr>
<td>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.</td>
<td>7,8-9</td>
</tr>
<tr>
<td>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.</td>
<td>5-9</td>
</tr>
<tr>
<td>Section</td>
<td>Paragraph</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Data management</td>
<td>19</td>
</tr>
<tr>
<td>Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8,9</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>20a</td>
</tr>
<tr>
<td>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.</td>
<td></td>
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<tr>
<td></td>
<td>8,9</td>
</tr>
<tr>
<td></td>
<td>20b</td>
</tr>
<tr>
<td>Methods for any additional analyses (e.g., subgroup and adjusted analyses)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9,10</td>
</tr>
<tr>
<td></td>
<td>20c</td>
</tr>
<tr>
<td>Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9,10</td>
</tr>
<tr>
<td>Methods: Monitoring</td>
<td>21a</td>
</tr>
<tr>
<td>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.</td>
<td></td>
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<tr>
<td></td>
<td>10,11</td>
</tr>
<tr>
<td></td>
<td>21b</td>
</tr>
<tr>
<td>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.</td>
<td></td>
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<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Harms</td>
<td>22</td>
</tr>
<tr>
<td>Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8-9</td>
</tr>
<tr>
<td>Auditing</td>
<td>23</td>
</tr>
<tr>
<td>Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8-9</td>
</tr>
<tr>
<td>Ethics and dissemination</td>
<td>24</td>
</tr>
<tr>
<td>Plans for seeking research ethics committee/institutional review board (REC/IRB) approval</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Protocol amendments</td>
<td>25</td>
</tr>
<tr>
<td>Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Item</td>
<td>Description</td>
</tr>
<tr>
<td>------</td>
<td>-------------</td>
</tr>
<tr>
<td>26a</td>
<td>Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) 5,7</td>
</tr>
<tr>
<td>26b</td>
<td>Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable N.A.</td>
</tr>
<tr>
<td>27</td>
<td>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 8,11</td>
</tr>
<tr>
<td>28</td>
<td>Financial and other competing interests for principal investigators for the overall trial and each study site 12</td>
</tr>
<tr>
<td>29</td>
<td>Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators 9</td>
</tr>
<tr>
<td>30</td>
<td>Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation In supplementary patient consent form</td>
</tr>
<tr>
<td>31a</td>
<td>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 11</td>
</tr>
<tr>
<td>31b</td>
<td>Authorship eligibility guidelines and any intended use of professional writers 11</td>
</tr>
<tr>
<td>31c</td>
<td>Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code 9</td>
</tr>
</tbody>
</table>

**Appendices**

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>Model consent form and other related documentation given to participants and authorised surrogates Supplement</td>
</tr>
<tr>
<td>33</td>
<td>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</td>
</tr>
</tbody>
</table>

*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.*