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Running title

NOTABLE study

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ABSTRACT

Introduction: Natural Orifice Transluminal Endoscopic Surgery(NOTES) uses natural orifices to access the cavities of the human body to perform surgical interventions. NOTES limits the magnitude of surgical trauma, and potentially reduces postoperative pain. Our group published a protocol on a randomized study comparing transvaginal NOTES(vNOTES) versus laparoscopy for hysterectomy(HALON). We simultaneously designed a similar RCT comparing vNOTES with laparoscopy for adnexectomy. To the best of our knowledge this is the first RCT comparing vNOTES with laparoscopy for adnexal surgery.

Methods and analysis: The methodology of the NOTABLE study is similar to that of the HALON trial. Women aged 18-70 years with an indication for benign adnexal surgery will be eligible. We will use stratification according to adnexal size. Entrants will be randomised to the laparoscopic treatment(control) or vNOTES(intervention). Participants will be evaluated on days 0-7, and at 3 and 6 months. The primary outcome will be the proportion of women successfully treated by removing an adnexa by the allocated technique without conversion. We will collect the following data(secondary outcomes): proportion of women hospitalized on the day of surgery; postoperative pain scores measured twice daily from day 1-7; total dosage of pain killers used from day 1-7; hospital readmission during the first six weeks; dyspareunia and sexual wellbeing at baseline, 3 and 6 months using a validated questionnaire(SSFS scale); health-related quality of life at baseline, 3 and 6 months after surgery using an validated questionnaire (EQ-5D-3L); duration of surgical intervention; infection or other surgical complications; direct costs up to 6 weeks following surgery. For the primary outcome measure, a one-sided 95% confidence interval of the difference in the proportions of women with a successful removal of the uterus by the randomised technique will be estimated. Non-inferiority will be concluded when 15% lies above the upper limit of this 95% CI.

Ethics and dissemination: The study was approved on December, 1st 2015 by the Ethics

Committee of the Imelda Hospital, Bonheiden, Belgium. We aim to present the final results of the NOTABLE trial in peer- reviewed journals and at scientific meetings within 4 years after the start of the recruitment.

Registration details:

Primary Registry and Trial Identifying Number**:** NCT02630329

Secondary Identifying Number**:** B689201526268

Date and version identifier: Version 5, 28 December 2015

Study dates:

The first patient was included on 15 January 2016.

On 22 May 2017 38 of the targeted 70 participants were recruited.

Anticipated date of study completion is estimated May 2018.

Strengths and limitations of this study:

Randomised controlled trial

Blinding of patients, outcome assessors and personnel

Single centre study

Limited generalisability

Use of non-therapeutic incisions for blinding may confound outcome pain

INTRODUCTION

Background

Laparoscopic surgery has reduced surgical morbidity and mortality. “Minimally invasive surgery” has moved even further forward with newer techniques such as single incision laparoscopic surgery (SILS) and natural orifice transluminal endoscopy (NOTES) with or without by robot assistance.

The NOTES technique uses any natural orifice (mouth, vagina, urethra or rectum) as a possible access route facilitating a surgical intervention in a cavity of the human body. Clinical researchers at Johns Hopkins University first reported its use in 2004 in a preclinical trial using an animal model (1). Ever since the clinical application of NOTES has been reported in many surgical procedures in ways that seem to defy human imagination: appendectomy and cholecystectomy have been performed using the mouth and the stomach as the access route (2, 3). The technique seems feasible and safe in the hands of experienced surgeons beyond their surgical learning curve. Observational evidence (mostly case reports) have reported moreover that NOTES may cause less postoperative pain, a shorter length of hospital stay, less complications and last but not least for female patients improved cosmetic results. The feasibility of scar-free surgery in combination with reduced wound (trocar) complications may be tempting for patients and their careproviders. This may be a strong facilitator for the widespread implementation of this new surgical approach.

NOTES has gained popularity amongst general surgeons, urologists and gastroenterologists over the past few years and its feasibility and safety in these domains have been reported (4). Although NOTES may be performed using various entries including the stomach, oesophagus, bladder and rectum, the majority of NOTES procedures in women have been performed through the vagina (5). This is not surprising because the colpotomy technique has been used widely vaginal prolapse surgery and for benign adnexal surgery involving the

extraction of large specimens. Its use has been reported as a safe access (6, 7). Two variants of NOTES have been described in the present literature. Hybrid NOTES combines the access through the vagina with transabdominal assistance; pure NOTES refers to procedures that involve only transluminal access.

The removal of one or both adnexa using a transvaginal NOTES (vNOTES) approach was described for the first time by Lee and co-workers in 2012 (8). vNOTES adnexectomy for benign pathology was introduced at our department by the first author (JB) in 2013. Our group published three small case series on adnexal removal (N=20) (9), salpingectomy (N=5) (10) and hysterectomy (N=10) (11) by vNOTES during the period between November 2013 and February 2015. We also published the protocol of the HALON study randomly comparing NOTES and laparoscopy for doing hysterectomy in women with benign gynaecological disease (12). The recruitment of the HALON study was finished recently (February 24th 2017). The final data analysis of the HALON study is foreseen for September 2017.

Objectives and hypotheses

We started our research by doing a systematic review of the literature. We searched MEDLINE, EMBASE and The Cochrane Library from inception to 1 August 2015 using a combination of MeSH terms and key words for '*colpotomy'* and '*adnexal diseases'* or *'adnexal mass'*. We aim to publish the results of this systematic search of the literature and a critical appraisal of the retrieved evidence in a separate systematic review (SR): we will adhere to the PRISMA-P guidelines (13) for the protocol of this SR. The protocol of the SR has been registered in PROSPERO- the international prospective register of systematic reviews, at the Centre for Reviews and Dissemination (CRD), University of York, United Kingdom (14), as CRD42016033670. To the best of our knowledge no randomised controlled

studies comparing vNOTES with the transabdominal laparoscopic approach for removal of one or both adnexa have been published in the literature. The main objective of the NOTABLE study is to study the effectiveness of vNOTES for successfully removing one or both adnexa for benign gynaecological disease using the classical laparoscopic approach as the established effective technique (EET). The rationale and the objectives of NOTABLE are in accordance with the principles outlined by the IDEAL collaboration (15-17).

Our primary study hypothesis is that vNOTES is not inferior to transabdominal laparoscopy for removing one or both adnexa for a benign gynaecological indication without having to convert to another technique. vNOTES may offer several advantages including the avoidance of abdominal scars, less need for hospital admission and possibly less postoperative pain.

METHODS

Trial design and study analysis

The NOTABLE study should be considered as a pilot study. It is a single-centre parallel-group double blinded (patient and outcome assessor) randomised trial conducted at the Department of Gynaecology of the Imelda Hospital in Bonheiden. This is a general hospital in Belgium serving an estimated population of 150,000 people. All women aged 18-70 years bound to undergo removal of one or both adnexa for benign gynaecological disease will be informed about the NOTABLE study and they will be invited to participate in the study, if eligible. The baseline characteristics of eligible women not wishing to give informed consent for participating in the study will be recorded as well as the reason for declining to participate. All surgical procedures (vNOTES and laparoscopy) will be done by one surgeon (JB) who is equally skilled in both techniques. The surgeon has been using the vNOTES approach for various interventions (salpingectomy for EUG, adnexectomy and hysterectomy) since November 2013. JB is also the surgeon performing the hysterectomies in the HALON trial. The surgeon cannot be blinded but the allocated treatment will be concealed. We will use a non-inferiority study design to test the effectiveness of vNOTES compared to laparoscopy. The protocol adheres to the SPIRIT standards (http://www.spirit-statement.org/). The study protocol of the NOTABLE trial is very similar to that of the earlier published HALON study (12).

Participants

NOTABLE will recruit eligible women aged 18-70 years, regardless of parity, who need the removal of one or both adnexa for a benign adnexal disease and who provide informed consent prior to surgery.

Exclusion criteria are as follows:

- history of rectal surgery

- suspected rectovaginal endometriosis
- suspected malignancy
- history of pelvic inflammatory disease (PID)
- active lower genital tract infection
- virginity
- pregnancy
- failure to provide written informed consent.

Intervention, procedures and standard care

On the day of the surgery, all patients are admitted to the day care unit. A nurse administers clindamycin vaginal cream on admission.

Under general anaesthesia, the patient is positioned in a vacuum mattress in the classical lithotomy. An alcoholic betadine solution is used for disinfection of the vagina, vulva and abdomen before draping. A Foley catheter is inserted into the bladder. The anaesthesiologist will administer cefazolin 2g and metronidazole 1.5g IV for prophylaxis against infection to all women of both treatment arms.

Control group: laparoscopic technique

The surgeon will start the procedure by making a small vertical intra-umbilical skin incision. A Veress needle is introduced into the peritoneal cavity; the tip position is checked with a Semm test before insufflating CO_2 until a maximal intraperitoneal pressure of 15mmHg. A 10mm trocar is inserted through the umbilicus after removal of the Veress needle. An optic is inserted to inspect the peritoneal cavity. The operating table is tilted in the Trendelenburg position. Two 5mm trocars are placed under direct vision in the suprapubic region and in the left iliac fossa lateral of the epigastric vessels. The small intestine is lifted out of the pelvis.

The ureter is identified, but no retroperitoneal dissection is performed unless indicated. The proximal end of the Fallopian tube is coagulated at its origin in the uterus using a reusable

bipolar grasping forceps before being cut with cold microscissors. The ovarian and infundibulopelvic ligament are coagulated and cut. After resection, the adnexa is placed in an endobag (Memobag, Teleflex). When indicated, the same procedure is repeated for the contralateral side.

After confirmation of haemostasis, the peritoneal cavity is rinsed. No drains are left in the peritoneal cavity unless necessary, e.g. problematic haemostasis. The 5 mm trocars are be removed under direct vision. The purse string of the endobag is pulled through the 10 mm trocar upon removal of the optic. The umbilical incision is extended vertically in caudal direction, but not more than 2.5 cm. The fascia and peritoneum are opened and the proximal end of the endobag is pulled through the incision without causing any rupture if possible. If not possible, the endobag will be opened and the content of the cyst will be aspirated to reduce the volume of the adnexa. The aspirated fluid will be sent for cytological evaluation. The endobag will then be removed with the adnexa inside it.

The fascia is closed using a Vicryl-1 running suture. The umbilicus and other incisions are disinfected with betadine solution. All skin incisions are closed with a Monocryl 3/0 intradermal suture and approximated using steri-strips. The wound sites are covered with a wound dressing. A vaginal plug (betadine gauze 10 cm x 5 m) is inserted into the vagina. After 3 hours the Foley catheter and the vaginal plug are removed.

Intervention group: vNOTES

The surgeon makes three non-therapeutic superficial skin incisions on exactly the same location as in the classical laparoscopic approach in all women allocated to the vNOTES group to blind study participants and the outcome assessor to the allocated technique. A 2.5 cm posterior colpotomy is made using a cold knife. The pouch of Douglas is opened using scissors. A Gelpoint Mini (Applied Medical), used as vNOTES port, is inserted into the pouch of Douglas. CO_2 is be insufflated until a maximal intraperitoneal pressure of 15mmHg. An

optic is inserted to inspect the peritoneal cavity. The operating table is tilted in the Trendelenburg position. The small intestine is lifted out of the pelvis.

The ureter is identified, but no retroperitoneal dissection is performed unless indicated. The proximal end of the Fallopian tube is coagulated at its origin into the uterus using a reusable bipolar grasping forceps and cut using microscissors. The ovarian and infundibulopelvic ligament are coagulated and cut. The adnex is removed. When indicated, the procedure is repeated for the contralateral side. After confirmation of haemostasis, the peritoneal cavity is rinsed.

Small benign looking adnexa are removed directly through the wound protector part of the vNOTES port. Large adnexa or adnexa that appear macroscopically suspicious, are placed in an endobag (Memobag, Teleflex). The purse string of the endobag is pulled through the wound protector and the purse string released. The content of the cyst is aspirated to reduce the volume of the adnexa. The endobag is then removed with the adnexa inside it. The vNOTES port is removed.

The colpotomy is closed using three interrupted figure-of-eight Vicryl 2/0 sutures. A vaginal plug (betadine gauze 10cmx5m) is inserted into the vagina. After 3 hours the Foley catheter and the vaginal plug are removed.

In the majority of patients it is feasible to perform a successful vNOTES or laparoscopic adnexectomy. Women in whom the intended approach has to be abandoned for an alternative intervention will not be excluded or withdrawn from the NOTABLE trial but will be followed up further. It is anticipated that most included patients with a normal CA125 value and benign features of the ovary on ultrasound, will not require other interventions besides the removal of the adnexa. If the responsible clinician judges that additional treatment is necessary at the time of the surgery or afterwards, this will be recorded and the patient will not be withdrawn

from the study. However, if there is a preoperative indication for additional surgery during the same procedure, these patients will be excluded from recruitment to the NOTABLE trial.

The anaesthesiologists involved in the clinical trial have developed a standardised protocol to insure that the pain management is identical for both groups. The outcome assessor (JJAB) and the patient are both blinded to the surgical approach used. The patient makes the decision to be discharged from the day care unit on the evening of the procedure or to be admitted to an in-hospital nursing ward for the night. The outcome assessor can only overrule the patient's decision in the interest of her health, e.g. when surgical complications were recorded in the surgical report or when vital parameters indicate a life-threatening condition. Before discharge all patients are given a standard list of instructions to avoid physical work, exercise and sexual intercourse for four weeks after the intervention.

All participants, regardless of being at home or in hospital, are requested to use a VAS scale twice daily to measure postoperative pain from day 1 until day 7 following surgery. Adequate instructions on how to use the VAS scale measuring tool are given on an individual basis by a dedicated nurse of the day care unit. One measurement is made in the evening before going to bed after physical activity (active) and another is made in the morning after bed rest at night (rest). All patients are asked to note the name, dosage, and route of administration of any analgesic drug taken from day 1-7 in a pain log book.

Outcome measure

We searched the COMET (18) database for a core outcome set for adnexectomy (general settings) in gynaecology (health area-disease category) in women (target population: sex) aged 18 to 70 years (target population: age): no core outcome set relevant to laparoscopic removal of adnexa was identified (19).

Primary outcome measure

The proportion of women successfully treated by removing one or both adnexa without spill by the allocated technique as randomized will be measured as the primary outcome of effectiveness.

Secondary outcome measures

The secondary outcomes are as follows:

- The proportion of women hospitalized on the day of surgery based on their own preference.
- Postoperative pain scores measured using a Visual Analogue Scale (VAS) scale (20) twice daily from day 1-7.
- The total dosage of pain killers taken during the first week following surgery.
- Postoperative infection defined by lower abdominal pain with fever > 38°C and positive clinical signs or laboratory findings detected during the first six weeks of surgery.
- Intra- or postoperative complications classified according to the Clavien- Dindo classification (20) detected during the first six weeks of surgery.
- Readmission to hospital during the first six weeks of surgery.
- Occurrence and severity of pain on sexual intercourse self-reported by the study participants at baseline, 3 and 6 months by using a simple questionnaire and VAS scale.
- Sexual wellbeing at baseline, at 3 and 6 months by self-reporting the Short Sexual Functioning Scale-SSFS (22).
- Health-related quality of life at baseline, 3 and 6 months after surgery by self-reporting using a validated questionnaire (EQ-5D-3L).
- The duration of the surgical intervention measured in minutes from the insertion of the bladder catheter to the end of vaginal/abdominal wound closure.

- Direct costs for both techniques up to 6 weeks following surgery.

Randomisation and blinding

Participants will be randomly allocated to one of both treatment arms (vNOTES versus laparoscopy) We will use a computer-generated randomisation schedule generated by the management assistant of our department. We will use a stratification into three categories (A, B or C) according to the size of the cyst on transvaginal ultrasound (0 to 5 cm, 5 to 10 cm, larger than 10 cm). Sequentially numbered, opaque, sealed envelopes will be used to ensure allocation concealment for the surgeon and the outcome assessor. The management assistant will safeguard the allocation code until the last visit of the last patient. The management assistant will not be involved in the outcome assessment or the data collection.

All participating women and the outcome assessor will be blinded to the allocation by the use of non-therapeutic skin incisions. It is impossible to blind the surgeon. In case of life-threatening adverse events, the outcome assessor will notify the surgeon to enable further treatment without the need for unblinding the patient. The use of the vNOTES technique avoids the use of abdominal incisions. Participants allocated to the vNOTES arm will have three superficial non-therapeutic skin incisions similar to those routinely done with the laparoscopic technique. This enables to blind all study participants, personnel and the outcome assessor. The wound dressings of all women will be left untouched until the postoperative visit on day 7. The practice of using non-therapeutic skin incisions has been reported in some surgical trials to minimise performance and detection bias when measuring subjective outcomes (e.g. pain) (23). The decision to use non-therapeutic skin incisions is justified by the risk/benefit ratio of the two interventions under comparison (24). Its use in the HALON and NOTABLE trial has been intensively discussed among the investigators and has been approved by the Ethical Committee of the Imelda Hospital Bonheiden (registration

number 689), Belgium on December 1, 2015. The written approval with the Belgian unique study identifier B689201526268 was sent to the FAMHP in Brussels.

Statistical methods

Sample size calculation

A sample size calculation was done for the primary outcome only. An appropriate level of statistical power was applied to preclude any clinically important inferiority of vNOTES compared to laparoscopy. The assumptions for the sample size calculation are based on evidence retrieved from one randomized study comparing the excision of mature dermoid cysts using colpotomy with laparoscopic assistance versus colpotomy without laparoscopy (25). An important consideration in any adnexal mass surgery is the inadvertent opening of the ovarian capsule of an unsuspected malignancy resulting in the spill of malignant cells into the abdominal cavity. Based on a 2.4% failure rate to remove dermoid cysts by colpotomy using laparoscopic assistance according to the findings from this singleton RCT (25) we assumed that the successful removal of adnexal cysts without spill would be feasible in 95% of all cases. The sample size was calculated with a one-sided test for non-inferiority for the primary outcome. The vNOTES approach may be the treatment of choice for women because it avoids scars. We assume that vNOTES would be the preferred technique even when 15% less women had in the end a successful removal of a benign adnexal mass by using vNOTES compared to laparoscopy with its unavoidable scars. Non-inferiority will be concluded when 15% lies above the upper limit of the 95% confidence interval calculated for the difference in the proportion of women successfully treated with either technique. To achieve 80% power to demonstrate non-inferiority under the assumption of similar success rates of 95% in both groups a sample size of 54 participants (27 women per group) will be required. We increased the target sample size to 64 participants (32 women per group) to account for a drop-out rate of 15%. Based on the power calculations for the primary outcome, the use of three strata for

the randomisation and assuming a loss-to-follow-up rate of 15 %, we decided to include 66 study participants in the NOTABLE trial.

Statistical analyses

GENERAL PRINCIPLES

For all baseline and outcome variables, the number of available measurements and the number of missing values will be given. A probability (p) less than 0.05 will be considered to be significant. Analysis will be performed by intention-to-treat, as recommended in the CONSORT statement (26). Since the study compares two regular interventions and is expected to recruit during a reasonably limited period, interim analyses will not be performed.

Categorical data will be reported as absolute numbers and percentages. Normally distributed continuous variables will be summarized as means with standard deviations and non-normally distributed continuous variables will be reported as medians with interquartile ranges (IQR). Main analyses will not impute missing values.

All analyses will be performed using SAS software (version 9.4 of the SAS System for Windows).

DESCRIPTIVE ANALYSES

Study population – baseline characteristics

- Mean age (± SD)
- Mean Body Mass Index (± SD)
- Mean number of natural vaginal births (± SD)
- Mean number of abdominal/pelvic surgical interventions (± SD)
- Mean weight of the uterus (± SD)

STUDY ENDPOINTS

Main study parameter/endpoint

Differences in the proportions of women successfully treated by removing the uterus by the intended technique without conversion to another approach

Secondary study parameters/endpoints

- Proportions of women hospitalized on the day of surgery
- Postoperative pain scores, measured using a VAS scale twice daily from day 1 till 7 self-reported by the study participants
- Total dose analgesics used during the first week following surgery
- Incidence of postoperative infection during the first six weeks of surgery
- Incidence of intra-operative complications
- Incidence of postoperative complications during the first 6 weeks following surgery
- Incidence of readmission during the first six weeks of
- Incidence of dyspareunia recorded by the participants at baseline, 3 and 6 months by self-reporting using a simple questionnaire
- Severity of dyspareunia recorded by the participants at baseline, 3 and 6 months by self-reporting using a VAS scale
- Sexual wellbeing at baseline, at 3 and 6 months by self-reporting the SSFS Quality of life (QoL) at baseline, at 3 and 6 months by self-reporting the EQ-5D-3L questionnaire.
- Duration of surgery
- Total costs of both interventions surgery

STATISTICAL ANALYSIS

For the primary outcome measure, a one-sided 95% confidence interval of the difference in the proportions of women with a successful removal of the uterus by the intended technique as randomised will be estimated. Non-inferiority will be concluded when 15% lies above the upper limit of this 95% CI.

For the manuscript all above listed secondary outcomes will be compared between the two groups. These data will be reported as vNOTES versus laparoscopy.

For dichotomous secondary outcome measures, comparisons between the two arms will be performed by applying Fisher exact test or Chi-square test, as appropriate.

Cross-sectionally measured continuous secondary outcomes will be analysed using an independent T-test or Mann–Whitney U- Test, as appropriate.

Longitudinally measured continuous secondary outcomes will be analysed using multilevel modelling. Differences in evolution between both treatment groups will be compared by means of a time by group interaction. In absence of such an interaction mean differences will be compared over all time points. Outcome scores will be transformed if required to meet model assumptions.

All statistical analyses will be done by an experienced biostatistician (AL) who is a co-investigator. After data cleaning the management secretary will send the unblinded data to the biostatistician after the last visit of the last patient. The biostatistician will do all the analyses without any assistance of the other investigators who will remain blinded until all data have been analysed.

The following strategy will be used in case of missing data. In case of a single item response missing, the data will be imputed from given values. In cases where more than one item is missing or an entire form is missing, imputation will not be attempted. We will assess whether

the obtained results are robust to the methods used to handle missing data, by performing a sensitivity analysis.

RESULTS

Participant flow diagram

Figure 1 shows the study flow reported as outlined by the Consolidated Standards of Reporting Trials (CONSORT).

Recruitment time frame

All potentially eligible women aged 18 to 70 years, regardless of parity, in need of adnexal surgery for benign gynaecological disease without exclusion criteria will be invited to participate in the trial. Only eligible women with written informed consent obtained before randomisation will be finally included in the NOTABLE trial.

We perform 36 interventions for adnexal surgery by laparoscopy for benign gynaecological disease at our Department of Gynaecology per year. The recruitment period of NOTABLE to meet the sample size will be approximately 2 years. Including the follow up period of 6 months after the LPLV (Last Patient Last Visit) and the time required to perform data analysis and reporting (6 months to 1 year) we estimate that the total study period will be at least 3 years.

Data collection

We will record the following patient characteristics at baseline: age, BMI, the number of vaginal births, previous abdominal or pelvic surgery (C-sections included), adnexal size, concomitant medication, dyspareunia questionnaire and the Short Sexual Functioning Scale (SSFS).

On the day of surgical intervention (day 0) we will record the following data: the duration of the surgical intervention, the successful removal of the adnexa by the technique as allocated without conversion to another technique with or without spilling (into the peritoneal cavity or the endobag), hospitalisation of the participant on the day of the surgical intervention based

on her own preference, the total dosage of analgesics used at the recovery and day care unit and the maximum VAS pain score on the day 0.

After one week at visit day 7 the outcome assessor will collect the pain scores as self-reported by the study participants twice daily from day 1 till day 7 using the VAS scale. The outcome assessor will also collect data on the total dosage of pain killers used during the first postoperative week.

At visit day 7 and day 42 the outcome assessor will record the following data: pelvic infection defined by lower abdominal pain with fever > 38°C and positive clinical signs or laboratory findings, readmission to hospital and the occurrence of other postoperative complications classified according to the Clavien- Dindo classification.

On month 3 and 6 following surgery the dyspareunia questionnaires, the EQ-5D-3L and the SSFS questionnaires will be filled in by the study participants and collected by regular mail. The management assistant will oversee this process and send reminders until all questionnaires have been received. We refer to Table 1 for an overview of the data collection process.

DISCUSSION

Interpretation, limitations and generalisability

The NOTABLE trial is a randomised pilot study on the efficacy of the vNOTES technique. All surgical procedures in the NOTABLE study are done by one single surgeon (JB) who is equally skilled in using both techniques under comparison. The surgeon has been using the vNOTES approach since November 2013. During this two-year period the new technique and suitable instruments used were pilot-tested and subsequently fine-tuned by the usual "trial and error" method used for centuries in surgical practice (17). The feasibility and preliminary safety of the new technique were reported in three observational studies performed at our department (9, 10, 11) in accordance with the principles outlined in the three article series on the IDEAL statement (15-17). According to the terminology used by the IDEAL collaboration (17) this study should be classified as an IDEAL stage 2b trial. The full PICO research question is as follows: will a surgeon who is equally skilled at performing both techniques, and beyond his learning curve for the new technique (vNOTES), succeed in removing one or both adnexa in women with benign gynaecological disease at least as often with the new pilot-tested transvaginal NOTES approach compared to the standard transabdominal laparoscopic approach without having to convert to any other technique

NOTABLE aims to measure efficacy of vNOTES for removing one or both adnexa (can vNOTES work under ideal experimental conditions?). The NOTABLE trial does not address the effectiveness of the new intervention at this moment (does vNOTES work in a real life setting?). The conditions in NOTABLE are truly experimental and in many instances opposed to 'real life' practice: all women are always treated by the most experienced surgeon equally skilled in using both techniques, all women receive more attention during this trial than the routine care given during standard clinical practice, the dosage of anaesthetic drugs is calculated to limit any side effect (nausea and vomiting) that may cause women to be

hospitalized on the day of the surgical intervention, all outcomes measured are very relevant for women in general, participants with adverse outcomes (e.g. dyspareunia and sexual dysfunction) will be recalled after the end of the study for counselling and therapy, etc…The results of the NOTABLE trial will therefore have a limited generalisability and their interpretation will be done cautiously. The testing of the safety and the (cost-) effectiveness will be needed in the longer term using pragmatic multi-centre RCTs or a prospective register. As suggested by the IDEAL collaboration more research (large multicentre trials performed by adequately trained surgeons in centres of clinical excellence and large prospective registries cumulating data on the safety of the new technique over many years) and adequate surgical training will be needed before vNOTES can be offered as a standard daily care surgical practice by a majority of gynaecological surgeons for all women bound to undergo removal of one or both adnexa for benign gynaecological disease.

ETHICS AND DISSEMINATION

The NOTABLE trial will be conducted in accordance with the ethical principles outlined in the latest version of the "Helsinki Declaration", the "Guideline for Good Clinical Practice" and the Belgian Law of 7 May 2004 related to experiments on humans.

All eligible women wishing to participate in the study will receive a detailed patient information document about the study protocol, the aims of the research and the possible adverse events related to the surgical techniques. We will request written informed consent from all participants before randomization. The principal investigator (JB) and the coordinating investigator (JJAB) will obtain these consents during a study intake. An adapted informed consent form was drafted based on the template proposed by the Federal Agency for Medicines and Health Products (FAMHP) for clinical research in Belgium (27).

The protocol of the NOTABLE trial is registered in ClinicalTrials.gov of the US National Institutes of Health as NCT02630329. The study protocol and the informed consent documents have been approved by the Ethics Committee of the Imelda Hospital Bonheiden (registration number 689), Belgium on December 1, 2015. The written approval with the Belgian unique study identifier B689201526268 was sent to the FAMHP in Brussels. All substantial protocol modifications will be communicated to all trial participants, the hospital's Ethics Committee, ClinicalTrials.gov, and the FAMHP.

The NOTABLE trial is a non-commercial and investigator-driven study. The investigators have taken out an insurance policy for medicolegal responsibility related with the conduct of the study from 01.12.2015 until 30.05.2018 in accordance with Article 29 of the Belgian Law of 7 May 204 related to experiments on humans.

The clinical research forms and all other study-related documents will be stored securely at the study site in locked file cabinets in an area with limited access. All records that contain names or other personal identifiers will be stored separately from study records identified by a

code number. Data collection, storage and dissemination will be in accordance with the Belgian Law of 8 December 1992 on the protection of privacy in relation to the processing of personal data and by the Law of 22 August 2002 on patient rights.

At the end of the NOTABLE trial the complete final data set will be accessible to all trial investigators (the nine authors of the study protocol).

Offering the surgical intervention identified as being most effective or most advantageous after the final analysis of the study data to those women that were allocated to the least effective technique is by nature of the surgical intervention not always possible except for women who had a unilateral surgical intervention. As part of good clinical practice, we will offer post-trial care to women with identified adverse.

The investigators declare that they have no conflict of interest with respect to the present research.

The NOTABLE trial results will in all circumstances be disseminated through scientific journals and at scientific conference presentations regardless of any positive or negative outcome in relation with the predefined study hypothesis is refuted by the data. All trial investigators will contribute to authorship, following the International Committee of Medical Journal Editors (ICMJE)'s authorship eligibility guidelines.

FOOTNOTES

Twitter: follow Jan Bosteels at @BosteelsJan.

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Contributors JB is the surgeon responsible for all interventions in all study participants. JBo is the outcome assessor. JB and JJAB conceived the study. PDM and IL are responsible for the draft of the pain protocol and the anaesthesia for all trial participants. JJAB, JB, PDM and IL will be responsible for data collection, quality analysis and storage. PE provided expertise for the sexuality research involved in this clinical trial design. SW provided external review as a content expert. CM provided external peer review on the scientific conduct of the study. AL is responsible for the biostatistics involved in the design and conduct of the trial. She has reviewed the SAP (Statistical Analysis Plan) of both HALON and NOTABLE. She will perform all data analysis for both studies without any involvement of the surgeon (JB) and the outcome assessor (JJAB). BWM provided external peer review as a methodology expert. All the authors contributed to the refinement of the study protocol and approved the final manuscript. For the economic analyses we will seek assistance from a Health Economist at the University of Ghent or at the Belgian Health Care Knowledge Centre.

Acknowledgements The vNOTES Investigators' team for taking care of the study participants; Amanda McPhail for language correction and editing of the manuscript.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval Ethics Committee Imelda hospital Bonheiden, protocol number B689201526268, 01/12/2015.

Provenance and peer review Not commissioned; externally peer reviewed.

Table 1

Table 1 Patient's characteristics and data collection													
Data collection	**Days**												
	BL*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**42**		**3 m**	**6m**
Age	X												
BMI**	X												
Uterine volume	X												
Concomitant medication	X	X	X	X	X	X	X	X	X	X			
Dyspareunia: frequency and intensity	X											X	X
SSFS***	X											X	X
Health related quality of life	X											X	X
Duration of surgery		X											
Successful removal		X											
Admission in hospital (for at least one night)		X											
Total amount of analgesics used		X	X	X	X	X	X	X	X				
VAS score****		X	X	X	X	X	X	X	X				
Readmission within six weeks										X			
Pelvic infection									X	X			
Other postoperative complications		X							X	X			
Direct and indirect costs (up to 6 weeks after surgery)										X			

* BL: baseline

** BMI: Body Mass Index

*** SSFS: Short Sexual Functioning Scale

**** VAS: Visual Analogue Scale

REFERENCES

1. Kalloo AN, Singh VK, Jagannath SB, et al. Flexible transgastric peritoneoscopy: a novel approach to diagnostic and therapeutic interventions in the peritoneal cavity. *Gastrointest Endosc* 2004; 60:114-7.

2. Rao GV, Reddy DN, Banerjee R. NOTES: Human experience. *Gastrointest Endosc Clin N Am* 2008; 18: 361–70.

3. Rolanda C, Lima E, Pêgo JM, et al. Third-generation cholecystectomy by natural orifices: transgastric and transvesical combined approach. *Gastrointest Endosc*. 2007; 65: 111-7.

4. Rattner D, Kalloo A. ASGE/SAGES working group on natural Orifice transluminal endoscopic surgery. *Surg Endosc* 2006; 20:329-33.

5. Santos BF, Hungness ES. Natural orifice translumenal endoscopic surgery: progress in humans since white paper. *World J Gastroenterol* 2011; 17:1655–65.

6. Tolcher MC, Kalogera E, Hopkins MR, et al. Safety of Culdotomy as a Surgical Approach: Implications for Natural Orifice Transluminal. *JSLS* 2012; 16:413–20

7. Uccella S, Cromi A, Bogani G, et al. Transvaginal specimen extraction at laparoscopy without concomitant hysterectomy: our experience and systematic review of the literature. *J Minim Invasive Gynecol* 2013; 20:583-90.

8. Lee CL, Wu KY, Su H, Ueng SH, Yen CH. Transvaginal Natural-Orifice Transluminal Endoscopic Surgery (NOTES) in Adnexal Procedures. *JMIG*. 2012;19: 509–513.

9. Reynders A, Baekelandt J. Adnexectomy by Poor Man's Transvaginal NOTES. Gynecological Surgery 2015; 12(3): 207-11.

10. Van Peer S, Baekelandt J. Natural orifice transluminal endoscopic surgery (NOTES) salpingectomy for ectopic pregnancy: a first series demonstrating how a new surgical technique can be applied in a low-resource setting. *Gynecol Surg* 2015; 12: 299-302.

11. Baekelandt J. Total Vaginal NOTES Hysterectomy: A New Approach to Hysterectomy. *J Minim Invasive Gynecol* 2015; 22:1088-94.

12. Baekelandt J, De Mulder PA, Le Roy I, et al. HALON –hysterectomy by transabdominal laparoscopy or natural orifice transluminal endoscopic surgery: a randomised controlled trial (study protocol). *BMJ Open* 2016; 6:e011546. Doi: 10.1136/bmjopen-2016-011546.

13. Shamseer L, Moher D, Clarke M, et al., the PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015; 349: g7647.

14. http://www.crd.york.ac.uk/prospero/

15. Barkun JS, Aronson JK, Feldman LS, et al., for the Balliol Collaboration. Evaluation and stages of surgical innovations. *The Lancet* 2009; 374:1089-96.

16. Ergina PL, Cook JA, Blazeby JM, et al., for the Balliol Collaboration. Challenges in evaluating surgical innovation. *The Lancet* 2009; 374:1097-1104.

17. Mc Culloch P, Altman DG, Campbell WB, et al., for the Balliol Collaboration. No surgical innovation without evaluation: the IDEAL recommendations. *The Lancet* 2009; 374:1105-12.

18. Gargon E, Gurung B, Medley N, et al. Choosing Important Health Outcomes for Comparative Effectiveness Research: A Systematic Review. *PLoS ONE* 2014; 9(6): e99111.

19. http://www.comet-initiative.org/studies/searchresults?

20. Todd KH, Funk KG, Funk JP, et al. Clinical significance of reported changes in pain severity. *Ann Emerg Med* 1996; 27: 485-9.

21. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; 240**:** 205–13.

22. Aerts L, Enzlin P, Verhaeghe J, et al. Psychologic, relational, and sexual functioning in women after surgical treatment of vulvar malignancy: a prospective controlled study. *Int J Gynecol Cancer* 2014; 24: 372-80.

23. Moseley JB, O'Malley K, Petersen NJ, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med* 2002; 347: 81-8.

24. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987; 317: 141-5.

25. Wang PH, Lee WL, Juang CM, Tsai WY, Chao HT, Yuan CC. Excision of mature teratoma using culdotomy, with and without laparoscopy: A prospective randomized trial. BJOG 2001; 108: 91-4.

26. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomized Trials. *Ann Intern Med.* 2010; 152: 1-8.

27. www.afmps.be

ClinicalTrials.gov PRS
Protocol Registration and Results System

ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 01/17/2016

ClinicalTrials.gov ID: NCT02630329

Study Identification

Unique Protocol ID:	B689201526268
Brief Title:	Notes Adnexectomy for Benign Pathology Compared to Laparoscopic Excision (NOTABLE)
Official Title:	Adnexectomy for Benign Gynaecological Pathology by Natural Orifice Transluminal Endoscopy or Laparoscopy
Secondary IDs:	

Study Status

Record Verification:	January 2016
Overall Status:	Recruiting
Study Start:	December 2015
Primary Completion:	May 2018 [Anticipated]
Study Completion:	May 2018 [Anticipated]

Sponsor/Collaborators

Sponsor:	Imelda Hospital, Bonheiden
Responsible Party:	Principal Investigator Investigator: Dr Jan Baekelandt, MD [jbaekelandt] Official Title: Dr Affiliation: Imelda Hospital, Bonheiden
Collaborators:	

Oversight

FDA Regulated?:	No
IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 689/151145 Board Name: Commissie Medische Ethiek Board Affiliation: Imelda Hospital Bonheiden Phone: + 3215505529 Email: marc.lambrechts@imelda.be
Data Monitoring?:	Yes
Plan to Share Data?:	No

	Interim analyses of major endpoints will be supplied, in strict confidence, to an independent Data Monitoring and Ethics Committee (DMEC) along with updates on results of other related studies, and any other analyses that the DMEC may request.
Oversight Authorities:	Belgium: Federal Agency for Medicines and Health Products, FAMHP

Study Description

Brief Summary:	Objective: To compare vNOTES (vaginal Natural Orifice Transluminal Endoscopic Surgery) and established laparoscopic removal of benign adnexal masses Study design: Randomized controlled/single center/single-blinded/parallel-group/non-inferiority/efficacy trial. Study population: Women aged 18 to 70 years with symptomatic or persistent benign adnexal masses detected by clinical examination and ultrasound. Randomization: Women will be randomly allocated to undergo one of two techniques for removal of the benign adnexal mass immediately before surgery by using a computer generated randomization list. The investigators will use stratified randomization according to the cyst diameter. Intervention: Women will be treated by a surgeon who is not blinded to the treatment allocation and who is equally skilled in performing both techniques. In the intervention group a vNOTES technique will be used. Control: In the control group surgery will be done by a classical laparoscopic technique. Participants, nursing staff and outcome assessors will be blinded. Main study parameters/endpoints: Primary outcomes: successful removal of a benign adnexal mass without spill. Secondary outcomes: the proportion of women discharged the same day based on their own preference; postoperative pain scores using a VAS (Visual Analogue Scale) measured between day 1 till 7 by the participating women following surgery and the total amount of analgesics used as described in the standardized pain treatment protocol between day 1 till 7; postoperative infection defined by lower abdominal pain with fever > 38°C and positive clinical signs or laboratory findings; per- or postoperative complications according to the Clavien- Dindo classification detected during the first six weeks of surgery; duration of the surgical procedure; incidence and intensity of dyspareunia recorded by the participants at 3 and 6 months by self-reporting using a simple questionnaire and VAS scale; sexual wellbeing recorded by the participants at 3 and 6 months by SSFS (Short Sexual Functioning Scale); direct costs associated up to 6 weeks after the surgical intervention with both procedures.
Detailed Description:	1. Objectives of the NOTABLE Trial The primary research questions of this IDEAL stage 2b efficacy trial are as follows: is a vNOTES adnexectomy at least as effective compared to the standard transabdominal laparoscopic approach (LSC) for removing a benign adnexal mass without spill? (non-inferiority design) Secondary research questions are: • Do more women treated by vNOTES prefer to leave the hospital on the day of surgery compared to LSC? • Do women treated by vNOTES suffer from less pain compared to women treated by LSC in the first postoperative week? • Is the removal of a benign adnexal mass by vNOTES faster compared to LSC? • Does a vNOTES cause more pelvic infection or other complications compared to LSC? • Does a vNOTES cause more hospital readmissions within 6 weeks following surgery compared to LSC?

- Does a vNOTES approach result in more women reporting dyspareunia or less sexual wellbeing at 3 or 6 months after surgery when compared to women treated by LSC?
- What are the direct costs up to 6 weeks of a vNOTES compared to LSC?

TRIAL DESIGN 2.1. Design A single center, single-blinded, parallel group randomized, non-inferiority efficacy trial.

2.2. Simple pilot randomized trial: minimal extra workload 2.3. Time schedule Based upon the mean number of laparoscopic adnexectomies performed annually at the department of Obstetrics and Gynecology of the participating center (36) the investigators estimate that the duration of recruitment will be 21 months. Based upon the follow up (6 months) and the period of analysis/reporting (3 months) the total study period will be 2.5 years.

2.4. Participating center Department of Obstetrics and Gynecology Imeldahospital Imeldalaan 9 2820 Bonheiden Belgium

- ELIGIBILITY, CONSENT AND RANDOMIZATION 3.1. Screening and consent prior to surgery All women aged 18 to 70 years regardless of parity presenting with a symptomatic or asymptomatic persistent benign adnexal mass on clinical examination confirmed by ultrasound are eligible for inclusion. The diagnosis of benign adnexal mass will be based upon the prospectively validated IOTA classification(International Ovarian Tumour Analysis Group) simple ultrasound rules to distinguish between benign and malignant adnexal masses.

  3.2. Determining eligibility All women aged 18 to 70 years regardless of parity presenting with a symptomatic or asymptomatic persistent benign adnexal mass on clinical examination who provide consent to participation are eligible in the NOTABLE trial based on the findings of the ultrasound findings and will be randomized before the procedure.

  3.3. Randomization If the woman is eligible for the NOTABLE trial, the trial secretary will obtain a randomized allocation the day before surgery. This will be done using a randomization list generated by a free computer software program offered by Research Randomizer (https://www.randomizer.org). The random sequence generation will be concealed using sequentially numbered opaque sealed envelopes. The envelope will be opened by the nurse assistant on the day before the surgical intervention for logistic reasons. The investigators will use stratified randomization in this small pilot RCT (randomized controlled trial) according to the cyst diameter.

  3.4. Patients with strong preference for treatment A minority of women will express a clear preference for one of both treatments (e.g. strong desire to have no scar) and for this reason will not wish to be randomized between surgical treatments. To investigate how outcomes vary by choice, these women could be followed up in exactly the same way as for those women randomized into the NOTABLE trial. A formal non-randomized follow-up of these women will not be done for simple logistical reasons.

  3.5. Stratification of randomization A blocked randomization procedure will be used to avoid chance imbalances for the parameter ‘cyst diameter’.

  To avoid any possibility of foreknowledge, the randomized allocation will not be given until all eligibility and stratification data have been given.
- TREATMENT ALLOCATIONS 4.1. Surgical procedures The principal investigator, who has training and experience in both laparoscopy and NOTES, will perform all surgical procedures. He is therefore not blinded. All vNOTES participants will be blinded by three superficial “mock” skin incisions similar to those routinely done with the laparoscopic technique.

  4.1.1 vNOTES adnexectomy This is the surgical procedure done in the intervention arm of the NOTABLE trial.

4.1.2 LSC adnexectomy This is the surgical procedure done in the control arm of the NOTABLE trial.

- FOLLOW-UP AND OUTCOME MEASURES 5.1. Clinical assessments 5.1.1 Format PROMs will be collected using a postal questionnaire, which will include a combination of disease specific and generic measurement instruments.

  The postal questionnaires will be sent from the NOTABLE Trial Office with postage paid envelopes two weeks before the due date. Reminders will be sent to the participants if the questionnaire is not returned within one week of the due date and attempts will be made to contact the women by phone if the questionnaire is not returned by two weeks after the due date.

  5.1.2 Timing of assessments The primary outcome will be measured clinically at the end of the surgical procedure. In addition PROMs will take place the evening of the surgical intervention (return home), during the first postoperative week (pain by VAS scores and analgetic drugs) and at 3 and 6 months (dyspareunia). Clinical physician assessment will take place the evening of the surgical intervention (return home) and during the first six weeks following surgery (pelvic infection, surgical complications, hospital readmission rate).

  5.2. Primary clinical outcome measure The proportion of women successfully treated by removing the adnexal mass without spill, using a dichotomous outcome measure, will be used as a measure of efficacy.

  5.3. Secondary clinical outcome measures

  The following secondary outcomes will be measured:

  - The proportion of women discharged the same day based on their own preference, as a dichotomous outcome.
  - Postoperative pain scores, as an ordinal outcome, measured using a VAS scale twice daily from day 1 till 7 self-reported by the participating women.
  - Postoperative pain defined by the total amount of analgesics used as described in the standardized pain treatment protocol, as a continuous outcome.
  - Postoperative infection as a dichotomous outcome.
  - Per- or postoperative complications according to the Clavien- Dindo classification detected during the first six weeks of surgery, as a dichotomous outcome.
  - Hospital readmission within 6 weeks following surgery, as a dichotomous outcome.
  - Incidence and intensity of dyspareunia recorded by the participants at 3 and 6 months by self-reporting using a simple questionnaire and VAS scale, as a dichotomous and ordinal outcome. .
  - Sexual wellbeing at baseline, at 3 and 6 months by self-reporting the SSFS.
  - Duration of surgery measured as the time in minutes from the insertion of the bladder catheter to the end of vaginal/abdominal wound closure, as a continuous outcome.

  5.4. Health economic outcomes The direct costs of both techniques up to 6 weeks after the surgical intervention will be calculated.

- ACCRUAL AND ANALYSIS 6.1. Sample size The sample size for this trial has been chosen to give good statistical power to preclude any clinically important inferiority of vNOTES compared to laparoscopy and is based on evidence retrieved from a systematic review of the literature and a RCT comparing the excision of mature teratoma using culdotomy with and without laparoscopy. Based on the power calculations for the primary outcome and two secondary outcomes and assuming a loss-to-follow-up rate of 10% the investigators decided to include 66 study participants in the NOTABLE trial.

6.2. Projected accrual and attrition rates It is anticipated that recruitment of participants will take two years. Based upon the mean number of laparoscopic adnexectomies performed annually at the department of Obstetrics and Gynecology of the participating center (36) the investigators estimate that the duration of recruitment will be 21 months. Based upon the follow up (6 months) and the period of analysis/reporting (3 months) the total study period will be 2.5 years. First publication will be possible within four years of trial commencement.

Conditions

Conditions: Natural Orifice Endoscopic Surgery
Disease, Adnexal
Laparoscopic Surgery

Keywords: NOTES
Benign adnexal disease
Laparoscopy

Study Design

Study Type: Interventional
Primary Purpose: Treatment
Study Phase: Phase 2
Intervention Model: Parallel Assignment
Number of Arms: 2
Masking: Double Blind (Subject, Outcomes Assessor)
Allocation: Randomized
Endpoint Classification: Efficacy Study
Enrollment: 66 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: vNOTES adnexectomy Vaginal Natural Orifice Transluminal Endoscopic Surgery	Procedure/Surgery: vNOTES adnexectomy Surgical removal of one or both adnexa by a natural orifice transluminal endoscopic surgical technique using a colpotomy (transvaginal incision)
Active Comparator: LSC adnexectomy Laparoscopic adnexectomy	Procedure/Surgery: Laparoscopic adnexectomy Surgical removal of one or both adnexa by transabdominal laparoscopy

Outcome Measures

Primary Outcome Measure:

1. Successful removal of adnexal mass without spill
   [Time Frame: Intraoperative] [Safety Issue: Yes]
   The proportion of women successfully treated by removing the adnexal mass without spill, using a dichotomous outcome measure, will be used as a measure of efficacy.

Secondary Outcome Measure:

2. Discharge from the hospital the day of the surgical intervention

[Time Frame: Dichotomous outcome measured on the day of the surgical intervention] [Safety Issue: Yes]
The proportion of women discharged the same day based on their own preference, as a dichotomous outcome. The decision to discharge or to admit to hospital for the night will be based solely on the choice of the woman to return home the same day or stay overnight.

3. Postoperative pain scores
[Time Frame: The first week after the surgical intervention] [Safety Issue: No]
Postoperative pain scores, as an ordinal outcome, measured using a VAS scale twice daily from day 1 till 7 self-reported by the participating women

4. The use of analgesics for postoperative pain
[Time Frame: The first week after the surgical intervention] [Safety Issue: No]
Postoperative pain defined by the total amount of analgesics used as described in the standardized pain treatment protocol, as a continuous outcome.

5. Postoperative infection
[Time Frame: The first six weeks after the surgical intervention] [Safety Issue: Yes]
Postoperative infection defined by lower abdominal pain with fever > 38°C and positive clinical signs or laboratory findings, detected during the first six weeks of surgery, as a dichotomous outcome.

6. Complications
[Time Frame: The first six weeks after the surgical intervention] [Safety Issue: Yes]
Per- or postoperative complications according to the Clavien- Dindo classification detected during the first six weeks of surgery, as a dichotomous outcome

7. Hospital readmission
[Time Frame: The first six weeks after the surgical intervention] [Safety Issue: Yes]
The proportion of women readmitted to hospital within six weeks of surgery, as a dichotomous outcome

8. Pain during sexual intercourse
[Time Frame: At baseline, 3 months and 6 months after the surgical intervention] [Safety Issue: No]
Incidence and intensity of dyspareunia recorded by the participants at 3 and 6 months by self-reporting using a simple questionnaire and VAS scale, as a dichotomous and ordinal outcome

9. Sexual well being
[Time Frame: At baseline, 3 months and 6 months after the surgical intervention] [Safety Issue: No]
Sexual wellbeing at baseline, at 3 and 6 months by self-reporting using the SSFS (Short Sexual Function Scale).

10. Duration of the surgical intervention
[Time Frame: Intraoperative] [Safety Issue: No]
Duration of surgery measured as the time in minutes from the insertion of the bladder catheter to the end of vaginal/ abdominal wound closure, as a continuous outcome

11. Direct costs
[Time Frame: Up to 6 weeks postoperative] [Safety Issue: No]
Calculating the comparative direct costs of both techniques up to 6 weeks after the surgical intervention

Eligibility

Minimum Age:	18 Years
Maximum Age:	70 Years
Gender:	Female
Accepts Healthy Volunteers?:	Yes
Criteria:	Inclusion Criteria:

- All women aged 18 to 70 years regardless of parity with a symptomatic adnexal mass presumed to be benign based on ultrasound examination by applying the IOTA simple rules

- All women aged 18 to 70 years regardless of parity with an asymptomatic persistent adnexal mass presumed to be benign based on ultrasound examination by applying the IOTA simple rules
- Written informed consent obtained prior to surgery

Exclusion Criteria:

- History of hysterectomy by any technique
- History of rectal surgery
- Suspected rectovaginal endometriosis
- Suspected endometriotic cyst
- Solid adnexal mass
- High suspicion of adnexal malignancy based on clinical, ultrasound or biochemical findings
- History of pelvic inflammatory disease, especially prior tubo-ovarian or pouch of Douglas abscess
- Active lower genital tract infection e.g. Chlamydia, N. gonorrhoeae
- Virgo
- Pregnancy
- Need for other uterine surgical intervention (i.e. endometrial ablation, resection, myomectomy or hysterectomy)
- Additional pathology necessitating hysterectomy
- Failure to provide written informed consent prior to surgery

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References

Citations: [Study Results] Baekelandt J. Poor man's NOTES: can it be a good approach for adhesiolysis? A first case report with video demonstration. J Minim Invasive Gynecol. 2015 Mar-Apr;22(3):319. doi: 10.1016/j.jmig.2014.11.001. Epub 2014 Nov 10. PubMed 25460516

[Study Results] Yang YS, Hur MH, Oh KY, Kim SY. Transvaginal natural orifice transluminal endoscopic surgery for adnexal masses. J Obstet Gynaecol Res. 2013 Dec;39(12):1604-9. doi: 10.1111/jog.12108. Epub 2013 Jul 22. PubMed 23875997

[Study Results] Ghezzi F, Cromi A, Uccella S, Bogani G, Serati M, Bolis P. Transumbilical versus transvaginal retrieval of surgical specimens at laparoscopy: a randomized trial. Am J Obstet Gynecol. 2012 Aug;207(2):112.e1-6. doi: 10.1016/j.ajog.2012.05.016. Epub 2012 May 23. PubMed 22704765

Wang PH, Lee WL, Juang CM, Tsai WY, Chao HT, Yuan CC. Excision of mature teratoma using culdotomy, with and without laparoscopy: a prospective randomised trial. BJOG. 2001 Jan;108(1):91-4. PubMed 11213011

[Study Results] Medeiros LR, Rosa DD, Bozzetti MC, Fachel JM, Furness S, Garry R, Rosa MI, Stein AT. Laparoscopy versus laparotomy for benign ovarian tumour. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD004751. doi: 10.1002/14651858.CD004751.pub3. Review. PubMed 19370607

Links:

Study Data/Documents:

Opdrachtgever: Afdeling Verloskunde/Gynaecologie Imeldaziekenhuis Bonheiden

Onderzoeksinstelling: Afdeling Verloskunde/Gynaecologie Imeldaziekenhuis Bonheiden

Comité voor Medische Ethiek: Commissie Medisch Ethiek Imeldaziekenhuis Bonheiden

Lokale artsen-onderzoekers: Dr Jan Baekelandt en Dr Jan Bosteels, Imeldaziekenhuis Bonheiden, tel 015 505011

Studie secretaresse: Mevrouw Sofie De Wit, Imeldaziekenhuis Bonheiden, tel 015 505926

I Noodzakelijke informatie voor Uw beslissing om deel te nemen aan de NOTABLE studie

Inleiding

U wordt uitgenodigd om deel te nemen aan een klinische studie voor het vergelijken van twee technieken voor het verwijderen van een goedaardige eierstokcyste.

De artsen-onderzoekers hopen dat deze blind vergelijkende studie voordelen kan bieden voor de behandeling van patiënten die getroffen zijn door dezelfde aandoening als u. Er is evenwel geen enkele garantie dat Uw deelname aan deze studie U voordeel zal opleveren.

Voordat U beslist over Uw deelname aan deze studie willen we U wat meer informatie geven over wat dit betekent op organisatorisch vlak en wat de eventuele voordelen en risico's voor U zijn. Zo kan U een beslissing nemen op basis van de juiste informatie. Dit wordt "geïnformeerde toestemming" genoemd.

Wij vragen U de volgende pagina's met informatie aandachtig te lezen. Hebt U vragen, dan kan U terecht bij de arts-onderzoeker of zijn of haar vertegenwoordiger. Dit document bestaat uit drie delen: essentiële informatie die U nodig heeft voor het nemen van Uw beslissing, Uw schriftelijke toestemming en bijlagen waarin U meer details terugvindt over bepaalde onderdelen van de basisinformatie.

Als U aan de NOTABLE studie deelneemt, dient U het volgende te weten:

- Deze klinische studie wordt opgestart na evaluatie door één of meerdere ethische comité(s).
- Uw deelname is vrijwillig; er kan op geen enkele manier sprake zijn van dwang. Voor deelname is Uw ondertekende toestemming nodig. Ook nadat U hebt getekend, kan u de arts-onderzoeker laten weten dat U Uw deelname wilt stopzetten. De beslissing om al dan niet (verder) deel te nemen zal geen enkele negatieve invloed hebben op de kwaliteit van de zorgen noch op de relatie met de behandelende arts(en).
- De gegevens die in het kader van Uw deelname worden verzameld, zijn vertrouwelijk. Bij de publicatie van de resultaten is Uw anonimiteit verzekerd.
- Er worden U geen bijkomende kosten aangerekend voor specifieke behandelingen, bezoeken / consultaties, onderzoeken in het kader van dit onderzoek. De uitgevoerde chirurgische procedures worden terugbetaald in het kader van de ziekteverzekering.
- Eventuele schade opgelopen in het kader van Uw deelname aan deze klinische studie valt onder de verzekeringspolis van Uw behandelende arts. Omdat het een niet-commerciële studie betreft, werd hiervoor een bijkomende verzekeringspolis afgesloten met de verzekeringsmaatschappij van de behandelende hoofdonderzoeker.
- Indien U extra informatie wenst, kan U altijd contact opnemen met de arts-onderzoekers of een medewerker van hun team.

Aanvullende informatie over Uw rechten als deelnemer aan een klinische studie kan U bekomen via de ombudsdienst van het Imeldaziekenhuis te Bonheiden bij mevrouw Ilse Creemers bereikbaar via telefoon 015 505015 of via e-mail ombudsdienst@imelda.be.

Doelstelling en beschrijving van het studieprotocol

Wij nodigen U uit om deel te nemen aan een klinische studie inzake de klassieke laparoscopische (via de navel in de buikwand) vergeleken met de transvaginale (doorheen de vagina) verwijdering van één of beide adnexen (eierstok én eileider) bij vermoeden van een goedaardige cyste van één of beide eierstokken bij ongeveer 66 vrouwelijke deelnemers in België.

Alle vrouwen met een op echografie vermoede goedaardige cyste van één of beide eierstokken kunnen deelnemen aan de studie ongeacht de leeftijd en het aantal bevallingen in de voorgeschiedenis. Deelname aan deze studie is niet mogelijk bij een voorgeschiedenis van verwijdering van de baarmoeder, heelkunde aan de endeldarm, endometriose van het rectovaginaal septum, vermoeden van eierstokkanker, voorgeschiedenis van PID of pelvien abces, actieve genitale infectie of vrouwen die nog nooit sexueel contact hebben gehad. Zwaarlijvigheid, nulliparitеit (nooit eerder langs natuurlijke weg bevallen) of grootte van de cyste zijn dan weer geen reden tot uitsluiten van deelname aan de studie.

Het is een gerandomizeerde studie die een alternatieve toegangsweg (NOTES transvaginaal) vergelijkt met de huidige gouden standaard van de klassieke transabdominale laparoscopische toegangsweg voor het verwijderen van één of beide adnexen (eierstok met eileider). In een eerdere pilootstudie werd de technische haalbaarheid van deze transvaginale toegangsweg beschreven. Deze gevallenreeks verzamelde de gegevens van 20 uitgevoerde procedures.Het bleek mogelijk om op een veilige manier cysten te verwijderen tot een doormeter van 11 cm. Men observeerde lagere pijnscores bij vrouwen behandeld via deze nieuwe toegangsweg. De hypothese van deze studie is dat de nieuwe techniek minstens even succesvol is dan de klassieke gouden standaard maar het voordeel zou kunnen bieden dat meer vrouwen die via de nieuwe techniek werden behandeld zelf zouden verkiezen om dezelfde dag van de ingreep naar huis terug te keren vergeleken met de standaardtechniek. Een tweede bijkomend voordeel zou kunnen zijn dat vrouwen behandeld met de nieuwe techniek minder pijn hebben vergeleken met de gouden standaard. In deze studie zal via een techniek van randomizatie worden beslist of een deelnemer behandeld wordt op de klassieke wijze dan wel via de nieuwe techniek. De ingreep wordt uitgevoerd door één chirurg die een even grote ervaring heeft in het uitvoeren van beide technieken. De studie verloopt geblindeerd voor de deelnemers en de effect beoordeelaars. Het meten van pijn is namelijk subjectief en kan worden verstoord wanneer de deelnemer aan de studie of de effectbeoordeelaar voorkennis heeft van de uitgevoerde procedure. In alle gevallen wordt daarom een insnede aangebracht in de navel zodat niemand behalve de chirurg weet welke ingreep werd uitgevoerd. Indien deze methodiek niet zou worden toegepast, zou het uiteiendelijk nooit mogelijk zijn om betrouwbaar de doeltreffendheid van de nieuwe techniek versus de standaardtechniek te vergelijken. Het oplossen van deze onzekerheid is net de hoofdbedoeling van de huidige studie. Na het uitvoeren van de ingreep wordt standaard medische en verpleegkundige zorg toegediend (antibiotica, pijnstilling, wondzorg,...). Deze is identiek in beide groepen. De avond van de ingreep komt de coördinerende onderzoeker (Dr Bosteels) langs om te vragen of U zich in staat voelt om naar huis te gaan. Deze beslissing wordt uitsluitend door U genomen. Uiteraard toetst de coördinerende onderzoeker deze beslissing aan de gegevens van temperatuur, pols, bloeddruk en urinedebiet (de zogenaamde vitale parameters). Bij twijfel wordt met U overlegd en wordt altijd beslist in het belang van Uw gezondheid. Uw deelname gaat dan onverminderd verder. U krijgt een formulier mee met beschrijving van mogelijke alarmsymptomen die dringend medisch nazicht via spoedgevallen vereisen. U ontvangt ook een lijst met telefoonnummers voor contact. Gedurende één week wordt U gevraagd om ’s morgens en ’s avonds de pijn zoals U die beleeft aan te geven via een score (de VAS pijnscore) via een meetlatje. Een pijnverpleegkundige zal U uitleg geven hoe U deze metingen dient uit te voeren en te noteren in het pijndagboek. Bij ontslag wordt U ook een afspraak gegeven voor een kontrole onderzoek na één week bij één van de twee hoofdonderzoekers. U mag gedurende 4 weken na de ingreep geen sexueel contact hebben. Er wordt tijdelijke werkonbekwaamheid voorgeschreven voor één maand. Een postoperatief kontrole onderzoek is voorzien na 6 weken. Bij aanvang van de studie en op 3 en 6 maanden na de ingreep moet U een zelfbeoordeling aangeven van pijn bij sexueel contact via een standaard vragenlijst. Tevens kan U een anonieme vragenlijst invullen voor het meten van het sexueel welbevinden bij aanvang van de studie en op 3 en 6 maanden: omdat deze vragenlijst gevoelige vragen bevat is het invullen ervan facultatief. Dit bekent dat het U vrij staat om deze vragenlijst wel of niet in te vullen zonder dat dit het verdere verloop van de studie of de kwaliteit van de toegediende zorg beïnvloedt.

Verloop van de studie

Uw deelname aan de studie neemt 6 maanden in beslag en omvat één bijkomende raadpleging vergeleken met een behandeling zonder deelname aan de studie.

Er worden geen bijkomende procedures vereist in het kader van de studie.

In het kader van Uw deelname aan de studie en rekening houdend met Uw medische situatie, zal de meerderheid van de bezoeken en onderzoeken die we zullen beschrijven, deel uitmaken van de standaardzorgen in ons ziekenhuis terwijl slechts één bijkomend bezoek wordt vereist in het kader van deze studie, namelijk de postoperatieve kontrole na één week.

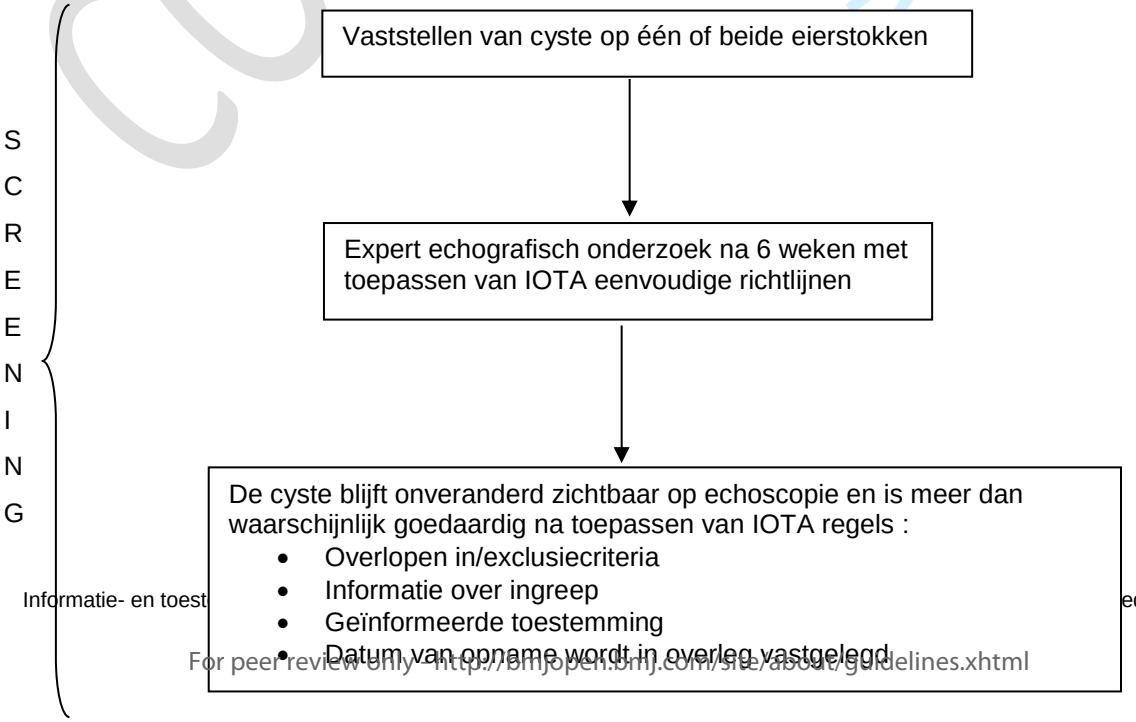
Screeningsfase: Bij een eerste raadpleging wordt de aanwezigheid van een cyste op één of beide eierstokken vastgesteld. De standaard praktijk is om de blijvende aanwezigheid van deze cyste te herkontroleren na 6 weken door een expert onderzoeker in de echografie. Blijkt de cyste blijvend aanwezig te zijn dan wordt tijdens het bezoek aan één van de beide lokale onderzoekers waarop de beslissing genomen om één of beide eierstokken te verwijderen overlopen of U voldoet aan de voorwaarden om te mogen deelnemen aan de studie (de in- en exclusiecriteria). De datum voor de geplande ingreep wordt vastgelegd. Het formulier voor geïnformeerde toestemming wordt ondertekend.

Onderzoeksfase: de nodige preoperatieve onderzoeken zijn deze welke volgens Uw leeftijd en voorgeschiedenis zijn vastgelegd in het werkdocument opgesteld door de dienst anesthesie. Deze kunnen voorafgaandelijk aan de ingreep door de huisarts worden uitgevoerd.De studie vereist geen bijkomende preoperatieve onderzoeken in vergelijking met de situatie waarin U zou hebben beslist om niet deel te nemen aan deze studie. U kan steeds uit vrije wil beslissen om niet langer deel te nemen aan de studie ook nadat U hiervoor Uw toestemming had gegeven. In dit geval wordt U steeds de standaard zorg verstrekt die dezelfde is als deze die U zou hebben ontvangen wanneer U had beslist om niet aan de studie deel te nemen. De studie wordt beëindigd na zes maanden. Op dat moment kan U van de hoofdonderzoeker (Dr Baekelandt) vernemen via welke techniek de ingreep werd uitgevoerd. Het eerder vrijgeven van deze informatie kan enkel om dringende medische redenen. In dergelijk dringend geval kan Uw deelname aan de studie voor het meten van de studie uitkomsten onveranderd doorgaan tenzij U op vrijwillige basis zou beslissen om verdere deelname aan de studie stop te zetten.

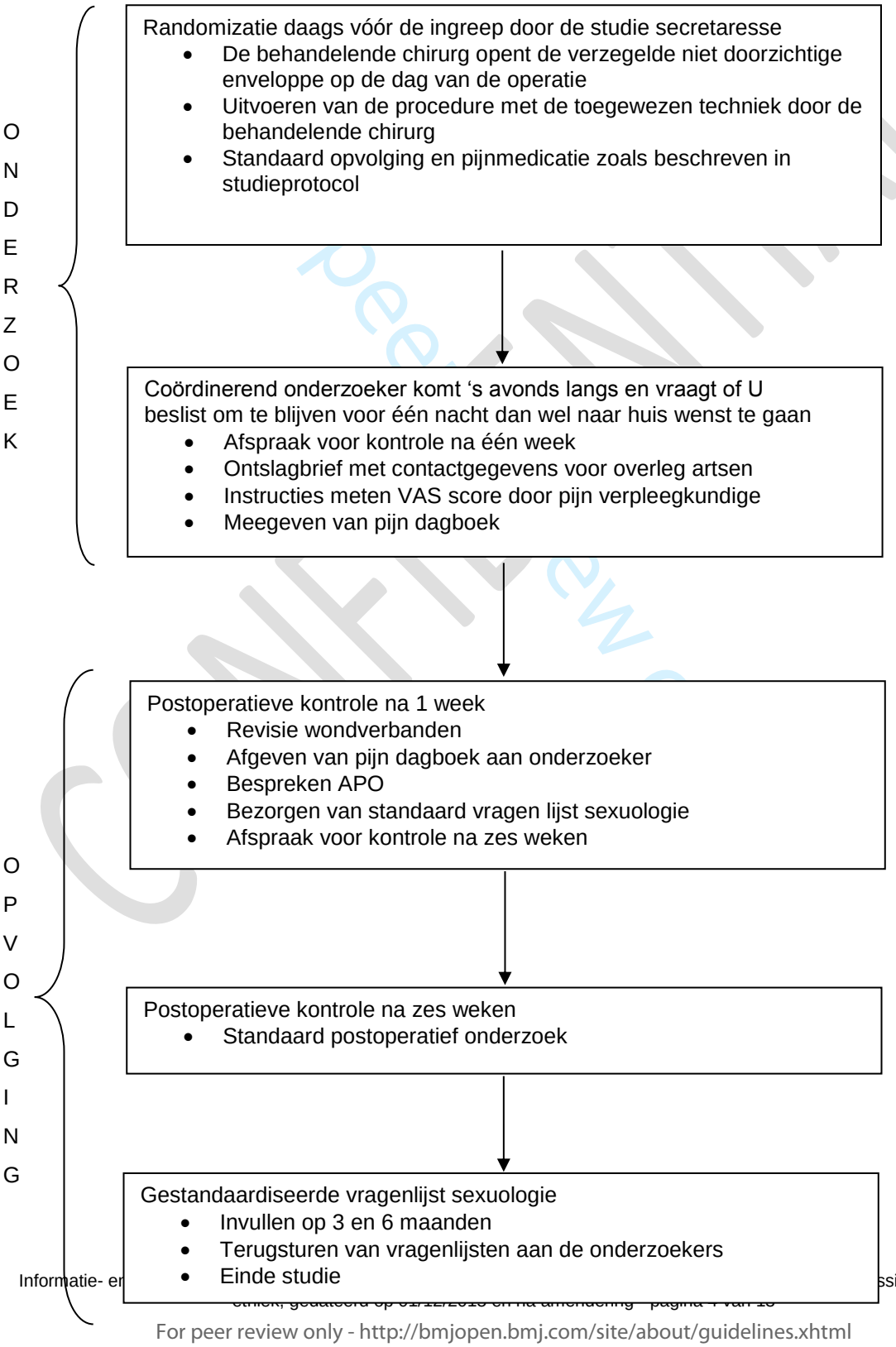
Opvolgingsfase: gedurende één week meet U thuis zelf s'morgens en 's avonds de VAS pijnscores en noteert U het gebruik van bijkomende pijnstillende medicatie met vermelding van naam, dosis en wijze van inname. Na één week en na zes weken volgen postoperatieve kontroles bij de onderzoekers. Op drie en zes maanden wordt U gevraagd om een door een universitair werkzame sexuoloog opgestelde standaard vragen lijst in te vullen en onder gesloten omslag met vermelding van "medisch geheim-verttrouwelijk" terug te zenden naar de onderzoekers.

De studie is volledig beëindigd wanneer U de vragenlijst op 6 maanden hebt teruggestuurd.

Indien u besluit deel te nemen aan de studie en aan alle voorwaarden voor deelname voldoet, ziet het schema van het verloop van Uw deelname aan de NOTABLE studie er uit als volgt:



Informatie- en toest edische



Risico's en ongemakken

A: Verwikkelingen van de vNOTES en laparoscopische techniek

Verwikkelingen tijdens en na minimaal invasieve chirurgie of MIS waartoe zowel de nieuwe vNOTES als de klassieke laparoscopische procedure behoren zijn zeldzaam. In een prospectief onderzoek gepubliceerd door Nederlandse onderzoekers werden 145 verwikkelingen vermeld bij 25 764 laparoscopische ingrepen [(1)]. Ook een groot Fins onderzoek rapporteerde minder dan 1% verwikkelingen na laparoscopische chirurgie [(2)].

De kansen op onderstaande verwikkelingen zijn als volgt:

- Tijdens de operatie:

- bloeding (slag)ader buikwand: 15 per 10 000 ingrepen
- letsel aan darm of maag: 11 per 10 000 ingrepen
- bloeding (slag) ader buikholte: 10 per 10 000 ingrepen
- bloeding vliezen rond eileider: 9 per 10 000 ingrepen
- blaasletsel: 2 per 10 000 ingrepen
- baarmoederletsel: 1 per 10 000 ingrepen
- laseraccident: 1 per 10 000 ingrepen
- overige: <1 per 10 000 ingrepen

- Na de operatie:

- abces: 35 per 100 000 ingrepen
- breuk: 8 per 100 000 ingrepen
- longembool: 4 per 100 000 ingrepen
- overlijden: 8 per 100 000 ingrepen

Ook is het mogelijk dat zich andere risico's en ongemakken voordoen die op dit moment nog onbekend zijn. Het is daarom van groot belang om elke nieuwe gezondheidsklacht zo snel mogelijk aan de arts-onderzoeker te melden, ongeacht of de klacht volgens U of Uw huisarts te maken heeft met de studie of niet.

B: Contraceptie, zwangerschap en borstvoeding

U mag niet deelnemen aan deze studie als u zwanger bent.Indien u kiest om aan deze studie deel te nemen, dient u gebruik te maken van één van de erkende contraceptiemethoden (om te voorkomen dat u zwanger wordt). Uw arts zal met u de verschillende doeltreffende opties bespreken.

C: Risico's in verband met de evaluatieprocedures in het kader van de studie.

Er zijn geen risico's/ongemakken verbonden aan de bijkomende kontrole één week na de ingreep die in het kader van de studie zal plaatsvinden. Het betreft een gebruikelijk klinisch onderzoek gelijkaardig aan het gewone preventief jaarlijks gynaecologisch onderzoek waarmee U waarschijnlijk voldoende vertrouwd bent.

(1) Jansen FW, Kapiteyn K, Trimbos-Kemper T, Hermans J, Trimbos-Kemper JB. Complications of laparoscopy: a prospective multicenter observational study. Br J Obstet Gynaeco 1997; 104: 595-600.

(2) Harkki-Siren P, Sjoberg J, Kurki T. Major complications of laparoscopy : a follow-up Finnish study. Obstet Gynecol 1999;94:94–98.

Melding van nieuwe informatie

Het is steeds mogelijk dat er tijdens het verloop van een klinische studie belangrijke nieuwe informatie over de transvaginale NOTES procedure beschikbaar wordt zoals dit het geval kan zijn met iedere klinische interventie studie. De onderzoekers verbindt er er zich toe om U desgevallend op de hoogte te brengen van nieuwe belangrijke informatie die een invloed kan hebben op Uw beslissing om Uw deelname aan de studie voort te zetten.

In dat geval zal men U vragen ofwel om een aanvulling bij de toestemmingsverklaring te ondertekenen ofwel om een nieuw informatie- en toestemmingsdocument te ondertekenen. Indien U in het licht van de nieuwe belangrijke informatie zou besluiten om Uw deelname aan de studie te beëindigen, zal Uw arts-onderzoeker erop toezien dat U ook nadien op de best mogelijke wijze behandeld wordt.

Voordelen

Indien U besluit om deze studie deel te nemen, kan de transvaginale NOTES techniek al dan niet gunstig blijken te zijn voor de behandeling van Uw aandoening, het verminderen van de symptomen ervan of het bespoedigen van het pijnvrije herstel na de ingreep.

De informatie, die dankzij dit onderzoek verkregen wordt, kan bijdragen tot een betere kennis van het gebruik van deze vernieuwende chirurgische techniek of tot de ontwikkeling van de NOTES transvaginale chirurgie voor de behandeling van gelijkaardige goedaardige gynaecologische aandoeningen bij toekomstige patiënten.

Andere behandelingen

Het meest gebruikte alternatief voor de nieuwe transvaginale vNOTES techniek is de laparoscopische techniek. Hierbij wordt via een kleine insnede via of onder het navellitteken een laparoscoop of kijkbuis ingebracht die toelaat om de bij U geplande heelkundige behandeling-het operatief verwijderen van één of beide eierstokken voor een goedaardige eierstokcyste- uit te voeren onder rechtstreeks zicht. Deze laparoscopische techniek vervangt de oudere klassieke open of laparotomische techniek, die heden hoofdzakelijk nog omwille van eierstokkanker of heel volumineuze eierstokcysten wordt toegepast.

De arts-onderzoeker zal deze alternatieve behandeling die als standaard klinische praktijk steeds in de controlegroep wordt toegepast eveneens met U bespreken.

Stopzetting van de deelname

Stopzetting van de deelname betekent simpelweg dat U als deelnemer Uw "praktische" deelname stopzet omdat U de aan de studie verbonden verplichtingen te zwaar vindt, de bijwerkingen te onaangenaam vindt of andere.

De deelname kan ook door de arts-onderzoeker worden stopgezet om veiligheidsredenen (evolutie van de ziekte) of andere redenen. Dit wil niet zeggen dat U als deelnemer Uw toestemming inzake de verzameling van aanvullende gegevens stopzet (indien U de arts-onderzoeker blijft bezoeken, die vaak ook Uw verwezen arts is voor de ziekte die in het kader van de klinische studie wordt behandeld).

Intrekking van de toestemming tot de studie betekent dat de deelnemer zijn/haar toestemming tot deelname aan de studie effectief intrekt. Dit kan zonder opgave van redenen en het kan betekenen dat de deelnemer zijn/haar toestemming inzake de verwerking van zijn/haar gezondheidsgegevens intrekt.

Uw deelname is vrijwillig. U hebt steeds het recht om Uw deelname aan de studie om eender welke reden en zonder opgave van redenen stop te zetten. Wel kan het voor de arts-onderzoeker en de opdrachtgever nuttig zijn om te weten of U zich terugtrekt omdat de aan de studiebehandeling verbonden beperkingen te zwaar zijn (bijvoorbeeld te veel onaangename bijwerkingen, te veel follow-up bezoeken).

Het is ook mogelijk dat de arts-onderzoeker Uw deelname aan de studie stopzet omdat hij van mening is dat dit beter is voor Uw gezondheid of omdat hij vaststelt dat U zich niet aan de voorschriften voor deelname houdt.

Ook gebeurt het soms dat de bevoegde nationale of internationale autoriteiten, de ethische comités die aanvankelijk goedkeuring hadden gegeven voor de studie of de opdrachtgever de studie stopzetten omdat uit de verzamelde informatie blijkt dat de behandeling niet werkt (de gezondheid van de deelnemers verbetert niet voldoende) of dat de onderzochte behandeling meer of ernstigere bijwerkingen veroorzaakt dan verwacht of voor een andere reden zoals bijvoorbeeld de beslissing om de studie en de ontwikkeling van het onderzochte studiegeneesmiddel stop te zetten.

Behandeling na stopzetting van de studie

In alle situaties waarbij de deelname aan de studie wordt stopgezet, maar ook wanneer de studie volgens planning is afgerond, zal Uw arts-onderzoeker Uw gezondheid onderzoeken en U de beste behandeling die beschikbaar is voorschrijven.

Biologische stalen die tijdens de studie worden afgenomen

De verwijderde weefsels worden volgens standaard klinische praktijk onderzocht op het labo pathologische ontleedkunde voor het microscopisch bevestigen van de goedaardigheid van de vastgestelde eierstokcyste. Hetzelfde geldt voor andere weefselvochten of biopsies. Deze worden standaard afgenomen als onderdeel van de behandeling (verwijderen van één of beide eierstokken) en deze praktijk zou ook worden toegepast indien U geen toestemming zou hebben gegeven voor deelname aan de studie.

Indien u aan deze studie deelneemt, vragen wij u het volgende:

- Tenvolle mee te werken voor een correct verloop van de studie.
- Geen informatie over Uw gezondheidstoestand, de geneesmiddelen die U gebruikt of de symptomen die U ervaart te minimaliseren of zelfs te verzwijgen.
- Niet deel te nemen aan een andere klinische studie met een experimentele behandeling - ongeacht of het een studiegeneesmiddel, medisch hulpmiddel of een procedure betreft- tijdens Uw deelname aan de huidige studie.
- Steeds uw “deelnemerskaart” bij u dragen. Dit is verplicht voor Uw veiligheid indien U een spoedbehandeling moet ondergaan in een ziekenhuis waar men U niet kent. Deze kaart vermeldt tevens de contactgegevens van de behandelende onderzoekers.

U moet eveneens weten dat:

het voor Uw veiligheid aangewezen is om Uw huisarts of andere behandelende artsen die bij Uw behandeling betrokken zijn te informeren over Uw deelname aan deze studie. Wij vragen U eveneens om hiervoor Uw toestemming te geven. Indien U echter niet wenst dat zij hierover worden geïnformeerd om welke reden ook, zullen wij Uw keuze respecteren.

Contact

Als U bijkomende informatie wenst, maar ook ingeval van problemen of als U zich zorgen maakt, kan U contact opnemen met de arts-onderzoekers Dr Jan Baekelandt of Dr. Jan Bosteels of de studiesecretaresse via de op de deelnemerskaart aangegeven contactgegevens of via het centraal telefoonnumer van het Imeldaziekenhuis (015 505011) of het onthaal van de dienst spoedgevallen buiten de klassieke werkuren (015 505040).

In geval van nood, kan U contact opnemen met de dienst spoedgevallen op het telefoonnummer 015 505040.

Buiten de consultatie-uren moet u zich aanmelden op de spoedafdeling van Uw ziekenhuis en vermelden dat U deelneemt aan een klinische studie. Uw dossier zal nuttige informatie bevatten voor de behandelde arts met betrekking tot de studie.

Als U vragen hebt met betrekking tot Uw rechten als deelnemer aan de studie, kan U contact opnemen met de ombudsdienst van het Imeldaziekenhuis (Mevrouw Ilse Creemers) op het telefoonnummer: 015 505015. Indien nodig kan de ombudsvrouw U in contact brengen met het Ethisch Comité

Titel van de studie: **NOTES adnexectomie voor benigne aandoeningen vergeleken met laparoscopische excisie**

II Geïnformeerde toestemming

Deelnemer

Ik verklaar dat ik geïnformeerd ben over de aard, het doel, de duur, de eventuele voordelen en risico's van de studie en dat ik weet wat van mij wordt verwacht. Ik heb kennis genomen van het informatiedocument en de bijlagen ervan.

Ik heb voldoende tijd gehad om na te denken en met een door mij gekozen persoon, zoals mijn huisarts of een familielid, te praten.

Ik heb alle vragen kunnen stellen die bij me opkwamen en ik heb een duidelijk antwoord gekregen op mijn vragen.

Ik begrijp dat mijn deelname aan deze studie vrijwillig is en dat ik vrij ben mijn deelname aan deze studie stop te zetten zonder dat dit mijn relatie schaadt met het therapeutisch team dat instaat voor mijn gezondheid.

Ik begrijp dat er tijdens mijn deelname aan deze studie gegevens over mij zullen worden verzameld en dat de arts-onderzoeker en de opdrachtgever de vertrouwelijkheid van deze gegevens verzekeren overeenkomstig de Belgische wetgeving ter zake.

Ik stem in met de verwerking van mijn persoonlijke gegevens volgens de modaliteiten die zijn beschreven in de rubriek over het verzekeren van de vertrouwelijkheid. Ik geef ook toestemming voor de overdracht naar en verwerking van mijn gecodeerde gegevens in andere landen dan België.

Ik ga ermee akkoord / Ik ga er niet mee akkoord (doorhalen wat niet van toepassing is) dat de studiegegevens die voor de hier vermelde studie worden verzameld, later zullen worden verwerkt, op voorwaarde dat deze verwerking beperkt blijft tot de context van de hier vermelde studie voor een betere kennis van de ziekte en de behandeling ervan.

Ik ga ermee akkoord / Ik ga er niet mee akkoord (doorhalen wat niet van toepassing is) dat mijn huisarts en andere specialisten die betrokken zijn bij mijn behandeling op de hoogte worden gesteld van mijn deelname aan deze klinische studie.

Ik heb een exemplaar ontvangen van de informatie aan de deelnemer en de geïnformeerde toestemming.

Naam, voornaam, datum en handtekening van de deelnemer

Wettelijke vertegenwoordiger

Ik verklaar dat men mij heeft geïnformeerd over de vraag om een beslissing te nemen over deelname aan de klinische studie door de persoon die ik in diens beste belang vertegenwoordig, rekening houdend met zijn of haar mogelijke wens. Mijn toestemming is van toepassing op alle items opgenomen in het toestemmingsformulier voor de deelnemer.

Ik ben eveneens geïnformeerd dat zodra de klinische situatie het toelaat, de persoon die ik vertegenwoordig op de hoogte zal worden gesteld van zijn/haar deelname aan een klinisch studie en op dat moment vrij is om toestemming te geven voor een verdere deelname of om deelname stop te zetten door het huidige toestemmingsformulier al dan niet te ondertekenen

Ik heb een exemplaar ontvangen van de informatie aan de deelnemer en de geïnformeerde toestemming.

Naam, voornaam en verwantschap met de vertegenwoordigde persoon:

Datum en handtekening van de wettelijke vertegenwoordiger

Getuige / Tolk

Ik ben tijdens het volledige proces van informatieverstrekking aan de deelnemer aanwezig geweest en ik bevestig dat de informatie over de doelstellingen en procedures van de studie op adequate wijze is verstrekt, dat de deelnemer (of diens wettelijke vertegenwoordiger) de studie naar alle waarschijnlijkheid heeft begrepen en dat de toestemming tot deelname aan de studie uit vrije wil is gegeven.

Naam, voornaam en hoedanigheid van de getuige:

Datum en handtekening van de getuige / tolk

Arts-onderzoeker

Ik ondergetekende, ..., arts-onderzoeker, verklaar de benodigde informatie inzake deze studie mondeling te hebben verstrekt evenals een exemplaar van het informatiedocument aan de deelnemer te hebben verstrekt.

Ik bevestig dat geen enkele druk op de deelnemer is uitgeoefend om haar te doen toestemmen tot deelname aan de studie en ik ben bereid om op alle eventuele bijkomende vragen te antwoorden.

Ik bevestig dat ik werk in overeenstemming met de ethische beginselen zoals vermeld in de laatste versie van de "Verklaring van Helsinki", de "Goede klinische praktijk" en de Belgische wet van 7 mei 2004 inzake experimenten op de menselijke persoon.

Naam, Voornaam, Datum en handtekening van de vertegenwoordiger van de arts-onderzoeker

Naam, Voornaam, Datum en handtekening van de vertegenwoordiger van de arts-onderzoeker

Naam, Voornaam, Datum en handtekening van de arts-onderzoeker

Titel van de studie: **NOTES adnexectomie voor benigne aandoeningen vergeleken met laparoscopische excisie**

III Aanvullende informatie

1 : Aanvullende informatie over de organisatie van de studie

Nagenoeg alle bezoeken / -consultaties en -procedures waarvan de resultaten eventueel voor de studie worden gebruikt vallen onder de huidige standaard klinische zorg. Enkel de het postoperatief bezoek één week na de ingreep is bijkomend in het kader van de studie. Hierbij worden geen bijkomende technische onderzoeken voorzien die belastend of gezondheidsrisico's inhouden voor de deelnemer. Bij vaststellen van postoperatieve verwikkelingen worden bijkomende bloednames of technische onderzoeken gepland analoog aan deze die ook zouden worden gepland voor een gelijkaardige verwikkeling indien de deelnemer geen geïnformeerde toestemming zou hebben gegeven voor deelname aan de studie.

2. Aanvullende informatie over de risico's die verbonden zijn aan deelname aan de studie

Verklarende begrippen over het voorkomen van verwikkelingen:

Zeer vaak	Bij meer dan 1 op de 10 patiënten
Vaak	Bij meer dan 1 op de 100, maar minder dan 1 op de 10 patiënten
Soms	Bij meer dan 1 op de 1000, maar minder dan 1 op de 100 patiënten
Zelden	Bij meer dan 1 op de 10 000, maar minder dan 1 op de 1000 patiënten

Wanneer gekozen wordt voor een ingreep langs vaginale weg, zal de buikholte worden geopend langs de schede door een insnede te maken in de omslagplooi van de Douglasholte. Men spreekt van een achterste colpotomie. Op deze plaats grenst het diepste punt van de buikholte aan het diepste punt van de schede. Vroeger werd deze toegang gebruikt om ingrepen aan de eierstokken of eileiders uit te voeren. Zo werd in het verleden voor de opkomst van de laparoscopie een sterilisatie uitgevoerd via een colpotomie. Precieze gegevens over het voorkomen van verwikkelingen na een colpotomie zijn bekend in het kader van een eileidersterilisatie:

- morbiditeit of totaal aantal verwikkelingen door bloeding, infectie: minder dan 5 op 100
- mortaliteit of sterfte: minder dan 4 op 100 000

Andere zeldzame verwikkelingen die in minder dan 1 op 100 ingrepen voorkomen zijn:

- acuut compartiment syndroom bij ingrepen die langer dan drie uur duren
- ileus of vertraagd of niet op gang komen van de darmactiviteit
- obstipatie of fecale impactie
- oligurie of minder goed kunnen plassen
- ernstige infecties zoals septische shock, necrotizerende fascitis
- longontsteking
- platvallen van de longbases of atelectasis
- openvallen van de colpotomie wonde of dehiscentie
- achterlaten van een vreemd voorwerp zoals een wondcompres
- niet vermoede kanker van eileider of eierstok
- ernstige emotionele of psychologische stoornissen zoals verwardheid of depressie

Contraceptie, zwangerschap bij de deelneemster.

Zwangere vrouwen kunnen niet deelnemen aan de studie.

Risico's in verband met de klinische onderzoeksprocedures

De **bloedafname** die nodig is voor het preoperatief onderzoek is hetzelfde als dat wat zou worden uitgevoerd indien U zou moeten worden behandeld zonder dat U geïnformeerde toestemming gaf voor deelname aan de studie. Deze bloedname kan (in zeldzame gevallen) pijn, bloedingen, bloeduitstortingen of een lokale infectie op de plek van bloedafname veroorzaken. Ook kunnen sommige deelnemers zich duizelig voelen of flauwvallen tijdens de afname. Het personeel dat de bloedafname uitvoert, zal alles in het werk stellen om deze ongemakken te beperken.

3 : Aanvullende informatie over de bescherming en de rechten van deelnemers aan een klinische studie

Ethische comités

Deze studie werd geëvalueerd door het onafhankelijk ethisch comité van het Imeldaziekenhuis dat een gunstig advies heeft uitgebracht op 1 december 2015. De ethische comités hebben als taak de personen die aan klinische studies deelnemen te beschermen. Ze controleren of uw rechten als patiënt en als deelnemer aan een studie gerespecteerd worden, of - uitgaande van de huidige kennis - de balans tussen risico's en voordelen gunstig is voor de deelnemers, of de studie wetenschappelijk relevant en ethisch verantwoord is.

Hierover brengen de ethische comités een advies uit in overeenstemming met de Belgische wet van 7 mei 2004.

U dient het positief advies van de Ethische Comités in geen geval te beschouwen als een aansporing om deel te nemen aan deze studie.

Vrijwillige deelname

Aarzel niet om alle vragen te stellen die bij U opkomen voordat U tekent. Neem de tijd om er over te praten met een vertrouwenspersoon indien U dat wenst.

U heeft het recht om niet deel te nemen aan deze studie of met deze studie te stoppen, zonder dat U hiervoor een reden hoeft te geven, zelfs al hebt U eerder toegestemd om aan deze studie deel te nemen. Uw beslissing zal in geen geval Uw relatie met de arts-onderzoeker beïnvloeden, noch de kwaliteit van uw verdere verzorging.

Als U aanvaardt om aan deze studie deel te nemen, ondertekent U het toestemmingsformulier. De arts-onderzoeker zal dit formulier ook ondertekenen en zal zo bevestigen dat hij U de noodzakelijke informatie over deze studie heeft gegeven. U zal het voor U bestemde exemplaar ontvangen.

Voor Uw veiligheid is het wel aanbevolen om de arts-onderzoeker op de hoogte te stellen indien U besluit Uw deelname aan de studie stop te zetten.

Kosten in verband met uw deelname

Deze studie is een niet-commerciële studie.

Alle kosten staan in verband met gebruikelijke medische prestaties in uw klinische situatie en deze worden na facturatie terugbetaald door de mutualiteiten en de verzekeringsmaatschappij. Het gaat namelijk om een heelkundige behandeling die standaard voor dit gezondheidsprobleem wordt toegepast en die eveneens zou moeten gebeuren indien U niet aan de huidige studie zou deelnemen.

De bijkomende postoperatieve kontrole na één week is buiten de standaard klinische praktijk: de kostprijs van deze raadpleging zal niet worden aangerekend behalve indien er tijdens dit onderzoek verwikkelingen zouden worden opgemerkt die verdere technische onderzoeken of behandeling zouden vereisen welke ook buiten Uw deelname aan deze studie op gelijkaardige manier zouden worden behandeld. Uw verplaatsingskosten voor deze bijkomende raadpleging worden niet vergoed. Neem contact op met het studieteam voor de praktische uitvoering.

Vertrouwelijkheidsgarantie

Uw deelname aan de studie betekent dat U ermee akkoord gaat dat de arts-onderzoeker gegevens over U verzamelt en dat de opdrachtgever van de studie die gebruikt voor onderzoek en in het kader van wetenschappelijke en medische publicaties.

U hebt het recht om aan de arts-onderzoeker te vragen welke gegevens hij over U heeft verzameld en waarvoor ze gebruikt worden in het kader van de studie. Deze gegevens hebben betrekking op Uw huidige klinische situatie maar ook op Uw medische voorgeschiedenis en op de resultaten van onderzoeken die werden uitgevoerd voor de behandeling van Uw gezondheid volgens de geldende zorgstandaard. U hebt het recht om deze gegevens in te kijken en om verbeteringen te laten aanbrengen indien ze foutief zouden zijn.

Uw recht op inzage wordt minstens tot één week na de ingreep uitgesteld (ideaal tot na afloop van de studie op zes maanden) om een correct verloop van de studie te garanderen. Het eerder bekend maken van de gebruikte techniek kan leiden to voorkennis die de resultaten van de pijnscore metingen die binnen de eerste week moeten worden gemeten, betekenisvol beïnvloeden wat leidt tot foutieve resultaten en besluiten over de doeltreffendheid van de transvaginale benadering vergeleken met de standaard laparoscopische benadering.

De arts-onderzoeker is verplicht om deze verzamelde gegevens vertrouwelijk te behandelen.

Dit betekent dat hij zich ertoe verbindt om Uw naam nooit bekend te maken bijvoorbeeld in het kader van een publicatie of een conferentie en dat hij Uw gegevens zal coderen (Uw identiteit zal worden vervangen door een identificatiecode in de studie). De data van Uw deelname aan de studie zijn klinische data die worden bewaard in Uw electronisch patiënten dossier.

De arts-onderzoeker en zijn team zullen gedurende de volledige klinische studie de enige personen zijn met toegang tot Uw studie dossier).

De gepubliceerde persoonlijke gegevens omvatten geen combinatie van elementen waarmee het mogelijk is U te identificeren.

Alle onderzoekers betrokken bij deze studie behandelen Uw gegevens in overeenstemming met de Belgische wet betreffende de bescherming van de persoonlijke levenssfeer.

Om de kwaliteit van de studie te controleren, kan uw medisch dossier worden ingekeken door personen die gebonden zijn aan het beroepsgeheim zoals vertegenwoordigers van de ethische comités of een extern auditbureau. Dit kan enkel gebeuren onder strikte voorwaarden, onder de verantwoordelijkheid van de arts-onderzoeker en onder zijn toezicht (of van één van zijn onderzoeksmedewerkers).

De (gecodeerde) onderzoeksgegevens kunnen doorgegeven worden aan Belgische of andere regelgevende instanties, aan de betrokken ethische comités, aan andere artsen en/of instellingen die samenwerken met de onderzoekers.

Uw toestemming om aan deze studie deel te nemen betekent dus ook dat U akkoord gaat dat Uw gecodeerde medische gegevens gebruikt worden voor doeleinden die in dit informatieformulier beschreven staan en dat ze overgedragen worden aan bovenvermelde personen en/of instellingen.

De onderzoekers zullen de verzamelde gegevens gebruiken in het kader van de studie waaraan U deelneemt, maar willen ze ook kunnen aanwenden in het kader van andere studies over dezelfde ziekte als de Uwe. Buiten de context die beschreven wordt in dit document, kunnen Uw gegevens enkel gebruikt worden als een ethisch comité haar goedkeuring heeft gegeven.

Indien u uw toestemming tot deelname aan de studie intrekt, zullen de gecodeerde gegevens die al verzameld waren vóór uw terugtrekking, bewaard worden. Hierdoor wordt de geldigheid van de studie gegarandeerd.

Verzekering

Elke deelname aan een studie houdt een risico in, hoe klein ook. De onderzoeker is - ook indien er geen sprake is van fout - aansprakelijk voor de schade die de deelnemer of in geval van overlijden haar rechthebbenden, oplopen en die rechtstreeks of onrechtstreeks verband houdt met diens deelname aan de studie. U moet hiervoor dus geen fout aantonen. De opdrachtgever heeft voor deze aansprakelijkheid een verzekering afgesloten

We verzoeken U daarom om elk nieuw gezondheidsprobleem aan de arts-onderzoeker te melden. Hij kan U aanvullende informatie verstrekken over mogelijke behandelingen.

Indien de arts-onderzoeker van mening is dat er een verband met de studie mogelijk is (er is geen verband met de studie bij schade ten gevolge van het natuurlijke verloop van Uw ziekte of ten gevolge van gekende bijwerkingen van uw standaardbehandeling), zal aangifteprocedure bij de verzekering worden opgestart. Deze zal, indien zij het nodig acht, een expert aanstellen om een oordeel uit te spreken over het verband tussen Uw nieuwe gezondheidsklachten en de studie.

In het geval van onenigheid met de arts-onderzoeker of met de door de verzekeringsmaatschappij aangestelde expert, en steeds wanneer U dit nodig acht, kunnen U of in geval van overlijden Uw rechthebbenden de verzekeraar rechtstreeks in België dagvaarden dagvaarden (NV VANBREDA RISK & BENEFITS (Liability / Fleet with premium), polisnummer LXX048196 , Plantin en Moretuslei 297, 2140 Borgerhout, Tel 03/2176767).

De wet voorziet dat de dagvaarding van de verzekeraar kan gebeuren ofwel voor de rechter van de plaats waar de schadeverwekkende feiten zich hebben voorgedaan, ofwel voor de rechter van Uw woonplaats, ofwel voor de rechter van de zetel van de verzekeraar.

RESEARCH PROTOCOL

NOTABLE trial

(NOTes Adnexectomy for Benign pathology compared to Laparoscopic Excision)

UNIQUE PROTOCOL ID: B689201526268

ClinicalTrials.govID: NCT02630329

Protocol ID	B689201526268 NCT02630329
Short title	NOTABLE trial
Version	5
Date	28-12-2015
Coordinating investigator	Dr. J. Bosteels Imeldaziekenhuis Department of Obstetrics and Gynaecology Imeldalaan 9, 2820 Bonheiden, Belgium T: + 32 15 505205 M: jan.bosteels@imelda.be
Principal investigator	Dr. J. Baekelandt Imeldaziekenhuis Department of Obstetrics and Gynaecology Imeldalaan 9, 2820 Bonheiden, Belgium T: + 32 15 505208 M: jbaekelandt@imelda.be
Sponsor	Investigator driven trial
Independent physician	Not applicable
Laboratory sites	Clinical laboratory Imeldaziekenhuis Imeldalaan 9, 2820 Bonheiden, Belgium T: + 32 15 505460
Pharmacy	Not applicable

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
For non-commercial research, Head of Department: Dr. Philippe Delattin, MD, Gynaecologist		
Coordinating Investigator: Dr. Jan Bosteels, MD, PhD, Gynaecologist		
Principal investigator/project leader: Dr. Jan Baekelandt, MD, Gynaecologist		
Assistant study investigators: Dr Jona Vercammen, MD Dr Sylvie De Rijdt, MD Dr. Siel Olbrecht, MD Dr. Judith De Coene, MD Dr. Maja Van Goitsenhoven, MD		

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ACOG	American College of Obstetricians and Gynecologists
AE	Adverse Event
CAT	Computerized Axial Tomography
CONSORT	Consolidated Standards of Reporting Trials
DMEC	Data Monitoring and Ethics Committee
EuroQoL	EQ-5D Health Questionnaire
GMT	Greenwich Mean Time
GP	General Practitioner
HTA	Health Technology Assessment
IOTA	International Ovarian Tumour Analysis
IV	intravenous
LSK	laparoscopy
MID	Minimally Important Difference
NHS	National Health Service
NOTABLE	NOTES Adnexectomy for Benign pathology compared to Laparoscopic Excision
NOTES	natural orifice transluminal endoscopy
vNOTES	vaginal natural orifice transluminal endoscopy
PROM	Patient Reported Outcome Measure
RCT	Randomised Controlled Trial
(S)AE	(Serious) Adverse Event
SD	Standard Deviation
SSFS	Short Sexual Functioning Scale
SILS	Single Incision Laparoscopic Surgery
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee
TU	Trans Umbilical
TV	Trans Vaginal
VAS	Visual analogue scale
QALY	Quality adjusted life year

SUMMARY

Rationale: Driven by the desire to minimalise surgical morbidity, the evolution from laparotomy to laparoscopic surgery has now extended to less invasive surgery such as robotics, mini- laparoscopy, single incision laparoscopic surgery (SILS), and natural orifice transluminal endoscopic surgery (NOTES). Minimally invasive surgery not only improves cosmetic outcome, it has the potential to restrict the magnitude of the surgical injury, which in turn can attenuate the inflammatory and neuroendocrine response resulting in less postoperative pain and quicker recovery (1, 2).

NOTES attempts to reach the abdominal cavity through an invisible scar, i.e. the surgical intervention is performed via a natural body orifice. Its popularity amongst general surgeons, urologists and gastroenterologist has increased over the past few years and its feasibility and safety has been reported in the medical literature (3).

NOTES can be done by various approaches including access via the stomach, oesophagus, bladder or rectum. The majority of NOTES procedures in women are done by the vagina as this site provides direct access to the lower abdominal cavity (4). Colpotomy has been used widely for several surgical procedures (by gynaecologists as well as general surgeons for the extraction of large specimens) and it has been reported as a safe access that is easy to close afterwards (5, 6).

In hybrid NOTES the surgical procedure is performed through a natural body orifice with transabdominal assistance, whereas the term pure NOTES refers to procedures that involve only transluminal access.

Given its potential benefits, including no visible scars, fewer port-related complications, and less painful and faster post-operative recovery, we have introduced transvaginal pure NOTES (vNOTES) for the treatment of benign adnexal masses in our surgical practice since November 2013. A case-series by our group describing the technical feasibility of removing benign adnexal masses by vNOTES in 20 women has been published recently (7). Most women reported a low postoperative pain score (range 0 to 2) measured at day 1 following surgery by a visual analogue scale (VAS). Based on these preliminary observational findings we decided to design a pilot randomized trial to study the effectiveness of the new vNOTES approach based on the hypothesis that the new technique is at least as effective for removing a benign adnexal mass without cyst rupture compared to the classical laparoscopic technique.

Objective: To compare vNOTES and established laparoscopic removal of benign adnexal masses

Study design: Randomised controlled/single centre/single-blinded/parallel-group/non-inferiority/efficacy trial.

Study population: Women with symptomatic or persistent benign adnexal masses detected by clinical examination and ultrasound.

Randomisation: After assessment of eligibility/ informed consent women will be randomly allocated to undergo one of two techniques for removal of the benign adnexal mass before surgery by using a computer generated randomisation list. We will use stratified randomisation according to the cyst diameter.

Intervention: Women will be treated by a surgeon who is not blinded to the treatment allocation and who is equally skilled in performing both techniques. In the intervention group a vNOTES technique will be used.

Control: In the control group surgery will be done by a classical laparoscopic technique.

Participants, nursing staff and outcome assessors will be blinded by the use of mock surgical skin incisions. Pre- and postoperative treatment will be provided by staff blinded for the allocated intervention using a standardized protocol that is identical for both techniques. All women will be advised not to work during a 4-week period and to abstain from sexual intercourse until their 6-week booked appointment for a postoperative assessment.

Main study parameters/endpoints:

Primary outcomes: successful removal of a benign adnexal mass without spill.

Secondary outcomes: the proportion of women discharged the same day based on their own preference; postoperative pain scores using a VAS scale measured between day 1 till 7 by the participating women following surgery and the total use of analgesics as described in the standardized pain treatment protocol; postoperative infection defined by lower abdominal pain with fever > 38°C and positive clinical signs or laboratory findings; per- or postoperative complications according to the Clavien- Dindo classification (8) detected during the first six weeks of surgery; hospital readmission during the first six weeks of surgery; duration of the surgical procedure; incidence and intensity of dyspareunia recorded by the participants at 3 and 6 months by self-reporting using a simple questionnaire and VAS scale; sexual wellbeing recorded by the participants at 3 and 6 months by SSFS; quality of life by self-reporting the EQ-5D-3L questionnaire at 3 and 6 months; direct costs associated with both procedures.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The burden and risks associated with the participation in the study are comparable with the risks related to the established technique of laparoscopic adnexectomy.

1. BACKGROUND

1.1. Disease: adnexal mass

An adnexal mass (mass of the ovary, fallopian tube, or surrounding connective tissues) is a common gynaecological problem. In the United States, it is estimated that there is a 5 to 10 percent lifetime risk for women undergoing surgery for a suspected ovarian neoplasm (9). Adnexal masses may be found in females of all ages, foetuses to the elderly, and there is a wide variety of types of masses. The management of an adnexal mass depends upon the type of mass, urgency of the presentation (e.g. ectopic pregnancy or ovarian torsion require immediate intervention), and degree of suspicion that the mass might be malignant.

1.1.1 Population to be studied

All women with a benign adnexal mass will be eligible for inclusion provided that they have no exclusion criteria and after giving fully informed consent.

The diagnosis of a benign adnexal mass will be based upon the prospectively IOTA validated simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery (10). All the ultrasound examinations will be reviewed before the randomisation by a named operator with competence in gynaecological ultrasound and experience in applying the simple rules. The need for additional examinations (CAT scan or CA-125) is based upon good clinical practice.

1.2. Current therapy for removal of an adnexal mass

Surgical exploration for an adnexal mass may be performed laparoscopically (conventional or robotic) or by laparotomy. The choice of surgical approach depends upon the degree of suspicion of malignancy and surgeon and patient preference. Ovarian cancer staging can be performed using an open or laparoscopic approach, although the majority of surgeons in current practice prefer laparotomy if there is a high degree of suspicion of malignancy. If there is a low or moderate suspicion of malignancy, a laparoscopic approach is typically used. Laparoscopy is associated with a shorter recovery and decreased perioperative morbidity compared with laparotomy.

The surgical technique used must minimise the potential for tumour disruption or dissemination. If malignancy is suspected, oophorectomy is required rather than ovarian cystectomy. Women with early stage ovarian cancer (i.e. no malignant cells in ascites or peritoneal cytology) benefit from removal of the adnexal mass intact, since opening the mass results in a more advanced stage and adversely affects prognosis (11, 12). In addition, every attempt must be made to provide the pathologist with an ovarian specimen with an intact cortex. If a laparoscopic approach is used, the ovary can be placed in a tissue recovery bag. If the specimen is too large to remove through the existing incisions, cyst fluid may be aspirated (but the collapsed cyst should not be disrupted) or the incision may be enlarged. The practice of morcellating ovarian masses in a bag is discouraged

because it may compromise pathology evaluation. In general, aspiration of cyst contents is not advisable as the sole surgical intervention because no tissue is obtained for histopathology and cytology of cyst fluid is not reliable for exclusion of malignancy, and there is a high rate of recurrence. Recent years have witnessed the use of a posterior colpotomy to retrieve large benign ovarian lesions since removal through the umbilicus may not be straightforward (13).

1.3. New therapy for removal of a benign adnexal mass

Natural orifice transluminal endoscopic surgery (NOTES) is a surgical technique whereby "scarless" abdominal operations can be performed with an endoscope passed through a natural orifice (mouth, urethra, anus, etc.) then through an internal incision in the stomach, vagina, bladder or colon, thus avoiding any external incisions or scars. NOTES was originally described in animals by researchers at Johns Hopkins University (Dr. Anthony Kalloo et al.), and was once upon a time used for transgastric appendectomy in humans in India (by Drs. G.V. Rao and N. Reddy). On June 25, 2007 Swanstrom and colleagues reported the first human transgastric cholecystectomy. The transvaginal access to NOTES seems to be the safest and most feasible approach for clinical application.

1.4. Literature review

1.4.1 Systematic Review

Health technology assessment (HTA) of surgical interventions requires an initial evaluation of the safety and feasibility followed by randomised controlled trials of effectiveness. We conducted a comprehensive systematic review on the efficacy of colpotomy in the treatment of benign adnexal mass. After searching three electronic databases (MEDLINE, EMBASE and The Cochrane Library) from inception to 1 August 2015 using '*colpotomy'* and '*adnexal diseases'* or *'adnexal mass'* as MeSH terms or key words, ten citations were identified, of which a total of four studies were eligible for inclusion. Two studies were observational including one very small case series (7 women) and one prospective cohort study (257 women); two studies were randomised controlled trials (66 women and 79 women respectively).

A summary of the evidence is given below:

We retrieved one observational study from Korea (14). The authors performed transvaginal NOTES in seven women with adnexal masses through a 2-cm incision in the posterior vaginal fornix. A transvaginal NOTES system comprising a wound protractor and a surgical glove with sheaths was used. Resection was performed according to the method of standard laparoscopic adnexal surgery. The adnexal mass was removed via the incision of the posterior vaginal fornix after complete resection. Since June 2011, seven women have undergone transvaginal NOTES for adnexal masses. All cases were completed successfully without conversion to standard laparoscopic approach. The median age of the women was 48 years (range: 36–60 years) and the median body mass index was 23.6 (range: 20.4–25.3). The median tumour size was 6 cm (range: 3.7–6.7 cm). The median

operative time was 45 min (range: 40–80 min). The estimated blood loss was minimal (range: 5–300 mL). The median postoperative hospital stay was 2 days (range: 1–3 days). No postoperative complications were observed at follow-up. All women were very satisfied with the cosmetic result. The authors conclude that transvaginal NOTES may be a feasible, safe and effective surgical technique that results in excellent cosmetic results. It may be an alternative technique for the treatment of properly selected patients with adnexal masses. The authors stress the need for further clinical research.

We retrieved a prospective cohort study from the United States (15). This descriptive study was conducted on women treated by a private gynaecological surgery practice in a community hospital setting from January 1, 2004 through April 30, 2011. Two-hundred fifty-seven consecutive women with adnexal masses of 8 cm to 13 cm on preoperative ultrasound examination not meeting triage criteria set forth in ACOG Committee Opinion 280 for referral to gynaecological oncologists were treated with operative laparoscopy, adnexal removal, bagging, and colpotomy. Laparoscopic surgery combined with posterior colpotomy has a low incidence of significant complications. Outcome data show that by observing the principals of minimally invasive surgery, 97% of women were successfully treated as outpatients: 98% of surgeries lasted <136 minutes; 97% had blood loss <200mL, and there were few consequential postoperative complications. Intraoperative rupture of the ovarian capsule was extremely uncommon: capsular rupture was noted in just 1.2% of cases. The most common lesions were cystadenomas, endometriotic cysts and mature teratomas accounting for 85% of all cases. Borderline tumours accounted for 5% of lesions, while invasive ovarian malignancy represented 3.7% of the specimens.

We retrieved one RCT from Italy (16). Women scheduled for a laparoscopic resection of an adnexal mass were randomised to have their surgical specimen removed either through a posterior colpotomy (n = 34) or the umbilical port site (n = 32). Group allocation was concealed from study participants and bedside clinicians. The primary outcome was postoperative incisional pain assessed by a 10-cm visual analogue scale at 1, 3, and 24 hours after surgery. Transvaginal retrieval caused less postoperative pain than transumbilical specimen extraction at each time point (visual analogue scale score at 1 hour: 2.6 ± 2.9 vs 1.2 ± 2.0, $P = 0.03$; at 3 hours: 2.4 ± 2.0 vs 1.4 ± 2.0, $P = 0.02$; and at 24 hours: 1.1 ± 1.5 vs 0.5 ± 1.4, $P = 0.02$). A higher proportion of women in the transumbilical group than in the transvaginal group indicated the umbilicus as the most painful area at 1 and 3 hours postoperatively. Two months after surgery, the participants scored similarly as to their overall satisfaction, cosmetic outcome, and dyspareunia upon resumption of intercourse. The authors conclude that a transvaginal approach for specimen removal after laparoscopic resection of adnexal masses may offer the advantage of less postoperative pain than the classical umbilical retrieval.

We retrieved one RCT from Taiwan (17). Seventy-nine women with mature teratomas identified by ultrasound examination and biochemical markers were randomly assigned to have their cysts removed via vaginal cystectomy without laparoscopy (n= 37, group A) or laparoscopic cystectomy via culdotomy (n=42, group B). Inclusion criteria were history of vaginal delivery, no previous abdominal surgery, no history of pelvic inflammatory disease, no medical illness, and no presenting symptoms. Eight women randomised to group A withdrew before surgery. The laparoscopically resected tumours were each put into a cellulose bag, and tumours without laparoscopic- assistance were removed directly via the vagina. Blood loss in group A (88± 37 ml) was significantly more than that in group B (64± 20 ml, P= 0.000). The post-operative recovery times were 20 and 17 hours, respectively (P= 0.030). The rates of successful surgery were 58.6 and 97.6%, respectively (P= 0.002). The spillage rates were 44.8% and 19.0%, respectively (P= 0.006). There were no significant differences in tumour size, patient age, and operative time between groups. The authors concluded that cystectomy without assistance of laparoscopy could be applied to manage mature teratoma of the ovary; however, because of the difficulty of this technique, there were high percentages of tumour spillage and more blood loss during operation and a high percentage of patients who required conversion to laparotomy compared with laparoscopic cystectomy. The authors favour laparoscopically assisted cystectomy to manage mature teratoma.

1.4.2 Current clinical practice

At the present the laparoscopic route is considered to be the gold standard for removing a benign adnexal mass compared to laparotomy. According to a Cochrane review (18), in women undergoing surgery for benign ovarian tumors, laparoscopy was associated with a reduction in fever, urinary tract infection, postoperative complications, postoperative pain, number of days in hospital, and total cost. These findings should be interpreted with caution since only a small number of studies (nine) were identified. These included a total of only 769 women and not all of the important outcomes were reported in each study.

In the days prior to widespread availability of laparoscopy, skilled gynaecological surgeons frequently used colpotomy for ready access to the pelvis (15). Unlike episiotomy that can cause dyspareunia, colpotomy does not transect muscles and, therefore, has less bleeding and negligible postoperative pain. Some surgeons may point out the potential disadvantages of colpotomy, including incisional infection, peritonitis, and technical complexity, particularly in patients after hysterectomy. Many gynaecologists seem reluctant to perform transvaginal surgery because this approach can be difficult for inexperienced surgeons and is occasionally unsuccessful. Moreover, conversion to conventional laparoscopy because of unsuccessful transvaginal approach is not acceptable to women who are expecting a minimally invasive surgery with no abdominal surgical scars. Therefore colpotomy is not used as the standard clinical practice in Belgium for removal of the adnexa.

1.4.3 Pilot studies

Given its apparent benefits, including no visible scars, fewer port-related complications, and less painful and faster post-operative recovery, we introduced transvaginal pure NOTES (vNOTES) for benign adnexal masses in our surgical practice since November 2013. Our group has recently published a case-series describing the feasibility of adnexectomy by vNOTES in 20 women for benign adnexal masses (7).

The purpose of the observational case-series was to describe the new technique as well as to demonstrate the feasibility of adnexectomy by transvaginal natural orifice transluminal endoscopic surgery (vNOTES) for the removal of benign adnexal masses. Conventional, reusable laparoscopic instruments were used, inserted through an inexpensive, self-designed single port device. Between November 2013 and November 2014, 20 adnexectomies by vNOTES were performed by a single surgeon (Dr. Jan Baekelandt).

We selected each participant based on the following inclusion criteria: no contraindication for general anaesthesia, pneumoperitoneum or Trendelenburg position; no fixed uterus, strong pelvic adhesions or nodularity in the pouch of Douglas on clinical examination; no history of pelvic inflammatory disease or moderate to severe endometriosis and mass not suspicious for malignancy. We excluded women with large fibroid uteri as these may impair visualization. Virginity and concomitant pregnancy were predefined as exclusion criteria whereas obesity (BMI ≥ 30) and nulliparity were not.

The self-designed single port device was made by assembling a surgical glove, a wound protector, one reusable 10 mm trocar, and four reusable 5 mm trocars. The adnexectomy was performed according to the technique for standard laparoscopic surgery and the specimen was removed through the colpotomy incision.

The following patient and perioperative data were collected and retrospectively analysed: patient age, body mass index (BMI), parity, history of vaginal delivery, previous pelvic surgery, type of surgery, total operating time, serum haemoglobin (Hb) drop (change between the preoperative Hb and postoperative Hb one day after surgery), (peri-) operative complications, postoperative pain score and size of the adnexal mass. The duration of surgery was defined as the time from the start of colpotomy to the end of vaginal closure. Bowel, bladder, ureteral or vascular injuries, as well as blood loss > 300 ml, were considered as intraoperative complications. Short-term postoperative complications were classified as urinary tract infection, postoperative ileus, vaginal vault bleeding or infection, or haematuria. Postoperative pain was assessed using the visual analogue pain scale (VAS) (scoring from 0 = no pain to 10 = worst imaginable pain). The VAS score was evaluated at 6 and 24 hours postoperatively. All women received the same intraoperative analgesia: intravenous

paracetamol 1000 mg and ketorolac trometamol 20 mg. Postoperative pain was managed by paracetamol 1000 mg and ketorolac trometamol was administered on patient's demand.

No bowel preparation was done prior to surgery. A Foley catheter was placed just before surgery and removed the morning after surgery (range 12-22 hours). Prophylactic intravenous antibiotic therapy, cefazoline 2 g and metronidazol 500 mg, was administrated during surgery. As this was a new technique the first patients were closely monitored post operatively. No vaginal intercourse was allowed for 6 weeks after the procedure. Each patient was re-assessed at the post-operative consultation 6 weeks after surgery.

Between November 2013 and November 2014, twenty procedures were successfully performed by Poor Man's vNOTES using conventional, reusable laparoscopic instruments. No conversion to standard multi incision laparoscopy or laparotomy was necessary. Fourteen women underwent a unilateral adnexectomy. In six women a bilateral salpingo-oophorectomy was performed.

Table 1 (Appendix I) gives a cumulative overview of patient characteristics and relevant perioperative data. Individual patient data are presented in Table 2 (Appendix II). Mean operation time was 32 minutes (range 20 to 50 minutes). Five women had had previous pelvic surgery. There were no intraoperative complications and only one patient had a postoperative cystitis for which oral antibiotic therapy was administered. The mean drop in haemoglobin level was 0.9 g/dl (range 0 to 2.1 g/dl). Most women reported a low postoperative pain score (range 0 to 2) measured at day 1 following surgery by a visual analogue scale (VAS). The mean size of the removed adnexal mass was 51.8 mm (35-110 mm). Each patient was examined six weeks after surgery. There was no vaginal wound infection nor dehiscence, and no patient complained of pain during pelvic examination. All women were in good health and were all satisfied with the result.

Based on this observational case-series we concluded that adnexectomy by vNOTES is feasible for masses up to 110 mm even when performed with reusable, conventional laparoscopic instruments. The potential benefits with vNOTES are better cosmetics, low postoperative pain scores, and easy removal of the specimen without spillage. We stated that this new technique may enable surgeons in low resource settings to perform procedures by vNOTES since no expensive devices or instruments are needed.

1.5. The need for a pilot trial of vNOTES versus LSK adnexectomy

Surgical innovation is an important part of surgical practice. Its assessment is complex because of idiosyncrasies related to surgical practice, but necessary so that introduction and adoption of surgical innovations can derive from evidence-based principles rather than trial and error. We decided to follow the principles and guidelines established by IDEAL. On four occasions between 2007 and 2009, invited international experts gathered at Balliol College, Oxford, to explore potential solutions concerning quality, innovation and evaluation in surgical practice and research. The conclusions and

guiding principles were published in The Lancet in 2009. Surgery lacks regulatory authorities that require studies of efficacy before a new procedure can be offered to patients. Nevertheless there is little difference between operations and other complex treatments delivered by individuals within teams. In each instance, the skill, experience, and judgment of the operator should be recognized, and outcomes are affected by the patient and the team. There was agreement between the experts that none of these factors is beyond the design of a clinical trial. The rationale for the resulting IDEAL framework (Idea–Development–Exploration–Assessment–Longterm study) for surgical research has been presented in a three article series in The Lancet (19, 20, 21). The central concept is that surgeons are regularly innovating and improving their skills. Because the point at which an innovation evolves into a novel procedure might not be obvious at the time, prospective open registration of new procedures and early ethical approval are encouraged. Evolution and evaluation can then occur simultaneously. The framework recognizes that at different stages of innovation, different study designs will be appropriate. According to the IDEAL framework the vNOTES approach has entered stage 2b (exploration) given that the technique of vNOTES has been described and the main technical aspects have been worked out. Even at this early stage a small efficacy RCT may be appropriate for the evaluation of the innovative surgical technique. The learning curve is likely to affect which surgeons participate in RCTs trials and when they become involved. We decided to use an RCT as the appropriate study design: the principal investigator had achieved his learning curve.

1.6. Objectives of the NOTABLE Trial

Is a vNOTES adnexectomy at least as effective compared to the standard transabdominal laparoscopic approach (LSC) for removing a benign adnexal mass without spill?

Secondary research questions are:

- Do more women treated by vNOTES prefer to leave the hospital on the day of surgery compared to LSC?
- Do women treated by vNOTES suffer from less pain compared to women treated by LSC in the first postoperative week?
- Is the removal of a benign adnexal mass by vNOTES faster compared to LSC?
- Does a vNOTES cause more pelvic infection or other complications compared to LSC?
- Does a vNOTES result in more hospital readmissions during the first six weeks following surgery compared to LSC?
- Does a vNOTES approach result in more women reporting dyspareunia, less quality of life or less sexual wellbeing at 3 or 6 months after surgery when compared to women treated by LSC?
- What are the costs of a vNOTES compared to LSC?

2. TRIAL DESIGN

2.1. Design

A single centre, single-blinded, parallel group randomised, non-inferiority efficacy trial.

2.2. Simple pilot randomised trial: minimal extra workload

This is a pilot randomised trial aiming to demonstrate that vNOTES is at least as effective compared to the classical gold standard approach of laparoscopy for successfully removing benign adnexal masses without spill (non-inferiority design). In this phase of HTA the trial will need the participation of only one centre. To make this practicable, trial procedures are kept simple, with the minimal extra workload placed on participating clinicians, beyond that required to treat their patients. This will be achieved by simple entry procedures, the use of standard local diagnostic and surgical regimens, routine follow-up of patients (with few additional hospital visits or tests to be performed above those done as part of standard care), minimising documentation and largely patient-based evaluation of outcome (PROM).

2.3. Time schedule

Based upon the mean number of laparoscopic adnexectomies performed annually at the department of Obstetrics and Gynaecology of the participating centre (36) we estimate that the duration of recruitment will be 21 months. Based upon the follow up (6 months) and the period of analysis/reporting (3 months) the total study period will be 2.5 years.

2.4. Participating centre

Department of Obstetrics and Gynaecology

Imelda Hospital

Imeldalaan 9

2820 Bonheiden

Belgium

3. ELIGIBILITY, CONSENT AND RANDOMISATION

3.1. Screening and consent prior to surgery

All women regardless of age and parity presenting with a symptomatic or asymptomatic persistent benign adnexal mass on clinical examination confirmed by ultrasound are eligible for inclusion. The diagnosis of benign adnexal mass will be based upon the prospectively IOTA validated simple ultrasound rules to distinguish between benign and malignant adnexal masses (10). All the ultrasound examinations will be reviewed before the randomisation by a named operator with competence in gynaecological ultrasound and experience in applying the simple rules. The need for additional examinations (CAT scan or CA-125) is based upon good clinical practice.

The trial will be introduced to the eligible women in the outpatient clinic and a comprehensive, evidence-based patient information sheet will be provided at the clinic visit. Participant information sheets and consent form will be provided in Dutch.

Before the procedure, the women will be given a chance to discuss the risks and benefits of vNOTES or laparoscopy for removing the adnexal mass, the process of randomisation and the follow-up requirements with the consultant gynaecologist. It will be carefully explained that the final decision about eligibility will be taken during the surgical procedure and is dependent on the findings; therefore consent will be required before the procedure, in every instance.

Over the past 4 years 145 laparoscopic adnexectomies were performed at the department of Obstetrics and Gynaecology of the participating centre. The mean number of procedures per year (SD) is 36 (± 13). About 69 % of the eligible women should be willing to participate in the proposed study to include the required amount of participants within 2.5 years (see: Section 6.1. Sample size on pages 31-32).

3.2. Determining eligibility

All women regardless of age and parity presenting with a symptomatic or asymptomatic persistent benign adnexal mass on clinical examination who provide consent to participation are eligible in the NOTABLE trial based on the findings of the ultrasound findings and will be randomised before the procedure.

The following inclusion/exclusion criteria will be applied to assess eligibility:

Inclusion criteria:

- All women regardless of age and parity with a symptomatic adnexal mass presumed to be benign based on ultrasound examination by applying the IOTA simple rules
- All women regardless of age and parity with an asymptomatic persistent adnexal mass presumed to be benign based on ultrasound examination by applying the IOTA simple rules

- Written informed consent obtained prior to surgery

Exclusion criteria:

- History of hysterectomy by any technique
- History of rectal surgery
- Suspected rectovaginal endometriosis
- Suspected endometriotic cyst
- Solid adnexal mass
- High suspicion of adnexal malignancy based on clinical, ultrasound or biochemical findings
- History of pelvic inflammatory disease, especially prior tubo-ovarian or pouch of Douglas abscess
- Active lower genital tract infection e.g. Chlamydia, N. gonorrhoeae
- Virginity
- Pregnancy
- Need for other uterine surgical intervention (i.e. endometrial ablation, resection, myomectomy or hysterectomy)
- Additional pathology necessitating hysterectomy
- Failure to provide written informed consent prior to surgery

Obesity (Body Mass Index or BMI > 30), nulliparity or large diameter of the cyst are not considered to be an exclusion criterion per se. We will only stratify for the diameter of the cyst because this parameter was perceived by the gynaecological surgeon as the most important one to influence the difficulty of the procedure. Stratification for three parameters in a small pilot randomised trial with a limited number of participants is not sensible.

3.3. Randomisation

If the woman is eligible for the NOTABLE trial, the trial secretary will obtain a randomised allocation the day before surgery. This will be done using a randomisation list generated by a free computer software program offered by Research Randomizer (https://www.randomizer.org). The random sequence generation will be concealed using sequentially numbered opaque sealed envelopes. The envelope will be opened by the nurse assistant on the day of surgery for practical logistic reasons. We will use stratified randomisation according to the cyst diameter. See 3.5 Stratification of randomisation.

3.4. Patients with strong preference for treatment

A minority of women will express a clear preference for one of both treatments (e.g. strong desire to have no scar) and for this reason will not wish to be randomised between surgical treatments. To investigate how outcomes vary by choice, these women could be followed up in exactly the same way as for those women randomised into the NOTABLE trial. We will however not do any formal non-randomised follow-up of these women for simple logistical reasons.

3.5. Stratification of randomisation

A blocked randomisation procedure will be used to avoid chance imbalances for the parameter 'cyst diameter'. We preferred not to use minimisation because this trial was not funded and we therefore could not afford to buy licenses for a computer-based algorithm for minimisation. Although parity and BMI may be prognostic parameters influencing the chances of the successful removal of the adnexal mass, we preferred to limit the stratification to one parameter for reasons of simplicity based on what is affordable to conduct the present research. It was not considered appropriate to use three strata in a small pilot study including a small number of participants.

To avoid any possibility of foreknowledge, the randomised allocation will not be given until all eligibility and stratification data have been given.

4. TREATMENT ALLOCATIONS

4.1. Surgical procedures

The principal investigator, who has training and experience in both laparoscopy and NOTES, will perform all surgical procedures. He is therefore not blinded. All vNOTES participants will be blinded by three superficial "mock" skin incisions similar to those routinely done with the laparoscopic technique. The wound bandages will be left in place until the day 7 postoperative control to be removed by the coordinating investigator who will state at that moment that the wound healing has left an almost invisible scar as expected. This procedure aims to blind the participants, personnel and outcome assessors. The practice of performing "mock" incisions should not be considered as unethical: it is a procedure that has already been used in some surgical trials to minimise performance and detection bias whenever a subjective outcome is measured (22). The decision to use "mock" surgery is based on the clinical equipoise regarding the balance between benefits and adverse events for the two interventions under comparison (23).

4.1.1 vNOTES adnexectomy

This is the surgical procedure done in the intervention arm of the NOTABLE trial.

Clindamycin vaginal cream is administered on admission of the study participant to the outpatient ward.

The patient is placed in lithotomy position in a vacuum mattress. The abdomen, the vulva and the vagina are disinfected with an alcoholic betadine solution and draped. A Foley catheter is inserted into the bladder.

Three superficial skin incisions are made, one deep in the umbilicus and one in the left and right iliac fossa lateral of the epigastric vessels, and in the suprapubic region. The small vertical intraumbilical skin incision is closed with a monocryl 3/0 intradermal suture. Wound bandages are applied to all three skin incisions.

A 2.5 cm posterior colpotomy is made using a cold knife. The pouch of Douglas is opened using cold scissors. A Gelpoint Mini (Applied Medical) is used as vNOTES port and is inserted into the pouch of Douglas. CO_2 is insufflated until a maximal intraperitoneal pressure of 15mmHg. An optic is inserted and the peritoneal cavity is inspected. The patient is now placed in Trendelenburg position. The small intestine is lifted out of the pelvis.

The ureter is identified, but not routinely dissected. It is only dissected if it cannot be identified transperitoneally. The proximal end of the Fallopian tube is coagulated at its origin into the uterus

using a reusable bipolar grasping forceps before being cut using cold scissors. The ovarian ligament is coagulated and cut. The infundibulopelvic ligament is coagulated and cut. The adnexa is resected. If necessary, the same procedure is repeated for the contralateral side. The peritoneal cavity is rinsed and haemostasis is checked.

Small and benign adnexa will be removed directly through the wound protector part of the NOTES port. Large adnexa or adnexa that are macroscopically suspicious, will be placed in an endobag (Memobag, Teleflex). The purse string of the endobag is pulled through the wound protector and the purse string is released. The content of the cyst is aspirated to reduce the volume of the adnexa. The endobag is now removed with the adnexa inside it. The vNOTES port is removed.

The colpotomy is closed using three interrupted figure-of-eight Vicryl 2/0 sutures. A vaginal plug (betadine gauze 10cmx5m) is placed to be removed after 3 hours together with the Foley catheter.

Antibiotic administration:

Cefazolin 2g and metronidazol 1.5g are administered IV during the procedure.

Analgesia at the recovery room and the nursing ward: The pain management for both groups was discussed with two senior staff members of the department of anaesthesiology of the hospital, who are co-investigators. The protocol will be standard for both comparison groups and is presented in appendix V.

The vaginal plug and the Foley catheter are removed 3 hours after the surgery. The bandages are left in place and not changed unless soaked by blood with a need to change. The personnel of the recovery room will be asked to replace bandages only for hygienic reasons and immediately to apply a new wound dressing without revealing any information to the participant or personnel on the outpatient or hospitalization ward.

The decision to discharge or to admit to hospital for the night will be based solely on the choice of the woman to return home the same day or stay overnight. The outcome assessor will report this decision in the patient record without consulting the results of the pain scoring or whether or not additional analgesics were administered. Every woman leaving the hospital will be given a standard list with instructions not to have intercourse during six weeks and not to work for a period of four weeks. Telephone numbers will be provided for contacting the staff members on call in case urgent medical care for treating any adverse event is needed. Cefazolin 2g is administered IV before discharge.

4.1.2 LSC adnexectomy

This is the surgical procedure done in the control arm of the NOTABLE trial.

Clindamycin vaginal cream is administered on admission of the study participant to the outpatient ward.

The woman is placed in lithotomy position in a vacuum mattress. The abdomen, the vulva and the vagina are disinfected with an alcoholic betadine solution and draped. A Foley catheter is inserted into the bladder.

A small vertical intra-umbilical skin incision is made. A Verress needle is inserted into the peritoneal cavity; the correct position of the needle tip is checked with Semm test. CO_2 is insufflated until a maximal intraperitoneal pressure of 15mmHg. The Verress needle is removed and replaced by a 10mm reusable trocar. An optic is inserted through the 10mm trocar and the peritoneal cavity is inspected. The patient is now placed in Trendelenburg position. Two reusable 5mm trocars are placed under direct vision in the left and right iliac fossa lateral of the epigastric vessels. The small intestine is lifted out of the pelvis.

The ureter is identified, but not routinely dissected. It is only dissected if it cannot be identified transperitoneally. The proximal end of the Fallopian tube is coagulated at its origin into the uterus using a reusable bipolar grasper and cut using cold scissors. The ovarian ligament is coagulated and cut. The infundibulopelvic ligament is coagulated and cut. The adnexa are resected and placed in an endobag (Memobag, Teleflex). If necessary, the same procedure is repeated for the contralateral side.

The peritoneal cavity is rinsed and haemostasis is checked. No drains are left in the peritoneal cavity except when there might be any uncertainty concerning the haemostasis. The 5 mm trocars are removed under direct vision. The purse string of the endobag is pulled through the 10 mm trocar upon removal of the optic. The umbilical incision is extended vertically in caudal direction, the size being not more than 2.5 cm. The fascia and peritoneum are opened and the proximal end of the endobag is pulled through the incision without causing any rupture if possible. If not possible, the endobag should be opened and the content of the cyst should be aspirated to reduce the volume of the adnexa. The aspirated fluid should be send for cytological examination. The endobag is now removed with the adnexa inside it.

The fascia is closed using a Vicryl-1 running suture. The umbilicus and the other incisions are disinfected with Betadine solution. The skin incisions are closed with a monocryl 3/0 intradermal

suture and steri-strips. The wound sites are covered with a standard bandage. A vaginal plug (betadine gauze 10 cm x 5 m) is placed to be removed after 3 hours together with the Foley catheter.

Antibiotic administration:

Cefazolin 2g and metronidazol 1.5g are administered IV during the procedure.

Analgesia at the recovery room and the nursing ward: The pain management for both groups was discussed with two senior staff member of the department of anaesthesiology of the hospital, who are co-investigators. The protocol will be standard for both comparison groups and is presented in appendix V.

The vaginal plug and the Foley catheter are removed 3 hours after the surgery. The bandages are left in place and not changed unless soaked by blood with a need to change. The personnel of the recovery room will be asked to replace bandages only for hygienic reasons and immediately to apply a new wound dressing without revealing any information to the participant or personnel on the day care unit or hospitalisation ward.

The decision to discharge or to admit to hospital for the night will be based solely on the choice of the woman to return home the same day or stay overnight. The outcome assessor will report this decision in the patient record without consulting the results of the pain scoring or whether or not additional analgesics were administered. Every woman leaving the hospital will be given a standard list with instructions not to have intercourse during six weeks and not to work for a period of four weeks. Telephone numbers will be provided for contacting the staff members on call in case urgent medical care for treating any adverse event is needed. Cefazolin 2g is administered IV before discharge.

4.1.3 Failure of procedure

Occasionally, surgical removal of a benign adnexal mass by any of the two techniques may not be completed according to the random sequence generation because of technical limitations or unexpected findings such as extensive adhesions or unexpected malignancy. Successful vNOTES or laparoscopic removal of a benign adnexal mass is possible in the majority of women, but the probability of success is not readily predictable. In cases where the intended procedure has to be abandoned, the appropriate technique (e.g. staging laparotomy for ovarian cancer) or a second procedure (e.g. laparoscopy or laparotomy after bowel preparation) under general anaesthesia should be scheduled as soon as possible. Women who require an alternative more appropriate intervention or a second procedure are not excluded or withdrawn from the NOTABLE trial. The investigators will sensitively explain to them that follow-up information is still very important,

despite the change in treatment, and unless they wish to withdrawn completely from the trial, they will be followed up.

4.2. Concomitant interventions and treatments

It is anticipated that most women presenting with a suspected benign adnexal mass will require no further intervention other that removal of the adnexa. However, in some circumstances additional treatments may be considered necessary by the responsible clinician at the time of adnexal removal or subsequently. Surgical interventions in the form of endometrial ablation or hysterectomy may subsequently be necessary and the need for such interventions will be recorded. However, if the need for additional surgery *at the time* of surgery is indicated, then such patients are excluded for recruitment to the NOTABLE trial. All therapeutic interventions additional to removal of one or both adnexa will be recorded and as the trial is randomised we anticipate that these further interventions will be symmetrically applicable.

4.3. Withdrawal from the NOTABLE trial

All women who consent to the randomised NOTABLE trial, should be followed up and asked to complete postal questionnaires, regardless of actual treatment received.

If a woman specifically requests a treatment setting *after* randomisation, then her choices should be respected. This does not necessitate withdrawal from the trial. Similarly, if one of both procedures fails, she will require subsequent treatment. In both circumstances, it should be sensitively explained to them that follow-up information is still very important, and unless they wish to withdrawn completely from the trial, they will be followed up. Any request to withdraw from follow-up should be notified to the NOTABLE study nurse.

4.4. Serious and unexpected adverse events

There may be mortality and morbidity associated with either procedure, therefore all serious adverse events (SAE) should be reported by fax to the NOTABLE Trial Office as soon as possible. This report should be followed within 2 days by a completed SAE form to the Ethics Committee and the Federal Agency for Medicines and Health Products (FAMHP). For the purposes of this study, “serious” adverse events are those which are fatal, life-threatening, disabling or prolong hospitalisation and have resulted from the surgical procedure, the anaesthetic or post-operative recovery e.g. deep vein thrombosis, hospital acquired infections.

5. FOLLOW-UP AND OUTCOME MEASURES

5.1. Clinical assessments

5.1.1 Format

PROMs will be collected using a postal questionnaire at baseline, at three and six months.

The postal questionnaires will be sent from the NOTABLE Trial Office with postage paid envelopes two weeks before the due date. Reminders will be sent to the participants if the questionnaire is not returned within one week of the due date and attempts will be made to contact the women by phone if the questionnaire is not returned by two weeks after the due date.

5.1.2 Timing of assessments

The primary outcome will be measured clinically at the end of the surgical procedure. In addition PROMs will take place the evening of the surgical intervention (return home), during the first postoperative week (pain by VAS scores and medication) and at 3 and 6 months (dyspareunia and sexual wellbeing). Clinical physician assessment will take place the evening of the surgical intervention (return home) and during the first six weeks following surgery (pelvic infection, surgical complications).

5.2. Primary clinical outcome measure

The proportion of women successfully treated by removing the adnexal mass without spill, using a dichotomous outcome measure, will be used as a measure of efficacy. An important consideration in adnexal mass surgery is the inadvertent opening of the ovarian capsule. The likelihood of cyst rupture during removal by laparotomy or laparoscopy ranges from 10.5% to 41.8% in published studies (15). We will consider any spontaneous rupture of the cyst or any need to aspirate the cyst to allow removal from the abdominal cavity as treatment failures, even if the content of the ruptured cyst does not spill freely inside the cavity but remains within the endobag. By avoiding any subjective interpretations this rigorous definition allows an objective measure of success. As the risk of rupture may be associated to the cyst size, due to the stratified random sequence generation we anticipate that the risk of rupture due to the cyst size rather than the technique used will be symmetrically applicable.

5.3. Secondary clinical outcome measures

We will measure the following secondary outcomes:

- The proportion of women discharged the same day based on their own preference, as a dichotomous outcome. The decision to discharge from the day care unit or to admit to hospital for the night will be based solely on the choice of the woman to return home the same day or stay overnight. The outcome assessor will report this decision in the patient record without consulting the results of the pain scoring or whether or not additional

analgesics were administered. In case of conflict (women wishing to return home against outcome assessor's advice based on clinical suspicion of possible complications for instance) the study participant is not excluded from further follow-up. Data will be analysed using a sensitivity analysis by imputing that the index participant would have agreed to stay overnight as dictated by the clinical judgement of the outcome assessor versus the available data analysis.

- Postoperative pain scores, as an ordinal outcome, measured using a VAS scale twice daily from day 1 till 7 self-reported by the participating women: one measurement will be done in the morning after bed rest at night (rest) and the other will be done in the evening before going to bed after physical activity (active). The participants should place the cursor of the VAS scale device available at the day care unit of the participating centre on the picture indicating the expression of pain sensation that according to their own experience best describes how they feel pain at the time point of measurement. By looking at the back of the scale they can measure the level of pain by recording the numbers immediately to the left and right of the red line: e.g. pain level 0 to 1, or pain level 5 to 6. The lowest number will be recorded by the outcome assessor for data analysis. The reliability of VAS has been established in the assessment of chronic gynaecological conditions like pain.
- Postoperative pain defined by the total use of analgesics during the first week following surgery as described in the standardized pain treatment protocol, as an ordinal outcome. The use of pain medication following surgery should be reported in the nursing file. At home the participants should note in their participant log book the name, dosage, route of administration of any analgesic drug that was taken from the moment they are at home until the assessment on day 7 irrespective of whether this was done on their own initiative or after consulting a family physician or any other medical specialist. The assessment of the total use of analgesics will be done on day 7 by the outcome assessor (the coordinating investigator), who is blinded for the intervention done by the principal investigator.
- Postoperative infection defined by lower abdominal pain with fever > 38°C and positive clinical signs or laboratory findings, detected during the first six weeks of surgery, as a dichotomous outcome.
- Per- or postoperative complications according to the Clavien- Dindo classification detected during the first six weeks of surgery, as a dichotomous outcome (Appendix III).
- Hospital readmission during the first six weeks of surgery, as a dichotomous outcome.
- Incidence and intensity of dyspareunia recorded by the participants at 3 and 6 months by self-reporting using a simple questionnaire and VAS scale, as a dichotomous and ordinal

outcome. A measurement of the prevalence and the intensity of dyspareunia will be done at baseline assessment.

- Sexual wellbeing at baseline, at 3 and 6 months by self-reporting the SSFS.
- Quality of life at baseline, at 3 and 6 months by self-reporting the EQ-5D-3L questionnaire.
- Duration of surgery measured as the time in minutes from the insertion of the bladder catheter to the end of vaginal/abdominal wound closure, as a continuous outcome.

5.4. Health economic outcomes

Costs and consequences of the treatment pathways will be collected from health care providers at the time of the procedure and at follow up in order to conduct the cost-effectiveness analyses.

Resource use data will include:

• Surgical treatment of benign adnexal mass

• Tests and investigations received

• The frequency and duration of out-patient visits and primary care consultations

• Inpatient stays

• Type and volume of medications received

• The number and duration of hospital readmissions and re-treatments.

These data will be collected prospectively from health care providers using a post-operative case report form and patient-completed questionnaires that assess patient health service utilisation at the follow-up time points throughout the trial. Costs incurred by patients will also be collected to conduct an evaluation from a wider societal perspective. Therefore, a patient cost questionnaire will be administered to all trial patients in order to consider the wider cost implications of the interventions which will contain questions to determine out of pocket expenses incurred when attending for treatment and private time costs including time lost from work.

Unit costs obtained from published sources and the trial centre will be used to estimate costs associated with resource use. Responses to the EuroQol EQ-5D-3L questionnaire will inform the effectiveness in terms of QALYs and clinical effectiveness will be measured in cured cases at six months. We obtained full approval of EUROQoL to use the questionnaire for free.

Data collection will be undertaken prospectively for all trial patients so that a stochastic cost analysis can be undertaken. The process of collecting resource use data will be undertaken separately from data collection on unit costs.

The main resource use to be monitored include the following:

1) Consultation time required prior for each procedure for explanation and consent.

2) Costs involved with each procedure including level of health care professional involvement in the procedure, equipment required, overheads, consumables and drugs including anaesthesia.

3) Any additional procedures required where initial treatment is unsuccessful or incomplete.

4) Duration of inpatient stay when women opt to stay overnight.

Information on any additional related primary or secondary care contacts will also be collected from all women to ensure any resulting resource use from additional complications is recorded. Unit costs will be obtained and attached to resource items in order that a cost can be calculated for each trial patient. Unit costs will be obtained from published sources and the centre participating in the trial. In addition, the set-up costs of NOTABLE will be estimated and additional analyses will be undertaken including these costs.

5.5. Data management and validation

5.5.1 Confidentiality of personal data

Personal data and sensitive information required for the NOTABLE Trial will be collected directly from participants, who will be informed about the transfer of this information to the trial office at the department of Obstetrics and Gynaecology of the participating centre and will be asked to consent to this. The data will be entered onto a secure computer database, either by staff or directly via a secure internet connection. Any data to be processed outside the trial office will be anonymised. All personal information obtained for the study will be held securely and treated as (strictly) confidential. All staff involved in the NOTABLE Trial (clinical, paramedical, administration) share the same duty of care to prevent unauthorized disclosure of personal information. No data that could be used to identify an individual will be published. We will handle all data confidentially in accordance with the Belgian law of 8 December 1992 on the protection of privacy with respect to the handling of individual personal data.

5.5.2 Long-term storage of data

In line with existing guidelines and Belgian legislation, all data will be stored for up to 15 years after the last participant has reached the 2.5 year follow-up to allow adequate time for review, reappraisal or further research, and to allow any queries or concerns about the data, conduct or conclusions of the study to be resolved.

5.6. Withdrawal from follow-up

Withdrawal from follow-up is the decision of the participant. However, withdrawn patients can bias clinical trial results and reduce the power of the study to detect important differences, so women should be encouraged to complete all follow-up questionnaires. Methods to reduce the burden of follow-up will be explored e.g. online data entry for participants. If the reason for withdrawal is known, it should be communicated to the NOTABLE Trial Office. To reduce loss to follow-up, we shall record patient's social security number, which allows us to track patients changing GP practice. With postal and telephone reminders we anticipate that, the completeness of data should surpass 90% although, as set out below incomplete follow-up is incorporated into the power calculations.

6. ACCRUAL AND ANALYSIS

6.1. Sample size

The sample size for the primary outcome of this trial has been chosen to give good statistical power to preclude any clinically important inferiority of vNOTES compared to laparoscopy and is based on evidence retrieved from a systematic review of the literature (15) and a RCT comparing the excision of mature teratoma using culdotomy with and without laparoscopy (17). An important consideration in adnexal mass surgery is the inadvertent opening of the ovarian capsule. The likelihood of cyst rupture during removal by laparotomy or laparoscopy ranges from 10.5% to 41.8% in published studies (15). Based on a low failure rate to remove dermoid cysts by colpotomy using laparoscopy (2.4%), according to the findings from a RCT (17) we assumed a successful removal of adnexal cysts without spill to be feasible in 95% of all cases. We calculated the sample size with a one-sided test for non-inferiority studies for the primary outcome. The vNOTES approach may be more convenient for women in that no scar in the abdominal wall is required. We believe, therefore, that vNOTES would be the treatment of choice even if 15% less women had successful removal of a benign adnexal mass by using the vNOTES approach. Non inferiority will be concluded when 15% lies above the upper limit of the 95% confidence interval calculated for the difference in the proportion of women successfully treated with either of both techniques. To achieve 80% power to demonstrate non-inferiority under the assumption of similar success rates of 95% in both groups a sample size of 54 participants (27 women per group) will be required. The target sample size was increased to 64 participants (32 women per group) to account for a drop-out rate of 15%.

(https://www.sealedenvelope.com/power/binary-noninferior/). Based on the power calculations for the primary outcome, the use of three strata for the randomisation and assuming a loss-to-follow-up rate of 15 % we decided to include 66 study participants in the NOTABLE trial.

6.2. Projected accrual and attrition rates

It is anticipated that recruitment of participants will take two years. Based upon the mean number of laparoscopic adnexectomies performed annually at the department of Obstetrics and Gynecology of the participating centre (36) we estimate that the duration of recruitment will be 21 months. Based upon the follow up (6 months) and the period of analysis/reporting (3 months) the total study period will be 2.5 years. First publication will be possible within four years of trial commencement.

Our sample size calculation has allowed for a 15% loss to follow up rate. In order to minimise rates of attrition we will employ a dedicated research secretary to optimize recruitment and follow up.

6.3. Statistical Analysis

We will calculate a 95% confidence interval of the difference in the proportions of women with a successful removal of an adnexal cyst. Non inferiority of the intervention (vNOTES) will be concluded

when 15% lies above the upper limit of this confidence interval. For this primary analysis, adjustments for prognostic factors will not be made in the first instance; the effect of the variables listed in Section 3.5 (Stratification of randomisation) will be explored as a secondary analysis. Continuous measures (VAS scores) will be analysed using analysis of covariance (adjusting for baseline value). Multilevel models for repeated measurements will also be used to compare the mean differences in VAS pain scores between groups overall at all time points, thereby maximising the power of the data available.

Analysis will be performed on an 'intention to treat' basis in the first instance as recommended in the CONSORT statement. A 'per protocol' analysis will also be performed to test the robustness of the results obtained. As a conservative measure, estimates of effect sizes between the two arms will be presented as point estimates with two-sided 95% confidence intervals. The trial can only conclude non-inferiority if 15% lies out of the upper band of the confidence interval (i.e. vNOTES 15% less successful than laparoscopic treatment).

Baseline characteristics of the patients enrolled in the two groups will be compared to ensure that randomisation has produced comparable groups of participants, and will be covariates in the modelling procedure.

6.3.1 Subgroup analyses

Subgroup analyses are limited by statistical power and can produce spurious results particularly if many are undertaken. We will not undertake any subgroup analyses in this pilot study.

6.3.2 Proposed frequency of analyses

1. Twice yearly review of recruitment, compliance and loss to follow-up for NOTABLE Trial Steering Committee.
2. Annual interim analyses of effectiveness for confidential review by Ethics Committee to determine whether the principal question has been answered and to monitor adverse events.
3. Main analyses of effectiveness of NOTABLE once all participants have reached 6-month follow up of the total study sample.
4. Additional analysis of longer term effects (completion of one and two years of follow-up).

6.3.3 Handling missing data

The interpretation of missing values in the analysis of clinical trials can be fraught with danger. The methods used to allow for missing data make assumptions about the reasons for data not being present, such as in the "observed case" analysis, where the presence or absence of data is viewed as unrelated to outcome, or in the "Last Observation Carried Forward" analysis where the assumption is that the condition does not improve or worsen following withdrawal from follow-up. To minimise possible biases, participants will continue to be followed up even after protocol treatment violation.

Missing data items will be imputed from given values if limited to a single item response. If a form is missing entirely or greater than one item imputation will not be attempted. Sensitivity analyses will be carried out to determine whether or not the results obtained are robust to the methods used to handle missing data. These approaches are in line with the recent recommendations from the European Agency for the Evaluation of Medicinal Products.

Questionnaires will only be treated as late if they are returned after the subsequent questionnaire has been sent to the participant. However if this form is the only form available at the later time point it will be included at the subsequent time.

6.4. Health Economic Analysis

6.4.1 Form of the economic evaluation

If vNOTES is found to be an effective treatment for the removal of benign adnexal mass, then it is likely that there can be cost implications for the health care sector. For example, as the woman will be treated as an outpatient, thus avoiding an inpatient stay, resources may be saved. However, vNOTES may incur costs due to equipment required and the specialist nature of health care professionals to perform this procedure. Therefore all costs incurred by both procedures need to be assessed in conjunction with measures of effectiveness.

The aim of the economic evaluation is to determine the cost-effectiveness of vNOTES compared with standard laparoscopic treatment. Although the trial has been designed as a non-inferiority trial, we feel the most appropriate type of analysis is a cost-effectiveness analysis. Cost-effectiveness will be determined in two ways. A cost-effectiveness analysis will be undertaken to calculate the cost per additional cured case adnexal removal at six months, utilizing the clinical outcome data collected within the trial. In addition, a cost-utility analysis will be undertaken to calculate the cost per additional quality-adjusted life year (QALY) gained. The utility values required to calculate QALYs will be obtained by administering the EuroQol EQ-5D-3L questionnaire to all study patients at baseline, three months and six months. In the first instance, the evaluation will consider costs incurred by the health service in the delivery of both treatment pathways. However, information on costs incurred by patients will also be collected in order that an evaluation from a wider societal perspective can also be undertaken.

6.4.2 Economic analysis

Given the objective of the trial and limited available evidence in support of the NOTABLE strategy, only a within trial economic analysis will be carried out. The analysis will adopt an incremental approach in that data collection will concentrate on resource use and outcome differences between trial arms. As the majority of cost data are skewed, and the mean cost of each procedure is of importance, a bootstrapping approach will be undertaken in order to calculate confidence intervals

around the mean costs. As the time frame of the economic evaluation is not greater than one year, discounting is not required.

Uncertainty in the confidence to be placed on the results of the economic analysis will be explored by estimating cost-effectiveness acceptability curves. These plot the probability that the intervention is cost-effective against threshold values for cost-effectiveness. The robustness of the results will be explored using sensitivity analysis. This will explore uncertainties in the trial based data itself, the methods employed to analyse the data and the generalizability of the results to other settings.

We will seek the assistance of an expert in health economics at the University of Ghent, Belgium.

6.5. Definition of the end of trial

The end of the NOTABLE trial will be defined as the time when the last participant recruited has completed 6 months of follow up.

7. ASSESSMENT OF PATIENT ACCEPTABILITY

7.1. Measurements for Patient Acceptability

The acceptability of vNOTES will principally be assessed using a questionnaire designed specifically for the study and administered within 24 hours of treatment to limit recall bias. Pilot testing will be carried out to make certain the questionnaire is usable. In addition to the questionnaire, data will be collected on the women who do not give consent to randomization (state a preference and agree to be registered for the NOTABLE study), and requested from those who decline to participate.

In order to aid interpretation and understanding of the questionnaire data, and to gain greater depth of experience, the acceptability of NOTABLE will further be assessed using a qualitative methodology. Interviewing after discharge will allow the woman time to reflect on her experience, and will also minimise the chance that gratitude to doctors and other hospital staff results in unduly positive responses. Honesty is also more likely to occur on neutral or the patient's home ground. Interviews will be recorded with patients' permission and transcribed verbatim. The interview schedule will be designed following a literature search on patient acceptability of surgical procedures, and from the focus group discussions. From these, a set of items will be derived which will seem relevant to the participants and cover all the areas thought to be important by participants. The latter will also ensure that the questionnaire is as discriminatory as possible. The interview schedule will be piloted with five women. These procedures will ensure face and content validity, and sending each woman the transcript of her interview with the opportunity to amend any inaccuracy will assess fair and accurate representation.

7.1.1 Sampling of Participants for In-depth Interview

We propose to select a 20% random sample (6 women) from each arm of the research for interview within one week of discharge either face to face, or by telephone.

7.2. Evaluation of Patient Acceptability

Analysis of data will be by content analysis with the development of analytical themes. The initial process will be the intensive reading and re-reading of interview transcripts, and a search for regularities, contradictions, patterns and themes by comparing the participants' statements using a coding frame. Inter-rater reliability on the coding of transcripts will be undertaken. A percentage of the transcripts will be coded independently by two members of the qualitative research team and discrepancies discussed and resolved. Emergent themes obtained by this process will be refined until final themes are agreed by all applicants as reflective of the data. 'Researcher triangulation' will offer the first step to verification of the findings. This will be achieved through the independent analysis of 20% of transcripts from the sample by the researchers. Verification occurs through discussion of their analyses, comparison and subsequent consensus. 'Respondent validation' will also be sought by

taking the tentative findings back to a sample of participants in order to be verified as reflective of their experience. A final form of verification is the comparison of findings with, and their embeddedness in the available literature.

It is anticipated that the questionnaire and the subsequent in depth interviews will measure and provide insight into acceptability and satisfaction in the following areas: the procedure(s) for diagnosis; the information provided when consent is obtained; procedures to protect confidentiality; preference for one arm of the trial over the other; experience of the procedure and the immediate post-operative phase; overall satisfaction with the process; acceptability for the same procedure if adnexal masses are diagnosed in the future; perceptions of being involved in an RCT.

8. DATA ACCESS AND QUALITY ASSURANCE

8.1. In-house Data Quality Assurance

The study will adopt a centralized approach to monitoring data quality and compliance. A computer database will be constructed specifically for the study data and will include range and logic checks to prevent erroneous data entry. Independent checking of data entry of paper questionnaires will be periodically undertaken on small sub-samples. The trial statistician will regularly check the balance of allocations by the stratification variables. Source data verification will only be employed if there is reason to believe data quality has been compromised.

8.2. Independent Trial Steering Committee

The Trial Steering Committee (TSC) provides independent supervision for the trial, providing advice to the Chief and Co- Investigators on all aspects of the trial and affording protection for patients by ensuring the trial is conducted according to the MRC Guidelines for Good Clinical Practice in Clinical Trials.

If the Chief and Co-Investigators are unable to resolve any concern satisfactorily, Principal Investigators, and all others associated with the study, may write through the Trial Office to the chairman of the TSC, drawing attention to any concerns they may have about the possibility of particular side-effects, or of particular categories of patient requiring special study, or about any other matters thought relevant.

8.3. Data Monitoring and Ethics Committee: Determining when clear answers have emerged

If vNOTES is clearly inferior to standard laparoscopic treatment, with respect to the primary endpoint, then this may become apparent before the target recruitment has been reached. Alternatively, new evidence might emerge from other sources that vNOTES definitely more, or less, effective than laparoscopy. To protect against this, during the period of recruitment to the study, interim analyses of major endpoints will be supplied, in strict confidence, to an independent Data Monitoring and Ethics Committee (DMEC) along with updates on results of other related studies, and any other analyses that the DMEC may request. The DMEC will advise the chair of the Trial Steering Committee if, in their view, any of the randomised comparisons in the trial have provided both (a) “proof beyond reasonable doubt” that for all, or some, women that vNOTES is so inferior from laparoscopy that non-inferiority can never be demonstrated, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. The TSC can then decide whether to close or modify any part of the trial. Unless this happens, however, the Trial

management group (TMG), TSC, the investigators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

9. ORGANIZATION AND RESPONSIBILITIES

All investigators are responsible for ensuring that any research they undertake follows the agreed protocol, for helping care professionals to ensure that participants receive appropriate care while involved in research, for protecting the integrity and confidentiality of clinical and other records and data generated by the research, and for reporting any failures in these respects, surgical complications and other events or suspected misconduct through the appropriate systems.

9.1. Centre eligibility

Not applicable since NOTABLE is a single centre RCT.

9.2. Local Coordinator

The responsibilities of the local Principal Investigator will be to ensure that all medical and nursing staff involved in the care of NOTABLE are well informed about the study and trained in trial procedures, including obtaining informed consent. The local Principal Investigator should liaise with the Trial Coordinator on logistic and administrative matters connected with the trial.

9.3. Nursing Coordinator

One nurse will be designated as *local Nursing Coordinator*. This person would be responsible for ensuring that all eligible patients are considered for the trial, that patients are provided with patient information sheets, and have an opportunity to discuss the study if required. The nurse may be responsible for collecting the baseline patient data and will act as a contact for obtaining missing follow-up evaluations. Again, this person would be sent updates and newsletters, and would be invited to training and progress meetings.

9.4. The NOTABLE Trial Office

The Trial Office at department of Obstetrics and Gynaecology of the participating centre is responsible for providing all trial materials, including the trial folders containing centre specific trial documentation, standard operating procedures and training materials. Additional supplies of any printed material can be obtained on request or downloaded from the NOTABLE trial website. The Trial Office is responsible for collection and checking of data (including reports of serious surgical complications), for reporting of serious adverse events to the sponsor and/ or regulatory authorities and for analyses. The Trial Office will help resolve any local problems that may be encountered in trial participation.

9.5. Research Governance

The study will be conducted according to the principles of the Declaration of Helsinki (Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000) and in accordance with the Belgian law of 7 May 2004 that regulates human experiments in Belgium.

All Principal Investigators will be required to sign an Investigator's Agreement, detailing their commitment to accrual, compliance, Good Clinical Practice, confidentiality and publication. Deviations from the agreement will be monitored and the TSC will decide whether any action needs to be taken, e.g. withdrawal of funding, suspension of centre.

9.6. Research Governance and Ethical Approval

As the trial does not involve an investigational medicinal product, clinical trial authorization from the Medicines and Healthcare products Regulatory Authority is not required.

In accordance to the Belgian law of 7 May 2004 that regulates human experiments, the investigator will inform the study participants and the medical ethical committee if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review, except insofar as suspension would jeopardize the subjects' health. The investigator will take care that all subjects are kept informed.

The principal investigator will report all adverse and serious events to the medical ethical committee.

Adverse events are defined as any undesirable experience occurring to a participant during the study, whether or not considered to be related to the intervention.

All adverse events reported spontaneously by the participant or observed by the investigator or his staff will be recorded.

A serious adverse event is any untoward medical occurrence or effect that:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

All SAEs will be reported to medical ethical committee that approved the protocol, within 15 days after the investigator has first knowledge of the serious adverse reactions.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur no later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

9.7. Funding and Cost implications

The research costs of this non-commercial trial are funded by the investigating team.

9.8. Indemnity

No additional preoperative examinations are needed when compared to the situation where the woman would not have given informed consent for study participation. One additional postoperative examination is needed for study participants compared to routine clinical practice: no risks or side effects are associated with this additional assessment. The risks and side effects for both types of surgical interventions have been extensively described in the consent form. According to two large prospective studies the incidence of complications associated with minimally invasive surgery are less than 1%. (26, 27) The benefit is an, as of yet, unknown increase in the chance of being discharged the same day as the surgical procedure with less postoperative pain.

The investigators have a 'no fault' liability insurance which is in accordance to the Belgian law of 7 May 2004 that regulates human experiments. The insurance aims to cover the financial consequences of the civil liability that the investigators may incur even when no fault has occurred as a result of the organization of medical experiments on the human person. All physical and material damage sustained by the participant in the experiment and/or his/her assignees and arising from the insured experiment are covered for an amount of 2 500 000 € per experiment. The insurance applies to the damage that becomes apparent during the study or within 36 months after the end of the study.

9.9. Publication

A meeting will be held after the end of the study to allow discussion of the main results among the collaborators prior to publication. The success of the study depends entirely on the wholehearted collaboration of a dedicated team of doctors, nurses and others.

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9.10. Ancillary studies

It is requested that any proposals for formal additional studies of the effects of the trial treatments on some participants (e.g. special investigations in selected hospitals) be referred to the Trial

Management Committee for consideration. In general, it would be preferable for the trial to be kept as simple as possible, and add-on studies will need to be fully justified.

10. REFERENCES

(1) Burpee SE, Kurian M, Murakame Y, Benevides S, Gagner M. The metabolic and immune response to laparoscopic versus open liver resection. Surg Endosc. 2002; 16(6):899 –904.

(2) Grande M, Tucci GF, Adorisio O, et al. Systemic acute-phase response after laparoscopic and open cholecystectomy. Surg Endosc. 2002; 16(2):313–6.

(3) Rattner D, Kalloo A. ASGE/SAGES working group on natural Orifice transluminal endoscopic surgery. October 2005. Surg Endosc. 2006; 20:329-33.

(4) Santos BF, Hungness ES. Natural orifice transluminal endoscopic surgery: progress in humans since white paper. World J Gastroenterol. 2011; 17:1655–65.

(5) Tolcher MC, Kalogera E, Hopkins MR, Weaver AL, Bingener J, Dowdy SC. Safety of Culdotomy as a Surgical Approach: Implications for Natural Orifice Transluminal. JSLS. 2012; 16:413–20

(6) Uccella S, Cromi A, Bogani G, Casarin J, Serati M, Ghezzi F. Transvaginal specimen extraction at laparoscopy without concomitant hysterectomy: our experience and systematic review of the literature. J Minim Invasive Gynecol. 2013; 20:583-90.

(7) Reynders A, Baekelandt J. Adnexectomy by Poor Man's Transvaginal NOTES. Gynecological Surgery 2015; 12(3): 207-11.

(8) Dindo D, Demartines N, Clavien PA. Classifi cation of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240**:** 205–13.

(9) Mc Williams GD, Hill MJ, Dietrich CS. Gynecologic emergencies. Surg Clin North Am 2008; 88(2): 265-83.

(10) Timmerman D, Ameye L, Fischerova D, Epstein E, Melis GB, Guerriero S, Van Holsbeke C, Savelli L, Fruscio R, Lissoni AA, Testa AC, Veldman J, Vergote I, Van Huffel S, Bourne T, Valentin L. Simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery: prospective validation by IOTA group. BMJ 2010; 341:c6839 doi:10.1136/bmj.c6839.

(11) Sainz de la Cuesta R, Goff BA, Fuller AF Jr, Nikrui N, Eichhorn JH, Rice LW. Prognostic importance of intraoperative rupture of malignant ovarian epithelial neoplasms. Obstet Gynecol. 1994;84(1):1.

(12) Webb MJ, Decker DG, Mussey E, Williams TJ. Factor influencing survival in Stage I ovarian cancer. Am J Obstet Gynecol. 1973;116(2):222.

(13) Pillai R, Yoong W. Posterior colpotomy revisited: a forgotten route for retrieving larger benign ovarian lesions following laparoscopic excision. Arch Gynecol Obstet. 2010; 281(4):609-11.

(14) Yang YS, Hur MH, Oh KY, Kim SY. Transvaginal natural orifice transluminal endoscopic surgery for adnexal masses. J Obstet Gynaecol Res. 2013 Dec; 39(12):1604-9.

(15)Demir RH, Marchand GJ. Adnexal masses suspected to be benign treated with laparoscopy. JSLS JSLS. 2012 Jan-Mar; 16(1): 71–84.

(16)Ghezzi F, Cromi A, Uccella S, Bogani G, Serati M, Bolis PF. Transumbilical versus transvaginal retrieval of surgical specimens at laparoscopy: a randomized trial. Am J Obstet Gynecol 2012; 207(2): 112.e1-112.e6.

(17) Wang PH, Lee WL, Juang CM, Tsai WY, Chao HT, Yuan CC. Excision of mature teratoma using culdotomy, with and without laparoscopy: A prospective randomized trial. BJOG 2001; 108: 91-4.

(18)Medeiros LR, Rosa DD, Bozzetti MC, Fachel JM, Furness S, Garry R, Rosa MI, Stein AT. Laparoscopy versus laparotomy for benign ovarian tumour. Cochrane Database Syst Rev. 2009 Apr 15; (2):CD004751.

(19)Barkun JS, Aronson JK, Feldman LS, Maddern GJ, Strasberg SM, for the Balliol Collaboration. Evaluation and stages of surgical innovations. The Lancet 2009; 374:1089-96.

(20)Ergina PL, Cook JA, Blazeby JM, Boutron I, Clavien PA, Reeves BC, Seiler CM, for the Balliol Collaboration. Challenges in evaluating surgical innovation. The Lancet 2009; 374:1097-1104.

(21)Mc Culloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, Nicholl J, for the Balliol Collaboration. No surgical intervention without evaluation: the IDEAL recommendations. The Lancet 2009; 374: 1105-12.

(22)Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykendall DH, Hollingsworth JC, Ashton CM, Wray NP. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med. 2002 Jul 11; 347(2):81-8.

(23)Freedman B. Equipoise and the ethics of clinical research. N Engl J Med 1987; 317: 141-145.

(24) Bird SB, Dickson EW. Clinically significant changes in pain along the visual analog scale. Ann Emerg Med 2001;38: 639-43.

(25) Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. Ann Emerg Med 1996; 27: 485-9.

(26) Jansen FW, Kapiteyn K, Trimbos-Kemper T, Hermans J, Trimbos-Kemper JB. Complications of laparoscopy: a prospective multicenter observational study. Br J Obstet Gynaeco 1997; 104: 595-600.

(27)Harrki-Sirén P, Sjoberg J, Kurki T. Major complications of laparoscopy: a follow-up Finnish study. Obstet Gynecol 1999; 94: 94-8.

APPENDIX I: TABLE I

Table 1 Overview of patient and perioperative characteristics

Data	Mean	Range
Age (years)	51	31 - 75
BMI (kg/m^2)	24.0	17.2 - 28.7
Total operating time (min)	32	20 - 50
Serum hemoglobine drop (g/dl)	0.9	0 - 2.1
Postoperative pain score		
6h	2.0	0 – 4
24h	1.3	0 – 2
Size of adnexal mass (mm)	51.8	35 - 110

APPENDIX II: TABLE II

Table 2 Patient and perioperative characteristics of consecutive patients

CE = cystectomy; CS = caesarean section; LS = laparoscopic sterilisation; USO = unilateral salpingo-oophorectomy; BSO = bilateral salpingo-oophorectomy; R = right; L = left.

Patient no.	Age (years)	BMI (kg/m^2)	Parity	History of vaginal delivery	Previous pelvic surgery	Type of surgery	Total operating time (min)	Serum hemo-globine drop (g/dl)	(Peri-) operative complications	Postoperative pain score		Size of adnexal mass (largest diameter, mm)
										6h	24h	
1	54	24.1	P4	Yes	LS	BSO	40	0.4	-	2	2	70
2	44	17.2	P1	Yes	-	USO R	35	0.8	-	2	2	62
3	56	21.5	P2	Yes	LS	BSO	35	0.5	Cystitis	2	2	35
4	47	27.1	P2	Yes	-	USO R	30	0	-	2	1	50
5	58	26.0	P0	No	-	BSO	35	0.6	-	4	1	40
6	52	28.3	P0	No	-	USO R	35	0.6	-	1	1	36
7	66	22.9	P2	Yes	-	BSO	40	0.7	-	2	1	45
8	46	20.8	P0	No	-	USO R	22	1.4	-	2	1	35
9	51	25.4	P2	Yes	-	USO L	22	0.5	-	2	1	35
10	56	24.2	P1	Yes	-	USO R	25	1.2	-	2	1	42
11	63	26.7	P2	Yes	-	BSO	30	2.0	-	3	0	40
12	56	25.0	P2	Yes	-	USO R	22	0.5	-	1	1	39
13	75	23.2	P1	Yes	-	USO R	20	0.6	-	2	2	38
14	31	21.5	P2	Yes	-	USO R	35	1.8	-	2	2	60
15	45	28.7	P1	Yes	-	USO R	20	0	-	2	2	40
16	43	24.4	P2	No	CS	USO R	50	0.9	-	2	2	100
17	45	23.7	P2	Yes	CE	USO R	45	0.7	-	0	0	110
18	36	22.8	P2	Yes	CS	USO R	40	1.7	-	2	1	39
19	55	23.4	P1	Yes	-	BSO	35	1.2	-	2	1	70
20	38	22.5	P2	Yes	-	USO L	32	2.1	-	2	2	49

APPENDIX III

CLAVIEN-DINDO CLASSIFICATION

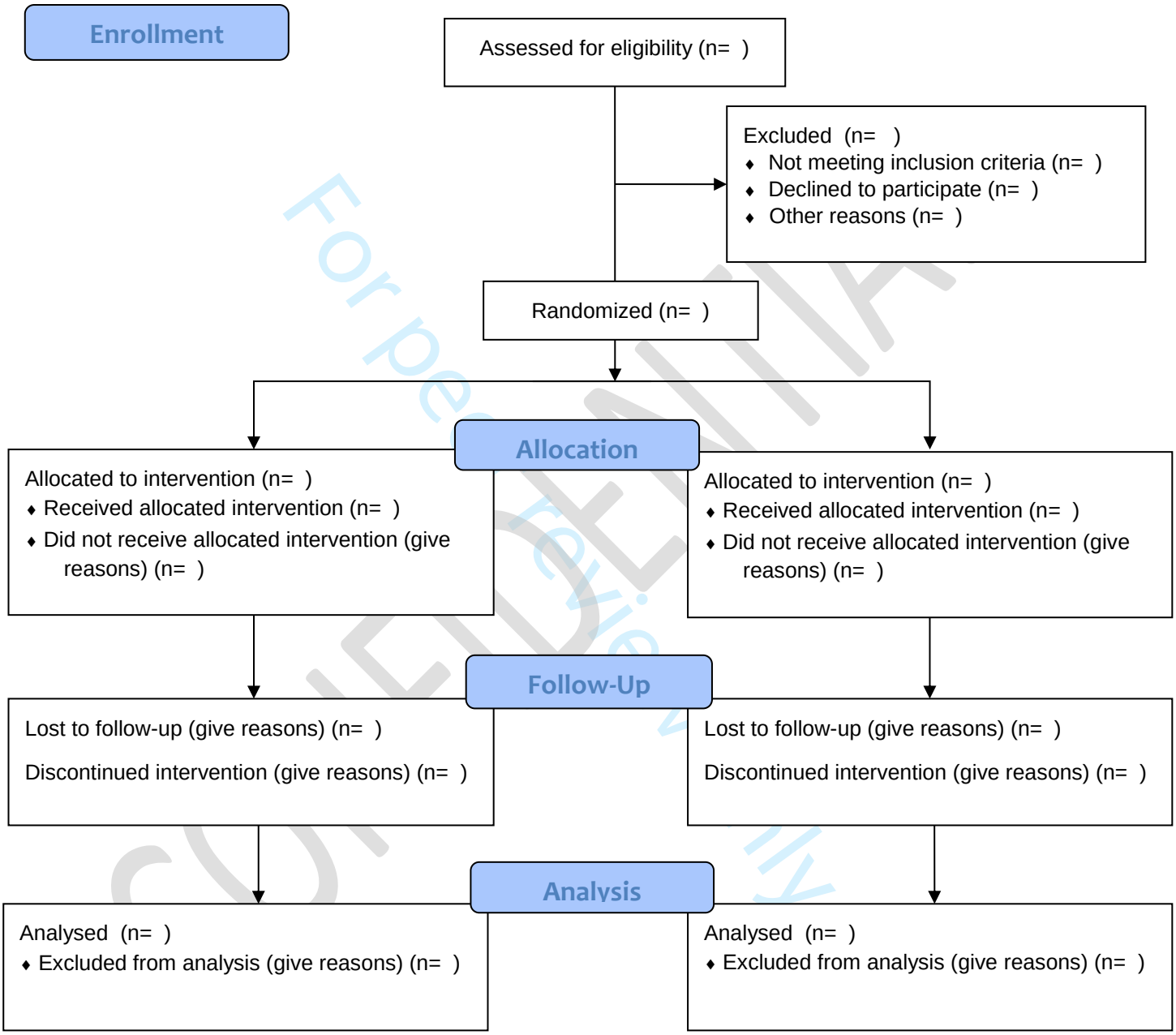
TABLE 1. Classification of Surgical Complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

APPENDIX IV

CONSORT 2010 Flow Diagram



APPENDIX V Pain protocol

PROTOCOL ADNEXECTOMIE – DR. BAEKELANDT

ASA I & ASA II PATIËNTEN

1. INDUCTIE ANESTHESIE

- Propolipid 2,5mg/kg
- Sufentanil 0,15µg/kg
- Rocurorium 0,6mg/kg
- Dexamethasone 5mg
-

2. ONDERHOUD ANESTHESIE

- O_2/ lucht 50/50
  DES 1 MAC

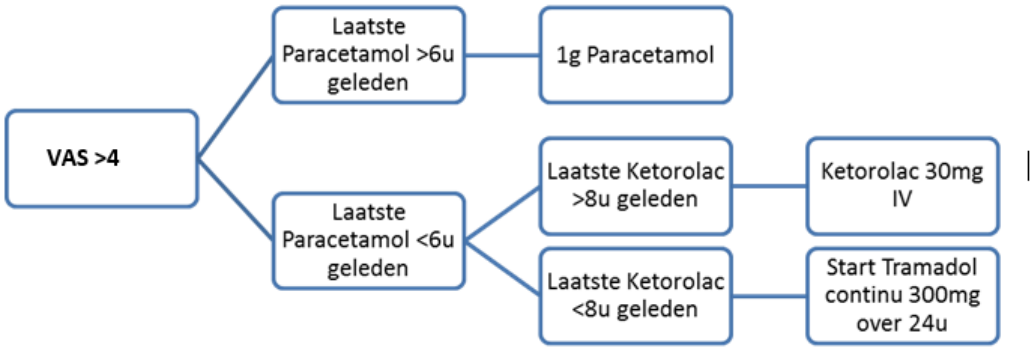
- Zo nodig bolus Alfentanil 5mg/kg
- 30min. voor einde IV toediening van
  - 1g Paracetamol
  - Ketorolac 0,5mg/kg met maximum van 30mg

3. POSTOPERATIEF

RECOVERY

- Bij VAS >4: 1g Paracetamol IV
- Herevaluatie na 30min.
  - Bij VAS >4: 2,5mg Piritramide IV

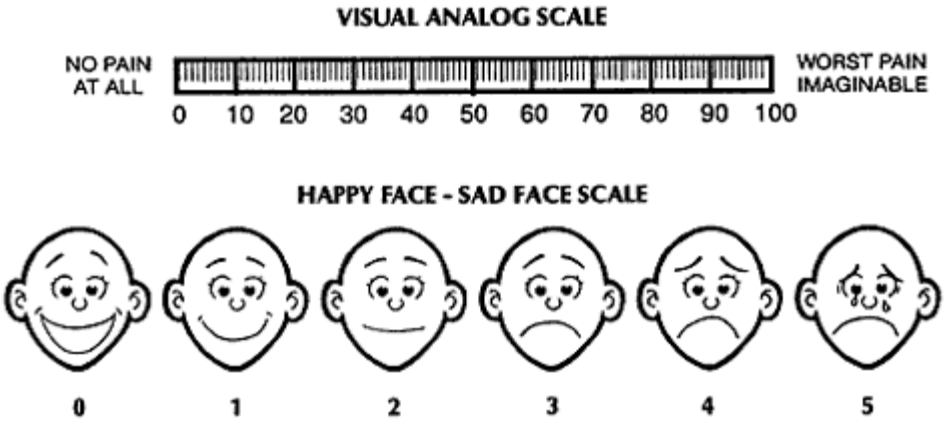
VERPLEEGAFDELING



Na 30min. herevaluatie + herstarten bovenstaand schema.

Indien VAS >4 blijft, ondanks starten van Tramadol continu: contacteer anesthesist

APPENDIX VI VAS scale



APPENDIX VII: Participant's pain log book

Notable trial

Naam en voornaam:	
Datum van de ingreep:	

Aankomst thuis:

uur van aankomst: .....

Pijnscore:

0	1	2	3	4	5	6	7	8	9	10

Pijnmedicatie:

	Aantal mg	Aantal comprimés	Tijdstip(pen) inname
Paracetamol			
Ibuprofen			
Andere			

Dag 1 na de ingreep:

Pijnscore ochtend:

0	1	2	3	4	5	6	7	8	9	10

Pijnscore avond:

0	1	2	3	4	5	6	7	8	9	10

Pijnmedicatie:

	Aantal mg	Aantal comprimés	Tijdstip(pen) inname
Paracetamol			
Ibuprofen			
Andere			

Dag 2 na de ingreep:

Pijnscore ochtend:

0	1	2	3	4	5	6	7	8	9	10

Pijnscore avond:

0	1	2	3	4	5	6	7	8	9	10

Pijnmedicatie:

	Aantal mg	Aantal comprimés	Tijdstip(pen) inname
Paracetamol			
Ibuprofen			
Andere			

Dag 3 na de ingreep:

Pijnscore ochtend:

0	1	2	3	4	5	6	7	8	9	10

Pijnscore avond:

0	1	2	3	4	5	6	7	8	9	10

Pijnmedicatie:

	Aantal mg	Aantal comprimés	Tijdstip(pen) inname
Paracetamol			
Ibuprofen			
Andere			

Dag 4 na de ingreep:

Pijnscore ochtend:

0	1	2	3	4	5	6	7	8	9	10

Pijnscore avond:

0	1	2	3	4	5	6	7	8	9	10

Pijnmedicatie:

	Aantal mg	Aantal comprimés	Tijdstip(pen) inname
Paracetamol			
Ibuprofen			
Andere			

Dag 5 na de ingreep:

Pijnscore ochtend:

0	1	2	3	4	5	6	7	8	9	10

Pijnscore avond:

0	1	2	3	4	5	6	7	8	9	10

Pijnmedicatie:

	Aantal mg	Aantal comprimés	Tijdstip(pen) inname
Paracetamol			
Ibuprofen			
Andere			

Dag 6 na de ingreep:

Pijnscore ochtend:

0	1	2	3	4	5	6	7	8	9	10

Pijnscore avond:

0	1	2	3	4	5	6	7	8	9	10

Pijnmedicatie:

	Aantal mg	Aantal comprimés	Tijdstip(pen) inname
Paracetamol			
Ibuprofen			
Andere			

APPENDIX VIII: Dyspareunia questionnaire

PIJN
lokatie en intensiteit

1) Ervaar je pijn bij het vrijen? Ja/Nee

2) Indien ja, waar ervaar je pijn bij het vrijen? Is er een specifieke plaats?
   a) ter hoogte van de vaginale opening
   b) ter hoogte van de schaamlippen
   c) in de vagina
   d) in the pelvische of abdominale regio

3) Geef een score voor de intensiteit van de pijn aan de ingang en/of the eerste deel van de vagina op deze schaal van 0 tot 10

0	1	2	3	4	5	6	7	8	9	10
geen pijn										ergste pijn ooit

4) Geef een score voor de intensiteit van de pijn in de pelvische en abdominale regio op deze schaal van 0 tot 10

0	1	2	3	4	5	6	7	8	9	10
geen pijn										ergste pijn ooit

APPENDIX IX: Short Sexual Functioning Scale

Short Sexual Functioning scale – female version

Met de volgende vragen wordt nagegaan of jij de voorbije 3 maanden bepaalde seksuele problemen hebt ervaren. Dit gebeurt door middel van vragen over lichamelijke reacties en gevoelens die kunnen optreden bij seksuele activiteiten. Als er zich een seksueel probleem heeft voorgedaan, vragen we telkens ook hoe lastig jij en jouw partner dat vinden én of dit op jullie relatie heeft gewogen.
Gelieve voor elke vraag het antwoord te omcirkelen dat het best jouw gevoel of ervaring weergeeft. Soms wordt er aangegeven dat je naar een volgende vraag mag gaan, dan hoef je de rest van de vraag niet verder in te vullen. Er zijn geen juiste of foute antwoorden. Let er op geen vragen over te slaan !

1. Had je - de voorbije 3 maanden - te weinig zin in seks, te weinig goesting in seksuele activiteiten, te weinig seksuele fantasieën of erotische gedachten (= te weinig seksueel verlangen)?

1. ik had niet te weinig zin ➔ *ga naar vraag 2*
2. ik had in lichte mate te weinig zin
3. ik had duidelijk te weinig zin
4. ik had in extreme mate te weinig zin

a) Indien ik te weinig zin in seks heb, is dit voor mij:
   1. geen probleem
   2. een licht probleem
   3. een duidelijk probleem
   4. en ernstig probleem

b) Indien ik te weinig zin in seks heb, is dit voor mijn partner:
   1. geen probleem
   2. een licht probleem
   3. een duidelijk probleem
   4. een ernstig probleem

c) Indien ik te weinig zin in seks heb, is dit voor onze relatie in het algemeen:
   1. geen probleem
   2. een licht probleem
   3. een duidelijk probleem
   4. een ernstig probleem

2. Had je - de voorbije 3 maanden - wanneer je zelf geen zin in seks had maar jouw partner wel initiatief nam tot seks, moeilijkheden om zin in seks te krijgen?

1. ik had dan geen moeilijkheden om zin in seks te krijgen ➔ *ga naar vraag 3*

2. ik had dan in lichte mate moeilijkheden om zin in seks te krijgen
3. ik had dan duidelijk moeilijkheden om zin in seks te krijgen
4. ik had dan in extreme mate moeilijkheden om zin in seks te krijgen

a) Indien ik moeilijkheden heb om zin in seks te krijgen wanneer mijn partner initiatief neemt tot seks, is dat <u>voor mij</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

b) Indien ik moeilijkheden heb om zin in seks te krijgen wanneer mijn partner initiatief neemt tot seks, is dat <u>voor mijn partner</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

c) Indien ik moeilijkheden heb om zin in seks te krijgen wanneer mijn partner initiatief neemt tot seks, is dat <u>voor onze relatie in het algemeen</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

3. Had je - de voorbije 3 maanden - wanneer jouw partner fijn met jou vrijde, <u>moeilijkheden met vochtig/nat worden</u> tijdens seks?

1. ik had geen moeilijkheden om vochtig/nat te worden ➔ ***ga naar vraag 4***
2. ik had in lichte mate moeilijkheden om vochtig/nat te worden
3. ik had duidelijk moeilijkheden om vochtig/nat te worden
4. ik had in extreme mate moeilijkheden om vochtig/nat te worden

a) Indien ik minder vochtig/nat word, is dit <u>voor mij</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

b) Indien ik minder vochtig/nat word, is dit <u>voor mijn partner</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

c) Indien ik minder vochtig/nat word, is dit <u>voor onze relatie</u> in het algemeen:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem

4. een ernstig probleem

4. Had je - de voorbije 3 maanden - wanneer je partner fijn met jou vrijde, geen of weinig gevoel van opwinding (emotioneel)?

1. ik had geen moeilijkheden met het krijgen van een gevoel van opwinding (emotioneel) ➔ ***ga naar vraag 5***
2. ik had in lichte mate moeilijkheden met het krijgen van een gevoel van opwinding (emotioneel)
3. ik had duidelijk moeilijkheden met het krijgen van een gevoel van opwinding (emotioneel)
4. ik had in extreme mate moeilijkheden met het krijgen van een gevoel van opwinding (emotioneel)

a) Indien ik geen of weinig gevoel van opwinding ervaar, is dit voor mij:
1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

b) Indien ik geen of weinig gevoel van opwinding ervaar, is dit voor mijn partner:
1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

c) Indien ik geen of weinig gevoel van opwinding ervaar, is dit voor onze relatie in het algemeen:
1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

5. Had je - de voorbije 3 maanden - wanneer jouw partner fijn met jou vrijde, moeilijkheden om klaar te komen (een orgasme te bereiken) ?

1. ik had geen moeite om klaar te komen of een orgasme te bereiken ➔ ***ga naar vraag 6***
2. ik had in lichte mate moeite om klaar te komen of een orgasme te bereiken
3. ik had duidelijk moeite om klaar te komen of een orgasme te bereiken
4. ik had in extreme mate moeite om klaar te komen of een orgasme te bereiken

a) Indien ik moeite heb om een orgasme te bereiken, is dit voor mij:
1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

b) Indien ik moeite heb om een orgasme te bereiken, is dit <u>voor mijn partner</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

c) Indien ik moeite heb om een orgasme te bereiken, is dit <u>voor onze relatie</u> in het algemeen:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

6. Had je - de voorbije 3 maanden - wanneer je met jezelf vrijde of masturbeerde, moeilijkheden om een orgasme te bereiken?

0. ik heb niet gemasturbeerd de laatste 4 weken ➔ ***ga naar vraag 7***
1. ik had geen moeite om bij masturbatie een orgasme te bereiken ➔ ***ga naar vraag 7***
2. ik had in lichte mate moeite om bij masturbatie een orgasme te bereiken
3. ik had duidelijk moeite om bij masturbatie een orgasme te bereiken
4. ik had in extreme mate moeite om bij masturbatie een orgasme te bereiken

a) Indien ik moeilijk kan klaarkomen bij masturbatie, is dit <u>voor mij</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

7. Kan je in de volgende lijst aangeven wat voor jou de voorbije 3 maanden van toepassing was? Je kan slechts één antwoord aanduiden.

1. vaginale penetratie (= het inbrengen van penis of vinger in de vagina) was mogelijk en niet pijnlijk ➔ ***einde van de vragenlijst***
2. vaginale penetratie was mogelijk, maar was pijnlijk
3. ➔ ***ga naar vraag 7a***
4. vaginale penetratie is (met mijn huidige partner) nog nooit gelukt ➔ ***einde van de vragenlijst***
5. vaginale penetratie was (met mijn huidige partner) vroeger mogelijk, maar nu niet meer ➔ ***einde van de vragenlijst***

7a. Had je - de voorbije 3 maanden - pijn voor, tijdens of na vaginale penetratie?

1. Ik had geen pijn voor, tijdens of na penetratie
2. Ik had een lichte pijn voor, tijdens of na penetratie
3. Ik had een duidelijke pijn voor, tijdens of na penetratie
4. Ik had een extreme pijn voor, tijdens of na penetratie

a) Indien ik pijn heb voor, tijdens of na vaginale penetratie, is dit <u>voor mij</u>:

1. geen probleem

2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

b) Indien ik pijn heb voor, tijdens of na vaginale penetratie, is dit <u>voor mijn partner</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

c) Indien ik pijn heb voor, tijdens of na penetratie, is dit <u>voor onze relatie</u> in het algemeen:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

Hartelijk dank voor het invullen van deze vragenlijst !

APPENDIX X: EQ-5D Health questionnaire

Gezondheidsvragenlijst

Nederlandse versie voor België

(Dutch version for Belgium)

Zet bij iedere hieronder vermelde groep een kruisje in één hokje achter de zin die het best uw gezondheidstoestand van vandaag weergeeft.

Mobiliteit

Ik heb geen problemen met rondwandelen ❑

Ik heb enige problemen met rondwandelen ❑

Ik ben bedlegerig ❑

Zelfzorg

Ik heb geen problemen om voor mezelf te zorgen ❑

Ik heb enige problemen om mezelf te wassen of aan te kleden ❑

Ik ben niet in staat mezelf te wassen of aan te kleden ❑

Dagelijkse activiteiten *(bijv. werk, studie, huishouden, gezins- of vrijetijdsactiviteiten)*

Ik heb geen problemen met mijn dagelijkse activiteiten ❑

Ik heb enige problemen met mijn dagelijkse activiteiten ❑

Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren ❑

Pijn/klachten

Ik heb geen pijn of andere klachten ❑

Ik heb matige pijn of andere klachten ❑

Ik heb zeer ernstige pijn of andere klachten ❑

Angst/depressie

Ik ben niet angstig of depressief ❑

Ik ben matig angstig of depressief ❑

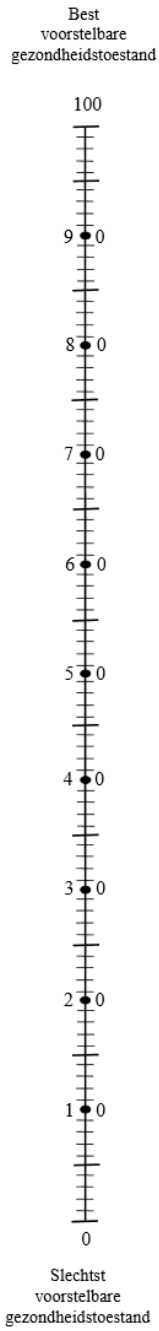
Ik ben erg angstig of depressief ❑

 2

Om mensen te helpen bij het aangeven hoe goed of hoe slecht een gezondheidstoestand is, hebben we een meetschaal (te vergelijken met een thermometer) gemaakt. Op de meetschaal hiernaast betekent "100" de beste gezondheidstoestand die u zich kunt voorstellen, en "0" de slechtste gezondheidstoestand die u zich kunt voorstellen.

We willen u vragen op deze meetschaal aan te geven hoe goed of hoe slecht volgens u uw eigen gezondheidstoestand vandaag is. Trek een lijn van het hokje hieronder naar het punt op de meetschaal dat volgens u aangeeft hoe goed of hoe slecht uw gezondheidstoestand vandaag is.

Uw gezondheidstoestand vandaag



 3

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_4_____
	2b	All items from the World Health Organization Trial Registration Data Set	_Appendix 1 ___
Protocol version	3	Date and version identifier	_3,4_____
Funding	4	Sources and types of financial, material, and other support	_25_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_1,2, 25_____
	5b	Name and contact information for the trial sponsor	_Not applicable__
	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	_Not applicable__
	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)	_Not applicable _____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__5,6_____
	6b	Explanation for choice of comparators	__6,7,22_____
Objectives	7	Specific objectives or hypotheses	__6,7_____
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)	___8_____
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	___8_____
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)	__8,9_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	___9,10,11,12,13
	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)	_11,12_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_11,12_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_11,12_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_12,13_____
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)	__Table 1_____

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_14,15_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__15_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__13,14_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	__13_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__13,14_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__14_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	__14_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__19,20_____
	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	__19,20_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__20_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__17,18_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___17,18_____
	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)	___17,18_____
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	_18,19_____
	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	__18,19_____
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	__18,19_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__18,19_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__23,24_____
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)	___24_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	__24_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_Not applicable__
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	_24,25_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__26_____
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	_25_____
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	__25_____
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	__25_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__25_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_24_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Appendix 2____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable__

*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.

BMJ Open

Transvaginal Natural Orifice Transluminal Endoscopic Surgery (vNOTES) adnexectomy for benign pathology compared to laparoscopic excision (NOTABLE): a protocol for a randomised controlled trial.

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Transvaginal Natural Orifice Transluminal Endoscopic Surgery (vNOTES) adnexectomy for benign pathology compared to laparoscopic excision (NOTABLE): a protocol for a randomised controlled trial.

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Running title

NOTABLE study

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ABSTRACT

Introduction: Natural Orifice Transluminal Endoscopic Surgery (NOTES) uses natural orifices to access the cavities of the human body to perform surgical interventions. NOTES limits the magnitude of surgical trauma, and potentially reduces postoperative pain. Our group published a protocol on a randomized study comparing transvaginal NOTES (vNOTES) versus laparoscopy for hysterectomy (HALON). We simultaneously designed a similar RCT comparing vNOTES with laparoscopy for adnexectomy. To the best of our knowledge this is the first RCT comparing vNOTES with laparoscopy for adnexal surgery.

Methods and analysis: The methodology of the NOTABLE study is similar to that of the HALON trial. Women aged 18-70 years with an indication for benign adnexal surgery will be eligible. We will use stratification according to adnexal size. Entrants will be randomised to the laparoscopic treatment (control) or vNOTES (intervention). Participants will be evaluated on days 0-7, and at 3 and 6 months. The primary outcome will be the proportion of women successfully treated by removing an adnexa by the allocated technique without conversion. We will collect the following data(secondary outcomes): proportion of women hospitalized on the day of surgery; postoperative pain scores measured twice daily from day 1-7; total dosage of pain killers used from day 1-7; hospital readmission during the first six weeks; dyspareunia and sexual wellbeing at baseline, 3 and 6 months using a validated questionnaire (SSFS scale); health-related quality of life at baseline, 3 and 6 months after surgery using an validated questionnaire (EQ-5D-3L); duration of surgical intervention; infection or other surgical complications; direct costs up to 6 weeks following surgery. For the primary outcome measure, a one-sided 95% confidence interval of the difference in the proportions of women with a successful removal of the uterus by the randomised technique will be estimated. Non-inferiority will be concluded when 15% lies above the upper limit of this 95% CI.

Ethics and dissemination: The study was approved on December, 1st 2015 by the Ethics

Committee of the Imelda Hospital, Bonheiden, Belgium. We aim to present the final results of the NOTABLE trial in peer- reviewed journals and at scientific meetings within 4 years after the start of the recruitment.

Registration details:

Primary Registry and Trial Identifying Number**:** NCT02630329

Secondary Identifying Number**:** B689201526268

Date and version identifier: Version 5, 28 December 2015

Study dates:

The first patient was included on 15 January 2016.

On 22 May 2017 38 of the targeted 70 participants were recruited.

Anticipated date of study completion is estimated May 2018.

Strengths and limitations of this study:

Strength: This study is a randomised controlled trial.

Strength: The patients, the outcome assessors and the personnel are blinded in this trial.

Limitation: This is a single centre study.

Limitation: The generalisability of this study to a "real-life" setting is limited due to the experimental setting of the study.

Limitation: The use of non-therapeutic incisions for blinding may confound the outcome pain.

INTRODUCTION

Background

Laparoscopic surgery has reduced surgical morbidity and mortality. “Minimally invasive surgery” has moved even further forward with newer techniques such as single incision laparoscopic surgery (SILS) and natural orifice transluminal endoscopy (NOTES) with or without by robot assistance.

The NOTES technique uses any natural orifice (mouth, vagina, urethra or rectum) as a possible access route facilitating a surgical intervention in a cavity of the human body. Clinical researchers at Johns Hopkins University first reported its use in 2004 in a preclinical trial using an animal model (1). Ever since the clinical application of NOTES has been reported in many surgical procedures in ways that seem to defy human imagination: appendectomy and cholecystectomy have been performed using the mouth and the stomach as the access route (2, 3). The technique seems feasible and safe in the hands of experienced surgeons beyond their surgical learning curve. Observational evidence (mostly case reports) have reported moreover that NOTES may cause less postoperative pain, a shorter length of hospital stay, less complications and last but not least for female patients improved cosmetic results. The feasibility of scar-free surgery in combination with reduced wound (trocar) complications may be tempting for patients and their care providers. This may be a strong facilitator for the widespread implementation of this new surgical approach.

NOTES has gained popularity amongst general surgeons, urologists and gastroenterologists over the past few years and its feasibility and safety in these domains have been reported (4). Although NOTES may be performed using various entries including the stomach, oesophagus, bladder and rectum, the majority of NOTES procedures in women have been performed through the vagina (5). This is not surprising because the colpotomy technique has been used widely vaginal prolapse surgery and for benign adnexal surgery involving the

extraction of large specimens. Its use has been reported as a safe access (6, 7). Two variants of NOTES have been described in the present literature. Hybrid NOTES combines the access through the vagina with transabdominal assistance; pure NOTES refers to procedures that involve only transluminal access.

The removal of one or both adnexa using a transvaginal NOTES (vNOTES) approach was described for the first time by Lee and co-workers in 2012 (8). vNOTES adnexectomy for benign pathology was introduced at our department by the first author (JB) in 2013. Our group published three small case series on adnexal removal (N=20) (9), salpingectomy (N=5) (10) and hysterectomy (N=10) (11) by vNOTES during the period between November 2013 and February 2015. We also published the protocol of the HALON study randomly comparing NOTES and laparoscopy for doing hysterectomy in women with benign gynaecological disease (12). The recruitment of the HALON study was finished recently (February 24th 2017). The final data analysis of the HALON study is foreseen for September 2017.

Objectives and hypotheses

We started our research by doing a systematic review of the literature. We searched MEDLINE, EMBASE and The Cochrane Library from inception to 1 August 2015 using a combination of MeSH terms and key words for '*colpotomy'* and '*adnexal diseases'* or *'adnexal mass'*. We aim to publish the results of this systematic search of the literature and a critical appraisal of the retrieved evidence in a separate systematic review (SR): we will adhere to the PRISMA-P guidelines (13) for the protocol of this SR. The protocol of the SR has been registered in PROSPERO- the international prospective register of systematic reviews, at the Centre for Reviews and Dissemination (CRD), University of York, United Kingdom (14), as CRD42016033670. To the best of our knowledge no randomised controlled

studies comparing vNOTES with the transabdominal laparoscopic approach for removal of one or both adnexa have been published in the literature. The main objective of the NOTABLE study is to study the effectiveness of vNOTES for successfully removing one or both adnexa for benign gynaecological disease using the classical laparoscopic approach as the established effective technique (EET). The rationale and the objectives of NOTABLE are in accordance with the principles outlined by the IDEAL collaboration (15-17).

Our primary study hypothesis is that vNOTES is not inferior to transabdominal laparoscopy for removing one or both adnexa for a benign gynaecological indication without having to convert to another technique. vNOTES may offer several advantages including the avoidance of abdominal scars, less need for hospital admission and possibly less postoperative pain.

METHODS

Trial design and study analysis

The NOTABLE study should be considered as a pilot study. It is a single-centre parallel-group double blinded (patient and outcome assessor) randomised trial conducted at the Department of Gynaecology of the Imelda Hospital in Bonheiden. This is a general hospital in Belgium serving an estimated population of 150,000 people. All women aged 18-70 years bound to undergo removal of one or both adnexa for benign gynaecological disease will be informed about the NOTABLE study and they will be invited to participate in the study, if eligible. The baseline characteristics of eligible women not wishing to give informed consent for participating in the study will be recorded as well as the reason for declining to participate. All surgical procedures (vNOTES and laparoscopy) will be done by one surgeon (JB) who is equally skilled in both techniques. The surgeon has been using the vNOTES approach for various interventions (salpingectomy for EUG, adnexectomy and hysterectomy) since November 2013. JB is also the surgeon performing the hysterectomies in the HALON trial. The surgeon cannot be blinded but the allocated treatment will be concealed. We will use a non-inferiority study design to test the effectiveness of vNOTES compared to laparoscopy. The protocol adheres to the SPIRIT standards (http://www.spirit-statement.org/). The study protocol of the NOTABLE trial is very similar to that of the earlier published HALON study (12).

Participants

NOTABLE will recruit eligible women aged 18-70 years, regardless of parity, who need the removal of one or both adnexa for a benign adnexal disease and who provide informed consent prior to surgery.

Exclusion criteria are as follows:

- history of rectal surgery

- suspected rectovaginal endometriosis
- suspected malignancy
- history of pelvic inflammatory disease (PID)
- active lower genital tract infection
- virginity
- pregnancy
- failure to provide written informed consent.

Intervention, procedures and standard care

On the day of the surgery, all patients are admitted to the day care unit. A nurse administers clindamycin vaginal cream on admission.

Under general anaesthesia, the patient is positioned in a vacuum mattress in the classical lithotomy. An alcoholic betadine solution is used for disinfection of the vagina, vulva and abdomen before draping. A Foley catheter is inserted into the bladder. In accordance with hospital protocol, the anaesthesiologist will administer cefazolin 2g and metronidazole 1.5g IV prior to incision for prophylaxis against infection to all women of both treatment arms. In both groups a 30° rigid endoscope is used.

Control group: laparoscopic technique

The surgeon will start the procedure by making a small vertical intra-umbilical skin incision. A Veress needle is introduced into the peritoneal cavity; the tip position is checked with a Semm test before insufflating CO_2 until a maximal intraperitoneal pressure of 15mmHg. A 10mm trocar is inserted through the umbilicus after removal of the Veress needle. An optic is inserted to inspect the peritoneal cavity. The operating table is tilted in the Trendelenburg position. Two 5mm trocars are placed under direct vision in the suprapubic region and in the left iliac fossa lateral of the epigastric vessels. The small intestine is lifted out of the pelvis.

The ureter is identified, but no retroperitoneal dissection is performed unless indicated. The proximal end of the Fallopian tube is coagulated at its origin in the uterus using a reusable bipolar grasping forceps before being cut with cold microscissors. The ovarian and infundibulopelvic ligament are coagulated and cut. After resection, the adnexa is placed in an endobag (Memobag, Teleflex). When indicated, the same procedure is repeated for the contralateral side.

After confirmation of haemostasis, the peritoneal cavity is rinsed. No drains are left in the peritoneal cavity unless necessary, e.g. problematic haemostasis. The 5 mm trocars are be removed under direct vision. The purse string of the endobag is pulled through the 10 mm trocar upon removal of the optic. The umbilical incision is extended vertically in caudal direction, but not more than 2.5 cm. The fascia and peritoneum are opened and the proximal end of the endobag is pulled through the incision without causing any rupture if possible. If not possible, the endobag will be opened and the content of the cyst will be aspirated to reduce the volume of the adnexa. The aspirated fluid will be sent for cytological evaluation. The endobag will then be removed with the adnexa inside it.

The fascia is closed using a Vicryl-1 running suture. The umbilicus and other incisions are disinfected with betadine solution. All skin incisions are closed with a Monocryl 3/0 intradermal suture and approximated using steri-strips. The wound sites are covered with a wound dressing. A vaginal plug (betadine gauze 10 cm x 5 m) is inserted into the vagina. After 3 hours the Foley catheter and the vaginal plug are removed.

Intervention group: vNOTES

The surgeon makes three non-therapeutic superficial skin incisions on exactly the same location as in the classical laparoscopic approach in all women allocated to the vNOTES group to blind study participants and the outcome assessor to the allocated technique. A 2.5 cm posterior colpotomy is made using a cold knife. The pouch of Douglas is opened using

scissors. A Gelpoint Mini (Applied Medical), used as vNOTES port, is inserted into the pouch of Douglas. CO_2 is insufflated until a maximal intraperitoneal pressure of 15mmHg. An optic is inserted to inspect the peritoneal cavity. The operating table is tilted in the Trendelenburg position. The small intestine is lifted out of the pelvis.

The ureter is identified, but no retroperitoneal dissection is performed unless indicated. The proximal end of the Fallopian tube is coagulated at its origin into the uterus using a reusable bipolar grasping forceps and cut using microscissors. The ovarian and infundibulopelvic ligament are coagulated and cut. The adnex is removed. When indicated, the procedure is repeated for the contralateral side. After confirmation of haemostasis, the peritoneal cavity is rinsed.

Small benign looking adnexa are removed directly through the wound protector part of the vNOTES port. Large adnexa or adnexa that appear macroscopically suspicious, are placed in an endobag (Memobag, Teleflex). The purse string of the endobag is pulled through the wound protector and the purse string released. The content of the cyst is aspirated to reduce the volume of the adnexa. The endobag is then removed with the adnexa inside it. The vNOTES port is removed.

The colpotomy is closed using three interrupted figure-of-eight Vicryl 2/0 sutures. A vaginal plug (betadine gauze 10cmx5m) is inserted into the vagina. After 3 hours the Foley catheter and the vaginal plug are removed.

In the majority of patients it is feasible to perform a successful vNOTES or laparoscopic adnexectomy. Women in whom the intended approach has to be abandoned for an alternative intervention will not be excluded or withdrawn from the NOTABLE trial but will be followed up further. It is anticipated that most included patients with a normal CA125 value and benign features of the ovary on ultrasound, will not require other interventions besides the removal of the adnexa. If the responsible clinician judges that additional treatment is necessary at the

time of the surgery or afterwards, this will be recorded and the patient will not be withdrawn from the study. However, if there is a preoperative indication for additional surgery during the same procedure, these patients will be excluded from recruitment to the NOTABLE trial.

The anaesthesiologists involved in the clinical trial have developed a standardised protocol to insure that the pain management is identical for both groups. The outcome assessor (JJAB) and the patient are both blinded to the surgical approach used. The patient makes the decision to be discharged from the day care unit on the evening of the procedure or to be admitted to an in-hospital nursing ward for the night. The outcome assessor can only overrule the patient's decision in the interest of her health, e.g. when surgical complications were recorded in the surgical report or when vital parameters indicate a life-threatening condition. Before discharge all patients are given a standard list of instructions to avoid physical work, exercise and sexual intercourse for four weeks after the intervention.

All participants, regardless of being at home or in hospital, are requested to use a VAS scale twice daily to measure postoperative pain from day 1 until day 7 following surgery. Adequate instructions on how to use the VAS scale measuring tool are given on an individual basis by a dedicated nurse of the day care unit. One measurement is made in the evening before going to bed after physical activity (active) and another is made in the morning after bed rest at night (rest). All patients are asked to note the name, dosage, and route of administration of any analgesic drug taken from day 1-7 in a pain log book.

Outcome measure

We searched the COMET (18) database for a core outcome set for adnexectomy (general settings) in gynaecology (health area-disease category) in women (target population: sex) aged 18 to 70 years (target population: age): no core outcome set relevant to laparoscopic removal of adnexa was identified (19).

Primary outcome measure

The proportion of women successfully treated by removing one or both adnexa without spill by the allocated technique as randomized will be measured as the primary outcome of effectiveness.

Secondary outcome measures

The secondary outcomes are as follows:

- The proportion of women hospitalized on the day of surgery based on their own preference.
- Postoperative pain scores measured using a Visual Analogue Scale (VAS) scale (20) twice daily from day 1-7.
- The total dosage of pain killers taken during the first week following surgery.
- Postoperative infection defined by lower abdominal pain with fever > 38°C and positive clinical signs or laboratory findings detected during the first six weeks of surgery.
- Intra- or postoperative complications classified according to the Clavien- Dindo classification (21) detected during the first six weeks of surgery.
- Readmission to hospital during the first six weeks of surgery.
- Occurrence and severity of pain on sexual intercourse self-reported by the study participants at baseline, 3 and 6 months by using a simple questionnaire and VAS scale.
- Sexual wellbeing at baseline, at 3 and 6 months by self-reporting the Short Sexual Functioning Scale-SSFS (22).
- Health-related quality of life at baseline, 3 and 6 months after surgery by self-reporting using a validated questionnaire (EQ-5D-3L).

- The duration of the surgical intervention measured in minutes from the insertion of the bladder catheter to the end of vaginal/abdominal wound closure.
- Direct costs for both techniques up to 6 weeks following surgery.

The SSFS and the EQ-5D-3L questionnaires were validated in Dutch and presented to the participants in their mother tongue

Randomisation and blinding

Participants will be randomly allocated to one of both treatment arms (vNOTES versus laparoscopy) We will use a computer-generated randomisation schedule generated by the management assistant of our department. We will use a stratification into three categories (A, B or C) according to the size of the cyst on transvaginal ultrasound (0 to 5 cm, 5 to 10 cm, larger than 10 cm). Sequentially numbered, opaque, sealed envelopes will be used to ensure allocation concealment for the surgeon and the outcome assessor. The management assistant will safeguard the allocation code until the last visit of the last patient. The management assistant will not be involved in the outcome assessment or the data collection.

All participating women and the outcome assessor will be blinded to the allocation by the use of non-therapeutic skin incisions. It is impossible to blind the surgeon. In case of life-threatening adverse events, the outcome assessor will notify the surgeon to enable further treatment without the need for unblinding the patient. The use of the vNOTES technique avoids the use of abdominal incisions. Participants allocated to the vNOTES arm will have three superficial non-therapeutic skin incisions similar to those routinely done with the laparoscopic technique. This enables blinding all study participants, personnel and the outcome assessor. The wound dressings of all women will be left untouched until the postoperative visit on day 7. The practice of using non-therapeutic skin incisions has been reported in some surgical trials to minimise performance and detection bias when measuring subjective outcomes (e.g. pain) (23). The decision to use non-therapeutic skin incisions is

justified by the risk/benefit ratio of the two interventions under comparison (24). Its use in the HALON and NOTABLE trial has been intensively discussed among the investigators and has been approved by the Ethical Committee of the Imelda Hospital Bonheiden (registration number 689), Belgium on December 1, 2015. The written approval with the Belgian unique study identifier B689201526268 was sent to the FAMHP in Brussels.

Statistical methods

Sample size calculation

A sample size calculation was done for the primary outcome only. An appropriate level of statistical power was applied to preclude any clinically important inferiority of vNOTES compared to laparoscopy. The assumptions for the sample size calculation are based on evidence retrieved from two sources: a randomized study comparing the excision of mature dermoid cysts using colpotomy with laparoscopic assistance versus colpotomy without laparoscopy (25) and a systematic review with meta-analysis comparing single port laparoscopy versus conventional laparoscopy in benign adnexal disease (26) An important consideration in any adnexal mass surgery is the inadvertent opening of the ovarian capsule of an unsuspected malignancy resulting in the spill of malignant cells into the abdominal cavity. Based on a 2.4% failure rate to remove dermoid cysts by colpotomy using laparoscopic assistance (25) and a 0% conversion rate from laparoscopy to laparotomy (26) we assumed that the successful removal of adnexal cysts without spill would be feasible in 95% of all cases. The sample size was calculated with a one-sided test for non-inferiority for the primary outcome. The vNOTES approach may be the treatment of choice for women because it avoids scars. We assume that vNOTES would be the preferred technique even when 15% less women had in the end a successful removal of a benign adnexal mass by using vNOTES compared to laparoscopy with its unavoidable scars. Non-inferiority will be concluded when 15% lies above the upper limit of the 95% confidence interval calculated for the difference in

the proportion of women successfully treated with either technique. To achieve 80% power to demonstrate non-inferiority under the assumption of similar success rates of 95% in both groups a sample size of 54 participants (27 women per group) will be required. We increased the target sample size to 64 participants (32 women per group) to account for a drop-out rate of 15%. Based on the power calculations for the primary outcome, the use of three strata for the randomisation and assuming a loss-to-follow-up rate of 15 %, we decided to include 66 study participants in the NOTABLE trial.

Statistical analyses

GENERAL PRINCIPLES

For all baseline and outcome variables, the number of available measurements and the number of missing values will be given. A probability (p) less than 0.05 will be considered to be significant. Analysis will be performed by intention-to-treat, as recommended in the CONSORT statement (27). Since the study compares two regular interventions and is expected to recruit during a reasonably limited period, interim analyses will not be performed.

Categorical data will be reported as absolute numbers and percentages. Normally distributed continuous variables will be summarized as means with standard deviations and non-normally distributed continuous variables will be reported as medians with interquartile ranges (IQR). Main analyses will not impute missing values.

All analyses will be performed using SAS software (version 9.4 of the SAS System for Windows).

DESCRIPTIVE ANALYSES

Study population – baseline characteristics

- Mean age (± SD)
- Mean Body Mass Index (± SD)

- Mean number of natural vaginal births (± SD)
- Mean number of abdominal/pelvic surgical interventions (± SD)
- Mean weight of the uterus (± SD)

STUDY ENDPOINTS

Main study parameter/endpoint

Differences in the proportions of women successfully treated by removing the uterus by the intended technique without conversion to another approach

Secondary study parameters/endpoints

- Proportions of women hospitalized on the day of surgery
- Postoperative pain scores, measured using a VAS scale twice daily from day 1 till 7 self-reported by the study participants
- Total dose analgesics used during the first week following surgery
- Incidence of postoperative infection during the first six weeks of surgery
- Incidence of intra-operative complications
- Incidence of postoperative complications during the first 6 weeks following surgery
- Incidence of readmission during the first six weeks of
- Incidence of dyspareunia recorded by the participants at baseline, 3 and 6 months by self-reporting using a simple questionnaire
- Severity of dyspareunia recorded by the participants at baseline, 3 and 6 months by self-reporting using a VAS scale

- Sexual wellbeing at baseline, at 3 and 6 months by self-reporting the SSFS Quality of life (QoL) at baseline, at 3 and 6 months by self-reporting the EQ-5D-3L questionnaire.
- Duration of surgery
- Total costs of both interventions surgery

STATISTICAL ANALYSIS

For the primary outcome measure, a one-sided 95% confidence interval of the difference in the proportions of women with a successful removal of the uterus by the intended technique as randomised will be estimated. Non-inferiority will be concluded when 15% lies above the upper limit of this 95% CI.

For the manuscript all above listed secondary outcomes will be compared between the two groups. These data will be reported as vNOTES versus laparoscopy.

For dichotomous secondary outcome measures, comparisons between the two arms will be performed by applying Fisher exact test or Chi-square test, as appropriate.

Cross-sectionally measured continuous secondary outcomes will be analysed using an independent T-test or Mann–Whitney U- Test, as appropriate.

Longitudinally measured continuous secondary outcomes will be analysed using multilevel modelling. Differences in evolution between both treatment groups will be compared by means of a time by group interaction. In absence of such an interaction mean differences will be compared over all time points. Outcome scores will be transformed if required to meet model assumptions.

All statistical analyses will be done by an experienced biostatistician (AL) who is a co-investigator. After data cleaning the management secretary will send the unblinded data to the biostatistician after the last visit of the last patient. The biostatistician will do all the analyses

without any assistance of the other investigators who will remain blinded until all data have been analysed.

The following strategy will be used in case of missing data. In case of a single item response missing, the data will be imputed from given values. In cases where more than one item is missing or an entire form is missing, imputation will not be attempted. We will assess whether the obtained results are robust to the methods used to handle missing data, by performing a sensitivity analysis.

MONITORING

NOTABLE is a small trial, therefore a data monitoring committee is not needed.

All adverse events reported spontaneously by the participant or observed by the investigator or his staff will be recorded. Infection and per- or postoperative complications will be assessed as secondary outcomes until 6 weeks after surgery. We will inform the family physician of all participants in order to assess all possible unintended effects of the trial intervention and promote to report all possible adverse events anonymously using the participant's unique study number to an e-mail address (NOTES@imelda.be). We will use descriptive statistics for data analysis although the trial is not adequately powered to detect important differences in rates of uncommon adverse events. Given the limited resources and the single-centre design there will be no auditing of the conduct of the trial. We will review patient enrollment, consent and eligibility on a regular basis to promote data quality and to preserve trial integrity. The distribution of the allocation to the study groups will be blindly checked by the study secretary at 30%, 60% and 90% of the recruitment and discussed with the study statistician and the principal investigators.

RESULTS

Participant flow diagram

Table 1 shows the study flow reported as outlined by the Consolidated Standards of Reporting Trials (CONSORT) (Table 1).

Recruitment time frame

All potentially eligible women aged 18 to 70 years, regardless of parity, in need of adnexal surgery for benign gynaecological disease without exclusion criteria will be invited to participate in the trial. Only eligible women with written informed consent obtained before randomisation will be finally included in the NOTABLE trial.

We perform 36 interventions for adnexal surgery by laparoscopy for benign gynaecological disease at our Department of Gynaecology per year. The recruitment period of NOTABLE to meet the sample size will be approximately 2 years. Including the follow up period of 6 months after the LPLV (Last Patient Last Visit) and the time required to perform data analysis and reporting (6 months to 1 year) we estimate that the total study period will be at least 3 years.

Data collection

We will record the following patient characteristics at baseline: age, BMI, the number of vaginal births, previous abdominal or pelvic surgery (C-sections included), adnexal size, concomitant medication, dyspareunia questionnaire and the Short Sexual Functioning Scale (SSFS).

On the day of surgical intervention (day 0) we will record the following data: the duration of the surgical intervention, the successful removal of the adnexa by the technique as allocated without conversion to another technique with or without spilling (into the peritoneal cavity or the endobag), hospitalisation of the participant on the day of the surgical intervention based

on her own preference, the total dosage of analgesics used at the recovery and day care unit and the maximum VAS pain score on the day 0.

After one week at visit day 7 the outcome assessor will collect the pain scores as self-reported by the study participants twice daily from day 1 till day 7 using the VAS scale. The outcome assessor will also collect data on the total dosage of pain killers used during the first postoperative week.

At visit day 7 and day 42 the outcome assessor will record the following data: pelvic infection defined by lower abdominal pain with fever > 38°C and positive clinical signs or laboratory findings, readmission to hospital and the occurrence of other postoperative complications classified according to the Clavien- Dindo classification.

On month 3 and 6 following surgery the dyspareunia questionnaires, the EQ-5D-3L and the SSFS questionnaires will be filled in by the study participants and collected by regular mail. The management assistant will oversee this process and send reminders until all questionnaires have been received. We refer to Table 2 for an overview of the data collection process (Table 2).

DISCUSSION

Interpretation, limitations and generalisability

The NOTABLE trial is a randomised pilot study on the efficacy of the vNOTES technique. All surgical procedures in the NOTABLE study are done by one single surgeon (JB) who is equally skilled in using both techniques under comparison. The surgeon has been using the vNOTES approach since November 2013. During this two-year period the new technique and suitable instruments used were pilot-tested and subsequently fine-tuned by the usual "trial and error" method used for centuries in surgical practice (17). The feasibility and preliminary safety of the new technique were reported in three observational studies performed at our department (9, 10, 11) in accordance with the principles outlined in the three article series on the IDEAL statement (15-17). According to the terminology used by the IDEAL collaboration (17) this study should be classified as an IDEAL stage 2b trial. The full PICO research question is as follows: will a surgeon who is equally skilled at performing both techniques, and beyond his learning curve for the new technique (vNOTES), succeed in removing one or both adnexa in women with benign gynaecological disease at least as often with the new pilot-tested transvaginal NOTES approach compared to the standard transabdominal laparoscopic approach without having to convert to any other technique

NOTABLE aims to measure efficacy of vNOTES for removing one or both adnexa (can vNOTES work under ideal experimental conditions?). The NOTABLE trial does not address the effectiveness of the new intervention at this moment (does vNOTES work in a real life setting?). The conditions in NOTABLE are truly experimental and in many instances opposed to 'real life' practice: all women are always treated by the most experienced surgeon equally skilled in using both techniques, all women receive more attention during this trial than the routine care given during standard clinical practice, the dosage of anaesthetic drugs is calculated to limit any side effect (nausea and vomiting) that may cause women to be

hospitalized on the day of the surgical intervention, all outcomes measured are very relevant for women in general, participants with adverse outcomes (e.g. dyspareunia and sexual dysfunction) will be recalled after the end of the study for counselling and therapy, etc…The results of the NOTABLE trial will therefore have a limited generalisability and their interpretation will be done cautiously. The testing of the safety and the (cost-) effectiveness will be needed in the longer term using pragmatic multi-centre RCTs or a prospective register. As suggested by the IDEAL collaboration more research (large multicentre trials performed by adequately trained surgeons in centres of clinical excellence and large prospective registries cumulating data on the safety of the new technique over many years) and adequate surgical training will be needed before vNOTES can be offered as a standard daily care surgical practice by a majority of gynaecological surgeons for all women bound to undergo removal of one or both adnexa for benign gynaecological disease.

ETHICS AND DISSEMINATION

The NOTABLE trial will be conducted in accordance with the ethical principles outlined in the latest version of the "Helsinki Declaration", the "Guideline for Good Clinical Practice" and the Belgian Law of 7 May 2004 related to experiments on humans.

All eligible women wishing to participate in the study will receive a detailed patient information document about the study protocol, the aims of the research and the possible adverse events related to the surgical techniques. We will request written informed consent from all participants before randomization. The principal investigator (JB) and the coordinating investigator (JJAB) will obtain these consents during a study intake. An adapted informed consent form (Appendix 1) was drafted based on the template proposed by the Federal Agency for Medicines and Health Products (FAMHP) for clinical research in Belgium (28).

The protocol of the NOTABLE trial is registered in ClinicalTrials.gov of the US National Institutes of Health as NCT02630329 (Appendix 2). The study protocol (Appendix 3) and the informed consent documents have been approved by the Ethics Committee of the Imelda Hospital Bonheiden (registration number 689), Belgium on December 1, 2015. The written approval with the Belgian unique study identifier B689201526268 was sent to the FAMHP in Brussels. All substantial protocol modifications will be communicated to all trial participants, the hospital's Ethics Committee, ClinicalTrials.gov, and the FAMHP.

The NOTABLE trial is a non-commercial and investigator-driven study. The investigators have taken out an insurance policy for medicolegal responsibility related with the conduct of the study from 01.12.2015 until 30.05.2018 in accordance with Article 29 of the Belgian Law of 7 May 204 related to experiments on humans.

The clinical research forms and all other study-related documents will be stored securely at the study site in locked file cabinets in an area with limited access. All records that contain

names or other personal identifiers will be stored separately from study records identified by a code number. Data collection, storage and dissemination will be in accordance with the Belgian Law of 8 December 1992 on the protection of privacy in relation to the processing of personal data and by the Law of 22 August 2002 on patient rights.

At the end of the NOTABLE trial the complete final data set will be accessible to all trial investigators (the nine authors of the study protocol).

Offering the surgical intervention identified as being most effective or most advantageous after the final analysis of the study data to those women that were allocated to the least effective technique is by nature of the surgical intervention not always possible except for women who had a unilateral surgical intervention. As part of good clinical practice, we will offer post-trial care to women with identified adverse events.

The investigators declare that they have no conflict of interest with respect to the present research.

The NOTABLE trial results will in all circumstances be disseminated through scientific journals and at scientific conference presentations regardless of any positive or negative outcome in relation with the predefined study hypothesis is refuted by the data. All trial investigators will contribute to authorship, following the International Committee of Medical Journal Editors (ICMJE)'s authorship eligibility guidelines.

FOOTNOTES

Twitter: follow Jan Bosteels at @BosteelsJan.

E-mail: NOTES@imelda.be

Contributors JB is the surgeon responsible for all interventions in all study participants. JBo is the outcome assessor. JB and JJAB conceived the study. PDM and IL are responsible for the draft of the pain protocol and the anaesthesia for all trial participants. JJAB, JB, PDM and IL will be responsible for data collection, quality analysis and storage. PE provided expertise for the sexuality research involved in this clinical trial design. SW provided external review as a content expert. CM provided external peer review on the scientific conduct of the study. AL is responsible for the biostatistics involved in the design and conduct of the trial. She has reviewed the SAP (Statistical Analysis Plan) of both HALON and NOTABLE. She will perform all data analysis for both studies without any involvement of the surgeon (JB) and the outcome assessor (JJAB). BWM provided external peer review as a methodology expert. All the authors contributed to the refinement of the study protocol and approved the final manuscript. For the economic analyses we will seek assistance from a Health Economist at the University of Ghent or at the Belgian Health Care Knowledge Centre.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval Ethics Committee Imelda hospital Bonheiden, protocol number B689201526268, 01/12/2015.

Provenance and peer review Not commissioned; externally peer reviewed.

Table 1

CONSORT 2010 Flow Diagram

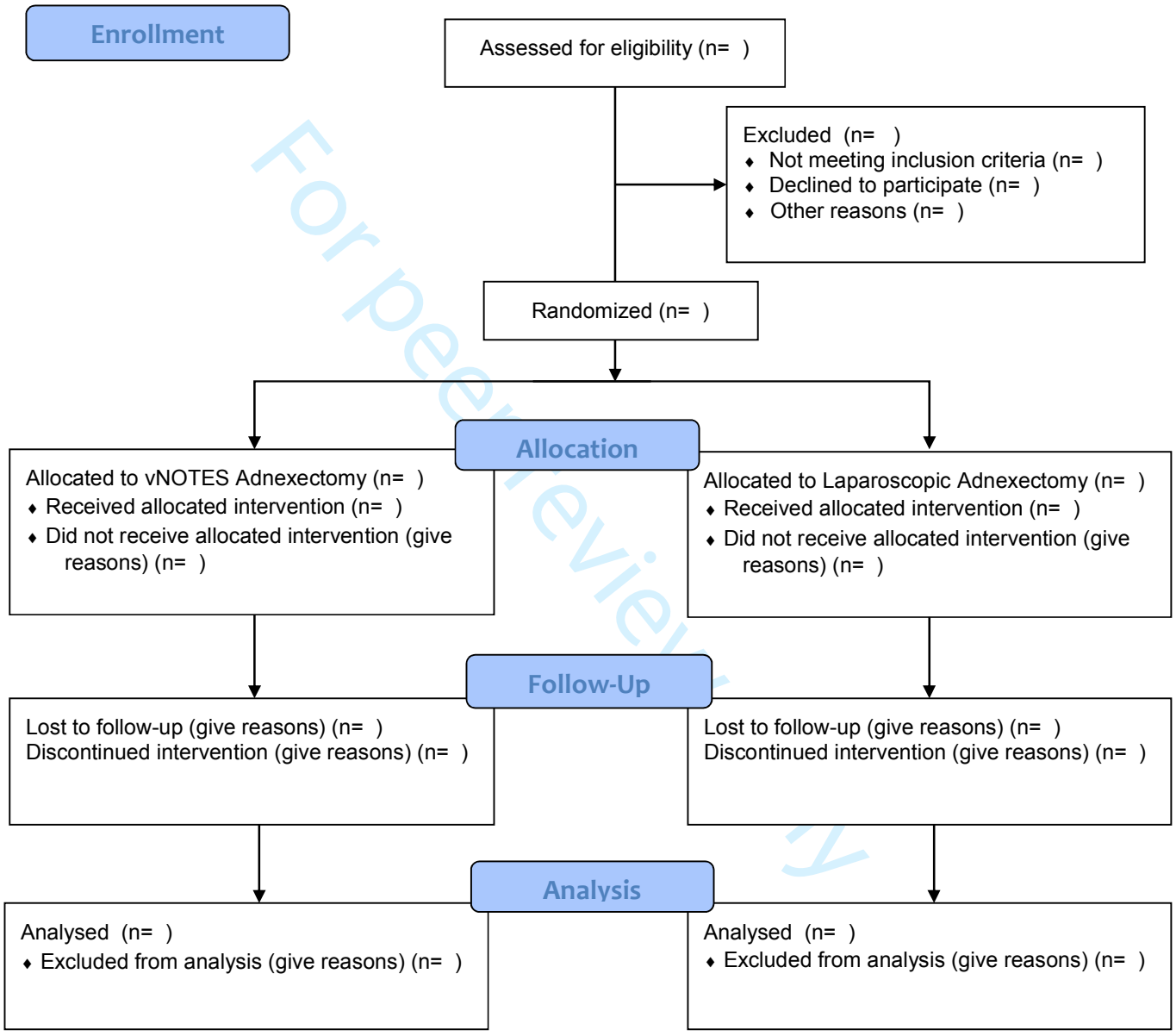


Table 2

Table 2 Patient's characteristics and data collection													
Data collection	**Days**												
	BL*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**42**		**3 m**	**6m**
Age	X												
BMI**	X												
Uterine volume	X												
Concomitant medication	X	X	X	X	X	X	X	X	X	X			
Dyspareunia: frequency and intensity	X											X	X
SSFS***	X											X	X
Health related quality of life	X											X	X
Duration of surgery		X											
Successful removal		X											
Admission in hospital (for at least one night)		X											
Total amount of analgesics used		X	X	X	X	X	X	X	X				
VAS score****		X	X	X	X	X	X	X	X				
Readmission within six weeks										X			
Pelvic infection									X	X			
Other postoperative complications		X							X	X			
Direct and indirect costs (up to 6 weeks after surgery)										X			

* BL: baseline

** BMI: Body Mass Index

*** SSFS: Short Sexual Functioning Scale

**** VAS: Visual Analogue Scale

REFERENCES

1. Kalloo AN, Singh VK, Jagannath SB, et al. Flexible transgastric peritoneoscopy: a novel approach to diagnostic and therapeutic interventions in the peritoneal cavity. *Gastrointest Endosc* 2004; 60:114-7.

2. Rao GV, Reddy DN, Banerjee R. NOTES: Human experience. *Gastrointest Endosc Clin N Am* 2008; 18: 361–70.

3. Rolanda C, Lima E, Pêgo JM, et al. Third-generation cholecystectomy by natural orifices: transgastric and transvesical combined approach. *Gastrointest Endosc*. 2007; 65: 111-7.

4. Rattner D, Kalloo A. ASGE/SAGES working group on natural Orifice transluminal endoscopic surgery. *Surg Endosc* 2006; 20:329-33.

5. Santos BF, Hungness ES. Natural orifice translumenal endoscopic surgery: progress in humans since white paper. *World J Gastroenterol* 2011; 17:1655–65.

6. Tolcher MC, Kalogera E, Hopkins MR, et al. Safety of Culdotomy as a Surgical Approach: Implications for Natural Orifice Transluminal. *JSLS* 2012; 16:413–20

7. Uccella S, Cromi A, Bogani G, et al. Transvaginal specimen extraction at laparoscopy without concomitant hysterectomy: our experience and systematic review of the literature. *J Minim Invasive Gynecol* 2013; 20:583-90.

8. Lee CL, Wu KY, Su H, Ueng SH, Yen CH. Transvaginal Natural-Orifice Transluminal Endoscopic Surgery (NOTES) in Adnexal Procedures. *JMIG*. 2012;19: 509–513.

9. Reynders A, Baekelandt J. Adnexectomy by Poor Man's Transvaginal NOTES. Gynecological Surgery 2015; 12(3): 207-11.

10. Van Peer S, Baekelandt J. Natural orifice transluminal endoscopic surgery (NOTES) salpingectomy for ectopic pregnancy: a first series demonstrating how a new surgical technique can be applied in a low-resource setting. *Gynecol Surg* 2015; 12: 299-302.

11. Baekelandt J. Total Vaginal NOTES Hysterectomy: A New Approach to Hysterectomy. *J Minim Invasive Gynecol* 2015; 22:1088-94.

12. Baekelandt J, De Mulder PA, Le Roy I, et al. HALON –hysterectomy by transabdominal laparoscopy or natural orifice transluminal endoscopic surgery: a randomised controlled trial (study protocol). *BMJ Open* 2016; 6:e011546. Doi: 10.1136/bmjopen-2016-011546.

13. Shamseer L, Moher D, Clarke M, et al., the PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015; 349: g7647.

14. http://www.crd.york.ac.uk/prospero/

15. Barkun JS, Aronson JK, Feldman LS, et al., for the Balliol Collaboration. Evaluation and stages of surgical innovations. *The Lancet* 2009; 374:1089-96.

16. Ergina PL, Cook JA, Blazeby JM, et al., for the Balliol Collaboration. Challenges in evaluating surgical innovation. *The Lancet* 2009; 374:1097-1104.

17. Mc Culloch P, Altman DG, Campbell WB, et al., for the Balliol Collaboration. No surgical innovation without evaluation: the IDEAL recommendations. *The Lancet* 2009; 374:1105-12.

18. Gargon E, Gurung B, Medley N, et al. Choosing Important Health Outcomes for Comparative Effectiveness Research: A Systematic Review. *PLoS ONE* 2014; 9(6): e99111.

19. http://www.comet-initiative.org/studies/searchresults?

20. Todd KH, Funk KG, Funk JP, et al. Clinical significance of reported changes in pain severity. *Ann Emerg Med* 1996; 27: 485-9.

21. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; 240**:** 205–13.

22. Aerts L, Enzlin P, Verhaeghe J, et al. Psychologic, relational, and sexual functioning in women after surgical treatment of vulvar malignancy: a prospective controlled study. *Int J Gynecol Cancer* 2014; 24: 372-80.

23. Moseley JB, O'Malley K, Petersen NJ, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med* 2002; 347: 81-8.

24. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987; 317: 141-5.

25. Wang PH, Lee WL, Juang CM, Tsai WY, Chao HT, Yuan CC. Excision of mature teratoma using culdotomy, with and without laparoscopy: A prospective randomized trial. BJOG 2001; 108: 91-4.

26. Schmitt A, Crochet P, Knight S, Tourette C, Loundou A, Agostini A. Single Port Laparoscopy Versus Conventional Laparoscopy in Benign Adnexal Diseases: a Systematic Review and Meta-Analysis., *J Minim Invasive Gynecol* 2017, ISSN 1553-4650, http://dx.doi.org/10.1016/j.jmig.2017.07.001.

27. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomized Trials. *Ann Intern Med.* 2010; 152: 1-8.

28. www.afmps.be

Opdrachtgever: Afdeling Verloskunde/Gynaecologie Imeldaziekenhuis Bonheiden
Onderzoeksinstelling: Afdeling Verloskunde/Gynaecologie Imeldaziekenhuis Bonheiden
Comité voor Medische Ethiek: Commissie Medisch Ethiek Imeldaziekenhuis Bonheiden
Lokale artsen-onderzoekers: Dr Jan Baekelandt en Dr Jan Bosteels, Imeldaziekenhuis Bonheiden, tel 015 505011
Studie secretaresse: Mevrouw Sofie De Wit, Imeldaziekenhuis Bonheiden, tel 015 505926

I Noodzakelijke informatie voor Uw beslissing om deel te nemen aan de NOTABLE studie

Inleiding

U wordt uitgenodigd om deel te nemen aan een klinische studie voor het vergelijken van twee technieken voor het verwijderen van een goedaardige eierstokcyste.

De artsen-onderzoekers hopen dat deze blind vergelijkende studie voordelen kan bieden voor de behandeling van patiënten die getroffen zijn door dezelfde aandoening als u. Er is evenwel geen enkele garantie dat Uw deelname aan deze studie U voordeel zal opleveren.

Voordat U beslist over Uw deelname aan deze studie willen we U wat meer informatie geven over wat dit betekent op organisatorisch vlak en wat de eventuele voordelen en risico's voor U zijn. Zo kan U een beslissing nemen op basis van de juiste informatie. Dit wordt "geïnformeerde toestemming" genoemd.

Wij vragen U de volgende pagina's met informatie aandachtig te lezen. Hebt U vragen, dan kan U terecht bij de arts-onderzoeker of zijn of haar vertegenwoordiger. Dit document bestaat uit drie delen: essentiële informatie die U nodig heeft voor het nemen van Uw beslissing, Uw schriftelijke toestemming en bijlagen waarin U meer details terugvindt over bepaalde onderdelen van de basisinformatie.

Als U aan de NOTABLE studie deelneemt, dient U het volgende te weten:

- Deze klinische studie wordt opgestart na evaluatie door één of meerdere ethische comité(s).
- Uw deelname is vrijwillig; er kan op geen enkele manier sprake zijn van dwang. Voor deelname is Uw ondertekende toestemming nodig. Ook nadat U hebt getekend, kan u de arts-onderzoeker laten weten dat U Uw deelname wilt stopzetten. De beslissing om al dan niet (verder) deel te nemen zal geen enkele negatieve invloed hebben op de kwaliteit van de zorgen noch op de relatie met de behandelende arts(en).
- De gegevens die in het kader van Uw deelname worden verzameld, zijn vertrouwelijk. Bij de publicatie van de resultaten is Uw anonimiteit verzekerd.
- Er worden U geen bijkomende kosten aangerekend voor specifieke behandelingen, bezoeken / consultaties, onderzoeken in het kader van dit onderzoek. De uitgevoerde chirurgische procedures worden terugbetaald in het kader van de ziekteverzekering.
- Eventuele schade opgelopen in het kader van Uw deelname aan deze klinische studie valt onder de verzekeringspolis van Uw behandelende arts. Omdat het een niet-commerciële studie betreft, werd hiervoor een bijkomende verzekeringspolis afgesloten met de verzekeringsmaatschappij van de behandelende hoofdonderzoeker.
- Indien U extra informatie wenst, kan U altijd contact opnemen met de arts-onderzoekers of een medewerker van hun team.

Aanvullende informatie over Uw rechten als deelnemer aan een klinische studie kan U bekomen via de ombudsdienst van het Imeldaziekenhuis te Bonheiden bij mevrouw Ilse Creemers bereikbaar via telefoon 015 505015 of via e-mail ombudsdienst@imelda.be.

Doelstelling en beschrijving van het studieprotocol

Wij nodigen U uit om deel te nemen aan een klinische studie inzake de klassieke laparoscopische (via de navel in de buikwand) vergeleken met de transvaginale (doorheen de vagina) verwijdering van één of beide adnexen (eierstok én eileider) bij vermoeden van een goedaardige cyste van één of beide eierstokken bij ongeveer 66 vrouwelijke deelnemers in België.

Alle vrouwen met een op echografie vermoede goedaardige cyste van één of beide eierstokken kunnen deelnemen aan de studie ongeacht de leeftijd en het aantal bevallingen in de voorgeschiedenis. Deelname aan deze studie is niet mogelijk bij een voorgeschiedenis van verwijdering van de baarmoeder, heelkunde aan de endeldarm, endometriose van het rectovaginaal septum, vermoeden van eierstokkanker, voorgeschiedenis van PID of pelvien abces, actieve genitale infectie of vrouwen die nog nooit sexueel contact hebben gehad. Zwaarlijvigheid, nulliparitеit (nooit eerder langs natuurlijke weg bevallen) of grootte van de cyste zijn dan weer geen reden tot uitsluiten van deelname aan de studie.

Het is een gerandomizeerde studie die een alternatieve toegangsweg (NOTES transvaginaal) vergelijkt met de huidige gouden standaard van de klassieke transabdominale laparoscopische toegangsweg voor het verwijderen van één of beide adnexen (eierstok met eileider). In een eerdere pilootstudie werd de technische haalbaarheid van deze transvaginale toegangsweg beschreven. Deze gevallenreeks verzamelde de gegevens van 20 uitgevoerde procedures.Het bleek mogelijk om op een veilige manier cysten te verwijderen tot een doormeter van 11 cm. Men observeerde lagere pijnscores bij vrouwen behandeld via deze nieuwe toegangsweg. De hypothese van deze studie is dat de nieuwe techniek minstens even succesvol is dan de klassieke gouden standaard maar het voordeel zou kunnen bieden dat meer vrouwen die via de nieuwe techniek werden behandeld zelf zouden verkiezen om dezelfde dag van de ingreep naar huis terug te keren vergeleken met de standaardtechniek. Een tweede bijkomend voordeel zou kunnen zijn dat vrouwen behandeld met de nieuwe techniek minder pijn hebben vergeleken met de gouden standaard. In deze studie zal via een techniek van randomizatie worden beslist of een deelnemer behandeld wordt op de klassieke wijze dan wel via de nieuwe techniek. De ingreep wordt uitgevoerd door één chirurg die een even grote ervaring heeft in het uitvoeren van beide technieken. De studie verloopt geblindeerd voor de deelnemers en de effect beoordeelaars. Het meten van pijn is namelijk subjectief en kan worden verstoord wanneer de deelnemer aan de studie of de effectbeoordeelaar voorkennis heeft van de uitgevoerde procedure. In alle gevallen wordt daarom een insnede aangebracht in de navel zodat niemand behalve de chirurg weet welke ingreep werd uitgevoerd. Indien deze methodiek niet zou worden toegepast, zou het uiteiendelijk nooit mogelijk zijn om betrouwbaar de doeltreffendheid van de nieuwe techniek versus de standaardtechniek te vergelijken. Het oplossen van deze onzekerheid is net de hoofdbedoeling van de huidige studie. Na het uitvoeren van de ingreep wordt standaard medische en verpleegkundige zorg toegediend (antibiotica, pijnstilling, wondzorg,...). Deze is identiek in beide groepen. De avond van de ingreep komt de coördinerende onderzoeker (Dr Bosteels) langs om te vragen of U zich in staat voelt om naar huis te gaan. Deze beslissing wordt uitsluitend door U genomen. Uiteraard toetst de coördinerende onderzoeker deze beslissing aan de gegevens van temperatuur, pols, bloeddruk en urinedebiet (de zogenaamde vitale parameters). Bij twijfel wordt met U overlegd en wordt altijd beslist in het belang van Uw gezondheid. Uw deelname gaat dan onverminderd verder. U krijgt een formulier mee met beschrijving van mogelijke alarmsymptomen die dringend medisch nazicht via spoedgevallen vereisen. U ontvangt ook een lijst met telefoonnummers voor contact. Gedurende één week wordt U gevraagd om ’s morgens en ’s avonds de pijn zoals U die beleeft aan te geven via een score (de VAS pijnscore) via een meetlatje. Een pijnverpleegkundige zal U uitleg geven hoe U deze metingen dient uit te voeren en te noteren in het pijndagboek. Bij ontslag wordt U ook een afspraak gegeven voor een kontrole onderzoek na één week bij één van de twee hoofdonderzoekers. U mag gedurende 4 weken na de ingreep geen sexueel contact hebben. Er wordt tijdelijke werkonbekwaamheid voorgeschreven voor één maand. Een postoperatief kontrole onderzoek is voorzien na 6 weken. Bij aanvang van de studie en op 3 en 6 maanden na de ingreep moet U een zelfbeoordeling aangeven van pijn bij sexueel contact via een standaard vragenlijst. Tevens kan U een anonieme vragenlijst invullen voor het meten van het sexueel welbevinden bij aanvang van de studie en op 3 en 6 maanden: omdat deze vragenlijst gevoelige vragen bevat is het invullen ervan facultatief. Dit bekent dat het U vrij staat om deze vragenlijst wel of niet in te vullen zonder dat dit het verdere verloop van de studie of de kwaliteit van de toegediende zorg beïnvloedt.

Verloop van de studie

Uw deelname aan de studie neemt 6 maanden in beslag en omvat één bijkomende raadpleging vergeleken met een behandeling zonder deelname aan de studie.

Er worden geen bijkomende procedures vereist in het kader van de studie.

In het kader van Uw deelname aan de studie en rekening houdend met Uw medische situatie, zal de meerderheid van de bezoeken en onderzoeken die we zullen beschrijven, deel uitmaken van de standaardzorgen in ons ziekenhuis terwijl slechts één bijkomend bezoek wordt vereist in het kader van deze studie, namelijk de postoperatieve kontrole na één week.

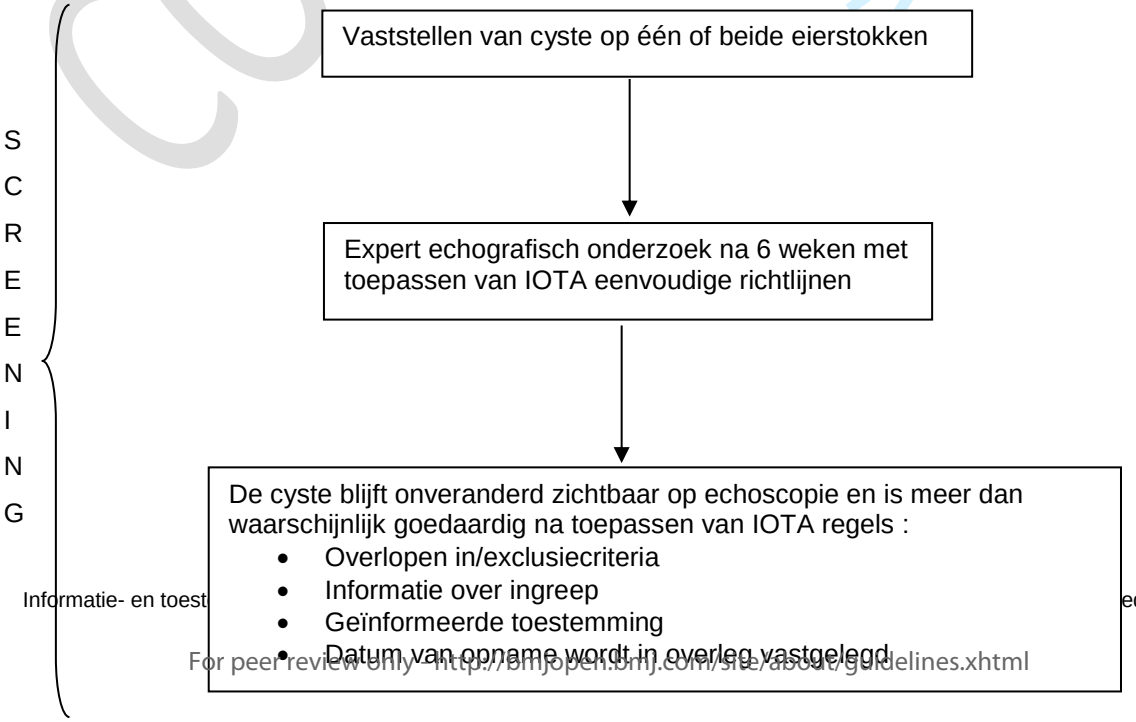
Screeningsfase: Bij een eerste raadpleging wordt de aanwezigheid van een cyste op één of beide eierstokken vastgesteld. De standaard praktijk is om de blijvende aanwezigheid van deze cyste te herkontroleren na 6 weken door een expert onderzoeker in de echografie. Blijkt de cyste blijvend aanwezig te zijn dan wordt tijdens het bezoek aan één van de beide lokale onderzoekers waarop de beslissing genomen om één of beide eierstokken te verwijderen overlopen of U voldoet aan de voorwaarden om te mogen deelnemen aan de studie (de in- en exclusiecriteria). De datum voor de geplande ingreep wordt vastgelegd. Het formulier voor geïnformeerde toestemming wordt ondertekend.

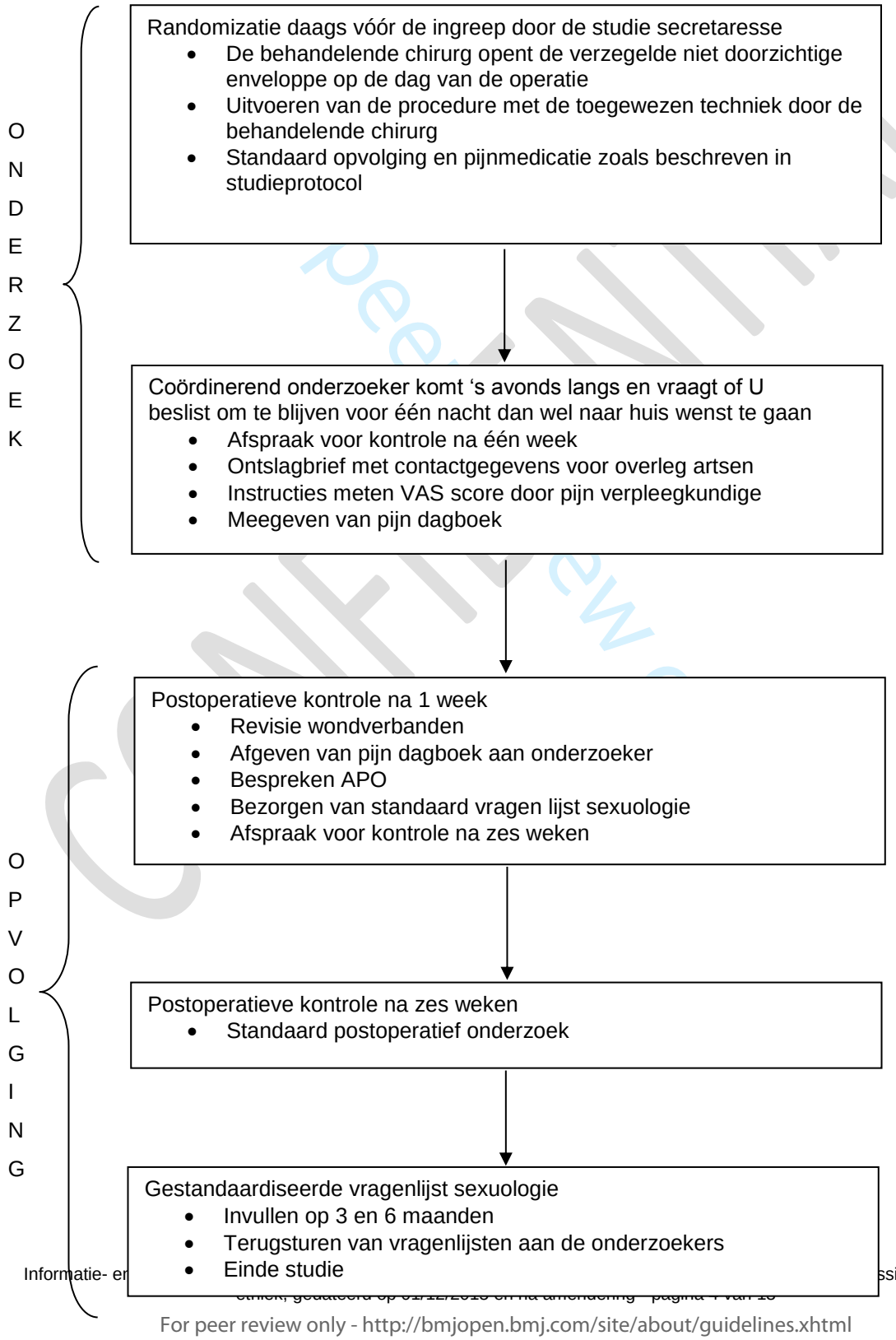
Onderzoeksfase: de nodige preoperatieve onderzoeken zijn deze welke volgens Uw leeftijd en voorgeschiedenis zijn vastgelegd in het werkdocument opgesteld door de dienst anesthesie. Deze kunnen voorafgaandelijk aan de ingreep door de huisarts worden uitgevoerd.De studie vereist geen bijkomende preoperatieve onderzoeken in vergelijking met de situatie waarin U zou hebben beslist om niet deel te nemen aan deze studie. U kan steeds uit vrije wil beslissen om niet langer deel te nemen aan de studie ook nadat U hiervoor Uw toestemming had gegeven. In dit geval wordt U steeds de standaard zorg verstrekt die dezelfde is als deze die U zou hebben ontvangen wanneer U had beslist om niet aan de studie deel te nemen. De studie wordt beëindigd na zes maanden. Op dat moment kan U van de hoofdonderzoeker (Dr Baekelandt) vernemen via welke techniek de ingreep werd uitgevoerd. Het eerder vrijgeven van deze informatie kan enkel om dringende medische redenen. In dergelijk dringend geval kan Uw deelname aan de studie voor het meten van de studie uitkomsten onveranderd doorgaan tenzij U op vrijwillige basis zou beslissen om verdere deelname aan de studie stop te zetten.

Opvolgingsfase: gedurende één week meet U thuis zelf s'morgens en 's avonds de VAS pijnscores en noteert U het gebruik van bijkomende pijnstillende medicatie met vermelding van naam, dosis en wijze van inname. Na één week en na zes weken volgen postoperatieve kontroles bij de onderzoekers. Op drie en zes maanden wordt U gevraagd om een door een universitair werkzame sexuoloog opgestelde standaard vragen lijst in te vullen en onder gesloten omslag met vermelding van "medisch geheim-verttrouwelijk" terug te zenden naar de onderzoekers.

De studie is volledig beëindigd wanneer U de vragenlijst op 6 maanden hebt teruggestuurd.

Indien u besluit deel te nemen aan de studie en aan alle voorwaarden voor deelname voldoet, ziet het schema van het verloop van Uw deelname aan de NOTABLE studie er uit als volgt:





Risico's en ongemakken

A: Verwikkelingen van de vNOTES en laparoscopische techniek

Verwikkelingen tijdens en na minimaal invasieve chirurgie of MIS waartoe zowel de nieuwe vNOTES als de klassieke laparoscopische procedure behoren zijn zeldzaam. In een prospectief onderzoek gepubliceerd door Nederlandse onderzoekers werden 145 verwikkelingen vermeld bij 25 764 laparoscopische ingrepen (1). Ook een groot Fins onderzoek rapporteerde minder dan 1% verwikkelingen na laparoscopische chirurgie (2).

De kansen op onderstaande verwikkelingen zijn als volgt:

- Tijdens de operatie:

- bloeding (slag)ader buikwand: 15 per 10 000 ingrepen
- letsel aan darm of maag: 11 per 10 000 ingrepen
- bloeding (slag) ader buikholte: 10 per 10 000 ingrepen
- bloeding vliezen rond eileider: 9 per 10 000 ingrepen
- blaasletsel: 2 per 10 000 ingrepen
- baarmoederletsel: 1 per 10 000 ingrepen
- laseraccident: 1 per 10 000 ingrepen
- overige: <1 per 10 000 ingrepen

- Na de operatie:

- abces: 35 per 100 000 ingrepen
- breuk: 8 per 100 000 ingrepen
- longembool: 4 per 100 000 ingrepen
- overlijden: 8 per 100 000 ingrepen

Ook is het mogelijk dat zich andere risico's en ongemakken voordoen die op dit moment nog onbekend zijn. Het is daarom van groot belang om elke nieuwe gezondheidsklacht zo snel mogelijk aan de arts-onderzoeker te melden, ongeacht of de klacht volgens U of Uw huisarts te maken heeft met de studie of niet.

B: Contraceptie, zwangerschap en borstvoeding

U mag niet deelnemen aan deze studie als u zwanger bent.Indien u kiest om aan deze studie deel te nemen, dient u gebruik te maken van één van de erkende contraceptiemethoden (om te voorkomen dat u zwanger wordt). Uw arts zal met u de verschillende doeltreffende opties bespreken.

C: Risico's in verband met de evaluatieprocedures in het kader van de studie.

Er zijn geen risico's/ongemakken verbonden aan de bijkomende kontrole één week na de ingreep die in het kader van de studie zal plaatsvinden. Het betreft een gebruikelijk klinisch onderzoek gelijkaardig aan het gewone preventief jaarlijks gynaecologisch onderzoek waarmee U waarschijnlijk voldoende vertrouwd bent.

(1) Jansen FW, Kapiteyn K, Trimbos-Kemper T, Hermans J, Trimbos-Kemper JB. Complications of laparoscopy: a prospective multicenter observational study. Br J Obstet Gynaeco 1997; 104: 595-600.

(2) Harkki-Siren P, Sjoberg J, Kurki T. Major complications of laparoscopy : a follow-up Finnish study. Obstet Gynecol 1999;94:94–98.

Melding van nieuwe informatie

Het is steeds mogelijk dat er tijdens het verloop van een klinische studie belangrijke nieuwe informatie over de transvaginale NOTES procedure beschikbaar wordt zoals dit het geval kan zijn met iedere klinische interventie studie. De onderzoekers verbindt er er zich toe om U desgevallend op de hoogte te brengen van nieuwe belangrijke informatie die een invloed kan hebben op Uw beslissing om Uw deelname aan de studie voort te zetten.

In dat geval zal men U vragen ofwel om een aanvulling bij de toestemmingsverklaring te ondertekenen ofwel om een nieuw informatie- en toestemmingsdocument te ondertekenen. Indien U in het licht van de nieuwe belangrijke informatie zou besluiten om Uw deelname aan de studie te beëindigen, zal Uw arts-onderzoeker erop toezien dat U ook nadien op de best mogelijke wijze behandeld wordt.

Voordelen

Indien U besluit om deze studie deel te nemen, kan de transvaginale NOTES techniek al dan niet gunstig blijken te zijn voor de behandeling van Uw aandoening, het verminderen van de symptomen ervan of het bespoedigen van het pijnvrije herstel na de ingreep.

De informatie, die dankzij dit onderzoek verkregen wordt, kan bijdragen tot een betere kennis van het gebruik van deze vernieuwende chirurgische techniek of tot de ontwikkeling van de NOTES transvaginale chirurgie voor de behandeling van gelijkaardige goedaardige gynaecologische aandoeningen bij toekomstige patiënten.

Andere behandelingen

Het meest gebruikte alternatief voor de nieuwe transvaginale vNOTES techniek is de laparoscopische techniek. Hierbij wordt via een kleine insnede via of onder het navellitteken een laparoscoop of kijkbuis ingebracht die toelaat om de bij U geplande heelkundige behandeling-het operatief verwijderen van één of beide eierstokken voor een goedaardige eierstokcyste- uit te voeren onder rechtstreeks zicht. Deze laparoscopische techniek vervangt de oudere klassieke open of laparotomische techniek, die heden hoofdzakelijk nog omwille van eierstokkanker of heel volumineuze eierstokcysten wordt toegepast.

De arts-onderzoeker zal deze alternatieve behandeling die als standaard klinische praktijk steeds in de controlegroep wordt toegepast eveneens met U bespreken.

Stopzetting van de deelname

Stopzetting van de deelname betekent simpelweg dat U als deelnemer Uw "praktische" deelname stopzet omdat U de aan de studie verbonden verplichtingen te zwaar vindt, de bijwerkingen te onaangenaam vindt of andere.

De deelname kan ook door de arts-onderzoeker worden stopgezet om veiligheidsredenen (evolutie van de ziekte) of andere redenen. Dit wil niet zeggen dat U als deelnemer Uw toestemming inzake de verzameling van aanvullende gegevens stopzet (indien U de arts-onderzoeker blijft bezoeken, die vaak ook Uw verwezen arts is voor de ziekte die in het kader van de klinische studie wordt behandeld).

Intrekking van de toestemming tot de studie betekent dat de deelnemer zijn/haar toestemming tot deelname aan de studie effectief intrekt. Dit kan zonder opgave van redenen en het kan betekenen dat de deelnemer zijn/haar toestemming inzake de verwerking van zijn/haar gezondheidsgegevens intrekt.

Uw deelname is vrijwillig. U hebt steeds het recht om Uw deelname aan de studie om eender welke reden en zonder opgave van redenen stop te zetten. Wel kan het voor de arts-onderzoeker en de opdrachtgever nuttig zijn om te weten of U zich terugtrekt omdat de aan de studiebehandeling verbonden beperkingen te zwaar zijn (bijvoorbeeld te veel onaangename bijwerkingen, te veel follow-up bezoeken).

Het is ook mogelijk dat de arts-onderzoeker Uw deelname aan de studie stopzet omdat hij van mening is dat dit beter is voor Uw gezondheid of omdat hij vaststelt dat U zich niet aan de voorschriften voor deelname houdt.

Ook gebeurt het soms dat de bevoegde nationale of internationale autoriteiten, de ethische comités die aanvankelijk goedkeuring hadden gegeven voor de studie of de opdrachtgever de studie stopzetten omdat uit de verzamelde informatie blijkt dat de behandeling niet werkt (de gezondheid van de deelnemers verbetert niet voldoende) of dat de onderzochte behandeling meer of ernstigere bijwerkingen veroorzaakt dan verwacht of voor een andere reden zoals bijvoorbeeld de beslissing om de studie en de ontwikkeling van het onderzochte studiegeneesmiddel stop te zetten.

Behandeling na stopzetting van de studie

In alle situaties waarbij de deelname aan de studie wordt stopgezet, maar ook wanneer de studie volgens planning is afgerond, zal Uw arts-onderzoeker Uw gezondheid onderzoeken en U de beste behandeling die beschikbaar is voorschrijven.

Biologische stalen die tijdens de studie worden afgenomen

De verwijderde weefsels worden volgens standaard klinische praktijk onderzocht op het labo pathologische ontleedkunde voor het microscopisch bevestigen van de goedaardigheid van de vastgestelde eierstokcyste. Hetzelfde geldt voor andere weefselvochten of biopsies. Deze worden standaard afgenomen als onderdeel van de behandeling (verwijderen van één of beide eierstokken) en deze praktijk zou ook worden toegepast indien U geen toestemming zou hebben gegeven voor deelname aan de studie.

Indien u aan deze studie deelneemt, vragen wij u het volgende:

- Tenvolle mee te werken voor een correct verloop van de studie.
- Geen informatie over Uw gezondheidstoestand, de geneesmiddelen die U gebruikt of de symptomen die U ervaart te minimaliseren of zelfs te verzwijgen.
- Niet deel te nemen aan een andere klinische studie met een experimentele behandeling - ongeacht of het een studiegeneesmiddel, medisch hulpmiddel of een procedure betreft- tijdens Uw deelname aan de huidige studie.
- Steeds uw “deelnemerskaart” bij u dragen. Dit is verplicht voor Uw veiligheid indien U een spoedbehandeling moet ondergaan in een ziekenhuis waar men U niet kent. Deze kaart vermeldt tevens de contactgegevens van de behandelende onderzoekers.

U moet eveneens weten dat:

het voor Uw veiligheid aangewezen is om Uw huisarts of andere behandelende artsen die bij Uw behandeling betrokken zijn te informeren over Uw deelname aan deze studie. Wij vragen U eveneens om hiervoor Uw toestemming te geven. Indien U echter niet wenst dat zij hierover worden geïnformeerd om welke reden ook, zullen wij Uw keuze respecteren.

Contact

Als U bijkomende informatie wenst, maar ook ingeval van problemen of als U zich zorgen maakt, kan U contact opnemen met de arts-onderzoekers Dr Jan Baekelandt of Dr. Jan Bosteels of de studiesecretaresse via de op de deelnemerskaart aangegeven contactgegevens of via het centraal telefoonnumer van het Imeldaziekenhuis (015 505011) of het onthaal van de dienst spoedgevallen buiten de klassieke werkuren (015 505040).

In geval van nood, kan U contact opnemen met de dienst spoedgevallen op het telefoonnummer 015 505040.

Buiten de consultatie-uren moet u zich aanmelden op de spoedafdeling van Uw ziekenhuis en vermelden dat U deelneemt aan een klinische studie. Uw dossier zal nuttige informatie bevatten voor de behandelde arts met betrekking tot de studie.

Als U vragen hebt met betrekking tot Uw rechten als deelnemer aan de studie, kan U contact opnemen met de ombudsdienst van het Imeldaziekenhuis (Mevrouw Ilse Creemers) op het telefoonnummer: 015 505015. Indien nodig kan de ombudsvrouw U in contact brengen met het Ethisch Comité

Titel van de studie: **NOTES adnexectomie voor benigne aandoeningen vergeleken met laparoscopische excisie**

II Geïnformeerde toestemming

Deelnemer

Ik verklaar dat ik geïnformeerd ben over de aard, het doel, de duur, de eventuele voordelen en risico's van de studie en dat ik weet wat van mij wordt verwacht. Ik heb kennis genomen van het informatiedocument en de bijlagen ervan.

Ik heb voldoende tijd gehad om na te denken en met een door mij gekozen persoon, zoals mijn huisarts of een familielid, te praten.

Ik heb alle vragen kunnen stellen die bij me opkwamen en ik heb een duidelijk antwoord gekregen op mijn vragen.

Ik begrijp dat mijn deelname aan deze studie vrijwillig is en dat ik vrij ben mijn deelname aan deze studie stop te zetten zonder dat dit mijn relatie schaadt met het therapeutisch team dat instaat voor mijn gezondheid.

Ik begrijp dat er tijdens mijn deelname aan deze studie gegevens over mij zullen worden verzameld en dat de arts-onderzoeker en de opdrachtgever de vertrouwelijkheid van deze gegevens verzekeren overeenkomstig de Belgische wetgeving ter zake.

Ik stem in met de verwerking van mijn persoonlijke gegevens volgens de modaliteiten die zijn beschreven in de rubriek over het verzekeren van de vertrouwelijkheid. Ik geef ook toestemming voor de overdracht naar en verwerking van mijn gecodeerde gegevens in andere landen dan België.

Ik ga ermee akkoord / Ik ga er niet mee akkoord (doorhalen wat niet van toepassing is) dat de studiegegevens die voor de hier vermelde studie worden verzameld, later zullen worden verwerkt, op voorwaarde dat deze verwerking beperkt blijft tot de context van de hier vermelde studie voor een betere kennis van de ziekte en de behandeling ervan.

Ik ga ermee akkoord / Ik ga er niet mee akkoord (doorhalen wat niet van toepassing is) dat mijn huisarts en andere specialisten die betrokken zijn bij mijn behandeling op de hoogte worden gesteld van mijn deelname aan deze klinische studie.

Ik heb een exemplaar ontvangen van de informatie aan de deelnemer en de geïnformeerde toestemming.

Naam, voornaam, datum en handtekening van de deelnemer

Wettelijke vertegenwoordiger

Ik verklaar dat men mij heeft geïnformeerd over de vraag om een beslissing te nemen over deelname aan de klinische studie door de persoon die ik in diens beste belang vertegenwoordig, rekening houdend met zijn of haar mogelijke wens. Mijn toestemming is van toepassing op alle items opgenomen in het toestemmingsformulier voor de deelnemer.

Ik ben eveneens geïnformeerd dat zodra de klinische situatie het toelaat, de persoon die ik vertegenwoordig op de hoogte zal worden gesteld van zijn/haar deelname aan een klinisch studie en op dat moment vrij is om toestemming te geven voor een verdere deelname of om deelname stop te zetten door het huidige toestemmingsformulier al dan niet te ondertekenen

Ik heb een exemplaar ontvangen van de informatie aan de deelnemer en de geïnformeerde toestemming.

Naam, voornaam en verwantschap met de vertegenwoordigde persoon:

Datum en handtekening van de wettelijke vertegenwoordiger

Getuige / Tolk

Ik ben tijdens het volledige proces van informatieverstrekking aan de deelnemer aanwezig geweest en ik bevestig dat de informatie over de doelstellingen en procedures van de studie op adequate wijze is verstrekt, dat de deelnemer (of diens wettelijke vertegenwoordiger) de studie naar alle waarschijnlijkheid heeft begrepen en dat de toestemming tot deelname aan de studie uit vrije wil is gegeven.

Naam, voornaam en hoedanigheid van de getuige:

Datum en handtekening van de getuige / tolk

Arts-onderzoeker

Ik ondergetekende, ..., arts-onderzoeker, verklaar de benodigde informatie inzake deze studie mondeling te hebben verstrekt evenals een exemplaar van het informatiedocument aan de deelnemer te hebben verstrekt.

Ik bevestig dat geen enkele druk op de deelnemer is uitgeoefend om haar te doen toestemmen tot deelname aan de studie en ik ben bereid om op alle eventuele bijkomende vragen te antwoorden.

Ik bevestig dat ik werk in overeenstemming met de ethische beginselen zoals vermeld in de laatste versie van de "Verklaring van Helsinki", de "Goede klinische praktijk" en de Belgische wet van 7 mei 2004 inzake experimenten op de menselijke persoon.

Naam, Voornaam, Datum en handtekening van de vertegenwoordiger van de arts-onderzoeker

Naam, Voornaam, Datum en handtekening van de vertegenwoordiger van de arts-onderzoeker

Naam, Voornaam, Datum en handtekening van de arts-onderzoeker

Titel van de studie: **NOTES adnexectomie voor benigne aandoeningen vergeleken met laparoscopische excisie**

III Aanvullende informatie

1 : Aanvullende informatie over de organisatie van de studie

Nagenoeg alle bezoeken / -consultaties en -procedures waarvan de resultaten eventueel voor de studie worden gebruikt vallen onder de huidige standaard klinische zorg. Enkel de het postoperatief bezoek één week na de ingreep is bijkomend in het kader van de studie. Hierbij worden geen bijkomende technische onderzoeken voorzien die belastend of gezondheidsrisico's inhouden voor de deelnemer. Bij vaststellen van postoperatieve verwikkelingen worden bijkomende bloednames of technische onderzoeken gepland analoog aan deze die ook zouden worden gepland voor een gelijkaardige verwikkeling indien de deelnemer geen geïnformeerde toestemming zou hebben gegeven voor deelname aan de studie.

2. Aanvullende informatie over de risico's die verbonden zijn aan deelname aan de studie

Verklarende begrippen over het voorkomen van verwikkelingen:

Zeer vaak	Bij meer dan 1 op de 10 patiënten
Vaak	Bij meer dan 1 op de 100, maar minder dan 1 op de 10 patiënten
Soms	Bij meer dan 1 op de 1000, maar minder dan 1 op de 100 patiënten
Zelden	Bij meer dan 1 op de 10 000, maar minder dan 1 op de 1000 patiënten

Wanneer gekozen wordt voor een ingreep langs vaginale weg, zal de buikholte worden geopend langs de schede door een insnede te maken in de omslagplooi van de Douglasholte. Men spreekt van een achterste colpotomie. Op deze plaats grenst het diepste punt van de buikholte aan het diepste punt van de schede. Vroeger werd deze toegang gebruikt om ingrepen aan de eierstokken of eileiders uit te voeren. Zo werd in het verleden voor de opkomst van de laparoscopie een sterilisatie uitgevoerd via een colpotomie. Precieze gegevens over het voorkomen van verwikkelingen na een colpotomie zijn bekend in het kader van een eileidersterilisatie:

- morbiditeit of totaal aantal verwikkelingen door bloeding, infectie: minder dan 5 op 100
- mortaliteit of sterfte: minder dan 4 op 100 000

Andere zeldzame verwikkelingen die in minder dan 1 op 100 ingrepen voorkomen zijn:

- acuut compartiment syndroom bij ingrepen die langer dan drie uur duren
- ileus of vertraagd of niet op gang komen van de darmactiviteit
- obstipatie of fecale impactie
- oligurie of minder goed kunnen plassen
- ernstige infecties zoals septische shock, necrotizerende fascitis
- longontsteking
- platvallen van de longbases of atelectasis
- openvallen van de colpotomie wonde of dehiscentie
- achterlaten van een vreemd voorwerp zoals een wondcompres
- niet vermoede kanker van eileider of eierstok
- ernstige emotionele of psychologische stoornissen zoals verwardheid of depressie

Contraceptie, zwangerschap bij de deelneemster.

Zwangere vrouwen kunnen niet deelnemen aan de studie.

Risico's in verband met de klinische onderzoeksprocedures

De **bloedafname** die nodig is voor het preoperatief onderzoek is hetzelfde als dat wat zou worden uitgevoerd indien U zou moeten worden behandeld zonder dat U geïnformeerde toestemming gaf voor deelname aan de studie. Deze bloedname kan (in zeldzame gevallen) pijn, bloedingen, bloeduitstortingen of een lokale infectie op de plek van bloedafname veroorzaken. Ook kunnen sommige deelnemers zich duizelig voelen of flauwvallen tijdens de afname. Het personeel dat de bloedafname uitvoert, zal alles in het werk stellen om deze ongemakken te beperken.

3 : Aanvullende informatie over de bescherming en de rechten van deelnemers aan een klinische studie

Ethische comités

Deze studie werd geëvalueerd door het onafhankelijk ethisch comité van het Imeldaziekenhuis dat een gunstig advies heeft uitgebracht op 1 december 2015. De ethische comités hebben als taak de personen die aan klinische studies deelnemen te beschermen. Ze controleren of uw rechten als patiënt en als deelnemer aan een studie gerespecteerd worden, of - uitgaande van de huidige kennis - de balans tussen risico's en voordelen gunstig is voor de deelnemers, of de studie wetenschappelijk relevant en ethisch verantwoord is.

Hierover brengen de ethische comités een advies uit in overeenstemming met de Belgische wet van 7 mei 2004.

U dient het positief advies van de Ethische Comités in geen geval te beschouwen als een aansporing om deel te nemen aan deze studie.

Vrijwillige deelname

Aarzel niet om alle vragen te stellen die bij U opkomen voordat U tekent. Neem de tijd om er over te praten met een vertrouwenspersoon indien U dat wenst.

U heeft het recht om niet deel te nemen aan deze studie of met deze studie te stoppen, zonder dat U hiervoor een reden hoeft te geven, zelfs al hebt U eerder toegestemd om aan deze studie deel te nemen. Uw beslissing zal in geen geval Uw relatie met de arts-onderzoeker beïnvloeden, noch de kwaliteit van uw verdere verzorging.

Als U aanvaardt om aan deze studie deel te nemen, ondertekent U het toestemmingsformulier. De arts-onderzoeker zal dit formulier ook ondertekenen en zal zo bevestigen dat hij U de noodzakelijke informatie over deze studie heeft gegeven. U zal het voor U bestemde exemplaar ontvangen.

Voor Uw veiligheid is het wel aanbevolen om de arts-onderzoeker op de hoogte te stellen indien U besluit Uw deelname aan de studie stop te zetten.

Kosten in verband met uw deelname

Deze studie is een niet-commerciële studie.

Alle kosten staan in verband met gebruikelijke medische prestaties in uw klinische situatie en deze worden na facturatie terugbetaald door de mutualiteiten en de verzekeringsmaatschappij. Het gaat namelijk om een heelkundige behandeling die standaard voor dit gezondheidsprobleem wordt toegepast en die eveneens zou moeten gebeuren indien U niet aan de huidige studie zou deelnemen.

De bijkomende postoperatieve kontrole na één week is buiten de standaard klinische praktijk: de kostprijs van deze raadpleging zal niet worden aangerekend behalve indien er tijdens dit onderzoek verwikkelingen zouden worden opgemerkt die verdere technische onderzoeken of behandeling zouden vereisen welke ook buiten Uw deelname aan deze studie op gelijkaardige manier zouden worden behandeld. Uw verplaatsingskosten voor deze bijkomende raadpleging worden niet vergoed. Neem contact op met het studieteam voor de praktische uitvoering.

Vertrouwelijkheidsgarantie

Uw deelname aan de studie betekent dat U ermee akkoord gaat dat de arts-onderzoeker gegevens over U verzamelt en dat de opdrachtgever van de studie die gebruikt voor onderzoek en in het kader van wetenschappelijke en medische publicaties.

U hebt het recht om aan de arts-onderzoeker te vragen welke gegevens hij over U heeft verzameld en waarvoor ze gebruikt worden in het kader van de studie. Deze gegevens hebben betrekking op Uw huidige klinische situatie maar ook op Uw medische voorgeschiedenis en op de resultaten van onderzoeken die werden uitgevoerd voor de behandeling van Uw gezondheid volgens de geldende zorgstandaard. U hebt het recht om deze gegevens in te kijken en om verbeteringen te laten aanbrengen indien ze foutief zouden zijn.

Uw recht op inzage wordt minstens tot één week na de ingreep uitgesteld (ideaal tot na afloop van de studie op zes maanden) om een correct verloop van de studie te garanderen. Het eerder bekend maken van de gebruikte techniek kan leiden to voorkennis die de resultaten van de pijnscore metingen die binnen de eerste week moeten worden gemeten, betekenisvol beïnvloeden wat leidt tot foutieve resultaten en besluiten over de doeltreffendheid van de transvaginale benadering vergeleken met de standaard laparoscopische benadering.

De arts-onderzoeker is verplicht om deze verzamelde gegevens vertrouwelijk te behandelen.

Dit betekent dat hij zich ertoe verbindt om Uw naam nooit bekend te maken bijvoorbeeld in het kader van een publicatie of een conferentie en dat hij Uw gegevens zal coderen (Uw identiteit zal worden vervangen door een identificatiecode in de studie). De data van Uw deelname aan de studie zijn klinische data die worden bewaard in Uw electronisch patiënten dossier.

De arts-onderzoeker en zijn team zullen gedurende de volledige klinische studie de enige personen zijn met toegang tot Uw studie dossier).

De gepubliceerde persoonlijke gegevens omvatten geen combinatie van elementen waarmee het mogelijk is U te identificeren.

Alle onderzoekers betrokken bij deze studie behandelen Uw gegevens in overeenstemming met de Belgische wet betreffende de bescherming van de persoonlijke levenssfeer.

Om de kwaliteit van de studie te controleren, kan uw medisch dossier worden ingekeken door personen die gebonden zijn aan het beroepsgeheim zoals vertegenwoordigers van de ethische comités of een extern auditbureau. Dit kan enkel gebeuren onder strikte voorwaarden, onder de verantwoordelijkheid van de arts-onderzoeker en onder zijn toezicht (of van één van zijn onderzoeksmedewerkers).

De (gecodeerde) onderzoeksgegevens kunnen doorgegeven worden aan Belgische of andere regelgevende instanties, aan de betrokken ethische comités, aan andere artsen en/of instellingen die samenwerken met de onderzoekers.

Uw toestemming om aan deze studie deel te nemen betekent dus ook dat U akkoord gaat dat Uw gecodeerde medische gegevens gebruikt worden voor doeleinden die in dit informatieformulier beschreven staan en dat ze overgedragen worden aan bovenvermelde personen en/of instellingen.

De onderzoekers zullen de verzamelde gegevens gebruiken in het kader van de studie waaraan U deelneemt, maar willen ze ook kunnen aanwenden in het kader van andere studies over dezelfde ziekte als de Uwe. Buiten de context die beschreven wordt in dit document, kunnen Uw gegevens enkel gebruikt worden als een ethisch comité haar goedkeuring heeft gegeven.

Indien u uw toestemming tot deelname aan de studie intrekt, zullen de gecodeerde gegevens die al verzameld waren vóór uw terugtrekking, bewaard worden. Hierdoor wordt de geldigheid van de studie gegarandeerd.

Verzekering

Elke deelname aan een studie houdt een risico in, hoe klein ook. De onderzoeker is - ook indien er geen sprake is van fout - aansprakelijk voor de schade die de deelnemer of in geval van overlijden haar rechthebbenden, oplopen en die rechtstreeks of onrechtstreeks verband houdt met diens deelname aan de studie. U moet hiervoor dus geen fout aantonen. De opdrachtgever heeft voor deze aansprakelijkheid een verzekering afgesloten

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In het geval van onenigheid met de arts-onderzoeker of met de door de verzekeringsmaatschappij aangestelde expert, en steeds wanneer U dit nodig acht, kunnen U of in geval van overlijden Uw rechthebbenden de verzekeraar rechtstreeks in België dagvaarden dagvaarden (NV VANBREDA RISK & BENEFITS (Liability / Fleet with premium), polisnummer LXX048196 , Plantin en Moretuslei 297, 2140 Borgerhout, Tel 03/2176767).

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ClinicalTrials.gov PRS
Protocol Registration and Results System

ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 01/17/2016

ClinicalTrials.gov ID: NCT02630329

Study Identification

Unique Protocol ID:	B689201526268
Brief Title:	Notes Adnexectomy for Benign Pathology Compared to Laparoscopic Excision (NOTABLE)
Official Title:	Adnexectomy for Benign Gynaecological Pathology by Natural Orifice Transluminal Endoscopy or Laparoscopy
Secondary IDs:	

Study Status

Record Verification:	January 2016
Overall Status:	Recruiting
Study Start:	December 2015
Primary Completion:	May 2018 [Anticipated]
Study Completion:	May 2018 [Anticipated]

Sponsor/Collaborators

Sponsor:	Imelda Hospital, Bonheiden
Responsible Party:	Principal Investigator Investigator: Dr Jan Baekelandt, MD [jbaekelandt] Official Title: Dr Affiliation: Imelda Hospital, Bonheiden
Collaborators:	

Oversight

FDA Regulated?:	No
IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 689/151145 Board Name: Commissie Medische Ethiek Board Affiliation: Imelda Hospital Bonheiden Phone: + 3215505529 Email: marc.lambrechts@imelda.be
Data Monitoring?:	Yes
Plan to Share Data?:	No

	Interim analyses of major endpoints will be supplied, in strict confidence, to an independent Data Monitoring and Ethics Committee (DMEC) along with updates on results of other related studies, and any other analyses that the DMEC may request.
Oversight Authorities:	Belgium: Federal Agency for Medicines and Health Products, FAMHP

Study Description

Brief Summary:	Objective: To compare vNOTES (vaginal Natural Orifice Transluminal Endoscopic Surgery) and established laparoscopic removal of benign adnexal masses Study design: Randomized controlled/single center/single-blinded/parallel-group/non-inferiority/efficacy trial. Study population: Women aged 18 to 70 years with symptomatic or persistent benign adnexal masses detected by clinical examination and ultrasound. Randomization: Women will be randomly allocated to undergo one of two techniques for removal of the benign adnexal mass immediately before surgery by using a computer generated randomization list. The investigators will use stratified randomization according to the cyst diameter. Intervention: Women will be treated by a surgeon who is not blinded to the treatment allocation and who is equally skilled in performing both techniques. In the intervention group a vNOTES technique will be used. Control: In the control group surgery will be done by a classical laparoscopic technique. Participants, nursing staff and outcome assessors will be blinded. Main study parameters/endpoints: Primary outcomes: successful removal of a benign adnexal mass without spill. Secondary outcomes: the proportion of women discharged the same day based on their own preference; postoperative pain scores using a VAS (Visual Analogue Scale) measured between day 1 till 7 by the participating women following surgery and the total amount of analgesics used as described in the standardized pain treatment protocol between day 1 till 7; postoperative infection defined by lower abdominal pain with fever > 38°C and positive clinical signs or laboratory findings; per- or postoperative complications according to the Clavien- Dindo classification detected during the first six weeks of surgery; duration of the surgical procedure; incidence and intensity of dyspareunia recorded by the participants at 3 and 6 months by self-reporting using a simple questionnaire and VAS scale; sexual wellbeing recorded by the participants at 3 and 6 months by SSFS (Short Sexual Functioning Scale); direct costs associated up to 6 weeks after the surgical intervention with both procedures.
Detailed Description:	1. Objectives of the NOTABLE Trial The primary research questions of this IDEAL stage 2b efficacy trial are as follows: is a vNOTES adnexectomy at least as effective compared to the standard transabdominal laparoscopic approach (LSC) for removing a benign adnexal mass without spill? (non-inferiority design) Secondary research questions are: • Do more women treated by vNOTES prefer to leave the hospital on the day of surgery compared to LSC? • Do women treated by vNOTES suffer from less pain compared to women treated by LSC in the first postoperative week? • Is the removal of a benign adnexal mass by vNOTES faster compared to LSC? • Does a vNOTES cause more pelvic infection or other complications compared to LSC? • Does a vNOTES cause more hospital readmissions within 6 weeks following surgery compared to LSC?

- Does a vNOTES approach result in more women reporting dyspareunia or less sexual wellbeing at 3 or 6 months after surgery when compared to women treated by LSC?
- What are the direct costs up to 6 weeks of a vNOTES compared to LSC?

TRIAL DESIGN 2.1. Design A single center, single-blinded, parallel group randomized, non-inferiority efficacy trial.

2.2. Simple pilot randomized trial: minimal extra workload 2.3. Time schedule Based upon the mean number of laparoscopic adnexectomies performed annually at the department of Obstetrics and Gynecology of the participating center (36) the investigators estimate that the duration of recruitment will be 21 months. Based upon the follow up (6 months) and the period of analysis/reporting (3 months) the total study period will be 2.5 years.

2.4. Participating center Department of Obstetrics and Gynecology Imeldahospital Imeldalaan 9 2820 Bonheiden Belgium

- ELIGIBILITY, CONSENT AND RANDOMIZATION 3.1. Screening and consent prior to surgery All women aged 18 to 70 years regardless of parity presenting with a symptomatic or asymptomatic persistent benign adnexal mass on clinical examination confirmed by ultrasound are eligible for inclusion. The diagnosis of benign adnexal mass will be based upon the prospectively validated IOTA classification(International Ovarian Tumour Analysis Group) simple ultrasound rules to distinguish between benign and malignant adnexal masses.

  3.2. Determining eligibility All women aged 18 to 70 years regardless of parity presenting with a symptomatic or asymptomatic persistent benign adnexal mass on clinical examination who provide consent to participation are eligible in the NOTABLE trial based on the findings of the ultrasound findings and will be randomized before the procedure.

  3.3. Randomization If the woman is eligible for the NOTABLE trial, the trial secretary will obtain a randomized allocation the day before surgery. This will be done using a randomization list generated by a free computer software program offered by Research Randomizer (https://www.randomizer.org). The random sequence generation will be concealed using sequentially numbered opaque sealed envelopes. The envelope will be opened by the nurse assistant on the day before the surgical intervention for logistic reasons. The investigators will use stratified randomization in this small pilot RCT (randomized controlled trial) according to the cyst diameter.

  3.4. Patients with strong preference for treatment A minority of women will express a clear preference for one of both treatments (e.g. strong desire to have no scar) and for this reason will not wish to be randomized between surgical treatments. To investigate how outcomes vary by choice, these women could be followed up in exactly the same way as for those women randomized into the NOTABLE trial. A formal non-randomized follow-up of these women will not be done for simple logistical reasons.

  3.5. Stratification of randomization A blocked randomization procedure will be used to avoid chance imbalances for the parameter ‘cyst diameter’.

  To avoid any possibility of foreknowledge, the randomized allocation will not be given until all eligibility and stratification data have been given.
- TREATMENT ALLOCATIONS 4.1. Surgical procedures The principal investigator, who has training and experience in both laparoscopy and NOTES, will perform all surgical procedures. He is therefore not blinded. All vNOTES participants will be blinded by three superficial “mock” skin incisions similar to those routinely done with the laparoscopic technique.

  4.1.1 vNOTES adnexectomy This is the surgical procedure done in the intervention arm of the NOTABLE trial.

4.1.2 LSC adnexectomy This is the surgical procedure done in the control arm of the NOTABLE trial.

- FOLLOW-UP AND OUTCOME MEASURES 5.1. Clinical assessments 5.1.1 Format PROMs will be collected using a postal questionnaire, which will include a combination of disease specific and generic measurement instruments.

  The postal questionnaires will be sent from the NOTABLE Trial Office with postage paid envelopes two weeks before the due date. Reminders will be sent to the participants if the questionnaire is not returned within one week of the due date and attempts will be made to contact the women by phone if the questionnaire is not returned by two weeks after the due date.

  5.1.2 Timing of assessments The primary outcome will be measured clinically at the end of the surgical procedure. In addition PROMs will take place the evening of the surgical intervention (return home), during the first postoperative week (pain by VAS scores and analgetic drugs) and at 3 and 6 months (dyspareunia). Clinical physician assessment will take place the evening of the surgical intervention (return home) and during the first six weeks following surgery (pelvic infection, surgical complications, hospital readmission rate).

  5.2. Primary clinical outcome measure The proportion of women successfully treated by removing the adnexal mass without spill, using a dichotomous outcome measure, will be used as a measure of efficacy.

  5.3. Secondary clinical outcome measures

  The following secondary outcomes will be measured:

  - The proportion of women discharged the same day based on their own preference, as a dichotomous outcome.
  - Postoperative pain scores, as an ordinal outcome, measured using a VAS scale twice daily from day 1 till 7 self-reported by the participating women.
  - Postoperative pain defined by the total amount of analgesics used as described in the standardized pain treatment protocol, as a continuous outcome.
  - Postoperative infection as a dichotomous outcome.
  - Per- or postoperative complications according to the Clavien- Dindo classification detected during the first six weeks of surgery, as a dichotomous outcome.
  - Hospital readmission within 6 weeks following surgery, as a dichotomous outcome.
  - Incidence and intensity of dyspareunia recorded by the participants at 3 and 6 months by self-reporting using a simple questionnaire and VAS scale, as a dichotomous and ordinal outcome. .
  - Sexual wellbeing at baseline, at 3 and 6 months by self-reporting the SSFS.
  - Duration of surgery measured as the time in minutes from the insertion of the bladder catheter to the end of vaginal/abdominal wound closure, as a continuous outcome.

  5.4. Health economic outcomes The direct costs of both techniques up to 6 weeks after the surgical intervention will be calculated.

- ACCRUAL AND ANALYSIS 6.1. Sample size The sample size for this trial has been chosen to give good statistical power to preclude any clinically important inferiority of vNOTES compared to laparoscopy and is based on evidence retrieved from a systematic review of the literature and a RCT comparing the excision of mature teratoma using culdotomy with and without laparoscopy. Based on the power calculations for the primary outcome and two secondary outcomes and assuming a loss-to-follow-up rate of 10% the investigators decided to include 66 study participants in the NOTABLE trial.

6.2. Projected accrual and attrition rates It is anticipated that recruitment of participants will take two years. Based upon the mean number of laparoscopic adnexectomies performed annually at the department of Obstetrics and Gynecology of the participating center (36) the investigators estimate that the duration of recruitment will be 21 months. Based upon the follow up (6 months) and the period of analysis/reporting (3 months) the total study period will be 2.5 years. First publication will be possible within four years of trial commencement.

Conditions

Conditions: Natural Orifice Endoscopic Surgery
Disease, Adnexal
Laparoscopic Surgery

Keywords: NOTES
Benign adnexal disease
Laparoscopy

Study Design

Study Type: Interventional
Primary Purpose: Treatment
Study Phase: Phase 2
Intervention Model: Parallel Assignment
Number of Arms: 2
Masking: Double Blind (Subject, Outcomes Assessor)
Allocation: Randomized
Endpoint Classification: Efficacy Study
Enrollment: 66 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: vNOTES adnexectomy Vaginal Natural Orifice Transluminal Endoscopic Surgery	Procedure/Surgery: vNOTES adnexectomy Surgical removal of one or both adnexa by a natural orifice transluminal endoscopic surgical technique using a colpotomy (transvaginal incision)
Active Comparator: LSC adnexectomy Laparoscopic adnexectomy	Procedure/Surgery: Laparoscopic adnexectomy Surgical removal of one or both adnexa by transabdominal laparoscopy

Outcome Measures

Primary Outcome Measure:

1. Successful removal of adnexal mass without spill
   [Time Frame: Intraoperative] [Safety Issue: Yes]
   The proportion of women successfully treated by removing the adnexal mass without spill, using a dichotomous outcome measure, will be used as a measure of efficacy.

Secondary Outcome Measure:

2. Discharge from the hospital the day of the surgical intervention

[Time Frame: Dichotomous outcome measured on the day of the surgical intervention] [Safety Issue: Yes]
The proportion of women discharged the same day based on their own preference, as a dichotomous outcome. The decision to discharge or to admit to hospital for the night will be based solely on the choice of the woman to return home the same day or stay overnight.

3. Postoperative pain scores
[Time Frame: The first week after the surgical intervention] [Safety Issue: No]
Postoperative pain scores, as an ordinal outcome, measured using a VAS scale twice daily from day 1 till 7 self-reported by the participating women

4. The use of analgesics for postoperative pain
[Time Frame: The first week after the surgical intervention] [Safety Issue: No]
Postoperative pain defined by the total amount of analgesics used as described in the standardized pain treatment protocol, as a continuous outcome.

5. Postoperative infection
[Time Frame: The first six weeks after the surgical intervention] [Safety Issue: Yes]
Postoperative infection defined by lower abdominal pain with fever > 38°C and positive clinical signs or laboratory findings, detected during the first six weeks of surgery, as a dichotomous outcome.

6. Complications
[Time Frame: The first six weeks after the surgical intervention] [Safety Issue: Yes]
Per- or postoperative complications according to the Clavien- Dindo classification detected during the first six weeks of surgery, as a dichotomous outcome

7. Hospital readmission
[Time Frame: The first six weeks after the surgical intervention] [Safety Issue: Yes]
The proportion of women readmitted to hospital within six weeks of surgery, as a dichotomous outcome

8. Pain during sexual intercourse
[Time Frame: At baseline, 3 months and 6 months after the surgical intervention] [Safety Issue: No]
Incidence and intensity of dyspareunia recorded by the participants at 3 and 6 months by self-reporting using a simple questionnaire and VAS scale, as a dichotomous and ordinal outcome

9. Sexual well being
[Time Frame: At baseline, 3 months and 6 months after the surgical intervention] [Safety Issue: No]
Sexual wellbeing at baseline, at 3 and 6 months by self-reporting using the SSFS (Short Sexual Function Scale).

10. Duration of the surgical intervention
[Time Frame: Intraoperative] [Safety Issue: No]
Duration of surgery measured as the time in minutes from the insertion of the bladder catheter to the end of vaginal/ abdominal wound closure, as a continuous outcome

11. Direct costs
[Time Frame: Up to 6 weeks postoperative] [Safety Issue: No]
Calculating the comparative direct costs of both techniques up to 6 weeks after the surgical intervention

Eligibility

Minimum Age:	18 Years
Maximum Age:	70 Years
Gender:	Female
Accepts Healthy Volunteers?:	Yes
Criteria:	Inclusion Criteria:

- All women aged 18 to 70 years regardless of parity with a symptomatic adnexal mass presumed to be benign based on ultrasound examination by applying the IOTA simple rules

- All women aged 18 to 70 years regardless of parity with an asymptomatic persistent adnexal mass presumed to be benign based on ultrasound examination by applying the IOTA simple rules
- Written informed consent obtained prior to surgery

Exclusion Criteria:

- History of hysterectomy by any technique
- History of rectal surgery
- Suspected rectovaginal endometriosis
- Suspected endometriotic cyst
- Solid adnexal mass
- High suspicion of adnexal malignancy based on clinical, ultrasound or biochemical findings
- History of pelvic inflammatory disease, especially prior tubo-ovarian or pouch of Douglas abscess
- Active lower genital tract infection e.g. Chlamydia, N. gonorrhoeae
- Virgo
- Pregnancy
- Need for other uterine surgical intervention (i.e. endometrial ablation, resection, myomectomy or hysterectomy)
- Additional pathology necessitating hysterectomy
- Failure to provide written informed consent prior to surgery

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References

Citations: [Study Results] Baekelandt J. Poor man's NOTES: can it be a good approach for adhesiolysis? A first case report with video demonstration. J Minim Invasive Gynecol. 2015 Mar-Apr;22(3):319. doi: 10.1016/j.jmig.2014.11.001. Epub 2014 Nov 10. PubMed 25460516

[Study Results] Yang YS, Hur MH, Oh KY, Kim SY. Transvaginal natural orifice transluminal endoscopic surgery for adnexal masses. J Obstet Gynaecol Res. 2013 Dec;39(12):1604-9. doi: 10.1111/jog.12108. Epub 2013 Jul 22. PubMed 23875997

[Study Results] Ghezzi F, Cromi A, Uccella S, Bogani G, Serati M, Bolis P. Transumbilical versus transvaginal retrieval of surgical specimens at laparoscopy: a randomized trial. Am J Obstet Gynecol. 2012 Aug;207(2):112.e1-6. doi: 10.1016/j.ajog.2012.05.016. Epub 2012 May 23. PubMed 22704765

Wang PH, Lee WL, Juang CM, Tsai WY, Chao HT, Yuan CC. Excision of mature teratoma using culdotomy, with and without laparoscopy: a prospective randomised trial. BJOG. 2001 Jan;108(1):91-4. PubMed 11213011

[Study Results] Medeiros LR, Rosa DD, Bozzetti MC, Fachel JM, Furness S, Garry R, Rosa MI, Stein AT. Laparoscopy versus laparotomy for benign ovarian tumour. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD004751. doi: 10.1002/14651858.CD004751.pub3. Review. PubMed 19370607

Links:

Study Data/Documents:

RESEARCH PROTOCOL

NOTABLE trial

(NOTes Adnexectomy for Benign pathology compared to Laparoscopic Excision)

UNIQUE PROTOCOL ID: B689201526268

ClinicalTrials.govID: NCT02630329

Protocol ID	B689201526268 NCT02630329
Short title	NOTABLE trial
Version	5
Date	28-12-2015
Coordinating investigator	Dr. J. Bosteels Imeldaziekenhuis Department of Obstetrics and Gynaecology Imeldalaan 9, 2820 Bonheiden, Belgium T: + 32 15 505205 M: jan.bosteels@imelda.be
Principal investigator	Dr. J. Baekelandt Imeldaziekenhuis Department of Obstetrics and Gynaecology Imeldalaan 9, 2820 Bonheiden, Belgium T: + 32 15 505208 M: jbaekelandt@imelda.be
Sponsor	Investigator driven trial
Independent physician	Not applicable
Laboratory sites	Clinical laboratory Imeldaziekenhuis Imeldalaan 9, 2820 Bonheiden, Belgium T: + 32 15 505460
Pharmacy	Not applicable

PROTOCOL SIGNATURE SHEET

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ACOG	American College of Obstetricians and Gynecologists
AE	Adverse Event
CAT	Computerized Axial Tomography
CONSORT	Consolidated Standards of Reporting Trials
DMEC	Data Monitoring and Ethics Committee
EuroQoL	EQ-5D Health Questionnaire
GMT	Greenwich Mean Time
GP	General Practitioner
HTA	Health Technology Assessment
IOTA	International Ovarian Tumour Analysis
IV	intravenous
LSK	laparoscopy
MID	Minimally Important Difference
NHS	National Health Service
NOTABLE	NOTES Adnexectomy for Benign pathology compared to Laparoscopic Excision
NOTES	natural orifice transluminal endoscopy
vNOTES	vaginal natural orifice transluminal endoscopy
PROM	Patient Reported Outcome Measure
RCT	Randomised Controlled Trial
(S)AE	(Serious) Adverse Event
SD	Standard Deviation
SSFS	Short Sexual Functioning Scale
SILS	Single Incision Laparoscopic Surgery
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee
TU	Trans Umbilical
TV	Trans Vaginal
VAS	Visual analogue scale
QALY	Quality adjusted life year

SUMMARY

Rationale: Driven by the desire to minimalise surgical morbidity, the evolution from laparotomy to laparoscopic surgery has now extended to less invasive surgery such as robotics, mini- laparoscopy, single incision laparoscopic surgery (SILS), and natural orifice transluminal endoscopic surgery (NOTES). Minimally invasive surgery not only improves cosmetic outcome, it has the potential to restrict the magnitude of the surgical injury, which in turn can attenuate the inflammatory and neuroendocrine response resulting in less postoperative pain and quicker recovery (1, 2).

NOTES attempts to reach the abdominal cavity through an invisible scar, i.e. the surgical intervention is performed via a natural body orifice. Its popularity amongst general surgeons, urologists and gastroenterologist has increased over the past few years and its feasibility and safety has been reported in the medical literature (3).

NOTES can be done by various approaches including access via the stomach, oesophagus, bladder or rectum. The majority of NOTES procedures in women are done by the vagina as this site provides direct access to the lower abdominal cavity (4). Colpotomy has been used widely for several surgical procedures (by gynaecologists as well as general surgeons for the extraction of large specimens) and it has been reported as a safe access that is easy to close afterwards (5, 6).

In hybrid NOTES the surgical procedure is performed through a natural body orifice with transabdominal assistance, whereas the term pure NOTES refers to procedures that involve only transluminal access.

Given its potential benefits, including no visible scars, fewer port-related complications, and less painful and faster post-operative recovery, we have introduced transvaginal pure NOTES (vNOTES) for the treatment of benign adnexal masses in our surgical practice since November 2013. A case-series by our group describing the technical feasibility of removing benign adnexal masses by vNOTES in 20 women has been published recently (7). Most women reported a low postoperative pain score (range 0 to 2) measured at day 1 following surgery by a visual analogue scale (VAS). Based on these preliminary observational findings we decided to design a pilot randomized trial to study the effectiveness of the new vNOTES approach based on the hypothesis that the new technique is at least as effective for removing a benign adnexal mass without cyst rupture compared to the classical laparoscopic technique.

Objective: To compare vNOTES and established laparoscopic removal of benign adnexal masses

Study design: Randomised controlled/single centre/single-blinded/parallel-group/non-inferiority/efficacy trial.

Study population: Women with symptomatic or persistent benign adnexal masses detected by clinical examination and ultrasound.

Randomisation: After assessment of eligibility/ informed consent women will be randomly allocated to undergo one of two techniques for removal of the benign adnexal mass before surgery by using a computer generated randomisation list. We will use stratified randomisation according to the cyst diameter.

Intervention: Women will be treated by a surgeon who is not blinded to the treatment allocation and who is equally skilled in performing both techniques. In the intervention group a vNOTES technique will be used.

Control: In the control group surgery will be done by a classical laparoscopic technique.

Participants, nursing staff and outcome assessors will be blinded by the use of mock surgical skin incisions. Pre- and postoperative treatment will be provided by staff blinded for the allocated intervention using a standardized protocol that is identical for both techniques. All women will be advised not to work during a 4-week period and to abstain from sexual intercourse until their 6-week booked appointment for a postoperative assessment.

Main study parameters/endpoints:

Primary outcomes: successful removal of a benign adnexal mass without spill.

Secondary outcomes: the proportion of women discharged the same day based on their own preference; postoperative pain scores using a VAS scale measured between day 1 till 7 by the participating women following surgery and the total use of analgesics as described in the standardized pain treatment protocol; postoperative infection defined by lower abdominal pain with fever > 38°C and positive clinical signs or laboratory findings; per- or postoperative complications according to the Clavien- Dindo classification (8) detected during the first six weeks of surgery; hospital readmission during the first six weeks of surgery; duration of the surgical procedure; incidence and intensity of dyspareunia recorded by the participants at 3 and 6 months by self-reporting using a simple questionnaire and VAS scale; sexual wellbeing recorded by the participants at 3 and 6 months by SSFS; quality of life by self-reporting the EQ-5D-3L questionnaire at 3 and 6 months; direct costs associated with both procedures.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The burden and risks associated with the participation in the study are comparable with the risks related to the established technique of laparoscopic adnexectomy.

1. BACKGROUND

1.1. Disease: adnexal mass

An adnexal mass (mass of the ovary, fallopian tube, or surrounding connective tissues) is a common gynaecological problem. In the United States, it is estimated that there is a 5 to 10 percent lifetime risk for women undergoing surgery for a suspected ovarian neoplasm (9). Adnexal masses may be found in females of all ages, foetuses to the elderly, and there is a wide variety of types of masses. The management of an adnexal mass depends upon the type of mass, urgency of the presentation (e.g. ectopic pregnancy or ovarian torsion require immediate intervention), and degree of suspicion that the mass might be malignant.

1.1.1 Population to be studied

All women with a benign adnexal mass will be eligible for inclusion provided that they have no exclusion criteria and after giving fully informed consent.

The diagnosis of a benign adnexal mass will be based upon the prospectively IOTA validated simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery (10). All the ultrasound examinations will be reviewed before the randomisation by a named operator with competence in gynaecological ultrasound and experience in applying the simple rules. The need for additional examinations (CAT scan or CA-125) is based upon good clinical practice.

1.2. Current therapy for removal of an adnexal mass

Surgical exploration for an adnexal mass may be performed laparoscopically (conventional or robotic) or by laparotomy. The choice of surgical approach depends upon the degree of suspicion of malignancy and surgeon and patient preference. Ovarian cancer staging can be performed using an open or laparoscopic approach, although the majority of surgeons in current practice prefer laparotomy if there is a high degree of suspicion of malignancy. If there is a low or moderate suspicion of malignancy, a laparoscopic approach is typically used. Laparoscopy is associated with a shorter recovery and decreased perioperative morbidity compared with laparotomy.

The surgical technique used must minimise the potential for tumour disruption or dissemination. If malignancy is suspected, oophorectomy is required rather than ovarian cystectomy. Women with early stage ovarian cancer (i.e. no malignant cells in ascites or peritoneal cytology) benefit from removal of the adnexal mass intact, since opening the mass results in a more advanced stage and adversely affects prognosis (11, 12). In addition, every attempt must be made to provide the pathologist with an ovarian specimen with an intact cortex. If a laparoscopic approach is used, the ovary can be placed in a tissue recovery bag. If the specimen is too large to remove through the existing incisions, cyst fluid may be aspirated (but the collapsed cyst should not be disrupted) or the incision may be enlarged. The practice of morcellating ovarian masses in a bag is discouraged

because it may compromise pathology evaluation. In general, aspiration of cyst contents is not advisable as the sole surgical intervention because no tissue is obtained for histopathology and cytology of cyst fluid is not reliable for exclusion of malignancy, and there is a high rate of recurrence. Recent years have witnessed the use of a posterior colpotomy to retrieve large benign ovarian lesions since removal through the umbilicus may not be straightforward (13).

1.3. New therapy for removal of a benign adnexal mass

Natural orifice transluminal endoscopic surgery (NOTES) is a surgical technique whereby "scarless" abdominal operations can be performed with an endoscope passed through a natural orifice (mouth, urethra, anus, etc.) then through an internal incision in the stomach, vagina, bladder or colon, thus avoiding any external incisions or scars. NOTES was originally described in animals by researchers at Johns Hopkins University (Dr. Anthony Kalloo et al.), and was once upon a time used for transgastric appendectomy in humans in India (by Drs. G.V. Rao and N. Reddy). On June 25, 2007 Swanstrom and colleagues reported the first human transgastric cholecystectomy. The transvaginal access to NOTES seems to be the safest and most feasible approach for clinical application.

1.4. Literature review

1.4.1 Systematic Review

Health technology assessment (HTA) of surgical interventions requires an initial evaluation of the safety and feasibility followed by randomised controlled trials of effectiveness. We conducted a comprehensive systematic review on the efficacy of colpotomy in the treatment of benign adnexal mass. After searching three electronic databases (MEDLINE, EMBASE and The Cochrane Library) from inception to 1 August 2015 using '*colpotomy'* and '*adnexal diseases'* or *'adnexal mass'* as MeSH terms or key words, ten citations were identified, of which a total of four studies were eligible for inclusion. Two studies were observational including one very small case series (7 women) and one prospective cohort study (257 women); two studies were randomised controlled trials (66 women and 79 women respectively).

A summary of the evidence is given below:

We retrieved one observational study from Korea (14). The authors performed transvaginal NOTES in seven women with adnexal masses through a 2-cm incision in the posterior vaginal fornix. A transvaginal NOTES system comprising a wound protractor and a surgical glove with sheaths was used. Resection was performed according to the method of standard laparoscopic adnexal surgery. The adnexal mass was removed via the incision of the posterior vaginal fornix after complete resection. Since June 2011, seven women have undergone transvaginal NOTES for adnexal masses. All cases were completed successfully without conversion to standard laparoscopic approach. The median age of the women was 48 years (range: 36–60 years) and the median body mass index was 23.6 (range: 20.4–25.3). The median tumour size was 6 cm (range: 3.7–6.7 cm). The median

operative time was 45 min (range: 40–80 min). The estimated blood loss was minimal (range: 5–300 mL). The median postoperative hospital stay was 2 days (range: 1–3 days). No postoperative complications were observed at follow-up. All women were very satisfied with the cosmetic result. The authors conclude that transvaginal NOTES may be a feasible, safe and effective surgical technique that results in excellent cosmetic results. It may be an alternative technique for the treatment of properly selected patients with adnexal masses. The authors stress the need for further clinical research.

We retrieved a prospective cohort study from the United States (15). This descriptive study was conducted on women treated by a private gynaecological surgery practice in a community hospital setting from January 1, 2004 through April 30, 2011. Two-hundred fifty-seven consecutive women with adnexal masses of 8 cm to 13 cm on preoperative ultrasound examination not meeting triage criteria set forth in ACOG Committee Opinion 280 for referral to gynaecological oncologists were treated with operative laparoscopy, adnexal removal, bagging, and colpotomy. Laparoscopic surgery combined with posterior colpotomy has a low incidence of significant complications. Outcome data show that by observing the principals of minimally invasive surgery, 97% of women were successfully treated as outpatients: 98% of surgeries lasted <136 minutes; 97% had blood loss <200mL, and there were few consequential postoperative complications. Intraoperative rupture of the ovarian capsule was extremely uncommon: capsular rupture was noted in just 1.2% of cases. The most common lesions were cystadenomas, endometriotic cysts and mature teratomas accounting for 85% of all cases. Borderline tumours accounted for 5% of lesions, while invasive ovarian malignancy represented 3.7% of the specimens.

We retrieved one RCT from Italy (16). Women scheduled for a laparoscopic resection of an adnexal mass were randomised to have their surgical specimen removed either through a posterior colpotomy (n = 34) or the umbilical port site (n = 32). Group allocation was concealed from study participants and bedside clinicians. The primary outcome was postoperative incisional pain assessed by a 10-cm visual analogue scale at 1, 3, and 24 hours after surgery. Transvaginal retrieval caused less postoperative pain than transumbilical specimen extraction at each time point (visual analogue scale score at 1 hour: 2.6 ± 2.9 vs 1.2 ± 2.0, $P = 0.03$; at 3 hours: 2.4 ± 2.0 vs 1.4 ± 2.0, $P = 0.02$; and at 24 hours: 1.1 ± 1.5 vs 0.5 ± 1.4, $P = 0.02$). A higher proportion of women in the transumbilical group than in the transvaginal group indicated the umbilicus as the most painful area at 1 and 3 hours postoperatively. Two months after surgery, the participants scored similarly as to their overall satisfaction, cosmetic outcome, and dyspareunia upon resumption of intercourse. The authors conclude that a transvaginal approach for specimen removal after laparoscopic resection of adnexal masses may offer the advantage of less postoperative pain than the classical umbilical retrieval.

We retrieved one RCT from Taiwan (17). Seventy-nine women with mature teratomas identified by ultrasound examination and biochemical markers were randomly assigned to have their cysts removed via vaginal cystectomy without laparoscopy (n= 37, group A) or laparoscopic cystectomy via culdotomy (n=42, group B). Inclusion criteria were history of vaginal delivery, no previous abdominal surgery, no history of pelvic inflammatory disease, no medical illness, and no presenting symptoms. Eight women randomised to group A withdrew before surgery. The laparoscopically resected tumours were each put into a cellulose bag, and tumours without laparoscopic- assistance were removed directly via the vagina. Blood loss in group A (88± 37 ml) was significantly more than that in group B (64± 20 ml, P= 0.000). The post-operative recovery times were 20 and 17 hours, respectively (P= 0.030). The rates of successful surgery were 58.6 and 97.6%, respectively (P= 0.002). The spillage rates were 44.8% and 19.0%, respectively (P= 0.006). There were no significant differences in tumour size, patient age, and operative time between groups. The authors concluded that cystectomy without assistance of laparoscopy could be applied to manage mature teratoma of the ovary; however, because of the difficulty of this technique, there were high percentages of tumour spillage and more blood loss during operation and a high percentage of patients who required conversion to laparotomy compared with laparoscopic cystectomy. The authors favour laparoscopically assisted cystectomy to manage mature teratoma.

1.4.2 Current clinical practice

At the present the laparoscopic route is considered to be the gold standard for removing a benign adnexal mass compared to laparotomy. According to a Cochrane review (18), in women undergoing surgery for benign ovarian tumors, laparoscopy was associated with a reduction in fever, urinary tract infection, postoperative complications, postoperative pain, number of days in hospital, and total cost. These findings should be interpreted with caution since only a small number of studies (nine) were identified. These included a total of only 769 women and not all of the important outcomes were reported in each study.

In the days prior to widespread availability of laparoscopy, skilled gynaecological surgeons frequently used colpotomy for ready access to the pelvis (15). Unlike episiotomy that can cause dyspareunia, colpotomy does not transect muscles and, therefore, has less bleeding and negligible postoperative pain. Some surgeons may point out the potential disadvantages of colpotomy, including incisional infection, peritonitis, and technical complexity, particularly in patients after hysterectomy. Many gynaecologists seem reluctant to perform transvaginal surgery because this approach can be difficult for inexperienced surgeons and is occasionally unsuccessful. Moreover, conversion to conventional laparoscopy because of unsuccessful transvaginal approach is not acceptable to women who are expecting a minimally invasive surgery with no abdominal surgical scars. Therefore colpotomy is not used as the standard clinical practice in Belgium for removal of the adnexa.

1.4.3 Pilot studies

Given its apparent benefits, including no visible scars, fewer port-related complications, and less painful and faster post-operative recovery, we introduced transvaginal pure NOTES (vNOTES) for benign adnexal masses in our surgical practice since November 2013. Our group has recently published a case-series describing the feasibility of adnexectomy by vNOTES in 20 women for benign adnexal masses (7).

The purpose of the observational case-series was to describe the new technique as well as to demonstrate the feasibility of adnexectomy by transvaginal natural orifice transluminal endoscopic surgery (vNOTES) for the removal of benign adnexal masses. Conventional, reusable laparoscopic instruments were used, inserted through an inexpensive, self-designed single port device. Between November 2013 and November 2014, 20 adnexectomies by vNOTES were performed by a single surgeon (Dr. Jan Baekelandt).

We selected each participant based on the following inclusion criteria: no contraindication for general anaesthesia, pneumoperitoneum or Trendelenburg position; no fixed uterus, strong pelvic adhesions or nodularity in the pouch of Douglas on clinical examination; no history of pelvic inflammatory disease or moderate to severe endometriosis and mass not suspicious for malignancy. We excluded women with large fibroid uteri as these may impair visualization. Virginity and concomitant pregnancy were predefined as exclusion criteria whereas obesity (BMI ≥ 30) and nulliparity were not.

The self-designed single port device was made by assembling a surgical glove, a wound protector, one reusable 10 mm trocar, and four reusable 5 mm trocars. The adnexectomy was performed according to the technique for standard laparoscopic surgery and the specimen was removed through the colpotomy incision.

The following patient and perioperative data were collected and retrospectively analysed: patient age, body mass index (BMI), parity, history of vaginal delivery, previous pelvic surgery, type of surgery, total operating time, serum haemoglobin (Hb) drop (change between the preoperative Hb and postoperative Hb one day after surgery), (peri-) operative complications, postoperative pain score and size of the adnexal mass. The duration of surgery was defined as the time from the start of colpotomy to the end of vaginal closure. Bowel, bladder, ureteral or vascular injuries, as well as blood loss > 300 ml, were considered as intraoperative complications. Short-term postoperative complications were classified as urinary tract infection, postoperative ileus, vaginal vault bleeding or infection, or haematuria. Postoperative pain was assessed using the visual analogue pain scale (VAS) (scoring from 0 = no pain to 10 = worst imaginable pain). The VAS score was evaluated at 6 and 24 hours postoperatively. All women received the same intraoperative analgesia: intravenous

paracetamol 1000 mg and ketorolac trometamol 20 mg. Postoperative pain was managed by paracetamol 1000 mg and ketorolac trometamol was administered on patient's demand.
No bowel preparation was done prior to surgery. A Foley catheter was placed just before surgery and removed the morning after surgery (range 12-22 hours). Prophylactic intravenous antibiotic therapy, cefazoline 2 g and metronidazol 500 mg, was administrated during surgery. As this was a new technique the first patients were closely monitored post operatively. No vaginal intercourse was allowed for 6 weeks after the procedure. Each patient was re-assessed at the post-operative consultation 6 weeks after surgery.
Between November 2013 and November 2014, twenty procedures were successfully performed by Poor Man's vNOTES using conventional, reusable laparoscopic instruments. No conversion to standard multi incision laparoscopy or laparotomy was necessary. Fourteen women underwent a unilateral adnexectomy. In six women a bilateral salpingo-oophorectomy was performed.
Table 1 (Appendix I) gives a cumulative overview of patient characteristics and relevant perioperative data. Individual patient data are presented in Table 2 (Appendix II). Mean operation time was 32 minutes (range 20 to 50 minutes). Five women had had previous pelvic surgery. There were no intraoperative complications and only one patient had a postoperative cystitis for which oral antibiotic therapy was administered. The mean drop in haemoglobin level was 0.9 g/dl (range 0 to 2.1 g/dl). Most women reported a low postoperative pain score (range 0 to 2) measured at day 1 following surgery by a visual analogue scale (VAS). The mean size of the removed adnexal mass was 51.8 mm (35-110 mm). Each patient was examined six weeks after surgery. There was no vaginal wound infection nor dehiscence, and no patient complained of pain during pelvic examination. All women were in good health and were all satisfied with the result.
Based on this observational case-series we concluded that adnexectomy by vNOTES is feasible for masses up to 110 mm even when performed with reusable, conventional laparoscopic instruments. The potential benefits with vNOTES are better cosmetics, low postoperative pain scores, and easy removal of the specimen without spillage. We stated that this new technique may enable surgeons in low resource settings to perform procedures by vNOTES since no expensive devices or instruments are needed.

1.5. The need for a pilot trial of vNOTES versus LSK adnexectomy

Surgical innovation is an important part of surgical practice. Its assessment is complex because of idiosyncrasies related to surgical practice, but necessary so that introduction and adoption of surgical innovations can derive from evidence-based principles rather than trial and error. We decided to follow the principles and guidelines established by IDEAL. On four occasions between 2007 and 2009, invited international experts gathered at Balliol College, Oxford, to explore potential solutions concerning quality, innovation and evaluation in surgical practice and research. The conclusions and

guiding principles were published in The Lancet in 2009. Surgery lacks regulatory authorities that require studies of efficacy before a new procedure can be offered to patients. Nevertheless there is little difference between operations and other complex treatments delivered by individuals within teams. In each instance, the skill, experience, and judgment of the operator should be recognized, and outcomes are affected by the patient and the team. There was agreement between the experts that none of these factors is beyond the design of a clinical trial. The rationale for the resulting IDEAL framework (Idea–Development–Exploration–Assessment–Longterm study) for surgical research has been presented in a three article series in The Lancet (19, 20, 21). The central concept is that surgeons are regularly innovating and improving their skills. Because the point at which an innovation evolves into a novel procedure might not be obvious at the time, prospective open registration of new procedures and early ethical approval are encouraged. Evolution and evaluation can then occur simultaneously. The framework recognizes that at different stages of innovation, different study designs will be appropriate. According to the IDEAL framework the vNOTES approach has entered stage 2b (exploration) given that the technique of vNOTES has been described and the main technical aspects have been worked out. Even at this early stage a small efficacy RCT may be appropriate for the evaluation of the innovative surgical technique. The learning curve is likely to affect which surgeons participate in RCTs trials and when they become involved. We decided to use an RCT as the appropriate study design: the principal investigator had achieved his learning curve.

1.6. Objectives of the NOTABLE Trial

Is a vNOTES adnexectomy at least as effective compared to the standard transabdominal laparoscopic approach (LSC) for removing a benign adnexal mass without spill?

Secondary research questions are:

- Do more women treated by vNOTES prefer to leave the hospital on the day of surgery compared to LSC?
- Do women treated by vNOTES suffer from less pain compared to women treated by LSC in the first postoperative week?
- Is the removal of a benign adnexal mass by vNOTES faster compared to LSC?
- Does a vNOTES cause more pelvic infection or other complications compared to LSC?
- Does a vNOTES result in more hospital readmissions during the first six weeks following surgery compared to LSC?
- Does a vNOTES approach result in more women reporting dyspareunia, less quality of life or less sexual wellbeing at 3 or 6 months after surgery when compared to women treated by LSC?
- What are the costs of a vNOTES compared to LSC?

2. TRIAL DESIGN

2.1. Design

A single centre, single-blinded, parallel group randomised, non-inferiority efficacy trial.

2.2. Simple pilot randomised trial: minimal extra workload

This is a pilot randomised trial aiming to demonstrate that vNOTES is at least as effective compared to the classical gold standard approach of laparoscopy for successfully removing benign adnexal masses without spill (non-inferiority design). In this phase of HTA the trial will need the participation of only one centre. To make this practicable, trial procedures are kept simple, with the minimal extra workload placed on participating clinicians, beyond that required to treat their patients. This will be achieved by simple entry procedures, the use of standard local diagnostic and surgical regimens, routine follow-up of patients (with few additional hospital visits or tests to be performed above those done as part of standard care), minimising documentation and largely patient-based evaluation of outcome (PROM).

2.3. Time schedule

Based upon the mean number of laparoscopic adnexectomies performed annually at the department of Obstetrics and Gynaecology of the participating centre (36) we estimate that the duration of recruitment will be 21 months. Based upon the follow up (6 months) and the period of analysis/reporting (3 months) the total study period will be 2.5 years.

2.4. Participating centre

Department of Obstetrics and Gynaecology

Imelda Hospital

Imeldalaan 9

2820 Bonheiden

Belgium

3. ELIGIBILITY, CONSENT AND RANDOMISATION

3.1. Screening and consent prior to surgery

All women regardless of age and parity presenting with a symptomatic or asymptomatic persistent benign adnexal mass on clinical examination confirmed by ultrasound are eligible for inclusion. The diagnosis of benign adnexal mass will be based upon the prospectively IOTA validated simple ultrasound rules to distinguish between benign and malignant adnexal masses (10). All the ultrasound examinations will be reviewed before the randomisation by a named operator with competence in gynaecological ultrasound and experience in applying the simple rules. The need for additional examinations (CAT scan or CA-125) is based upon good clinical practice.

The trial will be introduced to the eligible women in the outpatient clinic and a comprehensive, evidence-based patient information sheet will be provided at the clinic visit. Participant information sheets and consent form will be provided in Dutch.

Before the procedure, the women will be given a chance to discuss the risks and benefits of vNOTES or laparoscopy for removing the adnexal mass, the process of randomisation and the follow-up requirements with the consultant gynaecologist. It will be carefully explained that the final decision about eligibility will be taken during the surgical procedure and is dependent on the findings; therefore consent will be required before the procedure, in every instance.

Over the past 4 years 145 laparoscopic adnexectomies were performed at the department of Obstetrics and Gynaecology of the participating centre. The mean number of procedures per year (SD) is 36 (± 13). About 69 % of the eligible women should be willing to participate in the proposed study to include the required amount of participants within 2.5 years (see: Section 6.1. Sample size on pages 31-32).

3.2. Determining eligibility

All women regardless of age and parity presenting with a symptomatic or asymptomatic persistent benign adnexal mass on clinical examination who provide consent to participation are eligible in the NOTABLE trial based on the findings of the ultrasound findings and will be randomised before the procedure.

The following inclusion/exclusion criteria will be applied to assess eligibility:

Inclusion criteria:

- All women regardless of age and parity with a symptomatic adnexal mass presumed to be benign based on ultrasound examination by applying the IOTA simple rules
- All women regardless of age and parity with an asymptomatic persistent adnexal mass presumed to be benign based on ultrasound examination by applying the IOTA simple rules

- Written informed consent obtained prior to surgery

Exclusion criteria:

- History of hysterectomy by any technique
- History of rectal surgery
- Suspected rectovaginal endometriosis
- Suspected endometriotic cyst
- Solid adnexal mass
- High suspicion of adnexal malignancy based on clinical, ultrasound or biochemical findings
- History of pelvic inflammatory disease, especially prior tubo-ovarian or pouch of Douglas abscess
- Active lower genital tract infection e.g. Chlamydia, N. gonorrhoeae
- Virginity
- Pregnancy
- Need for other uterine surgical intervention (i.e. endometrial ablation, resection, myomectomy or hysterectomy)
- Additional pathology necessitating hysterectomy
- Failure to provide written informed consent prior to surgery

Obesity (Body Mass Index or BMI > 30), nulliparity or large diameter of the cyst are not considered to be an exclusion criterion per se. We will only stratify for the diameter of the cyst because this parameter was perceived by the gynaecological surgeon as the most important one to influence the difficulty of the procedure. Stratification for three parameters in a small pilot randomised trial with a limited number of participants is not sensible.

3.3. Randomisation

If the woman is eligible for the NOTABLE trial, the trial secretary will obtain a randomised allocation the day before surgery. This will be done using a randomisation list generated by a free computer software program offered by Research Randomizer (https://www.randomizer.org). The random sequence generation will be concealed using sequentially numbered opaque sealed envelopes. The envelope will be opened by the nurse assistant on the day of surgery for practical logistic reasons. We will use stratified randomisation according to the cyst diameter. See 3.5 Stratification of randomisation.

3.4. Patients with strong preference for treatment

A minority of women will express a clear preference for one of both treatments (e.g. strong desire to have no scar) and for this reason will not wish to be randomised between surgical treatments. To investigate how outcomes vary by choice, these women could be followed up in exactly the same way as for those women randomised into the NOTABLE trial. We will however not do any formal non-randomised follow-up of these women for simple logistical reasons.

3.5. Stratification of randomisation

A blocked randomisation procedure will be used to avoid chance imbalances for the parameter 'cyst diameter'. We preferred not to use minimisation because this trial was not funded and we therefore could not afford to buy licenses for a computer-based algorithm for minimisation. Although parity and BMI may be prognostic parameters influencing the chances of the successful removal of the adnexal mass, we preferred to limit the stratification to one parameter for reasons of simplicity based on what is affordable to conduct the present research. It was not considered appropriate to use three strata in a small pilot study including a small number of participants.

To avoid any possibility of foreknowledge, the randomised allocation will not be given until all eligibility and stratification data have been given.

4. TREATMENT ALLOCATIONS

4.1. Surgical procedures

The principal investigator, who has training and experience in both laparoscopy and NOTES, will perform all surgical procedures. He is therefore not blinded. All vNOTES participants will be blinded by three superficial "mock" skin incisions similar to those routinely done with the laparoscopic technique. The wound bandages will be left in place until the day 7 postoperative control to be removed by the coordinating investigator who will state at that moment that the wound healing has left an almost invisible scar as expected. This procedure aims to blind the participants, personnel and outcome assessors. The practice of performing "mock" incisions should not be considered as unethical: it is a procedure that has already been used in some surgical trials to minimise performance and detection bias whenever a subjective outcome is measured (22). The decision to use "mock" surgery is based on the clinical equipoise regarding the balance between benefits and adverse events for the two interventions under comparison (23).

4.1.1 vNOTES adnexectomy

This is the surgical procedure done in the intervention arm of the NOTABLE trial.

Clindamycin vaginal cream is administered on admission of the study participant to the outpatient ward.

The patient is placed in lithotomy position in a vacuum mattress. The abdomen, the vulva and the vagina are disinfected with an alcoholic betadine solution and draped. A Foley catheter is inserted into the bladder.

Three superficial skin incisions are made, one deep in the umbilicus and one in the left and right iliac fossa lateral of the epigastric vessels, and in the suprapubic region. The small vertical intraumbilical skin incision is closed with a monocryl 3/0 intradermal suture. Wound bandages are applied to all three skin incisions.

A 2.5 cm posterior colpotomy is made using a cold knife. The pouch of Douglas is opened using cold scissors. A Gelpoint Mini (Applied Medical) is used as vNOTES port and is inserted into the pouch of Douglas. CO_2 is insufflated until a maximal intraperitoneal pressure of 15mmHg. An optic is inserted and the peritoneal cavity is inspected. The patient is now placed in Trendelenburg position. The small intestine is lifted out of the pelvis.

The ureter is identified, but not routinely dissected. It is only dissected if it cannot be identified transperitoneally. The proximal end of the Fallopian tube is coagulated at its origin into the uterus

using a reusable bipolar grasping forceps before being cut using cold scissors. The ovarian ligament is coagulated and cut. The infundibulopelvic ligament is coagulated and cut. The adnexa is resected. If necessary, the same procedure is repeated for the contralateral side. The peritoneal cavity is rinsed and haemostasis is checked.

Small and benign adnexa will be removed directly through the wound protector part of the NOTES port. Large adnexa or adnexa that are macroscopically suspicious, will be placed in an endobag (Memobag, Teleflex). The purse string of the endobag is pulled through the wound protector and the purse string is released. The content of the cyst is aspirated to reduce the volume of the adnexa. The endobag is now removed with the adnexa inside it. The vNOTES port is removed.

The colpotomy is closed using three interrupted figure-of-eight Vicryl 2/0 sutures. A vaginal plug (betadine gauze 10cmx5m) is placed to be removed after 3 hours together with the Foley catheter.

Antibiotic administration:

Cefazolin 2g and metronidazol 1.5g are administered IV during the procedure.

Analgesia at the recovery room and the nursing ward: The pain management for both groups was discussed with two senior staff members of the department of anaesthesiology of the hospital, who are co-investigators. The protocol will be standard for both comparison groups and is presented in appendix V.

The vaginal plug and the Foley catheter are removed 3 hours after the surgery. The bandages are left in place and not changed unless soaked by blood with a need to change. The personnel of the recovery room will be asked to replace bandages only for hygienic reasons and immediately to apply a new wound dressing without revealing any information to the participant or personnel on the outpatient or hospitalization ward.

The decision to discharge or to admit to hospital for the night will be based solely on the choice of the woman to return home the same day or stay overnight. The outcome assessor will report this decision in the patient record without consulting the results of the pain scoring or whether or not additional analgesics were administered. Every woman leaving the hospital will be given a standard list with instructions not to have intercourse during six weeks and not to work for a period of four weeks. Telephone numbers will be provided for contacting the staff members on call in case urgent medical care for treating any adverse event is needed. Cefazolin 2g is administered IV before discharge.

4.1.2 LSC adnexectomy

This is the surgical procedure done in the control arm of the NOTABLE trial.

Clindamycin vaginal cream is administered on admission of the study participant to the outpatient ward.

The woman is placed in lithotomy position in a vacuum mattress. The abdomen, the vulva and the vagina are disinfected with an alcoholic betadine solution and draped. A Foley catheter is inserted into the bladder.

A small vertical intra-umbilical skin incision is made. A Verress needle is inserted into the peritoneal cavity; the correct position of the needle tip is checked with Semm test. CO_2 is insufflated until a maximal intraperitoneal pressure of 15mmHg. The Verress needle is removed and replaced by a 10mm reusable trocar. An optic is inserted through the 10mm trocar and the peritoneal cavity is inspected. The patient is now placed in Trendelenburg position. Two reusable 5mm trocars are placed under direct vision in the left and right iliac fossa lateral of the epigastric vessels. The small intestine is lifted out of the pelvis.

The ureter is identified, but not routinely dissected. It is only dissected if it cannot be identified transperitoneally. The proximal end of the Fallopian tube is coagulated at its origin into the uterus using a reusable bipolar grasper and cut using cold scissors. The ovarian ligament is coagulated and cut. The infundibulopelvic ligament is coagulated and cut. The adnexa are resected and placed in an endobag (Memobag, Teleflex). If necessary, the same procedure is repeated for the contralateral side.

The peritoneal cavity is rinsed and haemostasis is checked. No drains are left in the peritoneal cavity except when there might be any uncertainty concerning the haemostasis. The 5 mm trocars are removed under direct vision. The purse string of the endobag is pulled through the 10 mm trocar upon removal of the optic. The umbilical incision is extended vertically in caudal direction, the size being not more than 2.5 cm. The fascia and peritoneum are opened and the proximal end of the endobag is pulled through the incision without causing any rupture if possible. If not possible, the endobag should be opened and the content of the cyst should be aspirated to reduce the volume of the adnexa. The aspirated fluid should be send for cytological examination. The endobag is now removed with the adnexa inside it.

The fascia is closed using a Vicryl-1 running suture. The umbilicus and the other incisions are disinfected with Betadine solution. The skin incisions are closed with a monocryl 3/0 intradermal

suture and steri-strips. The wound sites are covered with a standard bandage. A vaginal plug (betadine gauze 10 cm x 5 m) is placed to be removed after 3 hours together with the Foley catheter.

Antibiotic administration:

Cefazolin 2g and metronidazol 1.5g are administered IV during the procedure.

Analgesia at the recovery room and the nursing ward: The pain management for both groups was discussed with two senior staff member of the department of anaesthesiology of the hospital, who are co-investigators. The protocol will be standard for both comparison groups and is presented in appendix V.

The vaginal plug and the Foley catheter are removed 3 hours after the surgery. The bandages are left in place and not changed unless soaked by blood with a need to change. The personnel of the recovery room will be asked to replace bandages only for hygienic reasons and immediately to apply a new wound dressing without revealing any information to the participant or personnel on the day care unit or hospitalisation ward.

The decision to discharge or to admit to hospital for the night will be based solely on the choice of the woman to return home the same day or stay overnight. The outcome assessor will report this decision in the patient record without consulting the results of the pain scoring or whether or not additional analgesics were administered. Every woman leaving the hospital will be given a standard list with instructions not to have intercourse during six weeks and not to work for a period of four weeks. Telephone numbers will be provided for contacting the staff members on call in case urgent medical care for treating any adverse event is needed. Cefazolin 2g is administered IV before discharge.

4.1.3 Failure of procedure

Occasionally, surgical removal of a benign adnexal mass by any of the two techniques may not be completed according to the random sequence generation because of technical limitations or unexpected findings such as extensive adhesions or unexpected malignancy. Successful vNOTES or laparoscopic removal of a benign adnexal mass is possible in the majority of women, but the probability of success is not readily predictable. In cases where the intended procedure has to be abandoned, the appropriate technique (e.g. staging laparotomy for ovarian cancer) or a second procedure (e.g. laparoscopy or laparotomy after bowel preparation) under general anaesthesia should be scheduled as soon as possible. Women who require an alternative more appropriate intervention or a second procedure are not excluded or withdrawn from the NOTABLE trial. The investigators will sensitively explain to them that follow-up information is still very important,

despite the change in treatment, and unless they wish to withdrawn completely from the trial, they will be followed up.

4.2. Concomitant interventions and treatments

It is anticipated that most women presenting with a suspected benign adnexal mass will require no further intervention other that removal of the adnexa. However, in some circumstances additional treatments may be considered necessary by the responsible clinician at the time of adnexal removal or subsequently. Surgical interventions in the form of endometrial ablation or hysterectomy may subsequently be necessary and the need for such interventions will be recorded. However, if the need for additional surgery *at the time* of surgery is indicated, then such patients are excluded for recruitment to the NOTABLE trial. All therapeutic interventions additional to removal of one or both adnexa will be recorded and as the trial is randomised we anticipate that these further interventions will be symmetrically applicable.

4.3. Withdrawal from the NOTABLE trial

All women who consent to the randomised NOTABLE trial, should be followed up and asked to complete postal questionnaires, regardless of actual treatment received.

If a woman specifically requests a treatment setting *after* randomisation, then her choices should be respected. This does not necessitate withdrawal from the trial. Similarly, if one of both procedures fails, she will require subsequent treatment. In both circumstances, it should be sensitively explained to them that follow-up information is still very important, and unless they wish to withdrawn completely from the trial, they will be followed up. Any request to withdraw from follow-up should be notified to the NOTABLE study nurse.

4.4. Serious and unexpected adverse events

There may be mortality and morbidity associated with either procedure, therefore all serious adverse events (SAE) should be reported by fax to the NOTABLE Trial Office as soon as possible. This report should be followed within 2 days by a completed SAE form to the Ethics Committee and the Federal Agency for Medicines and Health Products (FAMHP). For the purposes of this study, “serious” adverse events are those which are fatal, life-threatening, disabling or prolong hospitalisation and have resulted from the surgical procedure, the anaesthetic or post-operative recovery e.g. deep vein thrombosis, hospital acquired infections.

5. FOLLOW-UP AND OUTCOME MEASURES

5.1. Clinical assessments

5.1.1 Format

PROMs will be collected using a postal questionnaire at baseline, at three and six months.

The postal questionnaires will be sent from the NOTABLE Trial Office with postage paid envelopes two weeks before the due date. Reminders will be sent to the participants if the questionnaire is not returned within one week of the due date and attempts will be made to contact the women by phone if the questionnaire is not returned by two weeks after the due date.

5.1.2 Timing of assessments

The primary outcome will be measured clinically at the end of the surgical procedure. In addition PROMs will take place the evening of the surgical intervention (return home), during the first postoperative week (pain by VAS scores and medication) and at 3 and 6 months (dyspareunia and sexual wellbeing). Clinical physician assessment will take place the evening of the surgical intervention (return home) and during the first six weeks following surgery (pelvic infection, surgical complications).

5.2. Primary clinical outcome measure

The proportion of women successfully treated by removing the adnexal mass without spill, using a dichotomous outcome measure, will be used as a measure of efficacy. An important consideration in adnexal mass surgery is the inadvertent opening of the ovarian capsule. The likelihood of cyst rupture during removal by laparotomy or laparoscopy ranges from 10.5% to 41.8% in published studies (15). We will consider any spontaneous rupture of the cyst or any need to aspirate the cyst to allow removal from the abdominal cavity as treatment failures, even if the content of the ruptured cyst does not spill freely inside the cavity but remains within the endobag. By avoiding any subjective interpretations this rigorous definition allows an objective measure of success. As the risk of rupture may be associated to the cyst size, due to the stratified random sequence generation we anticipate that the risk of rupture due to the cyst size rather than the technique used will be symmetrically applicable.

5.3. Secondary clinical outcome measures

We will measure the following secondary outcomes:

- The proportion of women discharged the same day based on their own preference, as a dichotomous outcome. The decision to discharge from the day care unit or to admit to hospital for the night will be based solely on the choice of the woman to return home the same day or stay overnight. The outcome assessor will report this decision in the patient record without consulting the results of the pain scoring or whether or not additional

analgesics were administered. In case of conflict (women wishing to return home against outcome assessor's advice based on clinical suspicion of possible complications for instance) the study participant is not excluded from further follow-up. Data will be analysed using a sensitivity analysis by imputing that the index participant would have agreed to stay overnight as dictated by the clinical judgement of the outcome assessor versus the available data analysis.

- Postoperative pain scores, as an ordinal outcome, measured using a VAS scale twice daily from day 1 till 7 self-reported by the participating women: one measurement will be done in the morning after bed rest at night (rest) and the other will be done in the evening before going to bed after physical activity (active). The participants should place the cursor of the VAS scale device available at the day care unit of the participating centre on the picture indicating the expression of pain sensation that according to their own experience best describes how they feel pain at the time point of measurement. By looking at the back of the scale they can measure the level of pain by recording the numbers immediately to the left and right of the red line: e.g. pain level 0 to 1, or pain level 5 to 6. The lowest number will be recorded by the outcome assessor for data analysis. The reliability of VAS has been established in the assessment of chronic gynaecological conditions like pain.
- Postoperative pain defined by the total use of analgesics during the first week following surgery as described in the standardized pain treatment protocol, as an ordinal outcome. The use of pain medication following surgery should be reported in the nursing file. At home the participants should note in their participant log book the name, dosage, route of administration of any analgesic drug that was taken from the moment they are at home until the assessment on day 7 irrespective of whether this was done on their own initiative or after consulting a family physician or any other medical specialist. The assessment of the total use of analgesics will be done on day 7 by the outcome assessor (the coordinating investigator), who is blinded for the intervention done by the principal investigator.
- Postoperative infection defined by lower abdominal pain with fever > 38°C and positive clinical signs or laboratory findings, detected during the first six weeks of surgery, as a dichotomous outcome.
- Per- or postoperative complications according to the Clavien- Dindo classification detected during the first six weeks of surgery, as a dichotomous outcome (Appendix III).
- Hospital readmission during the first six weeks of surgery, as a dichotomous outcome.
- Incidence and intensity of dyspareunia recorded by the participants at 3 and 6 months by self-reporting using a simple questionnaire and VAS scale, as a dichotomous and ordinal

outcome. A measurement of the prevalence and the intensity of dyspareunia will be done at baseline assessment.

- Sexual wellbeing at baseline, at 3 and 6 months by self-reporting the SSFS.
- Quality of life at baseline, at 3 and 6 months by self-reporting the EQ-5D-3L questionnaire.
- Duration of surgery measured as the time in minutes from the insertion of the bladder catheter to the end of vaginal/abdominal wound closure, as a continuous outcome.

5.4. Health economic outcomes

Costs and consequences of the treatment pathways will be collected from health care providers at the time of the procedure and at follow up in order to conduct the cost-effectiveness analyses.

Resource use data will include:

• Surgical treatment of benign adnexal mass

• Tests and investigations received

• The frequency and duration of out-patient visits and primary care consultations

• Inpatient stays

• Type and volume of medications received

• The number and duration of hospital readmissions and re-treatments.

These data will be collected prospectively from health care providers using a post-operative case report form and patient-completed questionnaires that assess patient health service utilisation at the follow-up time points throughout the trial. Costs incurred by patients will also be collected to conduct an evaluation from a wider societal perspective. Therefore, a patient cost questionnaire will be administered to all trial patients in order to consider the wider cost implications of the interventions which will contain questions to determine out of pocket expenses incurred when attending for treatment and private time costs including time lost from work.

Unit costs obtained from published sources and the trial centre will be used to estimate costs associated with resource use. Responses to the EuroQol EQ-5D-3L questionnaire will inform the effectiveness in terms of QALYs and clinical effectiveness will be measured in cured cases at six months. We obtained full approval of EUROQoL to use the questionnaire for free.

Data collection will be undertaken prospectively for all trial patients so that a stochastic cost analysis can be undertaken. The process of collecting resource use data will be undertaken separately from data collection on unit costs.

The main resource use to be monitored include the following:

1) Consultation time required prior for each procedure for explanation and consent.

2) Costs involved with each procedure including level of health care professional involvement in the procedure, equipment required, overheads, consumables and drugs including anaesthesia.

3) Any additional procedures required where initial treatment is unsuccessful or incomplete.

4) Duration of inpatient stay when women opt to stay overnight.

Information on any additional related primary or secondary care contacts will also be collected from all women to ensure any resulting resource use from additional complications is recorded. Unit costs will be obtained and attached to resource items in order that a cost can be calculated for each trial patient. Unit costs will be obtained from published sources and the centre participating in the trial. In addition, the set-up costs of NOTABLE will be estimated and additional analyses will be undertaken including these costs.

5.5. Data management and validation

5.5.1 Confidentiality of personal data

Personal data and sensitive information required for the NOTABLE Trial will be collected directly from participants, who will be informed about the transfer of this information to the trial office at the department of Obstetrics and Gynaecology of the participating centre and will be asked to consent to this. The data will be entered onto a secure computer database, either by staff or directly via a secure internet connection. Any data to be processed outside the trial office will be anonymised. All personal information obtained for the study will be held securely and treated as (strictly) confidential. All staff involved in the NOTABLE Trial (clinical, paramedical, administration) share the same duty of care to prevent unauthorized disclosure of personal information. No data that could be used to identify an individual will be published. We will handle all data confidentially in accordance with the Belgian law of 8 December 1992 on the protection of privacy with respect to the handling of individual personal data.

5.5.2 Long-term storage of data

In line with existing guidelines and Belgian legislation, all data will be stored for up to 15 years after the last participant has reached the 2.5 year follow-up to allow adequate time for review, reappraisal or further research, and to allow any queries or concerns about the data, conduct or conclusions of the study to be resolved.

5.6. Withdrawal from follow-up

Withdrawal from follow-up is the decision of the participant. However, withdrawn patients can bias clinical trial results and reduce the power of the study to detect important differences, so women should be encouraged to complete all follow-up questionnaires. Methods to reduce the burden of follow-up will be explored e.g. online data entry for participants. If the reason for withdrawal is known, it should be communicated to the NOTABLE Trial Office. To reduce loss to follow-up, we shall record patient's social security number, which allows us to track patients changing GP practice. With postal and telephone reminders we anticipate that, the completeness of data should surpass 90% although, as set out below incomplete follow-up is incorporated into the power calculations.

6. ACCRUAL AND ANALYSIS

6.1. Sample size

The sample size for the primary outcome of this trial has been chosen to give good statistical power to preclude any clinically important inferiority of vNOTES compared to laparoscopy and is based on evidence retrieved from a systematic review of the literature (15) and a RCT comparing the excision of mature teratoma using culdotomy with and without laparoscopy (17). An important consideration in adnexal mass surgery is the inadvertent opening of the ovarian capsule. The likelihood of cyst rupture during removal by laparotomy or laparoscopy ranges from 10.5% to 41.8% in published studies (15). Based on a low failure rate to remove dermoid cysts by colpotomy using laparoscopy (2.4%), according to the findings from a RCT (17) we assumed a successful removal of adnexal cysts without spill to be feasible in 95% of all cases. We calculated the sample size with a one-sided test for non-inferiority studies for the primary outcome. The vNOTES approach may be more convenient for women in that no scar in the abdominal wall is required. We believe, therefore, that vNOTES would be the treatment of choice even if 15% less women had successful removal of a benign adnexal mass by using the vNOTES approach. Non inferiority will be concluded when 15% lies above the upper limit of the 95% confidence interval calculated for the difference in the proportion of women successfully treated with either of both techniques. To achieve 80% power to demonstrate non-inferiority under the assumption of similar success rates of 95% in both groups a sample size of 54 participants (27 women per group) will be required. The target sample size was increased to 64 participants (32 women per group) to account for a drop-out rate of 15%.

(https://www.sealedenvelope.com/power/binary-noninferior/). Based on the power calculations for the primary outcome, the use of three strata for the randomisation and assuming a loss-to-follow-up rate of 15 % we decided to include 66 study participants in the NOTABLE trial.

6.2. Projected accrual and attrition rates

It is anticipated that recruitment of participants will take two years. Based upon the mean number of laparoscopic adnexectomies performed annually at the department of Obstetrics and Gynecology of the participating centre (36) we estimate that the duration of recruitment will be 21 months. Based upon the follow up (6 months) and the period of analysis/reporting (3 months) the total study period will be 2.5 years. First publication will be possible within four years of trial commencement.

Our sample size calculation has allowed for a 15% loss to follow up rate. In order to minimise rates of attrition we will employ a dedicated research secretary to optimize recruitment and follow up.

6.3. Statistical Analysis

We will calculate a 95% confidence interval of the difference in the proportions of women with a successful removal of an adnexal cyst. Non inferiority of the intervention (vNOTES) will be concluded

when 15% lies above the upper limit of this confidence interval. For this primary analysis, adjustments for prognostic factors will not be made in the first instance; the effect of the variables listed in Section 3.5 (Stratification of randomisation) will be explored as a secondary analysis. Continuous measures (VAS scores) will be analysed using analysis of covariance (adjusting for baseline value). Multilevel models for repeated measurements will also be used to compare the mean differences in VAS pain scores between groups overall at all time points, thereby maximising the power of the data available.

Analysis will be performed on an 'intention to treat' basis in the first instance as recommended in the CONSORT statement. A 'per protocol' analysis will also be performed to test the robustness of the results obtained. As a conservative measure, estimates of effect sizes between the two arms will be presented as point estimates with two-sided 95% confidence intervals. The trial can only conclude non-inferiority if 15% lies out of the upper band of the confidence interval (i.e. vNOTES 15% less successful than laparoscopic treatment).

Baseline characteristics of the patients enrolled in the two groups will be compared to ensure that randomisation has produced comparable groups of participants, and will be covariates in the modelling procedure.

6.3.1 Subgroup analyses

Subgroup analyses are limited by statistical power and can produce spurious results particularly if many are undertaken. We will not undertake any subgroup analyses in this pilot study.

6.3.2 Proposed frequency of analyses

1. Twice yearly review of recruitment, compliance and loss to follow-up for NOTABLE Trial Steering Committee.
2. Annual interim analyses of effectiveness for confidential review by Ethics Committee to determine whether the principal question has been answered and to monitor adverse events.
3. Main analyses of effectiveness of NOTABLE once all participants have reached 6-month follow up of the total study sample.
4. Additional analysis of longer term effects (completion of one and two years of follow-up).

6.3.3 Handling missing data

The interpretation of missing values in the analysis of clinical trials can be fraught with danger. The methods used to allow for missing data make assumptions about the reasons for data not being present, such as in the "observed case" analysis, where the presence or absence of data is viewed as unrelated to outcome, or in the "Last Observation Carried Forward" analysis where the assumption is that the condition does not improve or worsen following withdrawal from follow-up. To minimise possible biases, participants will continue to be followed up even after protocol treatment violation.

Missing data items will be imputed from given values if limited to a single item response. If a form is missing entirely or greater than one item imputation will not be attempted. Sensitivity analyses will be carried out to determine whether or not the results obtained are robust to the methods used to handle missing data. These approaches are in line with the recent recommendations from the European Agency for the Evaluation of Medicinal Products.

Questionnaires will only be treated as late if they are returned after the subsequent questionnaire has been sent to the participant. However if this form is the only form available at the later time point it will be included at the subsequent time.

6.4. Health Economic Analysis

6.4.1 Form of the economic evaluation

If vNOTES is found to be an effective treatment for the removal of benign adnexal mass, then it is likely that there can be cost implications for the health care sector. For example, as the woman will be treated as an outpatient, thus avoiding an inpatient stay, resources may be saved. However, vNOTES may incur costs due to equipment required and the specialist nature of health care professionals to perform this procedure. Therefore all costs incurred by both procedures need to be assessed in conjunction with measures of effectiveness.

The aim of the economic evaluation is to determine the cost-effectiveness of vNOTES compared with standard laparoscopic treatment. Although the trial has been designed as a non-inferiority trial, we feel the most appropriate type of analysis is a cost-effectiveness analysis. Cost-effectiveness will be determined in two ways. A cost-effectiveness analysis will be undertaken to calculate the cost per additional cured case adnexal removal at six months, utilizing the clinical outcome data collected within the trial. In addition, a cost-utility analysis will be undertaken to calculate the cost per additional quality-adjusted life year (QALY) gained. The utility values required to calculate QALYs will be obtained by administering the EuroQol EQ-5D-3L questionnaire to all study patients at baseline, three months and six months. In the first instance, the evaluation will consider costs incurred by the health service in the delivery of both treatment pathways. However, information on costs incurred by patients will also be collected in order that an evaluation from a wider societal perspective can also be undertaken.

6.4.2 Economic analysis

Given the objective of the trial and limited available evidence in support of the NOTABLE strategy, only a within trial economic analysis will be carried out. The analysis will adopt an incremental approach in that data collection will concentrate on resource use and outcome differences between trial arms. As the majority of cost data are skewed, and the mean cost of each procedure is of importance, a bootstrapping approach will be undertaken in order to calculate confidence intervals

around the mean costs. As the time frame of the economic evaluation is not greater than one year, discounting is not required.

Uncertainty in the confidence to be placed on the results of the economic analysis will be explored by estimating cost-effectiveness acceptability curves. These plot the probability that the intervention is cost-effective against threshold values for cost-effectiveness. The robustness of the results will be explored using sensitivity analysis. This will explore uncertainties in the trial based data itself, the methods employed to analyse the data and the generalizability of the results to other settings.

We will seek the assistance of an expert in health economics at the University of Ghent, Belgium.

6.5. Definition of the end of trial

The end of the NOTABLE trial will be defined as the time when the last participant recruited has completed 6 months of follow up.

7. ASSESSMENT OF PATIENT ACCEPTABILITY

7.1. Measurements for Patient Acceptability

The acceptability of vNOTES will principally be assessed using a questionnaire designed specifically for the study and administered within 24 hours of treatment to limit recall bias. Pilot testing will be carried out to make certain the questionnaire is usable. In addition to the questionnaire, data will be collected on the women who do not give consent to randomization (state a preference and agree to be registered for the NOTABLE study), and requested from those who decline to participate.

In order to aid interpretation and understanding of the questionnaire data, and to gain greater depth of experience, the acceptability of NOTABLE will further be assessed using a qualitative methodology. Interviewing after discharge will allow the woman time to reflect on her experience, and will also minimise the chance that gratitude to doctors and other hospital staff results in unduly positive responses. Honesty is also more likely to occur on neutral or the patient's home ground. Interviews will be recorded with patients' permission and transcribed verbatim. The interview schedule will be designed following a literature search on patient acceptability of surgical procedures, and from the focus group discussions. From these, a set of items will be derived which will seem relevant to the participants and cover all the areas thought to be important by participants. The latter will also ensure that the questionnaire is as discriminatory as possible. The interview schedule will be piloted with five women. These procedures will ensure face and content validity, and sending each woman the transcript of her interview with the opportunity to amend any inaccuracy will assess fair and accurate representation.

7.1.1 Sampling of Participants for In-depth Interview

We propose to select a 20% random sample (6 women) from each arm of the research for interview within one week of discharge either face to face, or by telephone.

7.2. Evaluation of Patient Acceptability

Analysis of data will be by content analysis with the development of analytical themes. The initial process will be the intensive reading and re-reading of interview transcripts, and a search for regularities, contradictions, patterns and themes by comparing the participants' statements using a coding frame. Inter-rater reliability on the coding of transcripts will be undertaken. A percentage of the transcripts will be coded independently by two members of the qualitative research team and discrepancies discussed and resolved. Emergent themes obtained by this process will be refined until final themes are agreed by all applicants as reflective of the data. 'Researcher triangulation' will offer the first step to verification of the findings. This will be achieved through the independent analysis of 20% of transcripts from the sample by the researchers. Verification occurs through discussion of their analyses, comparison and subsequent consensus. 'Respondent validation' will also be sought by

taking the tentative findings back to a sample of participants in order to be verified as reflective of their experience. A final form of verification is the comparison of findings with, and their embeddedness in the available literature.

It is anticipated that the questionnaire and the subsequent in depth interviews will measure and provide insight into acceptability and satisfaction in the following areas: the procedure(s) for diagnosis; the information provided when consent is obtained; procedures to protect confidentiality; preference for one arm of the trial over the other; experience of the procedure and the immediate post-operative phase; overall satisfaction with the process; acceptability for the same procedure if adnexal masses are diagnosed in the future; perceptions of being involved in an RCT.

8. DATA ACCESS AND QUALITY ASSURANCE

8.1. In-house Data Quality Assurance

The study will adopt a centralized approach to monitoring data quality and compliance. A computer database will be constructed specifically for the study data and will include range and logic checks to prevent erroneous data entry. Independent checking of data entry of paper questionnaires will be periodically undertaken on small sub-samples. The trial statistician will regularly check the balance of allocations by the stratification variables. Source data verification will only be employed if there is reason to believe data quality has been compromised.

8.2. Independent Trial Steering Committee

The Trial Steering Committee (TSC) provides independent supervision for the trial, providing advice to the Chief and Co- Investigators on all aspects of the trial and affording protection for patients by ensuring the trial is conducted according to the MRC Guidelines for Good Clinical Practice in Clinical Trials.

If the Chief and Co-Investigators are unable to resolve any concern satisfactorily, Principal Investigators, and all others associated with the study, may write through the Trial Office to the chairman of the TSC, drawing attention to any concerns they may have about the possibility of particular side-effects, or of particular categories of patient requiring special study, or about any other matters thought relevant.

8.3. Data Monitoring and Ethics Committee: Determining when clear answers have emerged

If vNOTES is clearly inferior to standard laparoscopic treatment, with respect to the primary endpoint, then this may become apparent before the target recruitment has been reached. Alternatively, new evidence might emerge from other sources that vNOTES definitely more, or less, effective than laparoscopy. To protect against this, during the period of recruitment to the study, interim analyses of major endpoints will be supplied, in strict confidence, to an independent Data Monitoring and Ethics Committee (DMEC) along with updates on results of other related studies, and any other analyses that the DMEC may request. The DMEC will advise the chair of the Trial Steering Committee if, in their view, any of the randomised comparisons in the trial have provided both (a) “proof beyond reasonable doubt” that for all, or some, women that vNOTES is so inferior from laparoscopy that non-inferiority can never be demonstrated, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. The TSC can then decide whether to close or modify any part of the trial. Unless this happens, however, the Trial

management group (TMG), TSC, the investigators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

9. ORGANIZATION AND RESPONSIBILITIES

All investigators are responsible for ensuring that any research they undertake follows the agreed protocol, for helping care professionals to ensure that participants receive appropriate care while involved in research, for protecting the integrity and confidentiality of clinical and other records and data generated by the research, and for reporting any failures in these respects, surgical complications and other events or suspected misconduct through the appropriate systems.

9.1. Centre eligibility

Not applicable since NOTABLE is a single centre RCT.

9.2. Local Coordinator

The responsibilities of the local Principal Investigator will be to ensure that all medical and nursing staff involved in the care of NOTABLE are well informed about the study and trained in trial procedures, including obtaining informed consent. The local Principal Investigator should liaise with the Trial Coordinator on logistic and administrative matters connected with the trial.

9.3. Nursing Coordinator

One nurse will be designated as *local Nursing Coordinator*. This person would be responsible for ensuring that all eligible patients are considered for the trial, that patients are provided with patient information sheets, and have an opportunity to discuss the study if required. The nurse may be responsible for collecting the baseline patient data and will act as a contact for obtaining missing follow-up evaluations. Again, this person would be sent updates and newsletters, and would be invited to training and progress meetings.

9.4. The NOTABLE Trial Office

The Trial Office at department of Obstetrics and Gynaecology of the participating centre is responsible for providing all trial materials, including the trial folders containing centre specific trial documentation, standard operating procedures and training materials. Additional supplies of any printed material can be obtained on request or downloaded from the NOTABLE trial website. The Trial Office is responsible for collection and checking of data (including reports of serious surgical complications), for reporting of serious adverse events to the sponsor and/ or regulatory authorities and for analyses. The Trial Office will help resolve any local problems that may be encountered in trial participation.

9.5. Research Governance

The study will be conducted according to the principles of the Declaration of Helsinki (Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000) and in accordance with the Belgian law of 7 May 2004 that regulates human experiments in Belgium.

All Principal Investigators will be required to sign an Investigator's Agreement, detailing their commitment to accrual, compliance, Good Clinical Practice, confidentiality and publication. Deviations from the agreement will be monitored and the TSC will decide whether any action needs to be taken, e.g. withdrawal of funding, suspension of centre.

9.6. Research Governance and Ethical Approval

As the trial does not involve an investigational medicinal product, clinical trial authorization from the Medicines and Healthcare products Regulatory Authority is not required.

In accordance to the Belgian law of 7 May 2004 that regulates human experiments, the investigator will inform the study participants and the medical ethical committee if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review, except insofar as suspension would jeopardize the subjects' health. The investigator will take care that all subjects are kept informed.

The principal investigator will report all adverse and serious events to the medical ethical committee.

Adverse events are defined as any undesirable experience occurring to a participant during the study, whether or not considered to be related to the intervention.

All adverse events reported spontaneously by the participant or observed by the investigator or his staff will be recorded.

A serious adverse event is any untoward medical occurrence or effect that:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

All SAEs will be reported to medical ethical committee that approved the protocol, within 15 days after the investigator has first knowledge of the serious adverse reactions.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur no later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

9.7. Funding and Cost implications

The research costs of this non-commercial trial are funded by the investigating team.

9.8. Indemnity

No additional preoperative examinations are needed when compared to the situation where the woman would not have given informed consent for study participation. One additional postoperative examination is needed for study participants compared to routine clinical practice: no risks or side effects are associated with this additional assessment. The risks and side effects for both types of surgical interventions have been extensively described in the consent form. According to two large prospective studies the incidence of complications associated with minimally invasive surgery are less than 1%. (26, 27) The benefit is an, as of yet, unknown increase in the chance of being discharged the same day as the surgical procedure with less postoperative pain.

The investigators have a 'no fault' liability insurance which is in accordance to the Belgian law of 7 May 2004 that regulates human experiments. The insurance aims to cover the financial consequences of the civil liability that the investigators may incur even when no fault has occurred as a result of the organization of medical experiments on the human person. All physical and material damage sustained by the participant in the experiment and/or his/her assignees and arising from the insured experiment are covered for an amount of 2 500 000 € per experiment. The insurance applies to the damage that becomes apparent during the study or within 36 months after the end of the study.

9.9. Publication

A meeting will be held after the end of the study to allow discussion of the main results among the collaborators prior to publication. The success of the study depends entirely on the wholehearted collaboration of a dedicated team of doctors, nurses and others.

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9.10. Ancillary studies

It is requested that any proposals for formal additional studies of the effects of the trial treatments on some participants (e.g. special investigations in selected hospitals) be referred to the Trial

Management Committee for consideration. In general, it would be preferable for the trial to be kept as simple as possible, and add-on studies will need to be fully justified.

10. REFERENCES

(1) Burpee SE, Kurian M, Murakame Y, Benevides S, Gagner M. The metabolic and immune response to laparoscopic versus open liver resection. Surg Endosc. 2002; 16(6):899 –904.

(2) Grande M, Tucci GF, Adorisio O, et al. Systemic acute-phase response after laparoscopic and open cholecystectomy. Surg Endosc. 2002; 16(2):313–6.

(3) Rattner D, Kalloo A. ASGE/SAGES working group on natural Orifice transluminal endoscopic surgery. October 2005. Surg Endosc. 2006; 20:329-33.

(4) Santos BF, Hungness ES. Natural orifice transluminal endoscopic surgery: progress in humans since white paper. World J Gastroenterol. 2011; 17:1655–65.

(5) Tolcher MC, Kalogera E, Hopkins MR, Weaver AL, Bingener J, Dowdy SC. Safety of Culdotomy as a Surgical Approach: Implications for Natural Orifice Transluminal. JSLS. 2012; 16:413–20

(6) Uccella S, Cromi A, Bogani G, Casarin J, Serati M, Ghezzi F. Transvaginal specimen extraction at laparoscopy without concomitant hysterectomy: our experience and systematic review of the literature. J Minim Invasive Gynecol. 2013; 20:583-90.

(7) Reynders A, Baekelandt J. Adnexectomy by Poor Man's Transvaginal NOTES. Gynecological Surgery 2015; 12(3): 207-11.

(8) Dindo D, Demartines N, Clavien PA. Classifi cation of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240**:** 205–13.

(9) Mc Williams GD, Hill MJ, Dietrich CS. Gynecologic emergencies. Surg Clin North Am 2008; 88(2): 265-83.

(10) Timmerman D, Ameye L, Fischerova D, Epstein E, Melis GB, Guerriero S, Van Holsbeke C, Savelli L, Fruscio R, Lissoni AA, Testa AC, Veldman J, Vergote I, Van Huffel S, Bourne T, Valentin L. Simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery: prospective validation by IOTA group. BMJ 2010; 341:c6839 doi:10.1136/bmj.c6839.

(11) Sainz de la Cuesta R, Goff BA, Fuller AF Jr, Nikrui N, Eichhorn JH, Rice LW. Prognostic importance of intraoperative rupture of malignant ovarian epithelial neoplasms. Obstet Gynecol. 1994;84(1):1.

(12) Webb MJ, Decker DG, Mussey E, Williams TJ. Factor influencing survival in Stage I ovarian cancer. Am J Obstet Gynecol. 1973;116(2):222.

(13) Pillai R, Yoong W. Posterior colpotomy revisited: a forgotten route for retrieving larger benign ovarian lesions following laparoscopic excision. Arch Gynecol Obstet. 2010; 281(4):609-11.

(14) Yang YS, Hur MH, Oh KY, Kim SY. Transvaginal natural orifice transluminal endoscopic surgery for adnexal masses. J Obstet Gynaecol Res. 2013 Dec; 39(12):1604-9.

(15)Demir RH, Marchand GJ. Adnexal masses suspected to be benign treated with laparoscopy. JSLS JSLS. 2012 Jan-Mar; 16(1): 71–84.

(16)Ghezzi F, Cromi A, Uccella S, Bogani G, Serati M, Bolis PF. Transumbilical versus transvaginal retrieval of surgical specimens at laparoscopy: a randomized trial. Am J Obstet Gynecol 2012; 207(2): 112.e1-112.e6.

(17) Wang PH, Lee WL, Juang CM, Tsai WY, Chao HT, Yuan CC. Excision of mature teratoma using culdotomy, with and without laparoscopy: A prospective randomized trial. BJOG 2001; 108: 91-4.

(18)Medeiros LR, Rosa DD, Bozzetti MC, Fachel JM, Furness S, Garry R, Rosa MI, Stein AT. Laparoscopy versus laparotomy for benign ovarian tumour. Cochrane Database Syst Rev. 2009 Apr 15; (2):CD004751.

(19)Barkun JS, Aronson JK, Feldman LS, Maddern GJ, Strasberg SM, for the Balliol Collaboration. Evaluation and stages of surgical innovations. The Lancet 2009; 374:1089-96.

(20)Ergina PL, Cook JA, Blazeby JM, Boutron I, Clavien PA, Reeves BC, Seiler CM, for the Balliol Collaboration. Challenges in evaluating surgical innovation. The Lancet 2009; 374:1097-1104.

(21)Mc Culloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, Nicholl J, for the Balliol Collaboration. No surgical intervention without evaluation: the IDEAL recommendations. The Lancet 2009; 374: 1105-12.

(22)Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykendall DH, Hollingsworth JC, Ashton CM, Wray NP. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med. 2002 Jul 11; 347(2):81-8.

(23)Freedman B. Equipoise and the ethics of clinical research. N Engl J Med 1987; 317: 141-145.

(24) Bird SB, Dickson EW. Clinically significant changes in pain along the visual analog scale. Ann Emerg Med 2001;38: 639-43.

(25) Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. Ann Emerg Med 1996; 27: 485-9.

(26) Jansen FW, Kapiteyn K, Trimbos-Kemper T, Hermans J, Trimbos-Kemper JB. Complications of laparoscopy: a prospective multicenter observational study. Br J Obstet Gynaeco 1997; 104: 595-600.

(27)Harrki-Sirén P, Sjoberg J, Kurki T. Major complications of laparoscopy: a follow-up Finnish study. Obstet Gynecol 1999; 94: 94-8.

APPENDIX I: TABLE I

Table 1 Overview of patient and perioperative characteristics

Data	Mean	Range
Age (years)	51	31 - 75
BMI (kg/m^2)	24.0	17.2 - 28.7
Total operating time (min)	32	20 - 50
Serum hemoglobine drop (g/dl)	0.9	0 - 2.1
Postoperative pain score		
6h	2.0	0 – 4
24h	1.3	0 – 2
Size of adnexal mass (mm)	51.8	35 - 110

APPENDIX II: TABLE II

Table 2 Patient and perioperative characteristics of consecutive patients

CE = cystectomy; CS = caesarean section; LS = laparoscopic sterilisation; USO = unilateral salpingo-oophorectomy; BSO = bilateral salpingo-oophorectomy; R = right; L = left.

Patient no.	Age (years)	BMI (kg/m^2)	Parity	History of vaginal delivery	Previous pelvic surgery	Type of surgery	Total operating time (min)	Serum hemo-globine drop (g/dl)	(Peri-) operative complications	Postoperative pain score		Size of adnexal mass (largest diameter, mm)
										6h	24h	
1	54	24.1	P4	Yes	LS	BSO	40	0.4	-	2	2	70
2	44	17.2	P1	Yes	-	USO R	35	0.8	-	2	2	62
3	56	21.5	P2	Yes	LS	BSO	35	0.5	Cystitis	2	2	35
4	47	27.1	P2	Yes	-	USO R	30	0	-	2	1	50
5	58	26.0	P0	No	-	BSO	35	0.6	-	4	1	40
6	52	28.3	P0	No	-	USO R	35	0.6	-	1	1	36
7	66	22.9	P2	Yes	-	BSO	40	0.7	-	2	1	45
8	46	20.8	P0	No	-	USO R	22	1.4	-	2	1	35
9	51	25.4	P2	Yes	-	USO L	22	0.5	-	2	1	35
10	56	24.2	P1	Yes	-	USO R	25	1.2	-	2	1	42
11	63	26.7	P2	Yes	-	BSO	30	2.0	-	3	0	40
12	56	25.0	P2	Yes	-	USO R	22	0.5	-	1	1	39
13	75	23.2	P1	Yes	-	USO R	20	0.6	-	2	2	38
14	31	21.5	P2	Yes	-	USO R	35	1.8	-	2	2	60
15	45	28.7	P1	Yes	-	USO R	20	0	-	2	2	40
16	43	24.4	P2	No	CS	USO R	50	0.9	-	2	2	100
17	45	23.7	P2	Yes	CE	USO R	45	0.7	-	0	0	110
18	36	22.8	P2	Yes	CS	USO R	40	1.7	-	2	1	39
19	55	23.4	P1	Yes	-	BSO	35	1.2	-	2	1	70
20	38	22.5	P2	Yes	-	USO L	32	2.1	-	2	2	49

APPENDIX III

CLAVIEN-DINDO CLASSIFICATION

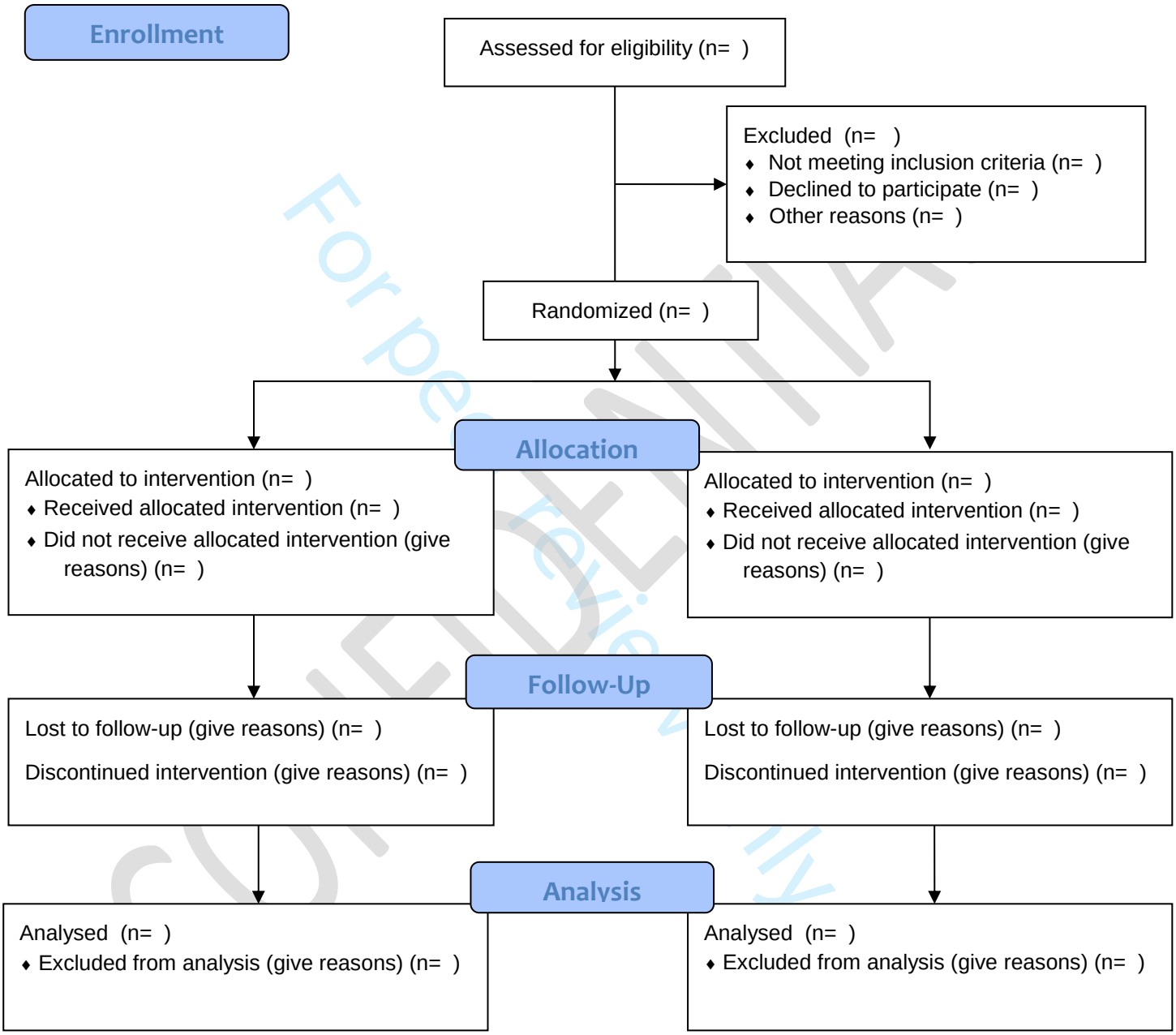
TABLE 1. Classification of Surgical Complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

APPENDIX IV

CONSORT 2010 Flow Diagram



APPENDIX V Pain protocol

PROTOCOL ADNEXECTOMIE – DR. BAEKELANDT

ASA I & ASA II PATIËNTEN

1. INDUCTIE ANESTHESIE

- Propolipid 2,5mg/kg
- Sufentanil 0,15µg/kg
- Rocurorium 0,6mg/kg
- Dexamethasone 5mg
-

2. ONDERHOUD ANESTHESIE

- O_2/ lucht 50/50
  DES 1 MAC

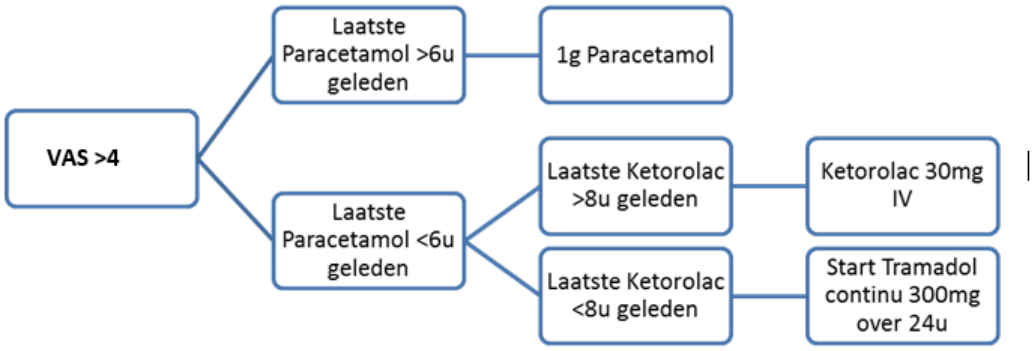
- Zo nodig bolus Alfentanil 5mg/kg
- 30min. voor einde IV toediening van
  - 1g Paracetamol
  - Ketorolac 0,5mg/kg met maximum van 30mg

3. POSTOPERATIEF

RECOVERY

- Bij VAS >4: 1g Paracetamol IV
- Herevaluatie na 30min.
  - Bij VAS >4: 2,5mg Piritramide IV

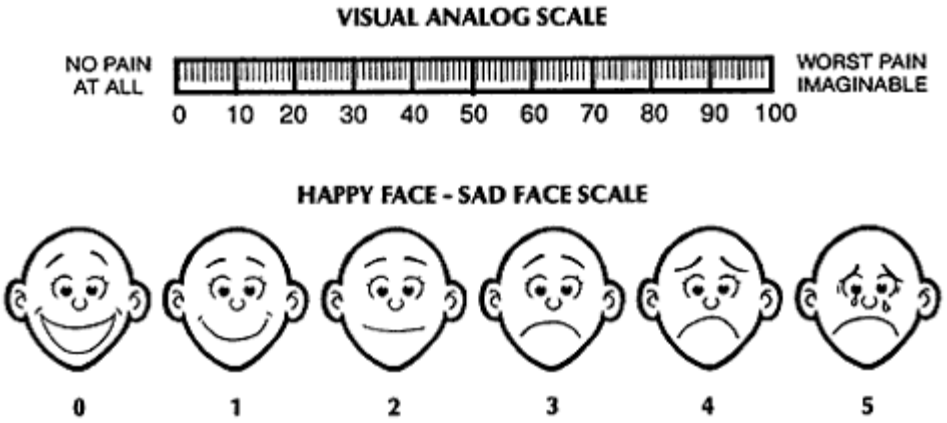
VERPLEEGAFDELING



Na 30min. herevaluatie + herstarten bovenstaand schema.

Indien VAS >4 blijft, ondanks starten van Tramadol continu: contacteer anesthesist

APPENDIX VI VAS scale



APPENDIX VII: Participant's pain log book

Notable trial

Naam en voornaam:	
Datum van de ingreep:	

Aankomst thuis:

uur van aankomst: .....

Pijnscore:

0	1	2	3	4	5	6	7	8	9	10

Pijnmedicatie:

	Aantal mg	Aantal comprimés	Tijdstip(pen) inname
Paracetamol			
Ibuprofen			
Andere			

Dag 1 na de ingreep:

Pijnscore ochtend:

0	1	2	3	4	5	6	7	8	9	10

Pijnscore avond:

0	1	2	3	4	5	6	7	8	9	10

Pijnmedicatie:

	Aantal mg	Aantal comprimés	Tijdstip(pen) inname
Paracetamol			
Ibuprofen			
Andere			

Dag 2 na de ingreep:

Pijnscore ochtend:

0	1	2	3	4	5	6	7	8	9	10

Pijnscore avond:

0	1	2	3	4	5	6	7	8	9	10

Pijnmedicatie:

	Aantal mg	Aantal comprimés	Tijdstip(pen) inname
Paracetamol			
Ibuprofen			
Andere			

Dag 3 na de ingreep:

Pijnscore ochtend:

0	1	2	3	4	5	6	7	8	9	10

Pijnscore avond:

0	1	2	3	4	5	6	7	8	9	10

Pijnmedicatie:

	Aantal mg	Aantal comprimés	Tijdstip(pen) inname
Paracetamol			
Ibuprofen			
Andere			

Dag 4 na de ingreep:

Pijnscore ochtend:

0	1	2	3	4	5	6	7	8	9	10

Pijnscore avond:

0	1	2	3	4	5	6	7	8	9	10

Pijnmedicatie:

	Aantal mg	Aantal comprimés	Tijdstip(pen) inname
Paracetamol			
Ibuprofen			
Andere			

Dag 5 na de ingreep:

Pijnscore ochtend:

0	1	2	3	4	5	6	7	8	9	10

Pijnscore avond:

0	1	2	3	4	5	6	7	8	9	10

Pijnmedicatie:

	Aantal mg	Aantal comprimés	Tijdstip(pen) inname
Paracetamol			
Ibuprofen			
Andere			

Dag 6 na de ingreep:

Pijnscore ochtend:

0	1	2	3	4	5	6	7	8	9	10

Pijnscore avond:

0	1	2	3	4	5	6	7	8	9	10

Pijnmedicatie:

	Aantal mg	Aantal comprimés	Tijdstip(pen) inname
Paracetamol			
Ibuprofen			
Andere			

APPENDIX VIII: Dyspareunia questionnaire

PIJN
lokatie en intensiteit

1) Ervaar je pijn bij het vrijen? Ja/Nee

2) Indien ja, waar ervaar je pijn bij het vrijen? Is er een specifieke plaats?
   a) ter hoogte van de vaginale opening
   b) ter hoogte van de schaamlippen
   c) in de vagina
   d) in the pelvische of abdominale regio

3) Geef een score voor de intensiteit van de pijn aan de ingang en/of the eerste deel van de vagina op deze schaal van 0 tot 10

0	1	2	3	4	5	6	7	8	9	10
geen pijn										ergste pijn ooit

4) Geef een score voor de intensiteit van de pijn in de pelvische en abdominale regio op deze schaal van 0 tot 10

0	1	2	3	4	5	6	7	8	9	10
geen pijn										ergste pijn ooit

APPENDIX IX: Short Sexual Functioning Scale

Short Sexual Functioning scale – female version

Met de volgende vragen wordt nagegaan of jij de voorbije 3 maanden bepaalde seksuele problemen hebt ervaren. Dit gebeurt door middel van vragen over lichamelijke reacties en gevoelens die kunnen optreden bij seksuele activiteiten. Als er zich een seksueel probleem heeft voorgedaan, vragen we telkens ook hoe lastig jij en jouw partner dat vinden én of dit op jullie relatie heeft gewogen.
Gelieve voor elke vraag het antwoord te omcirkelen dat het best jouw gevoel of ervaring weergeeft. Soms wordt er aangegeven dat je naar een volgende vraag mag gaan, dan hoef je de rest van de vraag niet verder in te vullen. Er zijn geen juiste of foute antwoorden. Let er op geen vragen over te slaan !

1. Had je - de voorbije 3 maanden - te weinig zin in seks, te weinig goesting in seksuele activiteiten, te weinig seksuele fantasieën of erotische gedachten (= te weinig seksueel verlangen)?

1. ik had niet te weinig zin ➔ *ga naar vraag 2*
2. ik had in lichte mate te weinig zin
3. ik had duidelijk te weinig zin
4. ik had in extreme mate te weinig zin

a) Indien ik te weinig zin in seks heb, is dit voor mij:
1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. en ernstig probleem

b) Indien ik te weinig zin in seks heb, is dit voor mijn partner:
1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

c) Indien ik te weinig zin in seks heb, is dit voor onze relatie in het algemeen:
1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

2. Had je - de voorbije 3 maanden - wanneer je zelf geen zin in seks had maar jouw partner wel initiatief nam tot seks, moeilijkheden om zin in seks te krijgen?

1. ik had dan geen moeilijkheden om zin in seks te krijgen ➔ *ga naar vraag 3*

2. ik had dan in lichte mate moeilijkheden om zin in seks te krijgen
3. ik had dan duidelijk moeilijkheden om zin in seks te krijgen
4. ik had dan in extreme mate moeilijkheden om zin in seks te krijgen

a) Indien ik moeilijkheden heb om zin in seks te krijgen wanneer mijn partner initiatief neemt tot seks, is dat <u>voor mij</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

b) Indien ik moeilijkheden heb om zin in seks te krijgen wanneer mijn partner initiatief neemt tot seks, is dat <u>voor mijn partner</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

c) Indien ik moeilijkheden heb om zin in seks te krijgen wanneer mijn partner initiatief neemt tot seks, is dat <u>voor onze relatie in het algemeen</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

3. Had je - de voorbije 3 maanden - wanneer jouw partner fijn met jou vrijde, <u>moeilijkheden met vochtig/nat worden</u> tijdens seks?

1. ik had geen moeilijkheden om vochtig/nat te worden ➔ ***ga naar vraag 4***
2. ik had in lichte mate moeilijkheden om vochtig/nat te worden
3. ik had duidelijk moeilijkheden om vochtig/nat te worden
4. ik had in extreme mate moeilijkheden om vochtig/nat te worden

a) Indien ik minder vochtig/nat word, is dit <u>voor mij</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

b) Indien ik minder vochtig/nat word, is dit <u>voor mijn partner</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

c) Indien ik minder vochtig/nat word, is dit <u>voor onze relatie</u> in het algemeen:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem

4. een ernstig probleem

4. Had je - de voorbije 3 maanden - wanneer je partner fijn met jou vrijde, geen of weinig gevoel van opwinding (emotioneel)?

1. ik had geen moeilijkheden met het krijgen van een gevoel van opwinding (emotioneel) ➔ ***ga naar vraag 5***
2. ik had in lichte mate moeilijkheden met het krijgen van een gevoel van opwinding (emotioneel)
3. ik had duidelijk moeilijkheden met het krijgen van een gevoel van opwinding (emotioneel)
4. ik had in extreme mate moeilijkheden met het krijgen van een gevoel van opwinding (emotioneel)

a) Indien ik geen of weinig gevoel van opwinding ervaar, is dit voor mij:
1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

b) Indien ik geen of weinig gevoel van opwinding ervaar, is dit voor mijn partner:
1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

c) Indien ik geen of weinig gevoel van opwinding ervaar, is dit voor onze relatie in het algemeen:
1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

5. Had je - de voorbije 3 maanden - wanneer jouw partner fijn met jou vrijde, moeilijkheden om klaar te komen (een orgasme te bereiken) ?

1. ik had geen moeite om klaar te komen of een orgasme te bereiken ➔ ***ga naar vraag 6***
2. ik had in lichte mate moeite om klaar te komen of een orgasme te bereiken
3. ik had duidelijk moeite om klaar te komen of een orgasme te bereiken
4. ik had in extreme mate moeite om klaar te komen of een orgasme te bereiken

a) Indien ik moeite heb om een orgasme te bereiken, is dit voor mij:
1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

b) Indien ik moeite heb om een orgasme te bereiken, is dit <u>voor mijn partner</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

c) Indien ik moeite heb om een orgasme te bereiken, is dit <u>voor onze relatie</u> in het algemeen:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

6. Had je - de voorbije 3 maanden - wanneer je met jezelf vrijde of masturbeerde, moeilijkheden om een orgasme te bereiken?

0. ik heb niet gemasturbeerd de laatste 4 weken ➔ ***ga naar vraag 7***

1. ik had geen moeite om bij masturbatie een orgasme te bereiken ➔ ***ga naar vraag 7***
2. ik had in lichte mate moeite om bij masturbatie een orgasme te bereiken
3. ik had duidelijk moeite om bij masturbatie een orgasme te bereiken
4. ik had in extreme mate moeite om bij masturbatie een orgasme te bereiken

a) Indien ik moeilijk kan klaarkomen bij masturbatie, is dit <u>voor mij</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

7. Kan je in de volgende lijst aangeven wat voor jou de voorbije 3 maanden van toepassing was? Je kan slechts één antwoord aanduiden.

1. vaginale penetratie (= het inbrengen van penis of vinger in de vagina) was mogelijk en niet pijnlijk ➔ ***einde van de vragenlijst***
2. vaginale penetratie was mogelijk, maar was pijnlijk
3. ➔ ***ga naar vraag 7a***
4. vaginale penetratie is (met mijn huidige partner) nog nooit gelukt ➔ ***einde van de vragenlijst***
5. vaginale penetratie was (met mijn huidige partner) vroeger mogelijk, maar nu niet meer ➔ ***einde van de vragenlijst***

7a. Had je - de voorbije 3 maanden - pijn voor, tijdens of na vaginale penetratie?

1. Ik had geen pijn voor, tijdens of na penetratie
2. Ik had een lichte pijn voor, tijdens of na penetratie
3. Ik had een duidelijke pijn voor, tijdens of na penetratie
4. Ik had een extreme pijn voor, tijdens of na penetratie

a) Indien ik pijn heb voor, tijdens of na vaginale penetratie, is dit <u>voor mij</u>:

1. geen probleem

2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

b) Indien ik pijn heb voor, tijdens of na vaginale penetratie, is dit <u>voor mijn partner</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

c) Indien ik pijn heb voor, tijdens of na penetratie, is dit <u>voor onze relatie</u> in het algemeen:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

Hartelijk dank voor het invullen van deze vragenlijst !

APPENDIX X: EQ-5D Health questionnaire

Gezondheidsvragenlijst

Nederlandse versie voor België

(Dutch version for Belgium)

Zet bij iedere hieronder vermelde groep een kruisje in één hokje achter de zin die het best uw gezondheidstoestand van vandaag weergeeft.

Mobiliteit

Ik heb geen problemen met rondwandelen ❑

Ik heb enige problemen met rondwandelen ❑

Ik ben bedlegerig ❑

Zelfzorg

Ik heb geen problemen om voor mezelf te zorgen ❑

Ik heb enige problemen om mezelf te wassen of aan te kleden ❑

Ik ben niet in staat mezelf te wassen of aan te kleden ❑

Dagelijkse activiteiten *(bijv. werk, studie, huishouden, gezins- of vrijetijdsactiviteiten)*

Ik heb geen problemen met mijn dagelijkse activiteiten ❑

Ik heb enige problemen met mijn dagelijkse activiteiten ❑

Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren ❑

Pijn/klachten

Ik heb geen pijn of andere klachten ❑

Ik heb matige pijn of andere klachten ❑

Ik heb zeer ernstige pijn of andere klachten ❑

Angst/depressie

Ik ben niet angstig of depressief ❑

Ik ben matig angstig of depressief ❑

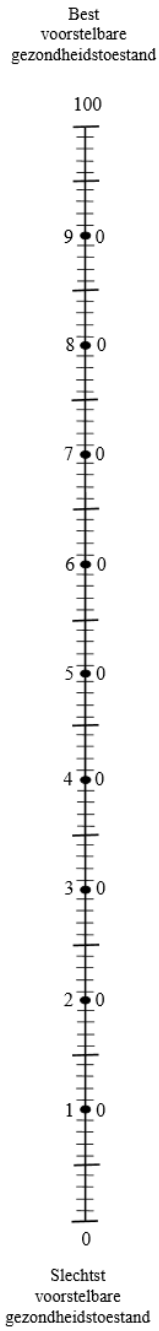
Ik ben erg angstig of depressief ❑

 2

Om mensen te helpen bij het aangeven hoe goed of hoe slecht een gezondheidstoestand is, hebben we een meetschaal (te vergelijken met een thermometer) gemaakt. Op de meetschaal hiernaast betekent "100" de beste gezondheidstoestand die u zich kunt voorstellen, en "0" de slechtste gezondheidstoestand die u zich kunt voorstellen.

We willen u vragen op deze meetschaal aan te geven hoe goed of hoe slecht volgens u uw eigen gezondheidstoestand vandaag is. Trek een lijn van het hokje hieronder naar het punt op de meetschaal dat volgens u aangeeft hoe goed of hoe slecht uw gezondheidstoestand vandaag is.

Uw gezondheidstoestand vandaag



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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_4_____
	2b	All items from the World Health Organization Trial Registration Data Set	_Appendix 1 ___
Protocol version	3	Date and version identifier	_4_____
Funding	4	Sources and types of financial, material, and other support	_24_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_1,2, 26_____
	5b	Name and contact information for the trial sponsor	_Not applicable__
	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	_Not applicable__
	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)	_Not applicable _____

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	__6,7_____
	6b	Explanation for choice of comparators	__6,7,22_____
Objectives	7	Specific objectives or hypotheses	__6,7_____
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)	___8_____

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	___8_____
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)	__8,9_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	___9,10,11,12
	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)	_11,12_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_11,12_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_9,10,11,12_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_12,13,14_____

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)	__Table 1_____
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_15_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__8_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__14_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	__14_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__14_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__14_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	__14_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__20_____

	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	__21_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__Appendix 3 protocol_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___16-19_____
-	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___16-19_____
	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)	___16-19_____
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	_19_____
	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	__19_____
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	__19_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__19_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__24_____

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)	___24_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	__24_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_Not applicable__
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	_24,25_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__26_____
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	_25_____
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	__25_____
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	__25_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__25_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_24_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Appendix 2____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable__

*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.

BMJ Open

Transvaginal Natural Orifice Transluminal Endoscopic Surgery (vNOTES) adnexectomy for benign pathology compared to laparoscopic excision (NOTABLE): a protocol for a randomised controlled trial.

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Transvaginal Natural Orifice Transluminal Endoscopic Surgery (vNOTES) adnexectomy for benign pathology compared to laparoscopic excision (NOTABLE): a protocol for a randomised controlled trial.

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Running title

NOTABLE study

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ABSTRACT

Introduction: Natural Orifice Transluminal Endoscopic Surgery (NOTES) uses natural orifices to access the cavities of the human body to perform surgical interventions. NOTES limits the magnitude of surgical trauma, and potentially reduces postoperative pain. Our group published a protocol on a randomized study comparing transvaginal NOTES (vNOTES) versus laparoscopy for hysterectomy (HALON). We simultaneously designed a similar RCT comparing vNOTES with laparoscopy for adnexectomy. To the best of our knowledge this is the first RCT comparing vNOTES with laparoscopy for adnexal surgery.

Methods and analysis: The methodology of the NOTABLE study is similar to that of the HALON trial. Women aged 18-70 years with an indication for benign adnexal surgery will be eligible. We will use stratification according to adnexal size. Entrants will be randomised to the laparoscopic treatment (control) or vNOTES (intervention). Participants will be evaluated on days 0-7, and at 3 and 6 months. The primary outcome will be the proportion of women successfully treated by removing an adnexa by the allocated technique without conversion. We will collect the following data(secondary outcomes): proportion of women hospitalized on the day of surgery; postoperative pain scores measured twice daily from day 1-7; total dosage of pain killers used from day 1-7; hospital readmission during the first six weeks; dyspareunia and sexual wellbeing at baseline, 3 and 6 months using a validated questionnaire (SSFS scale); health-related quality of life at baseline, 3 and 6 months after surgery using an validated questionnaire (EQ-5D-3L); duration of surgical intervention; infection or other surgical complications; direct costs up to 6 weeks following surgery. For the primary outcome measure, a one-sided 95% confidence interval of the difference in the proportions of women with a successful removal of the uterus by the randomised technique will be estimated. Non-inferiority will be concluded when 15% lies above the upper limit of this 95% CI.

Ethics and dissemination: The study was approved on December, 1st 2015 by the Ethics

Committee of the Imelda Hospital, Bonheiden, Belgium. We aim to present the final results of the NOTABLE trial in peer- reviewed journals and at scientific meetings within 4 years after the start of the recruitment.

Registration details:

Primary Registry and Trial Identifying Number**:** NCT02630329

Secondary Identifying Number**:** B689201526268

Date and version identifier: Version 5, 28 December 2015

Study dates:

The first patient was included on 15 January 2016.

On 22 May 2017 38 of the targeted 70 participants were recruited.

Anticipated date of study completion is estimated May 2018.

Strengths and limitations of this study:

Strength: This study is a randomised controlled trial.

Strength: The patients, the outcome assessors and the personnel are blinded in this trial.

Limitation: This is a single centre study.

Limitation: The generalisability of this study to a "real-life" setting is limited due to the experimental setting of the study.

Limitation: The use of non-therapeutic incisions for blinding may confound the outcome pain.

INTRODUCTION

Background

Laparoscopic surgery has reduced surgical morbidity and mortality. “Minimally invasive surgery” has moved even further forward with newer techniques such as single incision laparoscopic surgery (SILS) and natural orifice transluminal endoscopy (NOTES) with or without by robot assistance.

The NOTES technique uses any natural orifice (mouth, vagina, urethra or rectum) as a possible access route facilitating a surgical intervention in a cavity of the human body. Clinical researchers at Johns Hopkins University first reported its use in 2004 in a preclinical trial using an animal model (1). Ever since the clinical application of NOTES has been reported in many surgical procedures in ways that seem to defy human imagination: appendectomy and cholecystectomy have been performed using the mouth and the stomach as the access route (2, 3). The technique seems feasible and safe in the hands of experienced surgeons beyond their surgical learning curve. Observational evidence (mostly case reports) have reported moreover that NOTES may cause less postoperative pain, a shorter length of hospital stay, less complications and last but not least for female patients improved cosmetic results. The feasibility of scar-free surgery in combination with reduced wound (trocar) complications may be tempting for patients and their care providers. This may be a strong facilitator for the widespread implementation of this new surgical approach.

NOTES has gained popularity amongst general surgeons, urologists and gastroenterologists over the past few years and its feasibility and safety in these domains have been reported (4). Although NOTES may be performed using various entries including the stomach, oesophagus, bladder and rectum, the majority of NOTES procedures in women have been performed through the vagina (5). This is not surprising because the colpotomy technique has been used widely vaginal prolapse surgery and for benign adnexal surgery involving the

extraction of large specimens. Its use has been reported as a safe access (6, 7). Two variants of NOTES have been described in the present literature. Hybrid NOTES combines the access through the vagina with transabdominal assistance; pure NOTES refers to procedures that involve only transluminal access.

The removal of one or both adnexa using a transvaginal NOTES (vNOTES) approach was described for the first time by Lee and co-workers in 2012 (8). vNOTES adnexectomy for benign pathology was introduced at our department by the first author (JB) in 2013. Our group published three small case series on adnexal removal (N=20) (9), salpingectomy (N=5) (10) and hysterectomy (N=10) (11) by vNOTES during the period between November 2013 and February 2015. We also published the protocol of the HALON study randomly comparing NOTES and laparoscopy for doing hysterectomy in women with benign gynaecological disease (12). The recruitment of the HALON study was finished recently (February 24th 2017). The final data analysis of the HALON study is foreseen for September 2017.

Objectives and hypotheses

We started our research by doing a systematic review of the literature. We searched MEDLINE, EMBASE and The Cochrane Library from inception to 1 August 2015 using a combination of MeSH terms and key words for '*colpotomy'* and '*adnexal diseases'* or *'adnexal mass'*. We aim to publish the results of this systematic search of the literature and a critical appraisal of the retrieved evidence in a separate systematic review (SR): we will adhere to the PRISMA-P guidelines (13) for the protocol of this SR. The protocol of the SR has been registered in PROSPERO- the international prospective register of systematic reviews, at the Centre for Reviews and Dissemination (CRD), University of York, United Kingdom (14), as CRD42016033670. To the best of our knowledge no randomised controlled

studies comparing vNOTES with the transabdominal laparoscopic approach for removal of one or both adnexa have been published in the literature. The main objective of the NOTABLE study is to study the effectiveness of vNOTES for successfully removing one or both adnexa for benign gynaecological disease using the classical laparoscopic approach as the established effective technique (EET). The rationale and the objectives of NOTABLE are in accordance with the principles outlined by the IDEAL collaboration (15-17).

Our primary study hypothesis is that vNOTES is not inferior to transabdominal laparoscopy for removing one or both adnexa for a benign gynaecological indication without having to convert to another technique. vNOTES may offer several advantages including the avoidance of abdominal scars, less need for hospital admission and possibly less postoperative pain.

METHODS

Trial design and study analysis

The NOTABLE study should be considered as a pilot study. It is a single-centre parallel-group double blinded (patient and outcome assessor) randomised trial conducted at the Department of Gynaecology of the Imelda Hospital in Bonheiden. This is a general hospital in Belgium serving an estimated population of 150,000 people. All women aged 18-70 years bound to undergo removal of one or both adnexa for benign gynaecological disease will be informed about the NOTABLE study and they will be invited to participate in the study, if eligible. The baseline characteristics of eligible women not wishing to give informed consent for participating in the study will be recorded as well as the reason for declining to participate. All surgical procedures (vNOTES and laparoscopy) will be done by one surgeon (JB) who is equally skilled in both techniques. The surgeon has been using the vNOTES approach for various interventions (salpingectomy for EUG, adnexectomy and hysterectomy) since November 2013. JB is also the surgeon performing the hysterectomies in the HALON trial. The surgeon cannot be blinded but the allocated treatment will be concealed. We will use a non-inferiority study design to test the effectiveness of vNOTES compared to laparoscopy. The protocol adheres to the SPIRIT standards (http://www.spirit-statement.org/). The study protocol of the NOTABLE trial is very similar to that of the earlier published HALON study (12).

Participants

NOTABLE will recruit eligible women aged 18-70 years, regardless of parity, who need the removal of one or both adnexa for a benign adnexal disease and who provide informed consent prior to surgery.

Exclusion criteria are as follows:

- history of rectal surgery

- suspected rectovaginal endometriosis
- suspected malignancy
- history of pelvic inflammatory disease (PID)
- active lower genital tract infection
- virginity
- pregnancy
- failure to provide written informed consent.

Intervention, procedures and standard care

On the day of the surgery, all patients are admitted to the day care unit. A nurse administers clindamycin vaginal cream on admission.

Under general anaesthesia, the patient is positioned in a vacuum mattress in the classical lithotomy. An alcoholic betadine solution is used for disinfection of the vagina, vulva and abdomen before draping. A Foley catheter is inserted into the bladder. In accordance with hospital protocol, the anaesthesiologist will administer cefazolin 2g and metronidazole 1.5g IV prior to incision for prophylaxis against infection to all women of both treatment arms. In both groups a 30° rigid endoscope is used.

Control group: laparoscopic technique

The surgeon will start the procedure by making a small vertical intra-umbilical skin incision. A Veress needle is introduced into the peritoneal cavity; the tip position is checked with a Semm test before insufflating CO_2 until a maximal intraperitoneal pressure of 15mmHg. A 10mm trocar is inserted through the umbilicus after removal of the Veress needle. An optic is inserted to inspect the peritoneal cavity. The operating table is tilted in the Trendelenburg position. Two 5mm trocars are placed under direct vision in the suprapubic region and in the left iliac fossa lateral of the epigastric vessels. The small intestine is lifted out of the pelvis.

The ureter is identified, but no retroperitoneal dissection is performed unless indicated. The proximal end of the Fallopian tube is coagulated at its origin in the uterus using a reusable bipolar grasping forceps before being cut with cold microscissors. The ovarian and infundibulopelvic ligament are coagulated and cut. After resection, the adnexa is placed in an endobag (Memobag, Teleflex). When indicated, the same procedure is repeated for the contralateral side.

After confirmation of haemostasis, the peritoneal cavity is rinsed. No drains are left in the peritoneal cavity unless necessary, e.g. problematic haemostasis. The 5 mm trocars are be removed under direct vision. The purse string of the endobag is pulled through the 10 mm trocar upon removal of the optic. The umbilical incision is extended vertically in caudal direction, but not more than 2.5 cm. The fascia and peritoneum are opened and the proximal end of the endobag is pulled through the incision without causing any rupture if possible. If not possible, the endobag will be opened and the content of the cyst will be aspirated to reduce the volume of the adnexa. The aspirated fluid will be sent for cytological evaluation. The endobag will then be removed with the adnexa inside it.

The fascia is closed using a Vicryl-1 running suture. The umbilicus and other incisions are disinfected with betadine solution. All skin incisions are closed with a Monocryl 3/0 intradermal suture and approximated using steri-strips. The wound sites are covered with a wound dressing. A vaginal plug (betadine gauze 10 cm x 5 m) is inserted into the vagina. After 3 hours the Foley catheter and the vaginal plug are removed.

Intervention group: vNOTES

The surgeon makes three non-therapeutic superficial skin incisions on exactly the same location as in the classical laparoscopic approach in all women allocated to the vNOTES group to blind study participants and the outcome assessor to the allocated technique. A 2.5 cm posterior colpotomy is made using a cold knife. The pouch of Douglas is opened using

scissors. A Gelpoint Mini (Applied Medical), used as vNOTES port, is inserted into the pouch of Douglas. CO_2 is insufflated until a maximal intraperitoneal pressure of 15mmHg. An optic is inserted to inspect the peritoneal cavity. The operating table is tilted in the Trendelenburg position. The small intestine is lifted out of the pelvis.

The ureter is identified, but no retroperitoneal dissection is performed unless indicated. The proximal end of the Fallopian tube is coagulated at its origin into the uterus using a reusable bipolar grasping forceps and cut using microscissors. The ovarian and infundibulopelvic ligament are coagulated and cut. The adnex is removed. When indicated, the procedure is repeated for the contralateral side. After confirmation of haemostasis, the peritoneal cavity is rinsed.

Small benign looking adnexa are removed directly through the wound protector part of the vNOTES port. Large adnexa or adnexa that appear macroscopically suspicious, are placed in an endobag (Memobag, Teleflex). The purse string of the endobag is pulled through the wound protector and the purse string released. The content of the cyst is aspirated to reduce the volume of the adnexa. The endobag is then removed with the adnexa inside it. The vNOTES port is removed.

The colpotomy is closed using three interrupted figure-of-eight Vicryl 2/0 sutures. A vaginal plug (betadine gauze 10cmx5m) is inserted into the vagina. After 3 hours the Foley catheter and the vaginal plug are removed.

In the majority of patients it is feasible to perform a successful vNOTES or laparoscopic adnexectomy. Women in whom the intended approach has to be abandoned for an alternative intervention will not be excluded or withdrawn from the NOTABLE trial but will be followed up further. It is anticipated that most included patients with a normal CA125 value and benign features of the ovary on ultrasound, will not require other interventions besides the removal of the adnexa. If the responsible clinician judges that additional treatment is necessary at the

time of the surgery or afterwards, this will be recorded and the patient will not be withdrawn from the study. However, if there is a preoperative indication for additional surgery during the same procedure, these patients will be excluded from recruitment to the NOTABLE trial.

The anaesthesiologists involved in the clinical trial have developed a standardised protocol to insure that the pain management is identical for both groups. The outcome assessor (JJAB) and the patient are both blinded to the surgical approach used. The patient makes the decision to be discharged from the day care unit on the evening of the procedure or to be admitted to an in-hospital nursing ward for the night. The outcome assessor can only overrule the patient's decision in the interest of her health, e.g. when surgical complications were recorded in the surgical report or when vital parameters indicate a life-threatening condition. Before discharge all patients are given a standard list of instructions to avoid physical work, exercise and sexual intercourse for four weeks after the intervention.

All participants, regardless of being at home or in hospital, are requested to use a VAS scale twice daily to measure postoperative pain from day 1 until day 7 following surgery. Adequate instructions on how to use the VAS scale measuring tool are given on an individual basis by a dedicated nurse of the day care unit. One measurement is made in the evening before going to bed after physical activity (active) and another is made in the morning after bed rest at night (rest). All patients are asked to note the name, dosage, and route of administration of any analgesic drug taken from day 1-7 in a pain log book.

Outcome measure

We searched the COMET (18) database for a core outcome set for adnexectomy (general settings) in gynaecology (health area-disease category) in women (target population: sex) aged 18 to 70 years (target population: age): no core outcome set relevant to laparoscopic removal of adnexa was identified (19).

Primary outcome measure

The proportion of women successfully treated by removing one or both adnexa without spill by the allocated technique as randomized will be measured as the primary outcome of effectiveness.

Secondary outcome measures

The secondary outcomes are as follows:

- The proportion of women hospitalized on the day of surgery based on their own preference.
- Postoperative pain scores measured using a Visual Analogue Scale (VAS) scale (20) twice daily from day 1-7.
- The total dosage of pain killers taken during the first week following surgery.
- Postoperative infection defined by lower abdominal pain with fever > 38°C and positive clinical signs or laboratory findings detected during the first six weeks of surgery.
- Intra- or postoperative complications classified according to the Clavien- Dindo classification (21) detected during the first six weeks of surgery.
- Readmission to hospital during the first six weeks of surgery.
- Occurrence and severity of pain on sexual intercourse self-reported by the study participants at baseline, 3 and 6 months by using a simple questionnaire and VAS scale.
- Sexual wellbeing at baseline, at 3 and 6 months by self-reporting the Short Sexual Functioning Scale-SSFS (22).
- Health-related quality of life at baseline, 3 and 6 months after surgery by self-reporting using a validated questionnaire (EQ-5D-3L).

- The duration of the surgical intervention measured in minutes from the insertion of the bladder catheter to the end of vaginal/abdominal wound closure.
- Direct costs for both techniques up to 6 weeks following surgery.

The SSFS and the EQ-5D-3L questionnaires were validated in Dutch and presented to the participants in their mother tongue

Randomisation and blinding

Participants will be randomly allocated to one of both treatment arms (vNOTES versus laparoscopy) We will use a computer-generated randomisation schedule generated by the management assistant of our department. We will use a stratification into three categories (A, B or C) according to the size of the cyst on transvaginal ultrasound (0 to 5 cm, 5 to 10 cm, larger than 10 cm). Sequentially numbered, opaque, sealed envelopes will be used to ensure allocation concealment for the surgeon and the outcome assessor. The management assistant will safeguard the allocation code until the last visit of the last patient. The management assistant will not be involved in the outcome assessment or the data collection.

All participating women and the outcome assessor will be blinded to the allocation by the use of non-therapeutic skin incisions. It is impossible to blind the surgeon. In case of life-threatening adverse events, the outcome assessor will notify the surgeon to enable further treatment without the need for unblinding the patient. The use of the vNOTES technique avoids the use of abdominal incisions. Participants allocated to the vNOTES arm will have three superficial non-therapeutic skin incisions similar to those routinely done with the laparoscopic technique. This enables blinding all study participants, personnel and the outcome assessor. The wound dressings of all women will be left untouched until the postoperative visit on day 7. The practice of using non-therapeutic skin incisions has been reported in some surgical trials to minimise performance and detection bias when measuring subjective outcomes (e.g. pain) (23). The decision to use non-therapeutic skin incisions is

justified by the risk/benefit ratio of the two interventions under comparison (24). Its use in the HALON and NOTABLE trial has been intensively discussed among the investigators and has been approved by the Ethical Committee of the Imelda Hospital Bonheiden (registration number 689), Belgium on December 1, 2015. The written approval with the Belgian unique study identifier B689201526268 was sent to the FAMHP in Brussels.

Statistical methods

Sample size calculation

A sample size calculation was done for the primary outcome only. An appropriate level of statistical power was applied to preclude any clinically important inferiority of vNOTES compared to laparoscopy. The assumptions for the sample size calculation are based on evidence retrieved from two sources: a randomized study comparing the excision of mature dermoid cysts using colpotomy with laparoscopic assistance versus colpotomy without laparoscopy (25) and a systematic review with meta-analysis comparing single port laparoscopy versus conventional laparoscopy in benign adnexal disease (26) An important consideration in any adnexal mass surgery is the inadvertent opening of the ovarian capsule of an unsuspected malignancy resulting in the spill of malignant cells into the abdominal cavity. Based on a 2.4% failure rate to remove dermoid cysts by colpotomy using laparoscopic assistance (25) and a 0% conversion rate from laparoscopy to laparotomy (26) we assumed that the successful removal of adnexal cysts without spill would be feasible in 95% of all cases. The sample size was calculated with a one-sided test for non-inferiority for the primary outcome. The vNOTES approach may be the treatment of choice for women because it avoids scars. We assume that vNOTES would be the preferred technique even when 15% less women had in the end a successful removal of a benign adnexal mass by using vNOTES compared to laparoscopy with its unavoidable scars. Non-inferiority will be concluded when 15% lies above the upper limit of the 95% confidence interval calculated for the difference in

the proportion of women successfully treated with either technique. To achieve 80% power to demonstrate non-inferiority under the assumption of similar success rates of 95% in both groups a sample size of 54 participants (27 women per group) will be required. We increased the target sample size to 64 participants (32 women per group) to account for a drop-out rate of 15%. Based on the power calculations for the primary outcome, the use of three strata for the randomisation and assuming a loss-to-follow-up rate of 15 %, we decided to include 66 study participants in the NOTABLE trial.

Statistical analyses

GENERAL PRINCIPLES

For all baseline and outcome variables, the number of available measurements and the number of missing values will be given. A probability (p) less than 0.05 will be considered to be significant. Analysis will be performed by intention-to-treat, as recommended in the CONSORT statement (27). Since the study compares two regular interventions and is expected to recruit during a reasonably limited period, interim analyses will not be performed.

Categorical data will be reported as absolute numbers and percentages. Normally distributed continuous variables will be summarized as means with standard deviations and non-normally distributed continuous variables will be reported as medians with interquartile ranges (IQR). Main analyses will not impute missing values.

All analyses will be performed using SAS software (version 9.4 of the SAS System for Windows).

DESCRIPTIVE ANALYSES

Study population – baseline characteristics

- Mean age (± SD)
- Mean Body Mass Index (± SD)

- Mean number of natural vaginal births (± SD)
- Mean number of abdominal/pelvic surgical interventions (± SD)
- Mean weight of the uterus (± SD)

STUDY ENDPOINTS

Main study parameter/endpoint

Differences in the proportions of women successfully treated by removing the uterus by the intended technique without conversion to another approach

Secondary study parameters/endpoints

- Proportions of women hospitalized on the day of surgery
- Postoperative pain scores, measured using a VAS scale twice daily from day 1 till 7 self-reported by the study participants
- Total dose analgesics used during the first week following surgery
- Incidence of postoperative infection during the first six weeks of surgery
- Incidence of intra-operative complications
- Incidence of postoperative complications during the first 6 weeks following surgery
- Incidence of readmission during the first six weeks of
- Incidence of dyspareunia recorded by the participants at baseline, 3 and 6 months by self-reporting using a simple questionnaire
- Severity of dyspareunia recorded by the participants at baseline, 3 and 6 months by self-reporting using a VAS scale

- Sexual wellbeing at baseline, at 3 and 6 months by self-reporting the SSFS Quality of life (QoL) at baseline, at 3 and 6 months by self-reporting the EQ-5D-3L questionnaire.
- Duration of surgery
- Total costs of both interventions surgery

STATISTICAL ANALYSIS

For the primary outcome measure, a one-sided 95% confidence interval of the difference in the proportions of women with a successful removal of the uterus by the intended technique as randomised will be estimated. Non-inferiority will be concluded when 15% lies above the upper limit of this 95% CI.

For the manuscript all above listed secondary outcomes will be compared between the two groups. These data will be reported as vNOTES versus laparoscopy.

For dichotomous secondary outcome measures, comparisons between the two arms will be performed by applying Fisher exact test or Chi-square test, as appropriate.

Cross-sectionally measured continuous secondary outcomes will be analysed using an independent T-test or Mann–Whitney U- Test, as appropriate.

Longitudinally measured continuous secondary outcomes will be analysed using multilevel modelling. Differences in evolution between both treatment groups will be compared by means of a time by group interaction. In absence of such an interaction mean differences will be compared over all time points. Outcome scores will be transformed if required to meet model assumptions.

All statistical analyses will be done by an experienced biostatistician (AL) who is a co-investigator. After data cleaning the management secretary will send the unblinded data to the biostatistician after the last visit of the last patient. The biostatistician will do all the analyses

without any assistance of the other investigators who will remain blinded until all data have been analysed.

The following strategy will be used in case of missing data. In case of a single item response missing, the data will be imputed from given values. In cases where more than one item is missing or an entire form is missing, imputation will not be attempted. We will assess whether the obtained results are robust to the methods used to handle missing data, by performing a sensitivity analysis.

MONITORING

NOTABLE is a small trial, therefore a data monitoring committee is not needed.

All adverse events reported spontaneously by the participant or observed by the investigator or his staff will be recorded. Infection and per- or postoperative complications will be assessed as secondary outcomes until 6 weeks after surgery. We will inform the family physician of all participants in order to assess all possible unintended effects of the trial intervention and promote to report all possible adverse events anonymously using the participant's unique study number to an e-mail address (NOTES@imelda.be). We will use descriptive statistics for data analysis although the trial is not adequately powered to detect important differences in rates of uncommon adverse events. Given the limited resources and the single-centre design there will be no auditing of the conduct of the trial. We will review patient enrollment, consent and eligibility on a regular basis to promote data quality and to preserve trial integrity. The distribution of the allocation to the study groups will be blindly checked by the study secretary at 30%, 60% and 90% of the recruitment and discussed with the study statistician and the principal investigators.

RESULTS

Participant flow diagram

Figure 1 shows the study flow reported as outlined by the Consolidated Standards of Reporting Trials (CONSORT) (Figure 1).

Recruitment time frame

All potentially eligible women aged 18 to 70 years, regardless of parity, in need of adnexal surgery for benign gynaecological disease without exclusion criteria will be invited to participate in the trial. Only eligible women with written informed consent obtained before randomisation will be finally included in the NOTABLE trial.

We perform 36 interventions for adnexal surgery by laparoscopy for benign gynaecological disease at our Department of Gynaecology per year. The recruitment period of NOTABLE to meet the sample size will be approximately 2 years. Including the follow up period of 6 months after the LPLV (Last Patient Last Visit) and the time required to perform data analysis and reporting (6 months to 1 year) we estimate that the total study period will be at least 3 years.

Data collection

We will record the following patient characteristics at baseline: age, BMI, the number of vaginal births, previous abdominal or pelvic surgery (C-sections included), adnexal size, concomitant medication, dyspareunia questionnaire and the Short Sexual Functioning Scale (SSFS).

On the day of surgical intervention (day 0) we will record the following data: the duration of the surgical intervention, the successful removal of the adnexa by the technique as allocated without conversion to another technique with or without spilling (into the peritoneal cavity or the endobag), hospitalisation of the participant on the day of the surgical intervention based

on her own preference, the total dosage of analgesics used at the recovery and day care unit and the maximum VAS pain score on the day 0.

After one week at visit day 7 the outcome assessor will collect the pain scores as self-reported by the study participants twice daily from day 1 till day 7 using the VAS scale. The outcome assessor will also collect data on the total dosage of pain killers used during the first postoperative week.

At visit day 7 and day 42 the outcome assessor will record the following data: pelvic infection defined by lower abdominal pain with fever > 38°C and positive clinical signs or laboratory findings, readmission to hospital and the occurrence of other postoperative complications classified according to the Clavien- Dindo classification.

On month 3 and 6 following surgery the dyspareunia questionnaires, the EQ-5D-3L and the SSFS questionnaires will be filled in by the study participants and collected by regular mail. The management assistant will oversee this process and send reminders until all questionnaires have been received. We refer to Table 1 for an overview of the data collection process (Table 1).

DISCUSSION

Interpretation, limitations and generalisability

The NOTABLE trial is a randomised pilot study on the efficacy of the vNOTES technique. All surgical procedures in the NOTABLE study are done by one single surgeon (JB) who is equally skilled in using both techniques under comparison. The surgeon has been using the vNOTES approach since November 2013. During this two-year period the new technique and suitable instruments used were pilot-tested and subsequently fine-tuned by the usual "trial and error" method used for centuries in surgical practice (17). The feasibility and preliminary safety of the new technique were reported in three observational studies performed at our department (9, 10, 11) in accordance with the principles outlined in the three article series on the IDEAL statement (15-17). According to the terminology used by the IDEAL collaboration (17) this study should be classified as an IDEAL stage 2b trial. The full PICO research question is as follows: will a surgeon who is equally skilled at performing both techniques, and beyond his learning curve for the new technique (vNOTES), succeed in removing one or both adnexa in women with benign gynaecological disease at least as often with the new pilot-tested transvaginal NOTES approach compared to the standard transabdominal laparoscopic approach without having to convert to any other technique. An intraoperative decision to remove an adnexa via laparscopy and not via vNOTES due to e.g. a large specimen or an atrophic vagina may better be defined as a preemptive conversion, as it has less clinical implications than a conversion from laparoscopy to laparotomy. However, for the sake of unambiguity in this trial we decided to count as a conversion every case that was not treated by the allocated technique, whether the conversion was preemptive or not.

NOTABLE aims to measure efficacy of vNOTES for removing one or both adnexa (can vNOTES work under ideal experimental conditions?). The NOTABLE trial does not address the effectiveness of the new intervention at this moment (does vNOTES work in a real life

setting?). The conditions in NOTABLE are truly experimental and in many instances opposed to 'real life' practice: all women are always treated by the most experienced surgeon equally skilled in using both techniques, all women receive more attention during this trial than the routine care given during standard clinical practice, the dosage of anaesthetic drugs is calculated to limit any side effect (nausea and vomiting) that may cause women to be hospitalized on the day of the surgical intervention, all outcomes measured are very relevant for women in general, participants with adverse outcomes (e.g. dyspareunia and sexual dysfunction) will be recalled after the end of the study for counselling and therapy, etc…The results of the NOTABLE trial will therefore have a limited generalisability and their interpretation will be done cautiously. The testing of the safety and the (cost-) effectiveness will be needed in the longer term using pragmatic multi-centre RCTs or a prospective register. As suggested by the IDEAL collaboration more research (large multicentre trials performed by adequately trained surgeons in centres of clinical excellence and large prospective registries cumulating data on the safety of the new technique over many years) and adequate surgical training will be needed before vNOTES can be offered as a standard daily care surgical practice by a majority of gynaecological surgeons for all women bound to undergo removal of one or both adnexa for benign gynaecological disease.

ETHICS AND DISSEMINATION

The NOTABLE trial will be conducted in accordance with the ethical principles outlined in the latest version of the "Helsinki Declaration", the "Guideline for Good Clinical Practice" and the Belgian Law of 7 May 2004 related to experiments on humans.

All eligible women wishing to participate in the study will receive a detailed patient information document about the study protocol, the aims of the research and the possible adverse events related to the surgical techniques. We will request written informed consent from all participants before randomization. The principal investigator (JB) and the coordinating investigator (JJAB) will obtain these consents during a study intake. An adapted informed consent form (Appendix 1) was drafted based on the template proposed by the Federal Agency for Medicines and Health Products (FAMHP) for clinical research in Belgium (28).

The protocol of the NOTABLE trial is registered in ClinicalTrials.gov of the US National Institutes of Health as NCT02630329 (Appendix 2). The study protocol (Appendix 3) and the informed consent documents have been approved by the Ethics Committee of the Imelda Hospital Bonheiden (registration number 689), Belgium on December 1, 2015. The written approval with the Belgian unique study identifier B689201526268 was sent to the FAMHP in Brussels. All substantial protocol modifications will be communicated to all trial participants, the hospital's Ethics Committee, ClinicalTrials.gov, and the FAMHP.

The NOTABLE trial is a non-commercial and investigator-driven study. The investigators have taken out an insurance policy for medicolegal responsibility related with the conduct of the study from 01.12.2015 until 30.05.2018 in accordance with Article 29 of the Belgian Law of 7 May 204 related to experiments on humans.

The clinical research forms and all other study-related documents will be stored securely at the study site in locked file cabinets in an area with limited access. All records that contain

names or other personal identifiers will be stored separately from study records identified by a code number. Data collection, storage and dissemination will be in accordance with the Belgian Law of 8 December 1992 on the protection of privacy in relation to the processing of personal data and by the Law of 22 August 2002 on patient rights.

At the end of the NOTABLE trial the complete final data set will be accessible to all trial investigators (the nine authors of the study protocol).

Offering the surgical intervention identified as being most effective or most advantageous after the final analysis of the study data to those women that were allocated to the least effective technique is by nature of the surgical intervention not always possible except for women who had a unilateral surgical intervention. As part of good clinical practice, we will offer post-trial care to women with identified adverse events.

The investigators declare that they have no conflict of interest with respect to the present research.

The NOTABLE trial results will in all circumstances be disseminated through scientific journals and at scientific conference presentations regardless of any positive or negative outcome in relation with the predefined study hypothesis is refuted by the data. All trial investigators will contribute to authorship, following the International Committee of Medical Journal Editors (ICMJE)'s authorship eligibility guidelines.

FOOTNOTES

Twitter: follow Jan Bosteels at @BosteelsJan.

E-mail: NOTES@imelda.be

Contributors JB is the surgeon responsible for all interventions in all study participants. JBo is the outcome assessor. JB and JJAB conceived the study. PDM and IL are responsible for the draft of the pain protocol and the anaesthesia for all trial participants. JJAB, JB, PDM and IL will be responsible for data collection, quality analysis and storage. PE provided expertise for the sexuality research involved in this clinical trial design. SW provided external review as a content expert. CM provided external peer review on the scientific conduct of the study. AL is responsible for the biostatistics involved in the design and conduct of the trial. She has reviewed the SAP (Statistical Analysis Plan) of both HALON and NOTABLE. She will perform all data analysis for both studies without any involvement of the surgeon (JB) and the outcome assessor (JJAB). BWM provided external peer review as a methodology expert. All the authors contributed to the refinement of the study protocol and approved the final manuscript. For the economic analyses we will seek assistance from a Health Economist at the University of Ghent or at the Belgian Health Care Knowledge Centre.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval Ethics Committee Imelda hospital Bonheiden, protocol number B689201526268, 01/12/2015.

Provenance and peer review Not commissioned; externally peer reviewed.

Table 1

Table 1 Patient's characteristics and data collection													
Data collection	**Days**												
	BL*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**42**		**3 m**	**6m**
Age	X												
BMI**	X												
Uterine volume	X												
Concomitant medication	X	X	X	X	X	X	X	X	X	X			
Dyspareunia: frequency and intensity	X											X	X
SSFS***	X											X	X
Health related quality of life	X											X	X
Duration of surgery		X											
Successful removal		X											
Admission in hospital (for at least one night)		X											
Total amount of analgesics used		X	X	X	X	X	X	X	X				
VAS score****		X	X	X	X	X	X	X	X				
Readmission within six weeks										X			
Pelvic infection									X	X			
Other postoperative complications		X							X	X			
Direct and indirect costs (up to 6 weeks after surgery)										X			

* BL: baseline

** BMI: Body Mass Index

*** SSFS: Short Sexual Functioning Scale

**** VAS: Visual Analogue Scale

REFERENCES

1. Kalloo AN, Singh VK, Jagannath SB, et al. Flexible transgastric peritoneoscopy: a novel approach to diagnostic and therapeutic interventions in the peritoneal cavity. *Gastrointest Endosc* 2004; 60:114-7.

2. Rao GV, Reddy DN, Banerjee R. NOTES: Human experience. *Gastrointest Endosc Clin N Am* 2008; 18: 361–70.

3. Rolanda C, Lima E, Pêgo JM, et al. Third-generation cholecystectomy by natural orifices: transgastric and transvesical combined approach. *Gastrointest Endosc*. 2007; 65: 111-7.

4. Rattner D, Kalloo A. ASGE/SAGES working group on natural Orifice transluminal endoscopic surgery. *Surg Endosc* 2006; 20:329-33.

5. Santos BF, Hungness ES. Natural orifice translumenal endoscopic surgery: progress in humans since white paper. *World J Gastroenterol* 2011; 17:1655–65.

6. Tolcher MC, Kalogera E, Hopkins MR, et al. Safety of Culdotomy as a Surgical Approach: Implications for Natural Orifice Transluminal. *JSLS* 2012; 16:413–20

7. Uccella S, Cromi A, Bogani G, et al. Transvaginal specimen extraction at laparoscopy without concomitant hysterectomy: our experience and systematic review of the literature. *J Minim Invasive Gynecol* 2013; 20:583-90.

8. Lee CL, Wu KY, Su H, Ueng SH, Yen CH. Transvaginal Natural-Orifice Transluminal Endoscopic Surgery (NOTES) in Adnexal Procedures. *JMIG*. 2012;19: 509–513.

9. Reynders A, Baekelandt J. Adnexectomy by Poor Man's Transvaginal NOTES. Gynecological Surgery 2015; 12(3): 207-11.

10. Van Peer S, Baekelandt J. Natural orifice transluminal endoscopic surgery (NOTES) salpingectomy for ectopic pregnancy: a first series demonstrating how a new surgical technique can be applied in a low-resource setting. *Gynecol Surg* 2015; 12: 299-302.

11. Baekelandt J. Total Vaginal NOTES Hysterectomy: A New Approach to Hysterectomy. *J Minim Invasive Gynecol* 2015; 22:1088-94.

12. Baekelandt J, De Mulder PA, Le Roy I, et al. HALON –hysterectomy by transabdominal laparoscopy or natural orifice transluminal endoscopic surgery: a randomised controlled trial (study protocol). *BMJ Open* 2016; 6:e011546. Doi: 10.1136/bmjopen-2016-011546.

13. Shamseer L, Moher D, Clarke M, et al., the PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015; 349: g7647.

14. http://www.crd.york.ac.uk/prospero/

15. Barkun JS, Aronson JK, Feldman LS, et al., for the Balliol Collaboration. Evaluation and stages of surgical innovations. *The Lancet* 2009; 374:1089-96.

16. Ergina PL, Cook JA, Blazeby JM, et al., for the Balliol Collaboration. Challenges in evaluating surgical innovation. *The Lancet* 2009; 374:1097-1104.

17. Mc Culloch P, Altman DG, Campbell WB, et al., for the Balliol Collaboration. No surgical innovation without evaluation: the IDEAL recommendations. *The Lancet* 2009; 374:1105-12.

18. Gargon E, Gurung B, Medley N, et al. Choosing Important Health Outcomes for Comparative Effectiveness Research: A Systematic Review. *PLoS ONE* 2014; 9(6): e99111.

19. http://www.comet-initiative.org/studies/searchresults?

20. Todd KH, Funk KG, Funk JP, et al. Clinical significance of reported changes in pain severity. *Ann Emerg Med* 1996; 27: 485-9.

21. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; 240**:** 205–13.

22. Aerts L, Enzlin P, Verhaeghe J, et al. Psychologic, relational, and sexual functioning in women after surgical treatment of vulvar malignancy: a prospective controlled study. *Int J Gynecol Cancer* 2014; 24: 372-80.

23. Moseley JB, O'Malley K, Petersen NJ, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med* 2002; 347: 81-8.

24. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987; 317: 141-5.

25. Wang PH, Lee WL, Juang CM, Tsai WY, Chao HT, Yuan CC. Excision of mature teratoma using culdotomy, with and without laparoscopy: A prospective randomized trial. BJOG 2001; 108: 91-4.

26. Schmitt A, Crochet P, Knight S, Tourette C, Loundou A, Agostini A. Single Port Laparoscopy Versus Conventional Laparoscopy in Benign Adnexal Diseases: a Systematic Review and Meta-Analysis., *J Minim Invasive Gynecol* 2017, ISSN 1553-4650, http://dx.doi.org/10.1016/j.jmig.2017.07.001.

27. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomized Trials. *Ann Intern Med.* 2010; 152: 1-8.

28. www.afmps.be

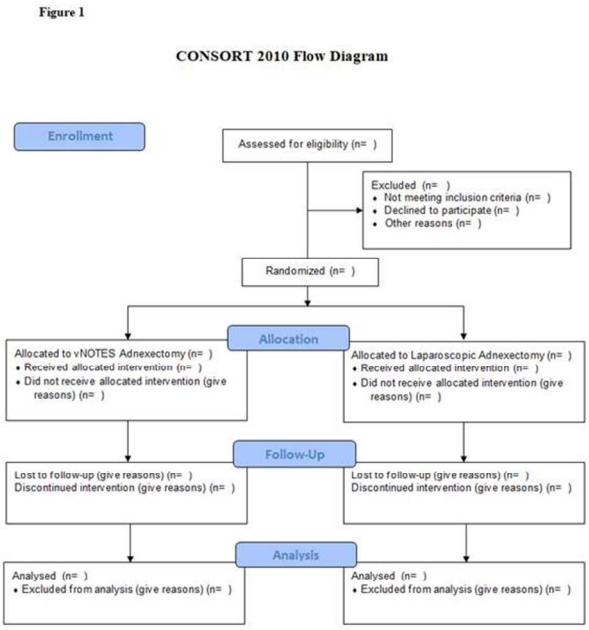


Figure 1: CONSORT 2010 Flow Diagram

254x190mm (96 x 96 DPI)

Opdrachtgever: Afdeling Verloskunde/Gynaecologie Imeldaziekenhuis Bonheiden
Onderzoeksinstelling: Afdeling Verloskunde/Gynaecologie Imeldaziekenhuis Bonheiden
Comité voor Medische Ethiek: Commissie Medisch Ethiek Imeldaziekenhuis Bonheiden
Lokale artsen-onderzoekers: Dr Jan Baekelandt en Dr Jan Bosteels, Imeldaziekenhuis Bonheiden, tel 015 505011
Studie secretaresse: Mevrouw Sofie De Wit, Imeldaziekenhuis Bonheiden, tel 015 505926

I Noodzakelijke informatie voor Uw beslissing om deel te nemen aan de NOTABLE studie

Inleiding

U wordt uitgenodigd om deel te nemen aan een klinische studie voor het vergelijken van twee technieken voor het verwijderen van een goedaardige eierstokcyste.

De artsen-onderzoekers hopen dat deze blind vergelijkende studie voordelen kan bieden voor de behandeling van patiënten die getroffen zijn door dezelfde aandoening als u. Er is evenwel geen enkele garantie dat Uw deelname aan deze studie U voordeel zal opleveren.

Voordat U beslist over Uw deelname aan deze studie willen we U wat meer informatie geven over wat dit betekent op organisatorisch vlak en wat de eventuele voordelen en risico's voor U zijn. Zo kan U een beslissing nemen op basis van de juiste informatie. Dit wordt "geïnformeerde toestemming" genoemd.

Wij vragen U de volgende pagina's met informatie aandachtig te lezen. Hebt U vragen, dan kan U terecht bij de arts-onderzoeker of zijn of haar vertegenwoordiger. Dit document bestaat uit drie delen: essentiële informatie die U nodig heeft voor het nemen van Uw beslissing, Uw schriftelijke toestemming en bijlagen waarin U meer details terugvindt over bepaalde onderdelen van de basisinformatie.

Als U aan de NOTABLE studie deelneemt, dient U het volgende te weten:

- Deze klinische studie wordt opgestart na evaluatie door één of meerdere ethische comité(s).
- Uw deelname is vrijwillig; er kan op geen enkele manier sprake zijn van dwang. Voor deelname is Uw ondertekende toestemming nodig. Ook nadat U hebt getekend, kan u de arts-onderzoeker laten weten dat U Uw deelname wilt stopzetten. De beslissing om al dan niet (verder) deel te nemen zal geen enkele negatieve invloed hebben op de kwaliteit van de zorgen noch op de relatie met de behandelende arts(en).
- De gegevens die in het kader van Uw deelname worden verzameld, zijn vertrouwelijk. Bij de publicatie van de resultaten is Uw anonimiteit verzekerd.
- Er worden U geen bijkomende kosten aangerekend voor specifieke behandelingen, bezoeken / consultaties, onderzoeken in het kader van dit onderzoek. De uitgevoerde chirurgische procedures worden terugbetaald in het kader van de ziekteverzekering.
- Eventuele schade opgelopen in het kader van Uw deelname aan deze klinische studie valt onder de verzekeringspolis van Uw behandelende arts. Omdat het een niet-commerciële studie betreft, werd hiervoor een bijkomende verzekeringspolis afgesloten met de verzekeringsmaatschappij van de behandelende hoofdonderzoeker.
- Indien U extra informatie wenst, kan U altijd contact opnemen met de arts-onderzoekers of een medewerker van hun team.

Aanvullende informatie over Uw rechten als deelnemer aan een klinische studie kan U bekomen via de ombudsdienst van het Imeldaziekenhuis te Bonheiden bij mevrouw Ilse Creemers bereikbaar via telefoon 015 505015 of via e-mail ombudsdienst@imelda.be.

Doelstelling en beschrijving van het studieprotocol

Wij nodigen U uit om deel te nemen aan een klinische studie inzake de klassieke laparoscopische (via de navel in de buikwand) vergeleken met de transvaginale (doorheen de vagina) verwijdering van één of beide adnexen (eierstok én eileider) bij vermoeden van een goedaardige cyste van één of beide eierstokken bij ongeveer 66 vrouwelijke deelnemers in België.

Alle vrouwen met een op echografie vermoede goedaardige cyste van één of beide eierstokken kunnen deelnemen aan de studie ongeacht de leeftijd en het aantal bevallingen in de voorgeschiedenis. Deelname aan deze studie is niet mogelijk bij een voorgeschiedenis van verwijdering van de baarmoeder, heelkunde aan de endeldarm, endometriose van het rectovaginaal septum, vermoeden van eierstokkanker, voorgeschiedenis van PID of pelvien abces, actieve genitale infectie of vrouwen die nog nooit sexueel contact hebben gehad. Zwaarlijvigheid, nulliparitеit (nooit eerder langs natuurlijke weg bevallen) of grootte van de cyste zijn dan weer geen reden tot uitsluiten van deelname aan de studie.

Het is een gerandomizeerde studie die een alternatieve toegangsweg (NOTES transvaginaal) vergelijkt met de huidige gouden standaard van de klassieke transabdominale laparoscopische toegangsweg voor het verwijderen van één of beide adnexen (eierstok met eileider). In een eerdere pilootstudie werd de technische haalbaarheid van deze transvaginale toegangsweg beschreven. Deze gevallenreeks verzamelde de gegevens van 20 uitgevoerde procedures.Het bleek mogelijk om op een veilige manier cysten te verwijderen tot een doormeter van 11 cm. Men observeerde lagere pijnscores bij vrouwen behandeld via deze nieuwe toegangsweg. De hypothese van deze studie is dat de nieuwe techniek minstens even succesvol is dan de klassieke gouden standaard maar het voordeel zou kunnen bieden dat meer vrouwen die via de nieuwe techniek werden behandeld zelf zouden verkiezen om dezelfde dag van de ingreep naar huis terug te keren vergeleken met de standaardtechniek. Een tweede bijkomend voordeel zou kunnen zijn dat vrouwen behandeld met de nieuwe techniek minder pijn hebben vergeleken met de gouden standaard. In deze studie zal via een techniek van randomizatie worden beslist of een deelnemer behandeld wordt op de klassieke wijze dan wel via de nieuwe techniek. De ingreep wordt uitgevoerd door één chirurg die een even grote ervaring heeft in het uitvoeren van beide technieken. De studie verloopt geblindeerd voor de deelnemers en de effect beoordeelaars. Het meten van pijn is namelijk subjectief en kan worden verstoord wanneer de deelnemer aan de studie of de effectbeoordeelaar voorkennis heeft van de uitgevoerde procedure. In alle gevallen wordt daarom een insnede aangebracht in de navel zodat niemand behalve de chirurg weet welke ingreep werd uitgevoerd. Indien deze methodiek niet zou worden toegepast, zou het uiteiendelijk nooit mogelijk zijn om betrouwbaar de doeltreffendheid van de nieuwe techniek versus de standaardtechniek te vergelijken. Het oplossen van deze onzekerheid is net de hoofdbedoeling van de huidige studie. Na het uitvoeren van de ingreep wordt standaard medische en verpleegkundige zorg toegediend (antibiotica, pijnstilling, wondzorg,...). Deze is identiek in beide groepen. De avond van de ingreep komt de coördinerende onderzoeker (Dr Bosteels) langs om te vragen of U zich in staat voelt om naar huis te gaan. Deze beslissing wordt uitsluitend door U genomen. Uiteraard toetst de coördinerende onderzoeker deze beslissing aan de gegevens van temperatuur, pols, bloeddruk en urinedebiet (de zogenaamde vitale parameters). Bij twijfel wordt met U overlegd en wordt altijd beslist in het belang van Uw gezondheid. Uw deelname gaat dan onverminderd verder. U krijgt een formulier mee met beschrijving van mogelijke alarmsymptomen die dringend medisch nazicht via spoedgevallen vereisen. U ontvangt ook een lijst met telefoonnummers voor contact. Gedurende één week wordt U gevraagd om ’s morgens en ’s avonds de pijn zoals U die beleeft aan te geven via een score (de VAS pijnscore) via een meetlatje. Een pijnverpleegkundige zal U uitleg geven hoe U deze metingen dient uit te voeren en te noteren in het pijndagboek. Bij ontslag wordt U ook een afspraak gegeven voor een kontrole onderzoek na één week bij één van de twee hoofdonderzoekers. U mag gedurende 4 weken na de ingreep geen sexueel contact hebben. Er wordt tijdelijke werkonbekwaamheid voorgeschreven voor één maand. Een postoperatief kontrole onderzoek is voorzien na 6 weken. Bij aanvang van de studie en op 3 en 6 maanden na de ingreep moet U een zelfbeoordeling aangeven van pijn bij sexueel contact via een standaard vragenlijst. Tevens kan U een anonieme vragenlijst invullen voor het meten van het sexueel welbevinden bij aanvang van de studie en op 3 en 6 maanden: omdat deze vragenlijst gevoelige vragen bevat is het invullen ervan facultatief. Dit bekent dat het U vrij staat om deze vragenlijst wel of niet in te vullen zonder dat dit het verdere verloop van de studie of de kwaliteit van de toegediende zorg beïnvloedt.

Verloop van de studie

Uw deelname aan de studie neemt 6 maanden in beslag en omvat één bijkomende raadpleging vergeleken met een behandeling zonder deelname aan de studie.

Er worden geen bijkomende procedures vereist in het kader van de studie.

In het kader van Uw deelname aan de studie en rekening houdend met Uw medische situatie, zal de meerderheid van de bezoeken en onderzoeken die we zullen beschrijven, deel uitmaken van de standaardzorgen in ons ziekenhuis terwijl slechts één bijkomend bezoek wordt vereist in het kader van deze studie, namelijk de postoperatieve kontrole na één week.

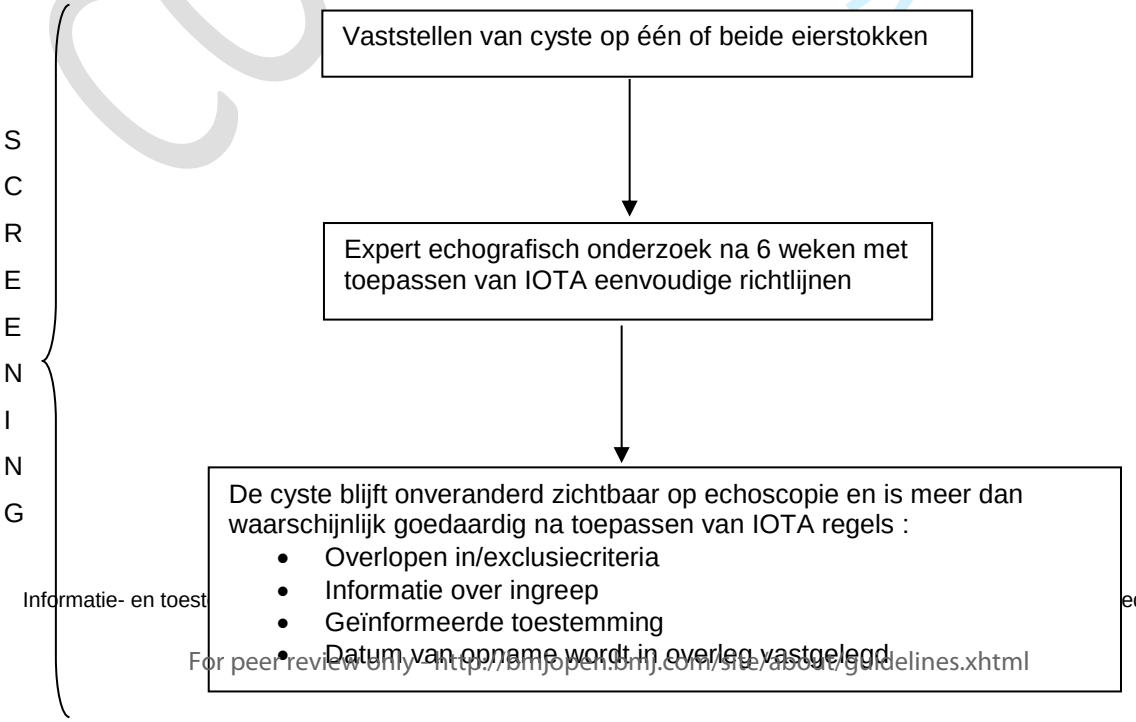
Screeningsfase: Bij een eerste raadpleging wordt de aanwezigheid van een cyste op één of beide eierstokken vastgesteld. De standaard praktijk is om de blijvende aanwezigheid van deze cyste te herkontroleren na 6 weken door een expert onderzoeker in de echografie. Blijkt de cyste blijvend aanwezig te zijn dan wordt tijdens het bezoek aan één van de beide lokale onderzoekers waarop de beslissing genomen om één of beide eierstokken te verwijderen overlopen of U voldoet aan de voorwaarden om te mogen deelnemen aan de studie (de in- en exclusiecriteria). De datum voor de geplande ingreep wordt vastgelegd. Het formulier voor geïnformeerde toestemming wordt ondertekend.

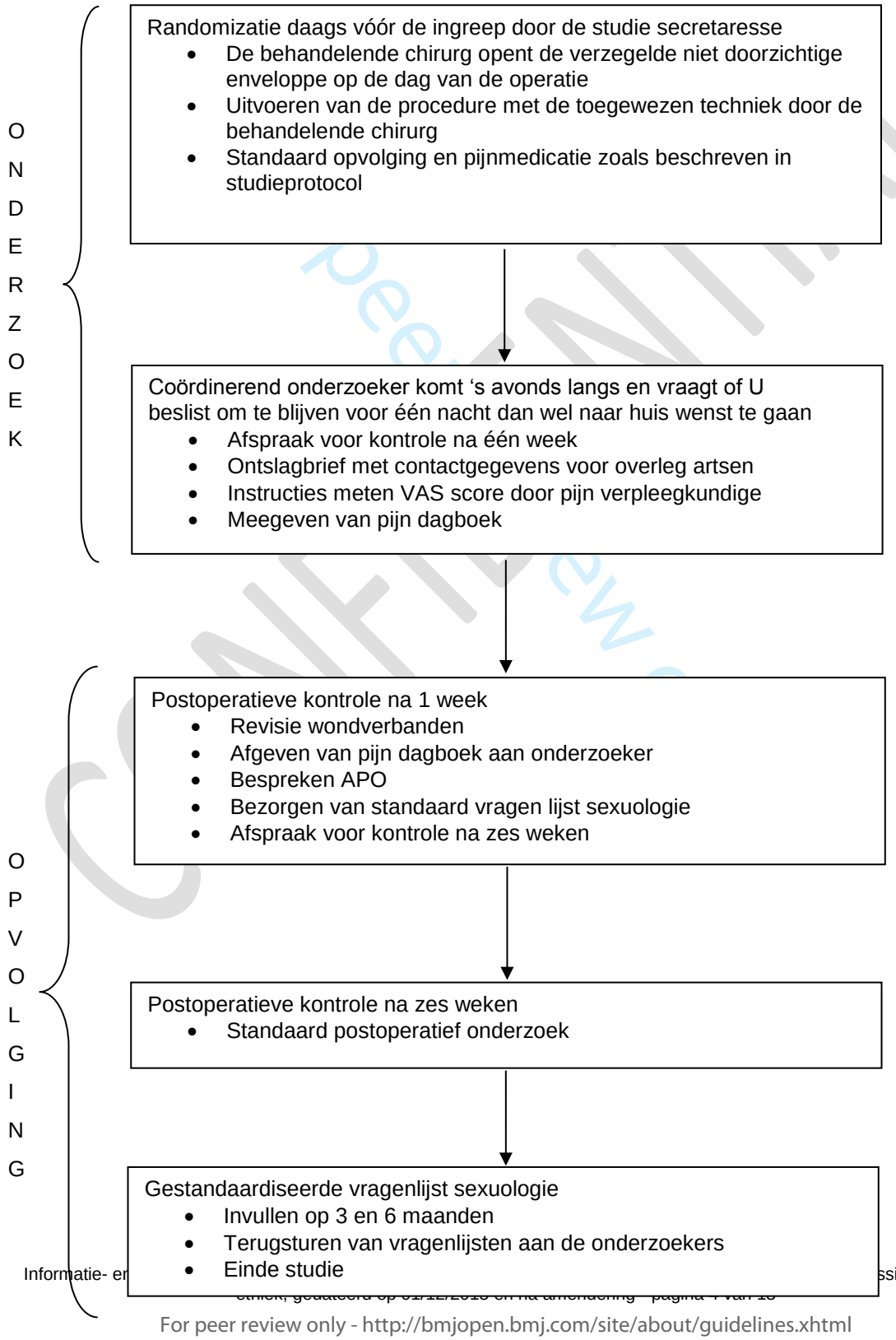
Onderzoeksfase: de nodige preoperatieve onderzoeken zijn deze welke volgens Uw leeftijd en voorgeschiedenis zijn vastgelegd in het werkdocument opgesteld door de dienst anesthesie. Deze kunnen voorafgaandelijk aan de ingreep door de huisarts worden uitgevoerd.De studie vereist geen bijkomende preoperatieve onderzoeken in vergelijking met de situatie waarin U zou hebben beslist om niet deel te nemen aan deze studie. U kan steeds uit vrije wil beslissen om niet langer deel te nemen aan de studie ook nadat U hiervoor Uw toestemming had gegeven. In dit geval wordt U steeds de standaard zorg verstrekt die dezelfde is als deze die U zou hebben ontvangen wanneer U had beslist om niet aan de studie deel te nemen. De studie wordt beëindigd na zes maanden. Op dat moment kan U van de hoofdonderzoeker (Dr Baekelandt) vernemen via welke techniek de ingreep werd uitgevoerd. Het eerder vrijgeven van deze informatie kan enkel om dringende medische redenen. In dergelijk dringend geval kan Uw deelname aan de studie voor het meten van de studie uitkomsten onveranderd doorgaan tenzij U op vrijwillige basis zou beslissen om verdere deelname aan de studie stop te zetten.

Opvolgingsfase: gedurende één week meet U thuis zelf s'morgens en 's avonds de VAS pijnscores en noteert U het gebruik van bijkomende pijnstillende medicatie met vermelding van naam, dosis en wijze van inname. Na één week en na zes weken volgen postoperatieve kontroles bij de onderzoekers. Op drie en zes maanden wordt U gevraagd om een door een universitair werkzame sexuoloog opgestelde standaard vragen lijst in te vullen en onder gesloten omslag met vermelding van "medisch geheim-verttrouwelijk" terug te zenden naar de onderzoekers.

De studie is volledig beëindigd wanneer U de vragenlijst op 6 maanden hebt teruggestuurd.

Indien u besluit deel te nemen aan de studie en aan alle voorwaarden voor deelname voldoet, ziet het schema van het verloop van Uw deelname aan de NOTABLE studie er uit als volgt:





Risico's en ongemakken

A: Verwikkelingen van de vNOTES en laparoscopische techniek

Verwikkelingen tijdens en na minimaal invasieve chirurgie of MIS waartoe zowel de nieuwe vNOTES als de klassieke laparoscopische procedure behoren zijn zeldzaam. In een prospectief onderzoek gepubliceerd door Nederlandse onderzoekers werden 145 verwikkelingen vermeld bij 25 764 laparoscopische ingrepen (1). Ook een groot Fins onderzoek rapporteerde minder dan 1% verwikkelingen na laparoscopische chirurgie (2).

De kansen op onderstaande verwikkelingen zijn als volgt:

- Tijdens de operatie:

- bloeding (slag)ader buikwand: 15 per 10 000 ingrepen
- letsel aan darm of maag: 11 per 10 000 ingrepen
- bloeding (slag) ader buikholte: 10 per 10 000 ingrepen
- bloeding vliezen rond eileider: 9 per 10 000 ingrepen
- blaasletsel: 2 per 10 000 ingrepen
- baarmoederletsel: 1 per 10 000 ingrepen
- laseraccident: 1 per 10 000 ingrepen
- overige: <1 per 10 000 ingrepen

- Na de operatie:

- abces: 35 per 100 000 ingrepen
- breuk: 8 per 100 000 ingrepen
- longembool: 4 per 100 000 ingrepen
- overlijden: 8 per 100 000 ingrepen

Ook is het mogelijk dat zich andere risico's en ongemakken voordoen die op dit moment nog onbekend zijn. Het is daarom van groot belang om elke nieuwe gezondheidsklacht zo snel mogelijk aan de arts-onderzoeker te melden, ongeacht of de klacht volgens U of Uw huisarts te maken heeft met de studie of niet.

B: Contraceptie, zwangerschap en borstvoeding

U mag niet deelnemen aan deze studie als u zwanger bent.Indien u kiest om aan deze studie deel te nemen, dient u gebruik te maken van één van de erkende contraceptiemethoden (om te voorkomen dat u zwanger wordt). Uw arts zal met u de verschillende doeltreffende opties bespreken.

C: Risico's in verband met de evaluatieprocedures in het kader van de studie.

Er zijn geen risico's/ongemakken verbonden aan de bijkomende kontrole één week na de ingreep die in het kader van de studie zal plaatsvinden. Het betreft een gebruikelijk klinisch onderzoek gelijkaardig aan het gewone preventief jaarlijks gynaecologisch onderzoek waarmee U waarschijnlijk voldoende vertrouwd bent.

(1) Jansen FW, Kapiteyn K, Trimbos-Kemper T, Hermans J, Trimbos-Kemper JB. Complications of laparoscopy: a prospective multicenter observational study. Br J Obstet Gynaeco 1997; 104: 595-600.

(2) Harkki-Siren P, Sjoberg J, Kurki T. Major complications of laparoscopy : a follow-up Finnish study. Obstet Gynecol 1999;94:94–98.

Melding van nieuwe informatie

Het is steeds mogelijk dat er tijdens het verloop van een klinische studie belangrijke nieuwe informatie over de transvaginale NOTES procedure beschikbaar wordt zoals dit het geval kan zijn met iedere klinische interventie studie. De onderzoekers verbindt er er zich toe om U desgevallend op de hoogte te brengen van nieuwe belangrijke informatie die een invloed kan hebben op Uw beslissing om Uw deelname aan de studie voort te zetten.

In dat geval zal men U vragen ofwel om een aanvulling bij de toestemmingsverklaring te ondertekenen ofwel om een nieuw informatie- en toestemmingsdocument te ondertekenen. Indien U in het licht van de nieuwe belangrijke informatie zou besluiten om Uw deelname aan de studie te beëindigen, zal Uw arts-onderzoeker erop toezien dat U ook nadien op de best mogelijke wijze behandeld wordt.

Voordelen

Indien U besluit om deze studie deel te nemen, kan de transvaginale NOTES techniek al dan niet gunstig blijken te zijn voor de behandeling van Uw aandoening, het verminderen van de symptomen ervan of het bespoedigen van het pijnvrije herstel na de ingreep.

De informatie, die dankzij dit onderzoek verkregen wordt, kan bijdragen tot een betere kennis van het gebruik van deze vernieuwende chirurgische techniek of tot de ontwikkeling van de NOTES transvaginale chirurgie voor de behandeling van gelijkaardige goedaardige gynaecologische aandoeningen bij toekomstige patiënten.

Andere behandelingen

Het meest gebruikte alternatief voor de nieuwe transvaginale vNOTES techniek is de laparoscopische techniek. Hierbij wordt via een kleine insnede via of onder het navellitteken een laparoscoop of kijkbuis ingebracht die toelaat om de bij U geplande heelkundige behandeling-het operatief verwijderen van één of beide eierstokken voor een goedaardige eierstokcyste- uit te voeren onder rechtstreeks zicht. Deze laparoscopische techniek vervangt de oudere klassieke open of laparotomische techniek, die heden hoofdzakelijk nog omwille van eierstokkanker of heel volumineuze eierstokcysten wordt toegepast.

De arts-onderzoeker zal deze alternatieve behandeling die als standaard klinische praktijk steeds in de controlegroep wordt toegepast eveneens met U bespreken.

Stopzetting van de deelname

Stopzetting van de deelname betekent simpelweg dat U als deelnemer Uw "praktische" deelname stopzet omdat U de aan de studie verbonden verplichtingen te zwaar vindt, de bijwerkingen te onaangenaam vindt of andere.

De deelname kan ook door de arts-onderzoeker worden stopgezet om veiligheidsredenen (evolutie van de ziekte) of andere redenen. Dit wil niet zeggen dat U als deelnemer Uw toestemming inzake de verzameling van aanvullende gegevens stopzet (indien U de arts-onderzoeker blijft bezoeken, die vaak ook Uw verwezen arts is voor de ziekte die in het kader van de klinische studie wordt behandeld).

Intrekking van de toestemming tot de studie betekent dat de deelnemer zijn/haar toestemming tot deelname aan de studie effectief intrekt. Dit kan zonder opgave van redenen en het kan betekenen dat de deelnemer zijn/haar toestemming inzake de verwerking van zijn/haar gezondheidsgegevens intrekt.

Uw deelname is vrijwillig. U hebt steeds het recht om Uw deelname aan de studie om eender welke reden en zonder opgave van redenen stop te zetten. Wel kan het voor de arts-onderzoeker en de opdrachtgever nuttig zijn om te weten of U zich terugtrekt omdat de aan de studiebehandeling verbonden beperkingen te zwaar zijn (bijvoorbeeld te veel onaangename bijwerkingen, te veel follow-up bezoeken).

Het is ook mogelijk dat de arts-onderzoeker Uw deelname aan de studie stopzet omdat hij van mening is dat dit beter is voor Uw gezondheid of omdat hij vaststelt dat U zich niet aan de voorschriften voor deelname houdt.

Ook gebeurt het soms dat de bevoegde nationale of internationale autoriteiten, de ethische comités die aanvankelijk goedkeuring hadden gegeven voor de studie of de opdrachtgever de studie stopzetten omdat uit de verzamelde informatie blijkt dat de behandeling niet werkt (de gezondheid van de deelnemers verbetert niet voldoende) of dat de onderzochte behandeling meer of ernstigere bijwerkingen veroorzaakt dan verwacht of voor een andere reden zoals bijvoorbeeld de beslissing om de studie en de ontwikkeling van het onderzochte studiegeneesmiddel stop te zetten.

Behandeling na stopzetting van de studie

In alle situaties waarbij de deelname aan de studie wordt stopgezet, maar ook wanneer de studie volgens planning is afgerond, zal Uw arts-onderzoeker Uw gezondheid onderzoeken en U de beste behandeling die beschikbaar is voorschrijven.

Biologische stalen die tijdens de studie worden afgenomen

De verwijderde weefsels worden volgens standaard klinische praktijk onderzocht op het labo pathologische ontleedkunde voor het microscopisch bevestigen van de goedaardigheid van de vastgestelde eierstokcyste. Hetzelfde geldt voor andere weefselvochten of biopsies. Deze worden standaard afgenomen als onderdeel van de behandeling (verwijderen van één of beide eierstokken) en deze praktijk zou ook worden toegepast indien U geen toestemming zou hebben gegeven voor deelname aan de studie.

Indien u aan deze studie deelneemt, vragen wij u het volgende:

- Tenvolle mee te werken voor een correct verloop van de studie.
- Geen informatie over Uw gezondheidstoestand, de geneesmiddelen die U gebruikt of de symptomen die U ervaart te minimaliseren of zelfs te verzwijgen.
- Niet deel te nemen aan een andere klinische studie met een experimentele behandeling - ongeacht of het een studiegeneesmiddel, medisch hulpmiddel of een procedure betreft- tijdens Uw deelname aan de huidige studie.
- Steeds uw “deelnemerskaart” bij u dragen. Dit is verplicht voor Uw veiligheid indien U een spoedbehandeling moet ondergaan in een ziekenhuis waar men U niet kent. Deze kaart vermeldt tevens de contactgegevens van de behandelende onderzoekers.

U moet eveneens weten dat:

het voor Uw veiligheid aangewezen is om Uw huisarts of andere behandelende artsen die bij Uw behandeling betrokken zijn te informeren over Uw deelname aan deze studie. Wij vragen U eveneens om hiervoor Uw toestemming te geven. Indien U echter niet wenst dat zij hierover worden geïnformeerd om welke reden ook, zullen wij Uw keuze respecteren.

Contact

Als U bijkomende informatie wenst, maar ook ingeval van problemen of als U zich zorgen maakt, kan U contact opnemen met de arts-onderzoekers Dr Jan Baekelandt of Dr. Jan Bosteels of de studiesecretaresse via de op de deelnemerskaart aangegeven contactgegevens of via het centraal telefoonnumer van het Imeldaziekenhuis (015 505011) of het onthaal van de dienst spoedgevallen buiten de klassieke werkuren (015 505040).

In geval van nood, kan U contact opnemen met de dienst spoedgevallen op het telefoonnummer 015 505040.

Buiten de consultatie-uren moet u zich aanmelden op de spoedafdeling van Uw ziekenhuis en vermelden dat U deelneemt aan een klinische studie. Uw dossier zal nuttige informatie bevatten voor de behandelde arts met betrekking tot de studie.

Als U vragen hebt met betrekking tot Uw rechten als deelnemer aan de studie, kan U contact opnemen met de ombudsdienst van het Imeldaziekenhuis (Mevrouw Ilse Creemers) op het telefoonnummer: 015 505015. Indien nodig kan de ombudsvrouw U in contact brengen met het Ethisch Comité

Titel van de studie: **NOTES adnexectomie voor benigne aandoeningen vergeleken met laparoscopische excisie**

II Geïnformeerde toestemming

Deelnemer

Ik verklaar dat ik geïnformeerd ben over de aard, het doel, de duur, de eventuele voordelen en risico's van de studie en dat ik weet wat van mij wordt verwacht. Ik heb kennis genomen van het informatiedocument en de bijlagen ervan.

Ik heb voldoende tijd gehad om na te denken en met een door mij gekozen persoon, zoals mijn huisarts of een familielid, te praten.

Ik heb alle vragen kunnen stellen die bij me opkwamen en ik heb een duidelijk antwoord gekregen op mijn vragen.

Ik begrijp dat mijn deelname aan deze studie vrijwillig is en dat ik vrij ben mijn deelname aan deze studie stop te zetten zonder dat dit mijn relatie schaadt met het therapeutisch team dat instaat voor mijn gezondheid.

Ik begrijp dat er tijdens mijn deelname aan deze studie gegevens over mij zullen worden verzameld en dat de arts-onderzoeker en de opdrachtgever de vertrouwelijkheid van deze gegevens verzekeren overeenkomstig de Belgische wetgeving ter zake.

Ik stem in met de verwerking van mijn persoonlijke gegevens volgens de modaliteiten die zijn beschreven in de rubriek over het verzekeren van de vertrouwelijkheid. Ik geef ook toestemming voor de overdracht naar en verwerking van mijn gecodeerde gegevens in andere landen dan België.

Ik ga ermee akkoord / Ik ga er niet mee akkoord (doorhalen wat niet van toepassing is) dat de studiegegevens die voor de hier vermelde studie worden verzameld, later zullen worden verwerkt, op voorwaarde dat deze verwerking beperkt blijft tot de context van de hier vermelde studie voor een betere kennis van de ziekte en de behandeling ervan.

Ik ga ermee akkoord / Ik ga er niet mee akkoord (doorhalen wat niet van toepassing is) dat mijn huisarts en andere specialisten die betrokken zijn bij mijn behandeling op de hoogte worden gesteld van mijn deelname aan deze klinische studie.

Ik heb een exemplaar ontvangen van de informatie aan de deelnemer en de geïnformeerde toestemming.

Naam, voornaam, datum en handtekening van de deelnemer

Wettelijke vertegenwoordiger

Ik verklaar dat men mij heeft geïnformeerd over de vraag om een beslissing te nemen over deelname aan de klinische studie door de persoon die ik in diens beste belang vertegenwoordig, rekening houdend met zijn of haar mogelijke wens. Mijn toestemming is van toepassing op alle items opgenomen in het toestemmingsformulier voor de deelnemer.

Ik ben eveneens geïnformeerd dat zodra de klinische situatie het toelaat, de persoon die ik vertegenwoordig op de hoogte zal worden gesteld van zijn/haar deelname aan een klinisch studie en op dat moment vrij is om toestemming te geven voor een verdere deelname of om deelname stop te zetten door het huidige toestemmingsformulier al dan niet te ondertekenen

Ik heb een exemplaar ontvangen van de informatie aan de deelnemer en de geïnformeerde toestemming.

Naam, voornaam en verwantschap met de vertegenwoordigde persoon:

Datum en handtekening van de wettelijke vertegenwoordiger

Getuige / Tolk

Ik ben tijdens het volledige proces van informatieverstrekking aan de deelnemer aanwezig geweest en ik bevestig dat de informatie over de doelstellingen en procedures van de studie op adequate wijze is verstrekt, dat de deelnemer (of diens wettelijke vertegenwoordiger) de studie naar alle waarschijnlijkheid heeft begrepen en dat de toestemming tot deelname aan de studie uit vrije wil is gegeven.

Naam, voornaam en hoedanigheid van de getuige:

Datum en handtekening van de getuige / tolk

Arts-onderzoeker

Ik ondergetekende, ..., arts-onderzoeker, verklaar de benodigde informatie inzake deze studie mondeling te hebben verstrekt evenals een exemplaar van het informatiedocument aan de deelnemer te hebben verstrekt.

Ik bevestig dat geen enkele druk op de deelnemer is uitgeoefend om haar te doen toestemmen tot deelname aan de studie en ik ben bereid om op alle eventuele bijkomende vragen te antwoorden.

Ik bevestig dat ik werk in overeenstemming met de ethische beginselen zoals vermeld in de laatste versie van de "Verklaring van Helsinki", de "Goede klinische praktijk" en de Belgische wet van 7 mei 2004 inzake experimenten op de menselijke persoon.

Naam, Voornaam, Datum en handtekening van de vertegenwoordiger van de arts-onderzoeker

Naam, Voornaam, Datum en handtekening van de vertegenwoordiger van de arts-onderzoeker

Naam, Voornaam, Datum en handtekening van de arts-onderzoeker

Titel van de studie: **NOTES adnexectomie voor benigne aandoeningen vergeleken met laparoscopische excisie**

III Aanvullende informatie

1 : Aanvullende informatie over de organisatie van de studie

Nagenoeg alle bezoeken / -consultaties en -procedures waarvan de resultaten eventueel voor de studie worden gebruikt vallen onder de huidige standaard klinische zorg. Enkel de het postoperatief bezoek één week na de ingreep is bijkomend in het kader van de studie. Hierbij worden geen bijkomende technische onderzoeken voorzien die belastend of gezondheidsrisico's inhouden voor de deelnemer. Bij vaststellen van postoperatieve verwikkelingen worden bijkomende bloednames of technische onderzoeken gepland analoog aan deze die ook zouden worden gepland voor een gelijkaardige verwikkeling indien de deelnemer geen geïnformeerde toestemming zou hebben gegeven voor deelname aan de studie.

2. Aanvullende informatie over de risico's die verbonden zijn aan deelname aan de studie

Verklarende begrippen over het voorkomen van verwikkelingen:

Zeer vaak	Bij meer dan 1 op de 10 patiënten
Vaak	Bij meer dan 1 op de 100, maar minder dan 1 op de 10 patiënten
Soms	Bij meer dan 1 op de 1000, maar minder dan 1 op de 100 patiënten
Zelden	Bij meer dan 1 op de 10 000, maar minder dan 1 op de 1000 patiënten

Wanneer gekozen wordt voor een ingreep langs vaginale weg, zal de buikholte worden geopend langs de schede door een insnede te maken in de omslagplooi van de Douglasholte. Men spreekt van een achterste colpotomie. Op deze plaats grenst het diepste punt van de buikholte aan het diepste punt van de schede. Vroeger werd deze toegang gebruikt om ingrepen aan de eierstokken of eileiders uit te voeren. Zo werd in het verleden voor de opkomst van de laparoscopie een sterilisatie uitgevoerd via een colpotomie. Precieze gegevens over het voorkomen van verwikkelingen na een colpotomie zijn bekend in het kader van een eileidersterilisatie:

- morbiditeit of totaal aantal verwikkelingen door bloeding, infectie: minder dan 5 op 100
- mortaliteit of sterfte: minder dan 4 op 100 000

Andere zeldzame verwikkelingen die in minder dan 1 op 100 ingrepen voorkomen zijn:

- acuut compartiment syndroom bij ingrepen die langer dan drie uur duren
- ileus of vertraagd of niet op gang komen van de darmactiviteit
- obstipatie of fecale impactie
- oligurie of minder goed kunnen plassen
- ernstige infecties zoals septische shock, necrotizerende fascitis
- longontsteking
- platvallen van de longbases of atelectasis
- openvallen van de colpotomie wonde of dehiscentie
- achterlaten van een vreemd voorwerp zoals een wondcompres
- niet vermoede kanker van eileider of eierstok
- ernstige emotionele of psychologische stoornissen zoals verwardheid of depressie

Contraceptie, zwangerschap bij de deelneemster.

Zwangere vrouwen kunnen niet deelnemen aan de studie.

Risico's in verband met de klinische onderzoeksprocedures

De **bloedafname** die nodig is voor het preoperatief onderzoek is hetzelfde als dat wat zou worden uitgevoerd indien U zou moeten worden behandeld zonder dat U geïnformeerde toestemming gaf voor deelname aan de studie. Deze bloedname kan (in zeldzame gevallen) pijn, bloedingen, bloeduitstortingen of een lokale infectie op de plek van bloedafname veroorzaken. Ook kunnen sommige deelnemers zich duizelig voelen of flauwvallen tijdens de afname. Het personeel dat de bloedafname uitvoert, zal alles in het werk stellen om deze ongemakken te beperken.

3 : Aanvullende informatie over de bescherming en de rechten van deelnemers aan een klinische studie

Ethische comités

Deze studie werd geëvalueerd door het onafhankelijk ethisch comité van het Imeldaziekenhuis dat een gunstig advies heeft uitgebracht op 1 december 2015. De ethische comités hebben als taak de personen die aan klinische studies deelnemen te beschermen. Ze controleren of uw rechten als patiënt en als deelnemer aan een studie gerespecteerd worden, of - uitgaande van de huidige kennis - de balans tussen risico's en voordelen gunstig is voor de deelnemers, of de studie wetenschappelijk relevant en ethisch verantwoord is.

Hierover brengen de ethische comités een advies uit in overeenstemming met de Belgische wet van 7 mei 2004.

U dient het positief advies van de Ethische Comités in geen geval te beschouwen als een aansporing om deel te nemen aan deze studie.

Vrijwillige deelname

Aarzel niet om alle vragen te stellen die bij U opkomen voordat U tekent. Neem de tijd om er over te praten met een vertrouwenspersoon indien U dat wenst.

U heeft het recht om niet deel te nemen aan deze studie of met deze studie te stoppen, zonder dat U hiervoor een reden hoeft te geven, zelfs al hebt U eerder toegestemd om aan deze studie deel te nemen. Uw beslissing zal in geen geval Uw relatie met de arts-onderzoeker beïnvloeden, noch de kwaliteit van uw verdere verzorging.

Als U aanvaardt om aan deze studie deel te nemen, ondertekent U het toestemmingsformulier. De arts-onderzoeker zal dit formulier ook ondertekenen en zal zo bevestigen dat hij U de noodzakelijke informatie over deze studie heeft gegeven. U zal het voor U bestemde exemplaar ontvangen.

Voor Uw veiligheid is het wel aanbevolen om de arts-onderzoeker op de hoogte te stellen indien U besluit Uw deelname aan de studie stop te zetten.

Kosten in verband met uw deelname

Deze studie is een niet-commerciële studie.

Alle kosten staan in verband met gebruikelijke medische prestaties in uw klinische situatie en deze worden na facturatie terugbetaald door de mutualiteiten en de verzekeringsmaatschappij. Het gaat namelijk om een heelkundige behandeling die standaard voor dit gezondheidsprobleem wordt toegepast en die eveneens zou moeten gebeuren indien U niet aan de huidige studie zou deelnemen.

De bijkomende postoperatieve kontrole na één week is buiten de standaard klinische praktijk: de kostprijs van deze raadpleging zal niet worden aangerekend behalve indien er tijdens dit onderzoek verwikkelingen zouden worden opgemerkt die verdere technische onderzoeken of behandeling zouden vereisen welke ook buiten Uw deelname aan deze studie op gelijkaardige manier zouden worden behandeld. Uw verplaatsingskosten voor deze bijkomende raadpleging worden niet vergoed. Neem contact op met het studieteam voor de praktische uitvoering.

Vertrouwelijkheidsgarantie

Uw deelname aan de studie betekent dat U ermee akkoord gaat dat de arts-onderzoeker gegevens over U verzamelt en dat de opdrachtgever van de studie die gebruikt voor onderzoek en in het kader van wetenschappelijke en medische publicaties.

U hebt het recht om aan de arts-onderzoeker te vragen welke gegevens hij over U heeft verzameld en waarvoor ze gebruikt worden in het kader van de studie. Deze gegevens hebben betrekking op Uw huidige klinische situatie maar ook op Uw medische voorgeschiedenis en op de resultaten van onderzoeken die werden uitgevoerd voor de behandeling van Uw gezondheid volgens de geldende zorgstandaard. U hebt het recht om deze gegevens in te kijken en om verbeteringen te laten aanbrengen indien ze foutief zouden zijn.

Uw recht op inzage wordt minstens tot één week na de ingreep uitgesteld (ideaal tot na afloop van de studie op zes maanden) om een correct verloop van de studie te garanderen. Het eerder bekend maken van de gebruikte techniek kan leiden to voorkennis die de resultaten van de pijnscore metingen die binnen de eerste week moeten worden gemeten, betekenisvol beïnvloeden wat leidt tot foutieve resultaten en besluiten over de doeltreffendheid van de transvaginale benadering vergeleken met de standaard laparoscopische benadering.

De arts-onderzoeker is verplicht om deze verzamelde gegevens vertrouwelijk te behandelen.

Dit betekent dat hij zich ertoe verbindt om Uw naam nooit bekend te maken bijvoorbeeld in het kader van een publicatie of een conferentie en dat hij Uw gegevens zal coderen (Uw identiteit zal worden vervangen door een identificatiecode in de studie). De data van Uw deelname aan de studie zijn klinische data die worden bewaard in Uw electronisch patiënten dossier.

De arts-onderzoeker en zijn team zullen gedurende de volledige klinische studie de enige personen zijn met toegang tot Uw studie dossier).

De gepubliceerde persoonlijke gegevens omvatten geen combinatie van elementen waarmee het mogelijk is U te identificeren.

Alle onderzoekers betrokken bij deze studie behandelen Uw gegevens in overeenstemming met de Belgische wet betreffende de bescherming van de persoonlijke levenssfeer.

Om de kwaliteit van de studie te controleren, kan uw medisch dossier worden ingekeken door personen die gebonden zijn aan het beroepsgeheim zoals vertegenwoordigers van de ethische comités of een extern auditbureau. Dit kan enkel gebeuren onder strikte voorwaarden, onder de verantwoordelijkheid van de arts-onderzoeker en onder zijn toezicht (of van één van zijn onderzoeksmedewerkers).

De (gecodeerde) onderzoeksgegevens kunnen doorgegeven worden aan Belgische of andere regelgevende instanties, aan de betrokken ethische comités, aan andere artsen en/of instellingen die samenwerken met de onderzoekers.

Uw toestemming om aan deze studie deel te nemen betekent dus ook dat U akkoord gaat dat Uw gecodeerde medische gegevens gebruikt worden voor doeleinden die in dit informatieformulier beschreven staan en dat ze overgedragen worden aan bovenvermelde personen en/of instellingen.

De onderzoekers zullen de verzamelde gegevens gebruiken in het kader van de studie waaraan U deelneemt, maar willen ze ook kunnen aanwenden in het kader van andere studies over dezelfde ziekte als de Uwe. Buiten de context die beschreven wordt in dit document, kunnen Uw gegevens enkel gebruikt worden als een ethisch comité haar goedkeuring heeft gegeven.

Indien u uw toestemming tot deelname aan de studie intrekt, zullen de gecodeerde gegevens die al verzameld waren vóór uw terugtrekking, bewaard worden. Hierdoor wordt de geldigheid van de studie gegarandeerd.

Verzekering

Elke deelname aan een studie houdt een risico in, hoe klein ook. De onderzoeker is - ook indien er geen sprake is van fout - aansprakelijk voor de schade die de deelnemer of in geval van overlijden haar rechthebbenden, oplopen en die rechtstreeks of onrechtstreeks verband houdt met diens deelname aan de studie. U moet hiervoor dus geen fout aantonen. De opdrachtgever heeft voor deze aansprakelijkheid een verzekering afgesloten

We verzoeken U daarom om elk nieuw gezondheidsprobleem aan de arts-onderzoeker te melden. Hij kan U aanvullende informatie verstrekken over mogelijke behandelingen.

Indien de arts-onderzoeker van mening is dat er een verband met de studie mogelijk is (er is geen verband met de studie bij schade ten gevolge van het natuurlijke verloop van Uw ziekte of ten gevolge van gekende bijwerkingen van uw standaardbehandeling), zal aangifteprocedure bij de verzekering worden opgestart. Deze zal, indien zij het nodig acht, een expert aanstellen om een oordeel uit te spreken over het verband tussen Uw nieuwe gezondheidsklachten en de studie.

In het geval van onenigheid met de arts-onderzoeker of met de door de verzekeringsmaatschappij aangestelde expert, en steeds wanneer U dit nodig acht, kunnen U of in geval van overlijden Uw rechthebbenden de verzekeraar rechtstreeks in België dagvaarden dagvaarden (NV VANBREDA RISK & BENEFITS (Liability / Fleet with premium), polisnummer LXX048196 , Plantin en Moretuslei 297, 2140 Borgerhout, Tel 03/2176767).

De wet voorziet dat de dagvaarding van de verzekeraar kan gebeuren ofwel voor de rechter van de plaats waar de schadeverwekkende feiten zich hebben voorgedaan, ofwel voor de rechter van Uw woonplaats, ofwel voor de rechter van de zetel van de verzekeraar.

ClinicalTrials.gov PRS
Protocol Registration and Results System

ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 01/17/2016

ClinicalTrials.gov ID: NCT02630329

Study Identification

Unique Protocol ID:	B689201526268
Brief Title:	Notes Adnexectomy for Benign Pathology Compared to Laparoscopic Excision (NOTABLE)
Official Title:	Adnexectomy for Benign Gynaecological Pathology by Natural Orifice Transluminal Endoscopy or Laparoscopy
Secondary IDs:	

Study Status

Record Verification:	January 2016
Overall Status:	Recruiting
Study Start:	December 2015
Primary Completion:	May 2018 [Anticipated]
Study Completion:	May 2018 [Anticipated]

Sponsor/Collaborators

Sponsor:	Imelda Hospital, Bonheiden
Responsible Party:	Principal Investigator Investigator: Dr Jan Baekelandt, MD [jbaekelandt] Official Title: Dr Affiliation: Imelda Hospital, Bonheiden
Collaborators:	

Oversight

FDA Regulated?:	No
IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 689/151145 Board Name: Commissie Medische Ethiek Board Affiliation: Imelda Hospital Bonheiden Phone: + 3215505529 Email: marc.lambrechts@imelda.be
Data Monitoring?:	Yes
Plan to Share Data?:	No

	Interim analyses of major endpoints will be supplied, in strict confidence, to an independent Data Monitoring and Ethics Committee (DMEC) along with updates on results of other related studies, and any other analyses that the DMEC may request.
Oversight Authorities:	Belgium: Federal Agency for Medicines and Health Products, FAMHP

Study Description

Brief Summary:	Objective: To compare vNOTES (vaginal Natural Orifice Transluminal Endoscopic Surgery) and established laparoscopic removal of benign adnexal masses Study design: Randomized controlled/single center/single-blinded/parallel-group/non-inferiority/efficacy trial. Study population: Women aged 18 to 70 years with symptomatic or persistent benign adnexal masses detected by clinical examination and ultrasound. Randomization: Women will be randomly allocated to undergo one of two techniques for removal of the benign adnexal mass immediately before surgery by using a computer generated randomization list. The investigators will use stratified randomization according to the cyst diameter. Intervention: Women will be treated by a surgeon who is not blinded to the treatment allocation and who is equally skilled in performing both techniques. In the intervention group a vNOTES technique will be used. Control: In the control group surgery will be done by a classical laparoscopic technique. Participants, nursing staff and outcome assessors will be blinded. Main study parameters/endpoints: Primary outcomes: successful removal of a benign adnexal mass without spill. Secondary outcomes: the proportion of women discharged the same day based on their own preference; postoperative pain scores using a VAS (Visual Analogue Scale) measured between day 1 till 7 by the participating women following surgery and the total amount of analgesics used as described in the standardized pain treatment protocol between day 1 till 7; postoperative infection defined by lower abdominal pain with fever > 38°C and positive clinical signs or laboratory findings; per- or postoperative complications according to the Clavien- Dindo classification detected during the first six weeks of surgery; duration of the surgical procedure; incidence and intensity of dyspareunia recorded by the participants at 3 and 6 months by self-reporting using a simple questionnaire and VAS scale; sexual wellbeing recorded by the participants at 3 and 6 months by SSFS (Short Sexual Functioning Scale); direct costs associated up to 6 weeks after the surgical intervention with both procedures.
Detailed Description:	1. Objectives of the NOTABLE Trial The primary research questions of this IDEAL stage 2b efficacy trial are as follows: is a vNOTES adnexectomy at least as effective compared to the standard transabdominal laparoscopic approach (LSC) for removing a benign adnexal mass without spill? (non-inferiority design) Secondary research questions are: • Do more women treated by vNOTES prefer to leave the hospital on the day of surgery compared to LSC? • Do women treated by vNOTES suffer from less pain compared to women treated by LSC in the first postoperative week? • Is the removal of a benign adnexal mass by vNOTES faster compared to LSC? • Does a vNOTES cause more pelvic infection or other complications compared to LSC? • Does a vNOTES cause more hospital readmissions within 6 weeks following surgery compared to LSC?

- Does a vNOTES approach result in more women reporting dyspareunia or less sexual wellbeing at 3 or 6 months after surgery when compared to women treated by LSC?
- What are the direct costs up to 6 weeks of a vNOTES compared to LSC?

TRIAL DESIGN 2.1. Design A single center, single-blinded, parallel group randomized, non-inferiority efficacy trial.

2.2. Simple pilot randomized trial: minimal extra workload 2.3. Time schedule Based upon the mean number of laparoscopic adnexectomies performed annually at the department of Obstetrics and Gynecology of the participating center (36) the investigators estimate that the duration of recruitment will be 21 months. Based upon the follow up (6 months) and the period of analysis/reporting (3 months) the total study period will be 2.5 years.

2.4. Participating center Department of Obstetrics and Gynecology Imeldahospital Imeldalaan 9 2820 Bonheiden Belgium

- ELIGIBILITY, CONSENT AND RANDOMIZATION 3.1. Screening and consent prior to surgery All women aged 18 to 70 years regardless of parity presenting with a symptomatic or asymptomatic persistent benign adnexal mass on clinical examination confirmed by ultrasound are eligible for inclusion. The diagnosis of benign adnexal mass will be based upon the prospectively validated IOTA classification(International Ovarian Tumour Analysis Group) simple ultrasound rules to distinguish between benign and malignant adnexal masses.

  3.2. Determining eligibility All women aged 18 to 70 years regardless of parity presenting with a symptomatic or asymptomatic persistent benign adnexal mass on clinical examination who provide consent to participation are eligible in the NOTABLE trial based on the findings of the ultrasound findings and will be randomized before the procedure.

  3.3. Randomization If the woman is eligible for the NOTABLE trial, the trial secretary will obtain a randomized allocation the day before surgery. This will be done using a randomization list generated by a free computer software program offered by Research Randomizer (https://www.randomizer.org). The random sequence generation will be concealed using sequentially numbered opaque sealed envelopes. The envelope will be opened by the nurse assistant on the day before the surgical intervention for logistic reasons. The investigators will use stratified randomization in this small pilot RCT (randomized controlled trial) according to the cyst diameter.

  3.4. Patients with strong preference for treatment A minority of women will express a clear preference for one of both treatments (e.g. strong desire to have no scar) and for this reason will not wish to be randomized between surgical treatments. To investigate how outcomes vary by choice, these women could be followed up in exactly the same way as for those women randomized into the NOTABLE trial. A formal non-randomized follow-up of these women will not be done for simple logistical reasons.

  3.5. Stratification of randomization A blocked randomization procedure will be used to avoid chance imbalances for the parameter ‘cyst diameter’.

  To avoid any possibility of foreknowledge, the randomized allocation will not be given until all eligibility and stratification data have been given.
- TREATMENT ALLOCATIONS 4.1. Surgical procedures The principal investigator, who has training and experience in both laparoscopy and NOTES, will perform all surgical procedures. He is therefore not blinded. All vNOTES participants will be blinded by three superficial “mock” skin incisions similar to those routinely done with the laparoscopic technique.

  4.1.1 vNOTES adnexectomy This is the surgical procedure done in the intervention arm of the NOTABLE trial.

4.1.2 LSC adnexectomy This is the surgical procedure done in the control arm of the NOTABLE trial.

- FOLLOW-UP AND OUTCOME MEASURES 5.1. Clinical assessments 5.1.1 Format PROMs will be collected using a postal questionnaire, which will include a combination of disease specific and generic measurement instruments.

  The postal questionnaires will be sent from the NOTABLE Trial Office with postage paid envelopes two weeks before the due date. Reminders will be sent to the participants if the questionnaire is not returned within one week of the due date and attempts will be made to contact the women by phone if the questionnaire is not returned by two weeks after the due date.

  5.1.2 Timing of assessments The primary outcome will be measured clinically at the end of the surgical procedure. In addition PROMs will take place the evening of the surgical intervention (return home), during the first postoperative week (pain by VAS scores and analgetic drugs) and at 3 and 6 months (dyspareunia). Clinical physician assessment will take place the evening of the surgical intervention (return home) and during the first six weeks following surgery (pelvic infection, surgical complications, hospital readmission rate).

  5.2. Primary clinical outcome measure The proportion of women successfully treated by removing the adnexal mass without spill, using a dichotomous outcome measure, will be used as a measure of efficacy.

  5.3. Secondary clinical outcome measures

  The following secondary outcomes will be measured:

  - The proportion of women discharged the same day based on their own preference, as a dichotomous outcome.
  - Postoperative pain scores, as an ordinal outcome, measured using a VAS scale twice daily from day 1 till 7 self-reported by the participating women.
  - Postoperative pain defined by the total amount of analgesics used as described in the standardized pain treatment protocol, as a continuous outcome.
  - Postoperative infection as a dichotomous outcome.
  - Per- or postoperative complications according to the Clavien- Dindo classification detected during the first six weeks of surgery, as a dichotomous outcome.
  - Hospital readmission within 6 weeks following surgery, as a dichotomous outcome.
  - Incidence and intensity of dyspareunia recorded by the participants at 3 and 6 months by self-reporting using a simple questionnaire and VAS scale, as a dichotomous and ordinal outcome. .
  - Sexual wellbeing at baseline, at 3 and 6 months by self-reporting the SSFS.
  - Duration of surgery measured as the time in minutes from the insertion of the bladder catheter to the end of vaginal/abdominal wound closure, as a continuous outcome.

  5.4. Health economic outcomes The direct costs of both techniques up to 6 weeks after the surgical intervention will be calculated.

- ACCRUAL AND ANALYSIS 6.1. Sample size The sample size for this trial has been chosen to give good statistical power to preclude any clinically important inferiority of vNOTES compared to laparoscopy and is based on evidence retrieved from a systematic review of the literature and a RCT comparing the excision of mature teratoma using culdotomy with and without laparoscopy. Based on the power calculations for the primary outcome and two secondary outcomes and assuming a loss-to-follow-up rate of 10% the investigators decided to include 66 study participants in the NOTABLE trial.

6.2. Projected accrual and attrition rates It is anticipated that recruitment of participants will take two years. Based upon the mean number of laparoscopic adnexectomies performed annually at the department of Obstetrics and Gynecology of the participating center (36) the investigators estimate that the duration of recruitment will be 21 months. Based upon the follow up (6 months) and the period of analysis/reporting (3 months) the total study period will be 2.5 years. First publication will be possible within four years of trial commencement.

Conditions

Conditions: Natural Orifice Endoscopic Surgery
Disease, Adnexal
Laparoscopic Surgery

Keywords: NOTES
Benign adnexal disease
Laparoscopy

Study Design

Study Type: Interventional
Primary Purpose: Treatment
Study Phase: Phase 2
Intervention Model: Parallel Assignment
Number of Arms: 2
Masking: Double Blind (Subject, Outcomes Assessor)
Allocation: Randomized
Endpoint Classification: Efficacy Study
Enrollment: 66 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: vNOTES adnexectomy Vaginal Natural Orifice Transluminal Endoscopic Surgery	Procedure/Surgery: vNOTES adnexectomy Surgical removal of one or both adnexa by a natural orifice transluminal endoscopic surgical technique using a colpotomy (transvaginal incision)
Active Comparator: LSC adnexectomy Laparoscopic adnexectomy	Procedure/Surgery: Laparoscopic adnexectomy Surgical removal of one or both adnexa by transabdominal laparoscopy

Outcome Measures

Primary Outcome Measure:

1. Successful removal of adnexal mass without spill
   [Time Frame: Intraoperative] [Safety Issue: Yes]
   The proportion of women successfully treated by removing the adnexal mass without spill, using a dichotomous outcome measure, will be used as a measure of efficacy.

Secondary Outcome Measure:

2. Discharge from the hospital the day of the surgical intervention

[Time Frame: Dichotomous outcome measured on the day of the surgical intervention] [Safety Issue: Yes]
The proportion of women discharged the same day based on their own preference, as a dichotomous outcome. The decision to discharge or to admit to hospital for the night will be based solely on the choice of the woman to return home the same day or stay overnight.

3. Postoperative pain scores
[Time Frame: The first week after the surgical intervention] [Safety Issue: No]
Postoperative pain scores, as an ordinal outcome, measured using a VAS scale twice daily from day 1 till 7 self-reported by the participating women

4. The use of analgesics for postoperative pain
[Time Frame: The first week after the surgical intervention] [Safety Issue: No]
Postoperative pain defined by the total amount of analgesics used as described in the standardized pain treatment protocol, as a continuous outcome.

5. Postoperative infection
[Time Frame: The first six weeks after the surgical intervention] [Safety Issue: Yes]
Postoperative infection defined by lower abdominal pain with fever > 38°C and positive clinical signs or laboratory findings, detected during the first six weeks of surgery, as a dichotomous outcome.

6. Complications
[Time Frame: The first six weeks after the surgical intervention] [Safety Issue: Yes]
Per- or postoperative complications according to the Clavien- Dindo classification detected during the first six weeks of surgery, as a dichotomous outcome

7. Hospital readmission
[Time Frame: The first six weeks after the surgical intervention] [Safety Issue: Yes]
The proportion of women readmitted to hospital within six weeks of surgery, as a dichotomous outcome

8. Pain during sexual intercourse
[Time Frame: At baseline, 3 months and 6 months after the surgical intervention] [Safety Issue: No]
Incidence and intensity of dyspareunia recorded by the participants at 3 and 6 months by self-reporting using a simple questionnaire and VAS scale, as a dichotomous and ordinal outcome

9. Sexual well being
[Time Frame: At baseline, 3 months and 6 months after the surgical intervention] [Safety Issue: No]
Sexual wellbeing at baseline, at 3 and 6 months by self-reporting using the SSFS (Short Sexual Function Scale).

10. Duration of the surgical intervention
[Time Frame: Intraoperative] [Safety Issue: No]
Duration of surgery measured as the time in minutes from the insertion of the bladder catheter to the end of vaginal/ abdominal wound closure, as a continuous outcome

11. Direct costs
[Time Frame: Up to 6 weeks postoperative] [Safety Issue: No]
Calculating the comparative direct costs of both techniques up to 6 weeks after the surgical intervention

Eligibility

Minimum Age:	18 Years
Maximum Age:	70 Years
Gender:	Female
Accepts Healthy Volunteers?:	Yes
Criteria:	Inclusion Criteria:

- All women aged 18 to 70 years regardless of parity with a symptomatic adnexal mass presumed to be benign based on ultrasound examination by applying the IOTA simple rules

- All women aged 18 to 70 years regardless of parity with an asymptomatic persistent adnexal mass presumed to be benign based on ultrasound examination by applying the IOTA simple rules
- Written informed consent obtained prior to surgery

Exclusion Criteria:

- History of hysterectomy by any technique
- History of rectal surgery
- Suspected rectovaginal endometriosis
- Suspected endometriotic cyst
- Solid adnexal mass
- High suspicion of adnexal malignancy based on clinical, ultrasound or biochemical findings
- History of pelvic inflammatory disease, especially prior tubo-ovarian or pouch of Douglas abscess
- Active lower genital tract infection e.g. Chlamydia, N. gonorrhoeae
- Virgo
- Pregnancy
- Need for other uterine surgical intervention (i.e. endometrial ablation, resection, myomectomy or hysterectomy)
- Additional pathology necessitating hysterectomy
- Failure to provide written informed consent prior to surgery

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References

Citations: [Study Results] Baekelandt J. Poor man's NOTES: can it be a good approach for adhesiolysis? A first case report with video demonstration. J Minim Invasive Gynecol. 2015 Mar-Apr;22(3):319. doi: 10.1016/j.jmig.2014.11.001. Epub 2014 Nov 10. PubMed 25460516

[Study Results] Yang YS, Hur MH, Oh KY, Kim SY. Transvaginal natural orifice transluminal endoscopic surgery for adnexal masses. J Obstet Gynaecol Res. 2013 Dec;39(12):1604-9. doi: 10.1111/jog.12108. Epub 2013 Jul 22. PubMed 23875997

[Study Results] Ghezzi F, Cromi A, Uccella S, Bogani G, Serati M, Bolis P. Transumbilical versus transvaginal retrieval of surgical specimens at laparoscopy: a randomized trial. Am J Obstet Gynecol. 2012 Aug;207(2):112.e1-6. doi: 10.1016/j.ajog.2012.05.016. Epub 2012 May 23. PubMed 22704765

Wang PH, Lee WL, Juang CM, Tsai WY, Chao HT, Yuan CC. Excision of mature teratoma using culdotomy, with and without laparoscopy: a prospective randomised trial. BJOG. 2001 Jan;108(1):91-4. PubMed 11213011

[Study Results] Medeiros LR, Rosa DD, Bozzetti MC, Fachel JM, Furness S, Garry R, Rosa MI, Stein AT. Laparoscopy versus laparotomy for benign ovarian tumour. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD004751. doi: 10.1002/14651858.CD004751.pub3. Review. PubMed 19370607

Links:

Study Data/Documents:

RESEARCH PROTOCOL

NOTABLE trial

(NOTes Adnexectomy for Benign pathology compared to Laparoscopic Excision)

UNIQUE PROTOCOL ID: B689201526268

ClinicalTrials.govID: NCT02630329

Protocol ID	B689201526268 NCT02630329
Short title	NOTABLE trial
Version	5
Date	28-12-2015
Coordinating investigator	Dr. J. Bosteels Imeldaziekenhuis Department of Obstetrics and Gynaecology Imeldalaan 9, 2820 Bonheiden, Belgium T: + 32 15 505205 M: jan.bosteels@imelda.be
Principal investigator	Dr. J. Baekelandt Imeldaziekenhuis Department of Obstetrics and Gynaecology Imeldalaan 9, 2820 Bonheiden, Belgium T: + 32 15 505208 M: jbaekelandt@imelda.be
Sponsor	Investigator driven trial
Independent physician	Not applicable
Laboratory sites	Clinical laboratory Imeldaziekenhuis Imeldalaan 9, 2820 Bonheiden, Belgium T: + 32 15 505460
Pharmacy	Not applicable

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
For non-commercial research, Head of Department: Dr. Philippe Delattin, MD, Gynaecologist		
Coordinating Investigator: Dr. Jan Bosteels, MD, PhD, Gynaecologist		
Principal investigator/project leader: Dr. Jan Baekelandt, MD, Gynaecologist		
Assistant study investigators: Dr Jona Vercammen, MD Dr Sylvie De Rijdt, MD Dr. Siel Olbrecht, MD Dr. Judith De Coene, MD Dr. Maja Van Goitsenhoven, MD		

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ACOG	American College of Obstetricians and Gynecologists
AE	Adverse Event
CAT	Computerized Axial Tomography
CONSORT	Consolidated Standards of Reporting Trials
DMEC	Data Monitoring and Ethics Committee
EuroQoL	EQ-5D Health Questionnaire
GMT	Greenwich Mean Time
GP	General Practitioner
HTA	Health Technology Assessment
IOTA	International Ovarian Tumour Analysis
IV	intravenous
LSK	laparoscopy
MID	Minimally Important Difference
NHS	National Health Service
NOTABLE	NOTES Adnexectomy for Benign pathology compared to Laparoscopic Excision
NOTES	natural orifice transluminal endoscopy
vNOTES	vaginal natural orifice transluminal endoscopy
PROM	Patient Reported Outcome Measure
RCT	Randomised Controlled Trial
(S)AE	(Serious) Adverse Event
SD	Standard Deviation
SSFS	Short Sexual Functioning Scale
SILS	Single Incision Laparoscopic Surgery
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee
TU	Trans Umbilical
TV	Trans Vaginal
VAS	Visual analogue scale
QALY	Quality adjusted life year

SUMMARY

Rationale: Driven by the desire to minimalise surgical morbidity, the evolution from laparotomy to laparoscopic surgery has now extended to less invasive surgery such as robotics, mini- laparoscopy, single incision laparoscopic surgery (SILS), and natural orifice transluminal endoscopic surgery (NOTES). Minimally invasive surgery not only improves cosmetic outcome, it has the potential to restrict the magnitude of the surgical injury, which in turn can attenuate the inflammatory and neuroendocrine response resulting in less postoperative pain and quicker recovery (1, 2).

NOTES attempts to reach the abdominal cavity through an invisible scar, i.e. the surgical intervention is performed via a natural body orifice. Its popularity amongst general surgeons, urologists and gastroenterologist has increased over the past few years and its feasibility and safety has been reported in the medical literature (3).

NOTES can be done by various approaches including access via the stomach, oesophagus, bladder or rectum. The majority of NOTES procedures in women are done by the vagina as this site provides direct access to the lower abdominal cavity (4). Colpotomy has been used widely for several surgical procedures (by gynaecologists as well as general surgeons for the extraction of large specimens) and it has been reported as a safe access that is easy to close afterwards (5, 6).

In hybrid NOTES the surgical procedure is performed through a natural body orifice with transabdominal assistance, whereas the term pure NOTES refers to procedures that involve only transluminal access.

Given its potential benefits, including no visible scars, fewer port-related complications, and less painful and faster post-operative recovery, we have introduced transvaginal pure NOTES (vNOTES) for the treatment of benign adnexal masses in our surgical practice since November 2013. A case-series by our group describing the technical feasibility of removing benign adnexal masses by vNOTES in 20 women has been published recently (7). Most women reported a low postoperative pain score (range 0 to 2) measured at day 1 following surgery by a visual analogue scale (VAS). Based on these preliminary observational findings we decided to design a pilot randomized trial to study the effectiveness of the new vNOTES approach based on the hypothesis that the new technique is at least as effective for removing a benign adnexal mass without cyst rupture compared to the classical laparoscopic technique.

Objective: To compare vNOTES and established laparoscopic removal of benign adnexal masses

Study design: Randomised controlled/single centre/single-blinded/parallel-group/non-inferiority/efficacy trial.

Study population: Women with symptomatic or persistent benign adnexal masses detected by clinical examination and ultrasound.

Randomisation: After assessment of eligibility/ informed consent women will be randomly allocated to undergo one of two techniques for removal of the benign adnexal mass before surgery by using a computer generated randomisation list. We will use stratified randomisation according to the cyst diameter.

Intervention: Women will be treated by a surgeon who is not blinded to the treatment allocation and who is equally skilled in performing both techniques. In the intervention group a vNOTES technique will be used.

Control: In the control group surgery will be done by a classical laparoscopic technique.

Participants, nursing staff and outcome assessors will be blinded by the use of mock surgical skin incisions. Pre- and postoperative treatment will be provided by staff blinded for the allocated intervention using a standardized protocol that is identical for both techniques. All women will be advised not to work during a 4-week period and to abstain from sexual intercourse until their 6-week booked appointment for a postoperative assessment.

Main study parameters/endpoints:

Primary outcomes: successful removal of a benign adnexal mass without spill.

Secondary outcomes: the proportion of women discharged the same day based on their own preference; postoperative pain scores using a VAS scale measured between day 1 till 7 by the participating women following surgery and the total use of analgesics as described in the standardized pain treatment protocol; postoperative infection defined by lower abdominal pain with fever > 38°C and positive clinical signs or laboratory findings; per- or postoperative complications according to the Clavien- Dindo classification (8) detected during the first six weeks of surgery; hospital readmission during the first six weeks of surgery; duration of the surgical procedure; incidence and intensity of dyspareunia recorded by the participants at 3 and 6 months by self-reporting using a simple questionnaire and VAS scale; sexual wellbeing recorded by the participants at 3 and 6 months by SSFS; quality of life by self-reporting the EQ-5D-3L questionnaire at 3 and 6 months; direct costs associated with both procedures.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The burden and risks associated with the participation in the study are comparable with the risks related to the established technique of laparoscopic adnexectomy.

1. BACKGROUND

1.1. Disease: adnexal mass

An adnexal mass (mass of the ovary, fallopian tube, or surrounding connective tissues) is a common gynaecological problem. In the United States, it is estimated that there is a 5 to 10 percent lifetime risk for women undergoing surgery for a suspected ovarian neoplasm (9). Adnexal masses may be found in females of all ages, foetuses to the elderly, and there is a wide variety of types of masses. The management of an adnexal mass depends upon the type of mass, urgency of the presentation (e.g. ectopic pregnancy or ovarian torsion require immediate intervention), and degree of suspicion that the mass might be malignant.

1.1.1 Population to be studied

All women with a benign adnexal mass will be eligible for inclusion provided that they have no exclusion criteria and after giving fully informed consent.

The diagnosis of a benign adnexal mass will be based upon the prospectively IOTA validated simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery (10). All the ultrasound examinations will be reviewed before the randomisation by a named operator with competence in gynaecological ultrasound and experience in applying the simple rules. The need for additional examinations (CAT scan or CA-125) is based upon good clinical practice.

1.2. Current therapy for removal of an adnexal mass

Surgical exploration for an adnexal mass may be performed laparoscopically (conventional or robotic) or by laparotomy. The choice of surgical approach depends upon the degree of suspicion of malignancy and surgeon and patient preference. Ovarian cancer staging can be performed using an open or laparoscopic approach, although the majority of surgeons in current practice prefer laparotomy if there is a high degree of suspicion of malignancy. If there is a low or moderate suspicion of malignancy, a laparoscopic approach is typically used. Laparoscopy is associated with a shorter recovery and decreased perioperative morbidity compared with laparotomy.

The surgical technique used must minimise the potential for tumour disruption or dissemination. If malignancy is suspected, oophorectomy is required rather than ovarian cystectomy. Women with early stage ovarian cancer (i.e. no malignant cells in ascites or peritoneal cytology) benefit from removal of the adnexal mass intact, since opening the mass results in a more advanced stage and adversely affects prognosis (11, 12). In addition, every attempt must be made to provide the pathologist with an ovarian specimen with an intact cortex. If a laparoscopic approach is used, the ovary can be placed in a tissue recovery bag. If the specimen is too large to remove through the existing incisions, cyst fluid may be aspirated (but the collapsed cyst should not be disrupted) or the incision may be enlarged. The practice of morcellating ovarian masses in a bag is discouraged

because it may compromise pathology evaluation. In general, aspiration of cyst contents is not advisable as the sole surgical intervention because no tissue is obtained for histopathology and cytology of cyst fluid is not reliable for exclusion of malignancy, and there is a high rate of recurrence. Recent years have witnessed the use of a posterior colpotomy to retrieve large benign ovarian lesions since removal through the umbilicus may not be straightforward (13).

1.3. New therapy for removal of a benign adnexal mass

Natural orifice transluminal endoscopic surgery (NOTES) is a surgical technique whereby "scarless" abdominal operations can be performed with an endoscope passed through a natural orifice (mouth, urethra, anus, etc.) then through an internal incision in the stomach, vagina, bladder or colon, thus avoiding any external incisions or scars. NOTES was originally described in animals by researchers at Johns Hopkins University (Dr. Anthony Kalloo et al.), and was once upon a time used for transgastric appendectomy in humans in India (by Drs. G.V. Rao and N. Reddy). On June 25, 2007 Swanstrom and colleagues reported the first human transgastric cholecystectomy. The transvaginal access to NOTES seems to be the safest and most feasible approach for clinical application.

1.4. Literature review

1.4.1 Systematic Review

Health technology assessment (HTA) of surgical interventions requires an initial evaluation of the safety and feasibility followed by randomised controlled trials of effectiveness. We conducted a comprehensive systematic review on the efficacy of colpotomy in the treatment of benign adnexal mass. After searching three electronic databases (MEDLINE, EMBASE and The Cochrane Library) from inception to 1 August 2015 using '*colpotomy'* and '*adnexal diseases'* or *'adnexal mass'* as MeSH terms or key words, ten citations were identified, of which a total of four studies were eligible for inclusion. Two studies were observational including one very small case series (7 women) and one prospective cohort study (257 women); two studies were randomised controlled trials (66 women and 79 women respectively).

A summary of the evidence is given below:

We retrieved one observational study from Korea (14). The authors performed transvaginal NOTES in seven women with adnexal masses through a 2-cm incision in the posterior vaginal fornix. A transvaginal NOTES system comprising a wound protractor and a surgical glove with sheaths was used. Resection was performed according to the method of standard laparoscopic adnexal surgery. The adnexal mass was removed via the incision of the posterior vaginal fornix after complete resection. Since June 2011, seven women have undergone transvaginal NOTES for adnexal masses. All cases were completed successfully without conversion to standard laparoscopic approach. The median age of the women was 48 years (range: 36–60 years) and the median body mass index was 23.6 (range: 20.4–25.3). The median tumour size was 6 cm (range: 3.7–6.7 cm). The median

operative time was 45 min (range: 40–80 min). The estimated blood loss was minimal (range: 5–300 mL). The median postoperative hospital stay was 2 days (range: 1–3 days). No postoperative complications were observed at follow-up. All women were very satisfied with the cosmetic result. The authors conclude that transvaginal NOTES may be a feasible, safe and effective surgical technique that results in excellent cosmetic results. It may be an alternative technique for the treatment of properly selected patients with adnexal masses. The authors stress the need for further clinical research.

We retrieved a prospective cohort study from the United States (15). This descriptive study was conducted on women treated by a private gynaecological surgery practice in a community hospital setting from January 1, 2004 through April 30, 2011. Two-hundred fifty-seven consecutive women with adnexal masses of 8 cm to 13 cm on preoperative ultrasound examination not meeting triage criteria set forth in ACOG Committee Opinion 280 for referral to gynaecological oncologists were treated with operative laparoscopy, adnexal removal, bagging, and colpotomy. Laparoscopic surgery combined with posterior colpotomy has a low incidence of significant complications. Outcome data show that by observing the principals of minimally invasive surgery, 97% of women were successfully treated as outpatients: 98% of surgeries lasted <136 minutes; 97% had blood loss <200mL, and there were few consequential postoperative complications. Intraoperative rupture of the ovarian capsule was extremely uncommon: capsular rupture was noted in just 1.2% of cases. The most common lesions were cystadenomas, endometriotic cysts and mature teratomas accounting for 85% of all cases. Borderline tumours accounted for 5% of lesions, while invasive ovarian malignancy represented 3.7% of the specimens.

We retrieved one RCT from Italy (16). Women scheduled for a laparoscopic resection of an adnexal mass were randomised to have their surgical specimen removed either through a posterior colpotomy (n = 34) or the umbilical port site (n = 32). Group allocation was concealed from study participants and bedside clinicians. The primary outcome was postoperative incisional pain assessed by a 10-cm visual analogue scale at 1, 3, and 24 hours after surgery. Transvaginal retrieval caused less postoperative pain than transumbilical specimen extraction at each time point (visual analogue scale score at 1 hour: 2.6 ± 2.9 vs 1.2 ± 2.0, $P = 0.03$; at 3 hours: 2.4 ± 2.0 vs 1.4 ± 2.0, $P = 0.02$; and at 24 hours: 1.1 ± 1.5 vs 0.5 ± 1.4, $P = 0.02$). A higher proportion of women in the transumbilical group than in the transvaginal group indicated the umbilicus as the most painful area at 1 and 3 hours postoperatively. Two months after surgery, the participants scored similarly as to their overall satisfaction, cosmetic outcome, and dyspareunia upon resumption of intercourse. The authors conclude that a transvaginal approach for specimen removal after laparoscopic resection of adnexal masses may offer the advantage of less postoperative pain than the classical umbilical retrieval.

We retrieved one RCT from Taiwan (17). Seventy-nine women with mature teratomas identified by ultrasound examination and biochemical markers were randomly assigned to have their cysts removed via vaginal cystectomy without laparoscopy (n= 37, group A) or laparoscopic cystectomy via culdotomy (n=42, group B). Inclusion criteria were history of vaginal delivery, no previous abdominal surgery, no history of pelvic inflammatory disease, no medical illness, and no presenting symptoms. Eight women randomised to group A withdrew before surgery. The laparoscopically resected tumours were each put into a cellulose bag, and tumours without laparoscopic- assistance were removed directly via the vagina. Blood loss in group A (88± 37 ml) was significantly more than that in group B (64± 20 ml, P= 0.000). The post-operative recovery times were 20 and 17 hours, respectively (P= 0.030). The rates of successful surgery were 58.6 and 97.6%, respectively (P= 0.002). The spillage rates were 44.8% and 19.0%, respectively (P= 0.006). There were no significant differences in tumour size, patient age, and operative time between groups. The authors concluded that cystectomy without assistance of laparoscopy could be applied to manage mature teratoma of the ovary; however, because of the difficulty of this technique, there were high percentages of tumour spillage and more blood loss during operation and a high percentage of patients who required conversion to laparotomy compared with laparoscopic cystectomy. The authors favour laparoscopically assisted cystectomy to manage mature teratoma.

1.4.2 Current clinical practice

At the present the laparoscopic route is considered to be the gold standard for removing a benign adnexal mass compared to laparotomy. According to a Cochrane review (18), in women undergoing surgery for benign ovarian tumors, laparoscopy was associated with a reduction in fever, urinary tract infection, postoperative complications, postoperative pain, number of days in hospital, and total cost. These findings should be interpreted with caution since only a small number of studies (nine) were identified. These included a total of only 769 women and not all of the important outcomes were reported in each study.

In the days prior to widespread availability of laparoscopy, skilled gynaecological surgeons frequently used colpotomy for ready access to the pelvis (15). Unlike episiotomy that can cause dyspareunia, colpotomy does not transect muscles and, therefore, has less bleeding and negligible postoperative pain. Some surgeons may point out the potential disadvantages of colpotomy, including incisional infection, peritonitis, and technical complexity, particularly in patients after hysterectomy. Many gynaecologists seem reluctant to perform transvaginal surgery because this approach can be difficult for inexperienced surgeons and is occasionally unsuccessful. Moreover, conversion to conventional laparoscopy because of unsuccessful transvaginal approach is not acceptable to women who are expecting a minimally invasive surgery with no abdominal surgical scars. Therefore colpotomy is not used as the standard clinical practice in Belgium for removal of the adnexa.

1.4.3 Pilot studies

Given its apparent benefits, including no visible scars, fewer port-related complications, and less painful and faster post-operative recovery, we introduced transvaginal pure NOTES (vNOTES) for benign adnexal masses in our surgical practice since November 2013. Our group has recently published a case-series describing the feasibility of adnexectomy by vNOTES in 20 women for benign adnexal masses (7).

The purpose of the observational case-series was to describe the new technique as well as to demonstrate the feasibility of adnexectomy by transvaginal natural orifice transluminal endoscopic surgery (vNOTES) for the removal of benign adnexal masses. Conventional, reusable laparoscopic instruments were used, inserted through an inexpensive, self-designed single port device. Between November 2013 and November 2014, 20 adnexectomies by vNOTES were performed by a single surgeon (Dr. Jan Baekelandt).

We selected each participant based on the following inclusion criteria: no contraindication for general anaesthesia, pneumoperitoneum or Trendelenburg position; no fixed uterus, strong pelvic adhesions or nodularity in the pouch of Douglas on clinical examination; no history of pelvic inflammatory disease or moderate to severe endometriosis and mass not suspicious for malignancy. We excluded women with large fibroid uteri as these may impair visualization. Virginity and concomitant pregnancy were predefined as exclusion criteria whereas obesity (BMI ≥ 30) and nulliparity were not.

The self-designed single port device was made by assembling a surgical glove, a wound protector, one reusable 10 mm trocar, and four reusable 5 mm trocars. The adnexectomy was performed according to the technique for standard laparoscopic surgery and the specimen was removed through the colpotomy incision.

The following patient and perioperative data were collected and retrospectively analysed: patient age, body mass index (BMI), parity, history of vaginal delivery, previous pelvic surgery, type of surgery, total operating time, serum haemoglobin (Hb) drop (change between the preoperative Hb and postoperative Hb one day after surgery), (peri-) operative complications, postoperative pain score and size of the adnexal mass. The duration of surgery was defined as the time from the start of colpotomy to the end of vaginal closure. Bowel, bladder, ureteral or vascular injuries, as well as blood loss > 300 ml, were considered as intraoperative complications. Short-term postoperative complications were classified as urinary tract infection, postoperative ileus, vaginal vault bleeding or infection, or haematuria. Postoperative pain was assessed using the visual analogue pain scale (VAS) (scoring from 0 = no pain to 10 = worst imaginable pain). The VAS score was evaluated at 6 and 24 hours postoperatively. All women received the same intraoperative analgesia: intravenous

paracetamol 1000 mg and ketorolac trometamol 20 mg. Postoperative pain was managed by paracetamol 1000 mg and ketorolac trometamol was administered on patient's demand.
No bowel preparation was done prior to surgery. A Foley catheter was placed just before surgery and removed the morning after surgery (range 12-22 hours). Prophylactic intravenous antibiotic therapy, cefazoline 2 g and metronidazol 500 mg, was administrated during surgery. As this was a new technique the first patients were closely monitored post operatively. No vaginal intercourse was allowed for 6 weeks after the procedure. Each patient was re-assessed at the post-operative consultation 6 weeks after surgery.
Between November 2013 and November 2014, twenty procedures were successfully performed by Poor Man's vNOTES using conventional, reusable laparoscopic instruments. No conversion to standard multi incision laparoscopy or laparotomy was necessary. Fourteen women underwent a unilateral adnexectomy. In six women a bilateral salpingo-oophorectomy was performed.
Table 1 (Appendix I) gives a cumulative overview of patient characteristics and relevant perioperative data. Individual patient data are presented in Table 2 (Appendix II). Mean operation time was 32 minutes (range 20 to 50 minutes). Five women had had previous pelvic surgery. There were no intraoperative complications and only one patient had a postoperative cystitis for which oral antibiotic therapy was administered. The mean drop in haemoglobin level was 0.9 g/dl (range 0 to 2.1 g/dl). Most women reported a low postoperative pain score (range 0 to 2) measured at day 1 following surgery by a visual analogue scale (VAS). The mean size of the removed adnexal mass was 51.8 mm (35-110 mm). Each patient was examined six weeks after surgery. There was no vaginal wound infection nor dehiscence, and no patient complained of pain during pelvic examination. All women were in good health and were all satisfied with the result.
Based on this observational case-series we concluded that adnexectomy by vNOTES is feasible for masses up to 110 mm even when performed with reusable, conventional laparoscopic instruments. The potential benefits with vNOTES are better cosmetics, low postoperative pain scores, and easy removal of the specimen without spillage. We stated that this new technique may enable surgeons in low resource settings to perform procedures by vNOTES since no expensive devices or instruments are needed.

1.5. The need for a pilot trial of vNOTES versus LSK adnexectomy

Surgical innovation is an important part of surgical practice. Its assessment is complex because of idiosyncrasies related to surgical practice, but necessary so that introduction and adoption of surgical innovations can derive from evidence-based principles rather than trial and error. We decided to follow the principles and guidelines established by IDEAL. On four occasions between 2007 and 2009, invited international experts gathered at Balliol College, Oxford, to explore potential solutions concerning quality, innovation and evaluation in surgical practice and research. The conclusions and

guiding principles were published in The Lancet in 2009. Surgery lacks regulatory authorities that require studies of efficacy before a new procedure can be offered to patients. Nevertheless there is little difference between operations and other complex treatments delivered by individuals within teams. In each instance, the skill, experience, and judgment of the operator should be recognized, and outcomes are affected by the patient and the team. There was agreement between the experts that none of these factors is beyond the design of a clinical trial. The rationale for the resulting IDEAL framework (Idea–Development–Exploration–Assessment–Longterm study) for surgical research has been presented in a three article series in The Lancet (19, 20, 21). The central concept is that surgeons are regularly innovating and improving their skills. Because the point at which an innovation evolves into a novel procedure might not be obvious at the time, prospective open registration of new procedures and early ethical approval are encouraged. Evolution and evaluation can then occur simultaneously. The framework recognizes that at different stages of innovation, different study designs will be appropriate. According to the IDEAL framework the vNOTES approach has entered stage 2b (exploration) given that the technique of vNOTES has been described and the main technical aspects have been worked out. Even at this early stage a small efficacy RCT may be appropriate for the evaluation of the innovative surgical technique. The learning curve is likely to affect which surgeons participate in RCTs trials and when they become involved. We decided to use an RCT as the appropriate study design: the principal investigator had achieved his learning curve.

1.6. Objectives of the NOTABLE Trial

Is a vNOTES adnexectomy at least as effective compared to the standard transabdominal laparoscopic approach (LSC) for removing a benign adnexal mass without spill?

Secondary research questions are:

- Do more women treated by vNOTES prefer to leave the hospital on the day of surgery compared to LSC?
- Do women treated by vNOTES suffer from less pain compared to women treated by LSC in the first postoperative week?
- Is the removal of a benign adnexal mass by vNOTES faster compared to LSC?
- Does a vNOTES cause more pelvic infection or other complications compared to LSC?
- Does a vNOTES result in more hospital readmissions during the first six weeks following surgery compared to LSC?
- Does a vNOTES approach result in more women reporting dyspareunia, less quality of life or less sexual wellbeing at 3 or 6 months after surgery when compared to women treated by LSC?
- What are the costs of a vNOTES compared to LSC?

2. TRIAL DESIGN

2.1. Design

A single centre, single-blinded, parallel group randomised, non-inferiority efficacy trial.

2.2. Simple pilot randomised trial: minimal extra workload

This is a pilot randomised trial aiming to demonstrate that vNOTES is at least as effective compared to the classical gold standard approach of laparoscopy for successfully removing benign adnexal masses without spill (non-inferiority design). In this phase of HTA the trial will need the participation of only one centre. To make this practicable, trial procedures are kept simple, with the minimal extra workload placed on participating clinicians, beyond that required to treat their patients. This will be achieved by simple entry procedures, the use of standard local diagnostic and surgical regimens, routine follow-up of patients (with few additional hospital visits or tests to be performed above those done as part of standard care), minimising documentation and largely patient-based evaluation of outcome (PROM).

2.3. Time schedule

Based upon the mean number of laparoscopic adnexectomies performed annually at the department of Obstetrics and Gynaecology of the participating centre (36) we estimate that the duration of recruitment will be 21 months. Based upon the follow up (6 months) and the period of analysis/reporting (3 months) the total study period will be 2.5 years.

2.4. Participating centre

Department of Obstetrics and Gynaecology

Imelda Hospital

Imeldalaan 9

2820 Bonheiden

Belgium

3. ELIGIBILITY, CONSENT AND RANDOMISATION

3.1. Screening and consent prior to surgery

All women regardless of age and parity presenting with a symptomatic or asymptomatic persistent benign adnexal mass on clinical examination confirmed by ultrasound are eligible for inclusion. The diagnosis of benign adnexal mass will be based upon the prospectively IOTA validated simple ultrasound rules to distinguish between benign and malignant adnexal masses (10). All the ultrasound examinations will be reviewed before the randomisation by a named operator with competence in gynaecological ultrasound and experience in applying the simple rules. The need for additional examinations (CAT scan or CA-125) is based upon good clinical practice.

The trial will be introduced to the eligible women in the outpatient clinic and a comprehensive, evidence-based patient information sheet will be provided at the clinic visit. Participant information sheets and consent form will be provided in Dutch.

Before the procedure, the women will be given a chance to discuss the risks and benefits of vNOTES or laparoscopy for removing the adnexal mass, the process of randomisation and the follow-up requirements with the consultant gynaecologist. It will be carefully explained that the final decision about eligibility will be taken during the surgical procedure and is dependent on the findings; therefore consent will be required before the procedure, in every instance.

Over the past 4 years 145 laparoscopic adnexectomies were performed at the department of Obstetrics and Gynaecology of the participating centre. The mean number of procedures per year (SD) is 36 (± 13). About 69 % of the eligible women should be willing to participate in the proposed study to include the required amount of participants within 2.5 years (see: Section 6.1. Sample size on pages 31-32).

3.2. Determining eligibility

All women regardless of age and parity presenting with a symptomatic or asymptomatic persistent benign adnexal mass on clinical examination who provide consent to participation are eligible in the NOTABLE trial based on the findings of the ultrasound findings and will be randomised before the procedure.

The following inclusion/exclusion criteria will be applied to assess eligibility:

Inclusion criteria:

- All women regardless of age and parity with a symptomatic adnexal mass presumed to be benign based on ultrasound examination by applying the IOTA simple rules
- All women regardless of age and parity with an asymptomatic persistent adnexal mass presumed to be benign based on ultrasound examination by applying the IOTA simple rules

- Written informed consent obtained prior to surgery

Exclusion criteria:

- History of hysterectomy by any technique
- History of rectal surgery
- Suspected rectovaginal endometriosis
- Suspected endometriotic cyst
- Solid adnexal mass
- High suspicion of adnexal malignancy based on clinical, ultrasound or biochemical findings
- History of pelvic inflammatory disease, especially prior tubo-ovarian or pouch of Douglas abscess
- Active lower genital tract infection e.g. Chlamydia, N. gonorrhoeae
- Virginity
- Pregnancy
- Need for other uterine surgical intervention (i.e. endometrial ablation, resection, myomectomy or hysterectomy)
- Additional pathology necessitating hysterectomy
- Failure to provide written informed consent prior to surgery

Obesity (Body Mass Index or BMI > 30), nulliparity or large diameter of the cyst are not considered to be an exclusion criterion per se. We will only stratify for the diameter of the cyst because this parameter was perceived by the gynaecological surgeon as the most important one to influence the difficulty of the procedure. Stratification for three parameters in a small pilot randomised trial with a limited number of participants is not sensible.

3.3. Randomisation

If the woman is eligible for the NOTABLE trial, the trial secretary will obtain a randomised allocation the day before surgery. This will be done using a randomisation list generated by a free computer software program offered by Research Randomizer (https://www.randomizer.org). The random sequence generation will be concealed using sequentially numbered opaque sealed envelopes. The envelope will be opened by the nurse assistant on the day of surgery for practical logistic reasons. We will use stratified randomisation according to the cyst diameter. See 3.5 Stratification of randomisation.

3.4. Patients with strong preference for treatment

A minority of women will express a clear preference for one of both treatments (e.g. strong desire to have no scar) and for this reason will not wish to be randomised between surgical treatments. To investigate how outcomes vary by choice, these women could be followed up in exactly the same way as for those women randomised into the NOTABLE trial. We will however not do any formal non-randomised follow-up of these women for simple logistical reasons.

3.5. Stratification of randomisation

A blocked randomisation procedure will be used to avoid chance imbalances for the parameter 'cyst diameter'. We preferred not to use minimisation because this trial was not funded and we therefore could not afford to buy licenses for a computer-based algorithm for minimisation. Although parity and BMI may be prognostic parameters influencing the chances of the successful removal of the adnexal mass, we preferred to limit the stratification to one parameter for reasons of simplicity based on what is affordable to conduct the present research. It was not considered appropriate to use three strata in a small pilot study including a small number of participants.

To avoid any possibility of foreknowledge, the randomised allocation will not be given until all eligibility and stratification data have been given.

4. TREATMENT ALLOCATIONS

4.1. Surgical procedures

The principal investigator, who has training and experience in both laparoscopy and NOTES, will perform all surgical procedures. He is therefore not blinded. All vNOTES participants will be blinded by three superficial "mock" skin incisions similar to those routinely done with the laparoscopic technique. The wound bandages will be left in place until the day 7 postoperative control to be removed by the coordinating investigator who will state at that moment that the wound healing has left an almost invisible scar as expected. This procedure aims to blind the participants, personnel and outcome assessors. The practice of performing "mock" incisions should not be considered as unethical: it is a procedure that has already been used in some surgical trials to minimise performance and detection bias whenever a subjective outcome is measured (22). The decision to use "mock" surgery is based on the clinical equipoise regarding the balance between benefits and adverse events for the two interventions under comparison (23).

4.1.1 vNOTES adnexectomy

This is the surgical procedure done in the intervention arm of the NOTABLE trial.

Clindamycin vaginal cream is administered on admission of the study participant to the outpatient ward.

The patient is placed in lithotomy position in a vacuum mattress. The abdomen, the vulva and the vagina are disinfected with an alcoholic betadine solution and draped. A Foley catheter is inserted into the bladder.

Three superficial skin incisions are made, one deep in the umbilicus and one in the left and right iliac fossa lateral of the epigastric vessels, and in the suprapubic region. The small vertical intraumbilical skin incision is closed with a monocryl 3/0 intradermal suture. Wound bandages are applied to all three skin incisions.

A 2.5 cm posterior colpotomy is made using a cold knife. The pouch of Douglas is opened using cold scissors. A Gelpoint Mini (Applied Medical) is used as vNOTES port and is inserted into the pouch of Douglas. CO_2 is insufflated until a maximal intraperitoneal pressure of 15mmHg. An optic is inserted and the peritoneal cavity is inspected. The patient is now placed in Trendelenburg position. The small intestine is lifted out of the pelvis.

The ureter is identified, but not routinely dissected. It is only dissected if it cannot be identified transperitoneally. The proximal end of the Fallopian tube is coagulated at its origin into the uterus

using a reusable bipolar grasping forceps before being cut using cold scissors. The ovarian ligament is coagulated and cut. The infundibulopelvic ligament is coagulated and cut. The adnexa is resected. If necessary, the same procedure is repeated for the contralateral side. The peritoneal cavity is rinsed and haemostasis is checked.

Small and benign adnexa will be removed directly through the wound protector part of the NOTES port. Large adnexa or adnexa that are macroscopically suspicious, will be placed in an endobag (Memobag, Teleflex). The purse string of the endobag is pulled through the wound protector and the purse string is released. The content of the cyst is aspirated to reduce the volume of the adnexa. The endobag is now removed with the adnexa inside it. The vNOTES port is removed.

The colpotomy is closed using three interrupted figure-of-eight Vicryl 2/0 sutures. A vaginal plug (betadine gauze 10cmx5m) is placed to be removed after 3 hours together with the Foley catheter.

Antibiotic administration:

Cefazolin 2g and metronidazol 1.5g are administered IV during the procedure.

Analgesia at the recovery room and the nursing ward: The pain management for both groups was discussed with two senior staff members of the department of anaesthesiology of the hospital, who are co-investigators. The protocol will be standard for both comparison groups and is presented in appendix V.

The vaginal plug and the Foley catheter are removed 3 hours after the surgery. The bandages are left in place and not changed unless soaked by blood with a need to change. The personnel of the recovery room will be asked to replace bandages only for hygienic reasons and immediately to apply a new wound dressing without revealing any information to the participant or personnel on the outpatient or hospitalization ward.

The decision to discharge or to admit to hospital for the night will be based solely on the choice of the woman to return home the same day or stay overnight. The outcome assessor will report this decision in the patient record without consulting the results of the pain scoring or whether or not additional analgesics were administered. Every woman leaving the hospital will be given a standard list with instructions not to have intercourse during six weeks and not to work for a period of four weeks. Telephone numbers will be provided for contacting the staff members on call in case urgent medical care for treating any adverse event is needed. Cefazolin 2g is administered IV before discharge.

4.1.2 LSC adnexectomy

This is the surgical procedure done in the control arm of the NOTABLE trial.

Clindamycin vaginal cream is administered on admission of the study participant to the outpatient ward.

The woman is placed in lithotomy position in a vacuum mattress. The abdomen, the vulva and the vagina are disinfected with an alcoholic betadine solution and draped. A Foley catheter is inserted into the bladder.

A small vertical intra-umbilical skin incision is made. A Verress needle is inserted into the peritoneal cavity; the correct position of the needle tip is checked with Semm test. CO_2 is insufflated until a maximal intraperitoneal pressure of 15mmHg. The Verress needle is removed and replaced by a 10mm reusable trocar. An optic is inserted through the 10mm trocar and the peritoneal cavity is inspected. The patient is now placed in Trendelenburg position. Two reusable 5mm trocars are placed under direct vision in the left and right iliac fossa lateral of the epigastric vessels. The small intestine is lifted out of the pelvis.

The ureter is identified, but not routinely dissected. It is only dissected if it cannot be identified transperitoneally. The proximal end of the Fallopian tube is coagulated at its origin into the uterus using a reusable bipolar grasper and cut using cold scissors. The ovarian ligament is coagulated and cut. The infundibulopelvic ligament is coagulated and cut. The adnexa are resected and placed in an endobag (Memobag, Teleflex). If necessary, the same procedure is repeated for the contralateral side.

The peritoneal cavity is rinsed and haemostasis is checked. No drains are left in the peritoneal cavity except when there might be any uncertainty concerning the haemostasis. The 5 mm trocars are removed under direct vision. The purse string of the endobag is pulled through the 10 mm trocar upon removal of the optic. The umbilical incision is extended vertically in caudal direction, the size being not more than 2.5 cm. The fascia and peritoneum are opened and the proximal end of the endobag is pulled through the incision without causing any rupture if possible. If not possible, the endobag should be opened and the content of the cyst should be aspirated to reduce the volume of the adnexa. The aspirated fluid should be send for cytological examination. The endobag is now removed with the adnexa inside it.

The fascia is closed using a Vicryl-1 running suture. The umbilicus and the other incisions are disinfected with Betadine solution. The skin incisions are closed with a monocryl 3/0 intradermal

suture and steri-strips. The wound sites are covered with a standard bandage. A vaginal plug (betadine gauze 10 cm x 5 m) is placed to be removed after 3 hours together with the Foley catheter.

Antibiotic administration:

Cefazolin 2g and metronidazol 1.5g are administered IV during the procedure.

Analgesia at the recovery room and the nursing ward: The pain management for both groups was discussed with two senior staff member of the department of anaesthesiology of the hospital, who are co-investigators. The protocol will be standard for both comparison groups and is presented in appendix V.

The vaginal plug and the Foley catheter are removed 3 hours after the surgery. The bandages are left in place and not changed unless soaked by blood with a need to change. The personnel of the recovery room will be asked to replace bandages only for hygienic reasons and immediately to apply a new wound dressing without revealing any information to the participant or personnel on the day care unit or hospitalisation ward.

The decision to discharge or to admit to hospital for the night will be based solely on the choice of the woman to return home the same day or stay overnight. The outcome assessor will report this decision in the patient record without consulting the results of the pain scoring or whether or not additional analgesics were administered. Every woman leaving the hospital will be given a standard list with instructions not to have intercourse during six weeks and not to work for a period of four weeks. Telephone numbers will be provided for contacting the staff members on call in case urgent medical care for treating any adverse event is needed. Cefazolin 2g is administered IV before discharge.

4.1.3 Failure of procedure

Occasionally, surgical removal of a benign adnexal mass by any of the two techniques may not be completed according to the random sequence generation because of technical limitations or unexpected findings such as extensive adhesions or unexpected malignancy. Successful vNOTES or laparoscopic removal of a benign adnexal mass is possible in the majority of women, but the probability of success is not readily predictable. In cases where the intended procedure has to be abandoned, the appropriate technique (e.g. staging laparotomy for ovarian cancer) or a second procedure (e.g. laparoscopy or laparotomy after bowel preparation) under general anaesthesia should be scheduled as soon as possible. Women who require an alternative more appropriate intervention or a second procedure are not excluded or withdrawn from the NOTABLE trial. The investigators will sensitively explain to them that follow-up information is still very important,

despite the change in treatment, and unless they wish to withdrawn completely from the trial, they will be followed up.

4.2. Concomitant interventions and treatments

It is anticipated that most women presenting with a suspected benign adnexal mass will require no further intervention other that removal of the adnexa. However, in some circumstances additional treatments may be considered necessary by the responsible clinician at the time of adnexal removal or subsequently. Surgical interventions in the form of endometrial ablation or hysterectomy may subsequently be necessary and the need for such interventions will be recorded. However, if the need for additional surgery *at the time* of surgery is indicated, then such patients are excluded for recruitment to the NOTABLE trial. All therapeutic interventions additional to removal of one or both adnexa will be recorded and as the trial is randomised we anticipate that these further interventions will be symmetrically applicable.

4.3. Withdrawal from the NOTABLE trial

All women who consent to the randomised NOTABLE trial, should be followed up and asked to complete postal questionnaires, regardless of actual treatment received.

If a woman specifically requests a treatment setting *after* randomisation, then her choices should be respected. This does not necessitate withdrawal from the trial. Similarly, if one of both procedures fails, she will require subsequent treatment. In both circumstances, it should be sensitively explained to them that follow-up information is still very important, and unless they wish to withdrawn completely from the trial, they will be followed up. Any request to withdraw from follow-up should be notified to the NOTABLE study nurse.

4.4. Serious and unexpected adverse events

There may be mortality and morbidity associated with either procedure, therefore all serious adverse events (SAE) should be reported by fax to the NOTABLE Trial Office as soon as possible. This report should be followed within 2 days by a completed SAE form to the Ethics Committee and the Federal Agency for Medicines and Health Products (FAMHP). For the purposes of this study, “serious” adverse events are those which are fatal, life-threatening, disabling or prolong hospitalisation and have resulted from the surgical procedure, the anaesthetic or post-operative recovery e.g. deep vein thrombosis, hospital acquired infections.

5. FOLLOW-UP AND OUTCOME MEASURES

5.1. Clinical assessments

5.1.1 Format

PROMs will be collected using a postal questionnaire at baseline, at three and six months.

The postal questionnaires will be sent from the NOTABLE Trial Office with postage paid envelopes two weeks before the due date. Reminders will be sent to the participants if the questionnaire is not returned within one week of the due date and attempts will be made to contact the women by phone if the questionnaire is not returned by two weeks after the due date.

5.1.2 Timing of assessments

The primary outcome will be measured clinically at the end of the surgical procedure. In addition PROMs will take place the evening of the surgical intervention (return home), during the first postoperative week (pain by VAS scores and medication) and at 3 and 6 months (dyspareunia and sexual wellbeing). Clinical physician assessment will take place the evening of the surgical intervention (return home) and during the first six weeks following surgery (pelvic infection, surgical complications).

5.2. Primary clinical outcome measure

The proportion of women successfully treated by removing the adnexal mass without spill, using a dichotomous outcome measure, will be used as a measure of efficacy. An important consideration in adnexal mass surgery is the inadvertent opening of the ovarian capsule. The likelihood of cyst rupture during removal by laparotomy or laparoscopy ranges from 10.5% to 41.8% in published studies (15). We will consider any spontaneous rupture of the cyst or any need to aspirate the cyst to allow removal from the abdominal cavity as treatment failures, even if the content of the ruptured cyst does not spill freely inside the cavity but remains within the endobag. By avoiding any subjective interpretations this rigorous definition allows an objective measure of success. As the risk of rupture may be associated to the cyst size, due to the stratified random sequence generation we anticipate that the risk of rupture due to the cyst size rather than the technique used will be symmetrically applicable.

5.3. Secondary clinical outcome measures

We will measure the following secondary outcomes:

- The proportion of women discharged the same day based on their own preference, as a dichotomous outcome. The decision to discharge from the day care unit or to admit to hospital for the night will be based solely on the choice of the woman to return home the same day or stay overnight. The outcome assessor will report this decision in the patient record without consulting the results of the pain scoring or whether or not additional

analgesics were administered. In case of conflict (women wishing to return home against outcome assessor's advice based on clinical suspicion of possible complications for instance) the study participant is not excluded from further follow-up. Data will be analysed using a sensitivity analysis by imputing that the index participant would have agreed to stay overnight as dictated by the clinical judgement of the outcome assessor versus the available data analysis.

- Postoperative pain scores, as an ordinal outcome, measured using a VAS scale twice daily from day 1 till 7 self-reported by the participating women: one measurement will be done in the morning after bed rest at night (rest) and the other will be done in the evening before going to bed after physical activity (active). The participants should place the cursor of the VAS scale device available at the day care unit of the participating centre on the picture indicating the expression of pain sensation that according to their own experience best describes how they feel pain at the time point of measurement. By looking at the back of the scale they can measure the level of pain by recording the numbers immediately to the left and right of the red line: e.g. pain level 0 to 1, or pain level 5 to 6. The lowest number will be recorded by the outcome assessor for data analysis. The reliability of VAS has been established in the assessment of chronic gynaecological conditions like pain.
- Postoperative pain defined by the total use of analgesics during the first week following surgery as described in the standardized pain treatment protocol, as an ordinal outcome. The use of pain medication following surgery should be reported in the nursing file. At home the participants should note in their participant log book the name, dosage, route of administration of any analgesic drug that was taken from the moment they are at home until the assessment on day 7 irrespective of whether this was done on their own initiative or after consulting a family physician or any other medical specialist. The assessment of the total use of analgesics will be done on day 7 by the outcome assessor (the coordinating investigator), who is blinded for the intervention done by the principal investigator.
- Postoperative infection defined by lower abdominal pain with fever > 38°C and positive clinical signs or laboratory findings, detected during the first six weeks of surgery, as a dichotomous outcome.
- Per- or postoperative complications according to the Clavien- Dindo classification detected during the first six weeks of surgery, as a dichotomous outcome (Appendix III).
- Hospital readmission during the first six weeks of surgery, as a dichotomous outcome.
- Incidence and intensity of dyspareunia recorded by the participants at 3 and 6 months by self-reporting using a simple questionnaire and VAS scale, as a dichotomous and ordinal

outcome. A measurement of the prevalence and the intensity of dyspareunia will be done at baseline assessment.

- Sexual wellbeing at baseline, at 3 and 6 months by self-reporting the SSFS.
- Quality of life at baseline, at 3 and 6 months by self-reporting the EQ-5D-3L questionnaire.
- Duration of surgery measured as the time in minutes from the insertion of the bladder catheter to the end of vaginal/abdominal wound closure, as a continuous outcome.

5.4. Health economic outcomes

Costs and consequences of the treatment pathways will be collected from health care providers at the time of the procedure and at follow up in order to conduct the cost-effectiveness analyses.

Resource use data will include:

• Surgical treatment of benign adnexal mass

• Tests and investigations received

• The frequency and duration of out-patient visits and primary care consultations

• Inpatient stays

• Type and volume of medications received

• The number and duration of hospital readmissions and re-treatments.

These data will be collected prospectively from health care providers using a post-operative case report form and patient-completed questionnaires that assess patient health service utilisation at the follow-up time points throughout the trial. Costs incurred by patients will also be collected to conduct an evaluation from a wider societal perspective. Therefore, a patient cost questionnaire will be administered to all trial patients in order to consider the wider cost implications of the interventions which will contain questions to determine out of pocket expenses incurred when attending for treatment and private time costs including time lost from work.

Unit costs obtained from published sources and the trial centre will be used to estimate costs associated with resource use. Responses to the EuroQol EQ-5D-3L questionnaire will inform the effectiveness in terms of QALYs and clinical effectiveness will be measured in cured cases at six months. We obtained full approval of EUROQoL to use the questionnaire for free.

Data collection will be undertaken prospectively for all trial patients so that a stochastic cost analysis can be undertaken. The process of collecting resource use data will be undertaken separately from data collection on unit costs.

The main resource use to be monitored include the following:

1) Consultation time required prior for each procedure for explanation and consent.

2) Costs involved with each procedure including level of health care professional involvement in the procedure, equipment required, overheads, consumables and drugs including anaesthesia.

3) Any additional procedures required where initial treatment is unsuccessful or incomplete.

4) Duration of inpatient stay when women opt to stay overnight.

Information on any additional related primary or secondary care contacts will also be collected from all women to ensure any resulting resource use from additional complications is recorded. Unit costs will be obtained and attached to resource items in order that a cost can be calculated for each trial patient. Unit costs will be obtained from published sources and the centre participating in the trial. In addition, the set-up costs of NOTABLE will be estimated and additional analyses will be undertaken including these costs.

5.5. Data management and validation

5.5.1 Confidentiality of personal data

Personal data and sensitive information required for the NOTABLE Trial will be collected directly from participants, who will be informed about the transfer of this information to the trial office at the department of Obstetrics and Gynaecology of the participating centre and will be asked to consent to this. The data will be entered onto a secure computer database, either by staff or directly via a secure internet connection. Any data to be processed outside the trial office will be anonymised. All personal information obtained for the study will be held securely and treated as (strictly) confidential. All staff involved in the NOTABLE Trial (clinical, paramedical, administration) share the same duty of care to prevent unauthorized disclosure of personal information. No data that could be used to identify an individual will be published. We will handle all data confidentially in accordance with the Belgian law of 8 December 1992 on the protection of privacy with respect to the handling of individual personal data.

5.5.2 Long-term storage of data

In line with existing guidelines and Belgian legislation, all data will be stored for up to 15 years after the last participant has reached the 2.5 year follow-up to allow adequate time for review, reappraisal or further research, and to allow any queries or concerns about the data, conduct or conclusions of the study to be resolved.

5.6. Withdrawal from follow-up

Withdrawal from follow-up is the decision of the participant. However, withdrawn patients can bias clinical trial results and reduce the power of the study to detect important differences, so women should be encouraged to complete all follow-up questionnaires. Methods to reduce the burden of follow-up will be explored e.g. online data entry for participants. If the reason for withdrawal is known, it should be communicated to the NOTABLE Trial Office. To reduce loss to follow-up, we shall record patient's social security number, which allows us to track patients changing GP practice. With postal and telephone reminders we anticipate that, the completeness of data should surpass 90% although, as set out below incomplete follow-up is incorporated into the power calculations.

6. ACCRUAL AND ANALYSIS

6.1. Sample size

The sample size for the primary outcome of this trial has been chosen to give good statistical power to preclude any clinically important inferiority of vNOTES compared to laparoscopy and is based on evidence retrieved from a systematic review of the literature (15) and a RCT comparing the excision of mature teratoma using culdotomy with and without laparoscopy (17). An important consideration in adnexal mass surgery is the inadvertent opening of the ovarian capsule. The likelihood of cyst rupture during removal by laparotomy or laparoscopy ranges from 10.5% to 41.8% in published studies (15). Based on a low failure rate to remove dermoid cysts by colpotomy using laparoscopy (2.4%), according to the findings from a RCT (17) we assumed a successful removal of adnexal cysts without spill to be feasible in 95% of all cases. We calculated the sample size with a one-sided test for non-inferiority studies for the primary outcome. The vNOTES approach may be more convenient for women in that no scar in the abdominal wall is required. We believe, therefore, that vNOTES would be the treatment of choice even if 15% less women had successful removal of a benign adnexal mass by using the vNOTES approach. Non inferiority will be concluded when 15% lies above the upper limit of the 95% confidence interval calculated for the difference in the proportion of women successfully treated with either of both techniques. To achieve 80% power to demonstrate non-inferiority under the assumption of similar success rates of 95% in both groups a sample size of 54 participants (27 women per group) will be required. The target sample size was increased to 64 participants (32 women per group) to account for a drop-out rate of 15%.

(https://www.sealedenvelope.com/power/binary-noninferior/). Based on the power calculations for the primary outcome, the use of three strata for the randomisation and assuming a loss-to-follow-up rate of 15 % we decided to include 66 study participants in the NOTABLE trial.

6.2. Projected accrual and attrition rates

It is anticipated that recruitment of participants will take two years. Based upon the mean number of laparoscopic adnexectomies performed annually at the department of Obstetrics and Gynecology of the participating centre (36) we estimate that the duration of recruitment will be 21 months. Based upon the follow up (6 months) and the period of analysis/reporting (3 months) the total study period will be 2.5 years. First publication will be possible within four years of trial commencement.

Our sample size calculation has allowed for a 15% loss to follow up rate. In order to minimise rates of attrition we will employ a dedicated research secretary to optimize recruitment and follow up.

6.3. Statistical Analysis

We will calculate a 95% confidence interval of the difference in the proportions of women with a successful removal of an adnexal cyst. Non inferiority of the intervention (vNOTES) will be concluded

when 15% lies above the upper limit of this confidence interval. For this primary analysis, adjustments for prognostic factors will not be made in the first instance; the effect of the variables listed in Section 3.5 (Stratification of randomisation) will be explored as a secondary analysis. Continuous measures (VAS scores) will be analysed using analysis of covariance (adjusting for baseline value). Multilevel models for repeated measurements will also be used to compare the mean differences in VAS pain scores between groups overall at all time points, thereby maximising the power of the data available.

Analysis will be performed on an 'intention to treat' basis in the first instance as recommended in the CONSORT statement. A 'per protocol' analysis will also be performed to test the robustness of the results obtained. As a conservative measure, estimates of effect sizes between the two arms will be presented as point estimates with two-sided 95% confidence intervals. The trial can only conclude non-inferiority if 15% lies out of the upper band of the confidence interval (i.e. vNOTES 15% less successful than laparoscopic treatment).

Baseline characteristics of the patients enrolled in the two groups will be compared to ensure that randomisation has produced comparable groups of participants, and will be covariates in the modelling procedure.

6.3.1 Subgroup analyses

Subgroup analyses are limited by statistical power and can produce spurious results particularly if many are undertaken. We will not undertake any subgroup analyses in this pilot study.

6.3.2 Proposed frequency of analyses

1. Twice yearly review of recruitment, compliance and loss to follow-up for NOTABLE Trial Steering Committee.
2. Annual interim analyses of effectiveness for confidential review by Ethics Committee to determine whether the principal question has been answered and to monitor adverse events.
3. Main analyses of effectiveness of NOTABLE once all participants have reached 6-month follow up of the total study sample.
4. Additional analysis of longer term effects (completion of one and two years of follow-up).

6.3.3 Handling missing data

The interpretation of missing values in the analysis of clinical trials can be fraught with danger. The methods used to allow for missing data make assumptions about the reasons for data not being present, such as in the "observed case" analysis, where the presence or absence of data is viewed as unrelated to outcome, or in the "Last Observation Carried Forward" analysis where the assumption is that the condition does not improve or worsen following withdrawal from follow-up. To minimise possible biases, participants will continue to be followed up even after protocol treatment violation.

Missing data items will be imputed from given values if limited to a single item response. If a form is missing entirely or greater than one item imputation will not be attempted. Sensitivity analyses will be carried out to determine whether or not the results obtained are robust to the methods used to handle missing data. These approaches are in line with the recent recommendations from the European Agency for the Evaluation of Medicinal Products.

Questionnaires will only be treated as late if they are returned after the subsequent questionnaire has been sent to the participant. However if this form is the only form available at the later time point it will be included at the subsequent time.

6.4. Health Economic Analysis

6.4.1 Form of the economic evaluation

If vNOTES is found to be an effective treatment for the removal of benign adnexal mass, then it is likely that there can be cost implications for the health care sector. For example, as the woman will be treated as an outpatient, thus avoiding an inpatient stay, resources may be saved. However, vNOTES may incur costs due to equipment required and the specialist nature of health care professionals to perform this procedure. Therefore all costs incurred by both procedures need to be assessed in conjunction with measures of effectiveness.

The aim of the economic evaluation is to determine the cost-effectiveness of vNOTES compared with standard laparoscopic treatment. Although the trial has been designed as a non-inferiority trial, we feel the most appropriate type of analysis is a cost-effectiveness analysis. Cost-effectiveness will be determined in two ways. A cost-effectiveness analysis will be undertaken to calculate the cost per additional cured case adnexal removal at six months, utilizing the clinical outcome data collected within the trial. In addition, a cost-utility analysis will be undertaken to calculate the cost per additional quality-adjusted life year (QALY) gained. The utility values required to calculate QALYs will be obtained by administering the EuroQol EQ-5D-3L questionnaire to all study patients at baseline, three months and six months. In the first instance, the evaluation will consider costs incurred by the health service in the delivery of both treatment pathways. However, information on costs incurred by patients will also be collected in order that an evaluation from a wider societal perspective can also be undertaken.

6.4.2 Economic analysis

Given the objective of the trial and limited available evidence in support of the NOTABLE strategy, only a within trial economic analysis will be carried out. The analysis will adopt an incremental approach in that data collection will concentrate on resource use and outcome differences between trial arms. As the majority of cost data are skewed, and the mean cost of each procedure is of importance, a bootstrapping approach will be undertaken in order to calculate confidence intervals

around the mean costs. As the time frame of the economic evaluation is not greater than one year, discounting is not required.

Uncertainty in the confidence to be placed on the results of the economic analysis will be explored by estimating cost-effectiveness acceptability curves. These plot the probability that the intervention is cost-effective against threshold values for cost-effectiveness. The robustness of the results will be explored using sensitivity analysis. This will explore uncertainties in the trial based data itself, the methods employed to analyse the data and the generalizability of the results to other settings.

We will seek the assistance of an expert in health economics at the University of Ghent, Belgium.

6.5. Definition of the end of trial

The end of the NOTABLE trial will be defined as the time when the last participant recruited has completed 6 months of follow up.

7. ASSESSMENT OF PATIENT ACCEPTABILITY

7.1. Measurements for Patient Acceptability

The acceptability of vNOTES will principally be assessed using a questionnaire designed specifically for the study and administered within 24 hours of treatment to limit recall bias. Pilot testing will be carried out to make certain the questionnaire is usable. In addition to the questionnaire, data will be collected on the women who do not give consent to randomization (state a preference and agree to be registered for the NOTABLE study), and requested from those who decline to participate.

In order to aid interpretation and understanding of the questionnaire data, and to gain greater depth of experience, the acceptability of NOTABLE will further be assessed using a qualitative methodology. Interviewing after discharge will allow the woman time to reflect on her experience, and will also minimise the chance that gratitude to doctors and other hospital staff results in unduly positive responses. Honesty is also more likely to occur on neutral or the patient's home ground. Interviews will be recorded with patients' permission and transcribed verbatim. The interview schedule will be designed following a literature search on patient acceptability of surgical procedures, and from the focus group discussions. From these, a set of items will be derived which will seem relevant to the participants and cover all the areas thought to be important by participants. The latter will also ensure that the questionnaire is as discriminatory as possible. The interview schedule will be piloted with five women. These procedures will ensure face and content validity, and sending each woman the transcript of her interview with the opportunity to amend any inaccuracy will assess fair and accurate representation.

7.1.1 Sampling of Participants for In-depth Interview

We propose to select a 20% random sample (6 women) from each arm of the research for interview within one week of discharge either face to face, or by telephone.

7.2. Evaluation of Patient Acceptability

Analysis of data will be by content analysis with the development of analytical themes. The initial process will be the intensive reading and re-reading of interview transcripts, and a search for regularities, contradictions, patterns and themes by comparing the participants' statements using a coding frame. Inter-rater reliability on the coding of transcripts will be undertaken. A percentage of the transcripts will be coded independently by two members of the qualitative research team and discrepancies discussed and resolved. Emergent themes obtained by this process will be refined until final themes are agreed by all applicants as reflective of the data. 'Researcher triangulation' will offer the first step to verification of the findings. This will be achieved through the independent analysis of 20% of transcripts from the sample by the researchers. Verification occurs through discussion of their analyses, comparison and subsequent consensus. 'Respondent validation' will also be sought by

taking the tentative findings back to a sample of participants in order to be verified as reflective of their experience. A final form of verification is the comparison of findings with, and their embeddedness in the available literature.

It is anticipated that the questionnaire and the subsequent in depth interviews will measure and provide insight into acceptability and satisfaction in the following areas: the procedure(s) for diagnosis; the information provided when consent is obtained; procedures to protect confidentiality; preference for one arm of the trial over the other; experience of the procedure and the immediate post-operative phase; overall satisfaction with the process; acceptability for the same procedure if adnexal masses are diagnosed in the future; perceptions of being involved in an RCT.

8. DATA ACCESS AND QUALITY ASSURANCE

8.1. In-house Data Quality Assurance

The study will adopt a centralized approach to monitoring data quality and compliance. A computer database will be constructed specifically for the study data and will include range and logic checks to prevent erroneous data entry. Independent checking of data entry of paper questionnaires will be periodically undertaken on small sub-samples. The trial statistician will regularly check the balance of allocations by the stratification variables. Source data verification will only be employed if there is reason to believe data quality has been compromised.

8.2. Independent Trial Steering Committee

The Trial Steering Committee (TSC) provides independent supervision for the trial, providing advice to the Chief and Co- Investigators on all aspects of the trial and affording protection for patients by ensuring the trial is conducted according to the MRC Guidelines for Good Clinical Practice in Clinical Trials.

If the Chief and Co-Investigators are unable to resolve any concern satisfactorily, Principal Investigators, and all others associated with the study, may write through the Trial Office to the chairman of the TSC, drawing attention to any concerns they may have about the possibility of particular side-effects, or of particular categories of patient requiring special study, or about any other matters thought relevant.

8.3. Data Monitoring and Ethics Committee: Determining when clear answers have emerged

If vNOTES is clearly inferior to standard laparoscopic treatment, with respect to the primary endpoint, then this may become apparent before the target recruitment has been reached. Alternatively, new evidence might emerge from other sources that vNOTES definitely more, or less, effective than laparoscopy. To protect against this, during the period of recruitment to the study, interim analyses of major endpoints will be supplied, in strict confidence, to an independent Data Monitoring and Ethics Committee (DMEC) along with updates on results of other related studies, and any other analyses that the DMEC may request. The DMEC will advise the chair of the Trial Steering Committee if, in their view, any of the randomised comparisons in the trial have provided both (a) “proof beyond reasonable doubt” that for all, or some, women that vNOTES is so inferior from laparoscopy that non-inferiority can never be demonstrated, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. The TSC can then decide whether to close or modify any part of the trial. Unless this happens, however, the Trial

management group (TMG), TSC, the investigators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

9. ORGANIZATION AND RESPONSIBILITIES

All investigators are responsible for ensuring that any research they undertake follows the agreed protocol, for helping care professionals to ensure that participants receive appropriate care while involved in research, for protecting the integrity and confidentiality of clinical and other records and data generated by the research, and for reporting any failures in these respects, surgical complications and other events or suspected misconduct through the appropriate systems.

9.1. Centre eligibility

Not applicable since NOTABLE is a single centre RCT.

9.2. Local Coordinator

The responsibilities of the local Principal Investigator will be to ensure that all medical and nursing staff involved in the care of NOTABLE are well informed about the study and trained in trial procedures, including obtaining informed consent. The local Principal Investigator should liaise with the Trial Coordinator on logistic and administrative matters connected with the trial.

9.3. Nursing Coordinator

One nurse will be designated as *local Nursing Coordinator*. This person would be responsible for ensuring that all eligible patients are considered for the trial, that patients are provided with patient information sheets, and have an opportunity to discuss the study if required. The nurse may be responsible for collecting the baseline patient data and will act as a contact for obtaining missing follow-up evaluations. Again, this person would be sent updates and newsletters, and would be invited to training and progress meetings.

9.4. The NOTABLE Trial Office

The Trial Office at department of Obstetrics and Gynaecology of the participating centre is responsible for providing all trial materials, including the trial folders containing centre specific trial documentation, standard operating procedures and training materials. Additional supplies of any printed material can be obtained on request or downloaded from the NOTABLE trial website. The Trial Office is responsible for collection and checking of data (including reports of serious surgical complications), for reporting of serious adverse events to the sponsor and/ or regulatory authorities and for analyses. The Trial Office will help resolve any local problems that may be encountered in trial participation.

9.5. Research Governance

The study will be conducted according to the principles of the Declaration of Helsinki (Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000) and in accordance with the Belgian law of 7 May 2004 that regulates human experiments in Belgium.

All Principal Investigators will be required to sign an Investigator's Agreement, detailing their commitment to accrual, compliance, Good Clinical Practice, confidentiality and publication. Deviations from the agreement will be monitored and the TSC will decide whether any action needs to be taken, e.g. withdrawal of funding, suspension of centre.

9.6. Research Governance and Ethical Approval

As the trial does not involve an investigational medicinal product, clinical trial authorization from the Medicines and Healthcare products Regulatory Authority is not required.

In accordance to the Belgian law of 7 May 2004 that regulates human experiments, the investigator will inform the study participants and the medical ethical committee if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review, except insofar as suspension would jeopardize the subjects' health. The investigator will take care that all subjects are kept informed.

The principal investigator will report all adverse and serious events to the medical ethical committee.

Adverse events are defined as any undesirable experience occurring to a participant during the study, whether or not considered to be related to the intervention.

All adverse events reported spontaneously by the participant or observed by the investigator or his staff will be recorded.

A serious adverse event is any untoward medical occurrence or effect that:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

All SAEs will be reported to medical ethical committee that approved the protocol, within 15 days after the investigator has first knowledge of the serious adverse reactions.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur no later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

9.7. Funding and Cost implications

The research costs of this non-commercial trial are funded by the investigating team.

9.8. Indemnity

No additional preoperative examinations are needed when compared to the situation where the woman would not have given informed consent for study participation. One additional postoperative examination is needed for study participants compared to routine clinical practice: no risks or side effects are associated with this additional assessment. The risks and side effects for both types of surgical interventions have been extensively described in the consent form. According to two large prospective studies the incidence of complications associated with minimally invasive surgery are less than 1%. (26, 27) The benefit is an, as of yet, unknown increase in the chance of being discharged the same day as the surgical procedure with less postoperative pain.

The investigators have a 'no fault' liability insurance which is in accordance to the Belgian law of 7 May 2004 that regulates human experiments. The insurance aims to cover the financial consequences of the civil liability that the investigators may incur even when no fault has occurred as a result of the organization of medical experiments on the human person. All physical and material damage sustained by the participant in the experiment and/or his/her assignees and arising from the insured experiment are covered for an amount of 2 500 000 € per experiment. The insurance applies to the damage that becomes apparent during the study or within 36 months after the end of the study.

9.9. Publication

A meeting will be held after the end of the study to allow discussion of the main results among the collaborators prior to publication. The success of the study depends entirely on the wholehearted collaboration of a dedicated team of doctors, nurses and others.

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9.10. Ancillary studies

It is requested that any proposals for formal additional studies of the effects of the trial treatments on some participants (e.g. special investigations in selected hospitals) be referred to the Trial

Management Committee for consideration. In general, it would be preferable for the trial to be kept as simple as possible, and add-on studies will need to be fully justified.

10. REFERENCES

(1) Burpee SE, Kurian M, Murakame Y, Benevides S, Gagner M. The metabolic and immune response to laparoscopic versus open liver resection. Surg Endosc. 2002; 16(6):899 –904.

(2) Grande M, Tucci GF, Adorisio O, et al. Systemic acute-phase response after laparoscopic and open cholecystectomy. Surg Endosc. 2002; 16(2):313–6.

(3) Rattner D, Kalloo A. ASGE/SAGES working group on natural Orifice transluminal endoscopic surgery. October 2005. Surg Endosc. 2006; 20:329-33.

(4) Santos BF, Hungness ES. Natural orifice transluminal endoscopic surgery: progress in humans since white paper. World J Gastroenterol. 2011; 17:1655–65.

(5) Tolcher MC, Kalogera E, Hopkins MR, Weaver AL, Bingener J, Dowdy SC. Safety of Culdotomy as a Surgical Approach: Implications for Natural Orifice Transluminal. JSLS. 2012; 16:413–20

(6) Uccella S, Cromi A, Bogani G, Casarin J, Serati M, Ghezzi F. Transvaginal specimen extraction at laparoscopy without concomitant hysterectomy: our experience and systematic review of the literature. J Minim Invasive Gynecol. 2013; 20:583-90.

(7) Reynders A, Baekelandt J. Adnexectomy by Poor Man's Transvaginal NOTES. Gynecological Surgery 2015; 12(3): 207-11.

(8) Dindo D, Demartines N, Clavien PA. Classifi cation of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240**:** 205–13.

(9) Mc Williams GD, Hill MJ, Dietrich CS. Gynecologic emergencies. Surg Clin North Am 2008; 88(2): 265-83.

(10) Timmerman D, Ameye L, Fischerova D, Epstein E, Melis GB, Guerriero S, Van Holsbeke C, Savelli L, Fruscio R, Lissoni AA, Testa AC, Veldman J, Vergote I, Van Huffel S, Bourne T, Valentin L. Simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery: prospective validation by IOTA group. BMJ 2010; 341:c6839 doi:10.1136/bmj.c6839.

(11) Sainz de la Cuesta R, Goff BA, Fuller AF Jr, Nikrui N, Eichhorn JH, Rice LW. Prognostic importance of intraoperative rupture of malignant ovarian epithelial neoplasms. Obstet Gynecol. 1994;84(1):1.

(12) Webb MJ, Decker DG, Mussey E, Williams TJ. Factor influencing survival in Stage I ovarian cancer. Am J Obstet Gynecol. 1973;116(2):222.

(13) Pillai R, Yoong W. Posterior colpotomy revisited: a forgotten route for retrieving larger benign ovarian lesions following laparoscopic excision. Arch Gynecol Obstet. 2010; 281(4):609-11.

(14) Yang YS, Hur MH, Oh KY, Kim SY. Transvaginal natural orifice transluminal endoscopic surgery for adnexal masses. J Obstet Gynaecol Res. 2013 Dec; 39(12):1604-9.

(15)Demir RH, Marchand GJ. Adnexal masses suspected to be benign treated with laparoscopy. JSLS JSLS. 2012 Jan-Mar; 16(1): 71–84.

(16)Ghezzi F, Cromi A, Uccella S, Bogani G, Serati M, Bolis PF. Transumbilical versus transvaginal retrieval of surgical specimens at laparoscopy: a randomized trial. Am J Obstet Gynecol 2012; 207(2): 112.e1-112.e6.

(17) Wang PH, Lee WL, Juang CM, Tsai WY, Chao HT, Yuan CC. Excision of mature teratoma using culdotomy, with and without laparoscopy: A prospective randomized trial. BJOG 2001; 108: 91-4.

(18)Medeiros LR, Rosa DD, Bozzetti MC, Fachel JM, Furness S, Garry R, Rosa MI, Stein AT. Laparoscopy versus laparotomy for benign ovarian tumour. Cochrane Database Syst Rev. 2009 Apr 15; (2):CD004751.

(19)Barkun JS, Aronson JK, Feldman LS, Maddern GJ, Strasberg SM, for the Balliol Collaboration. Evaluation and stages of surgical innovations. The Lancet 2009; 374:1089-96.

(20)Ergina PL, Cook JA, Blazeby JM, Boutron I, Clavien PA, Reeves BC, Seiler CM, for the Balliol Collaboration. Challenges in evaluating surgical innovation. The Lancet 2009; 374:1097-1104.

(21)Mc Culloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, Nicholl J, for the Balliol Collaboration. No surgical intervention without evaluation: the IDEAL recommendations. The Lancet 2009; 374: 1105-12.

(22)Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykendall DH, Hollingsworth JC, Ashton CM, Wray NP. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med. 2002 Jul 11; 347(2):81-8.

(23)Freedman B. Equipoise and the ethics of clinical research. N Engl J Med 1987; 317: 141-145.

(24) Bird SB, Dickson EW. Clinically significant changes in pain along the visual analog scale. Ann Emerg Med 2001;38: 639-43.

(25) Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. Ann Emerg Med 1996; 27: 485-9.

(26) Jansen FW, Kapiteyn K, Trimbos-Kemper T, Hermans J, Trimbos-Kemper JB. Complications of laparoscopy: a prospective multicenter observational study. Br J Obstet Gynaeco 1997; 104: 595-600.

(27)Harrki-Sirén P, Sjoberg J, Kurki T. Major complications of laparoscopy: a follow-up Finnish study. Obstet Gynecol 1999; 94: 94-8.

APPENDIX I: TABLE I

Table 1 Overview of patient and perioperative characteristics

Data	Mean	Range
Age (years)	51	31 - 75
BMI (kg/m^2)	24.0	17.2 - 28.7
Total operating time (min)	32	20 - 50
Serum hemoglobine drop (g/dl)	0.9	0 - 2.1
Postoperative pain score		
6h	2.0	0 – 4
24h	1.3	0 – 2
Size of adnexal mass (mm)	51.8	35 - 110

APPENDIX II: TABLE II

Table 2 Patient and perioperative characteristics of consecutive patients

CE = cystectomy; CS = caesarean section; LS = laparoscopic sterilisation; USO = unilateral salpingo-oophorectomy; BSO = bilateral salpingo-oophorectomy; R = right; L = left.

Patient no.	Age (years)	BMI (kg/m^2)	Parity	History of vaginal delivery	Previous pelvic surgery	Type of surgery	Total operating time (min)	Serum hemo-globine drop (g/dl)	(Peri-) operative complications	Postoperative pain score		Size of adnexal mass (largest diameter, mm)
										6h	24h	
1	54	24.1	P4	Yes	LS	BSO	40	0.4	-	2	2	70
2	44	17.2	P1	Yes	-	USO R	35	0.8	-	2	2	62
3	56	21.5	P2	Yes	LS	BSO	35	0.5	Cystitis	2	2	35
4	47	27.1	P2	Yes	-	USO R	30	0	-	2	1	50
5	58	26.0	P0	No	-	BSO	35	0.6	-	4	1	40
6	52	28.3	P0	No	-	USO R	35	0.6	-	1	1	36
7	66	22.9	P2	Yes	-	BSO	40	0.7	-	2	1	45
8	46	20.8	P0	No	-	USO R	22	1.4	-	2	1	35
9	51	25.4	P2	Yes	-	USO L	22	0.5	-	2	1	35
10	56	24.2	P1	Yes	-	USO R	25	1.2	-	2	1	42
11	63	26.7	P2	Yes	-	BSO	30	2.0	-	3	0	40
12	56	25.0	P2	Yes	-	USO R	22	0.5	-	1	1	39
13	75	23.2	P1	Yes	-	USO R	20	0.6	-	2	2	38
14	31	21.5	P2	Yes	-	USO R	35	1.8	-	2	2	60
15	45	28.7	P1	Yes	-	USO R	20	0	-	2	2	40
16	43	24.4	P2	No	CS	USO R	50	0.9	-	2	2	100
17	45	23.7	P2	Yes	CE	USO R	45	0.7	-	0	0	110
18	36	22.8	P2	Yes	CS	USO R	40	1.7	-	2	1	39
19	55	23.4	P1	Yes	-	BSO	35	1.2	-	2	1	70
20	38	22.5	P2	Yes	-	USO L	32	2.1	-	2	2	49

APPENDIX III

CLAVIEN-DINDO CLASSIFICATION

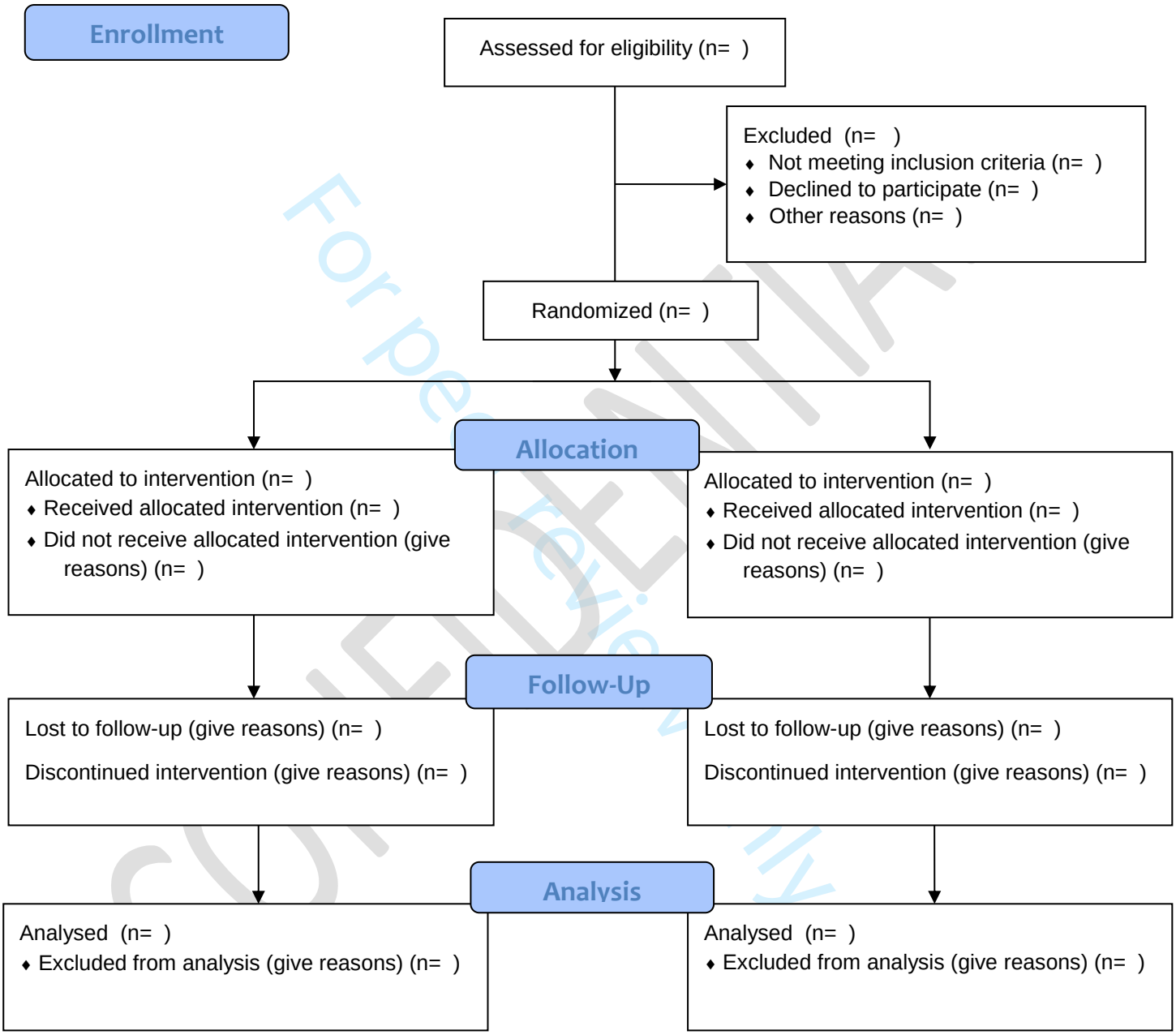
TABLE 1. Classification of Surgical Complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

APPENDIX IV

CONSORT 2010 Flow Diagram



APPENDIX V Pain protocol

PROTOCOL ADNEXECTOMIE – DR. BAEKELANDT

ASA I & ASA II PATIËNTEN

1. INDUCTIE ANESTHESIE

- Propolipid 2,5mg/kg
- Sufentanil 0,15µg/kg
- Rocurorium 0,6mg/kg
- Dexamethasone 5mg
-

2. ONDERHOUD ANESTHESIE

- O_2/ lucht 50/50
  DES 1 MAC

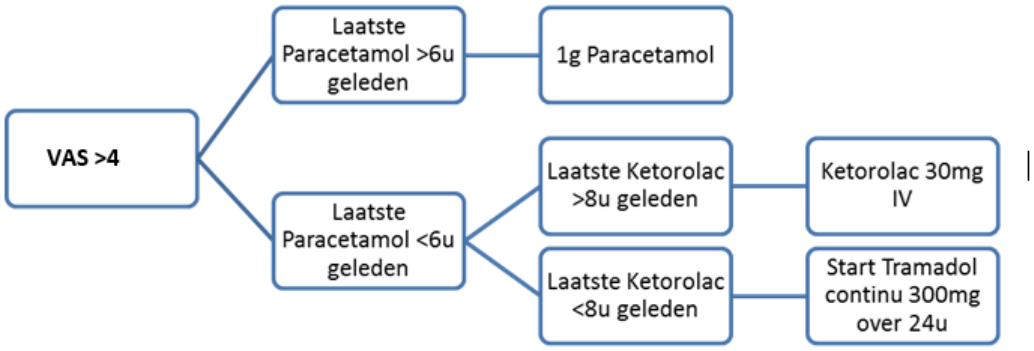
- Zo nodig bolus Alfentanil 5mg/kg
- 30min. voor einde IV toediening van
  - 1g Paracetamol
  - Ketorolac 0,5mg/kg met maximum van 30mg

3. POSTOPERATIEF

RECOVERY

- Bij VAS >4: 1g Paracetamol IV
- Herevaluatie na 30min.
  - Bij VAS >4: 2,5mg Piritramide IV

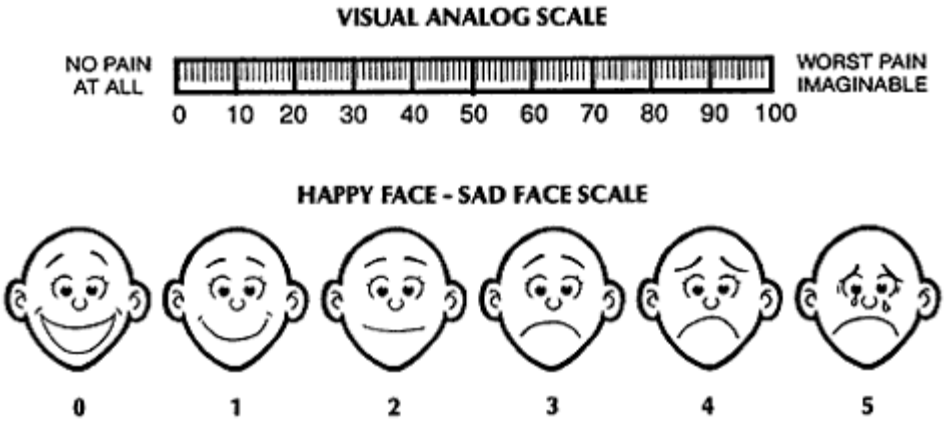
VERPLEEGAFDELING



Na 30min. herevaluatie + herstarten bovenstaand schema.

Indien VAS >4 blijft, ondanks starten van Tramadol continu: contacteer anesthesist

APPENDIX VI VAS scale



APPENDIX VII: Participant's pain log book

Notable trial

Naam en voornaam:	
Datum van de ingreep:	

Aankomst thuis:

uur van aankomst: .....

Pijnscore:

0	1	2	3	4	5	6	7	8	9	10

Pijnmedicatie:

	Aantal mg	Aantal comprimés	Tijdstip(pen) inname
Paracetamol			
Ibuprofen			
Andere			

Dag 1 na de ingreep:

Pijnscore ochtend:

0	1	2	3	4	5	6	7	8	9	10

Pijnscore avond:

0	1	2	3	4	5	6	7	8	9	10

Pijnmedicatie:

	Aantal mg	Aantal comprimés	Tijdstip(pen) inname
Paracetamol			
Ibuprofen			
Andere			

Dag 2 na de ingreep:

Pijnscore ochtend:

0	1	2	3	4	5	6	7	8	9	10

Pijnscore avond:

0	1	2	3	4	5	6	7	8	9	10

Pijnmedicatie:

	Aantal mg	Aantal comprimés	Tijdstip(pen) inname
Paracetamol			
Ibuprofen			
Andere			

Dag 3 na de ingreep:

Pijnscore ochtend:

0	1	2	3	4	5	6	7	8	9	10

Pijnscore avond:

0	1	2	3	4	5	6	7	8	9	10

Pijnmedicatie:

	Aantal mg	Aantal comprimés	Tijdstip(pen) inname
Paracetamol			
Ibuprofen			
Andere			

Dag 4 na de ingreep:

Pijnscore ochtend:

0	1	2	3	4	5	6	7	8	9	10

Pijnscore avond:

0	1	2	3	4	5	6	7	8	9	10

Pijnmedicatie:

	Aantal mg	Aantal comprimés	Tijdstip(pen) inname
Paracetamol			
Ibuprofen			
Andere			

Dag 5 na de ingreep:

Pijnscore ochtend:

0	1	2	3	4	5	6	7	8	9	10

Pijnscore avond:

0	1	2	3	4	5	6	7	8	9	10

Pijnmedicatie:

	Aantal mg	Aantal comprimés	Tijdstip(pen) inname
Paracetamol			
Ibuprofen			
Andere			

Dag 6 na de ingreep:

Pijnscore ochtend:

0	1	2	3	4	5	6	7	8	9	10

Pijnscore avond:

0	1	2	3	4	5	6	7	8	9	10

Pijnmedicatie:

	Aantal mg	Aantal comprimés	Tijdstip(pen) inname
Paracetamol			
Ibuprofen			
Andere			

APPENDIX VIII: Dyspareunia questionnaire

PIJN
lokatie en intensiteit

1) Ervaar je pijn bij het vrijen? Ja/Nee

2) Indien ja, waar ervaar je pijn bij het vrijen? Is er een specifieke plaats?
   a) ter hoogte van de vaginale opening
   b) ter hoogte van de schaamlippen
   c) in de vagina
   d) in the pelvische of abdominale regio

3) Geef een score voor de intensiteit van de pijn aan de ingang en/of the eerste deel van de vagina op deze schaal van 0 tot 10

0	1	2	3	4	5	6	7	8	9	10
geen pijn										ergste pijn ooit

4) Geef een score voor de intensiteit van de pijn in de pelvische en abdominale regio op deze schaal van 0 tot 10

0	1	2	3	4	5	6	7	8	9	10
geen pijn										ergste pijn ooit

APPENDIX IX: Short Sexual Functioning Scale

Short Sexual Functioning scale – female version

Met de volgende vragen wordt nagegaan of jij de voorbije 3 maanden bepaalde seksuele problemen hebt ervaren. Dit gebeurt door middel van vragen over lichamelijke reacties en gevoelens die kunnen optreden bij seksuele activiteiten. Als er zich een seksueel probleem heeft voorgedaan, vragen we telkens ook hoe lastig jij en jouw partner dat vinden én of dit op jullie relatie heeft gewogen.
Gelieve voor elke vraag het antwoord te omcirkelen dat het best jouw gevoel of ervaring weergeeft. Soms wordt er aangegeven dat je naar een volgende vraag mag gaan, dan hoef je de rest van de vraag niet verder in te vullen. Er zijn geen juiste of foute antwoorden. Let er op geen vragen over te slaan !

1. Had je - de voorbije 3 maanden - te weinig zin in seks, te weinig goesting in seksuele activiteiten, te weinig seksuele fantasieën of erotische gedachten (= te weinig seksueel verlangen)?

1. ik had niet te weinig zin ➔ *ga naar vraag 2*
2. ik had in lichte mate te weinig zin
3. ik had duidelijk te weinig zin
4. ik had in extreme mate te weinig zin

a) Indien ik te weinig zin in seks heb, is dit voor mij:
1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. en ernstig probleem

b) Indien ik te weinig zin in seks heb, is dit voor mijn partner:
1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

c) Indien ik te weinig zin in seks heb, is dit voor onze relatie in het algemeen:
1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

2. Had je - de voorbije 3 maanden - wanneer je zelf geen zin in seks had maar jouw partner wel initiatief nam tot seks, moeilijkheden om zin in seks te krijgen?

1. ik had dan geen moeilijkheden om zin in seks te krijgen ➔ *ga naar vraag 3*

2. ik had dan in lichte mate moeilijkheden om zin in seks te krijgen
3. ik had dan duidelijk moeilijkheden om zin in seks te krijgen
4. ik had dan in extreme mate moeilijkheden om zin in seks te krijgen

a) Indien ik moeilijkheden heb om zin in seks te krijgen wanneer mijn partner initiatief neemt tot seks, is dat <u>voor mij</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

b) Indien ik moeilijkheden heb om zin in seks te krijgen wanneer mijn partner initiatief neemt tot seks, is dat <u>voor mijn partner</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

c) Indien ik moeilijkheden heb om zin in seks te krijgen wanneer mijn partner initiatief neemt tot seks, is dat <u>voor onze relatie in het algemeen</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

3. Had je - de voorbije 3 maanden - wanneer jouw partner fijn met jou vrijde, <u>moeilijkheden met vochtig/nat worden</u> tijdens seks?

1. ik had geen moeilijkheden om vochtig/nat te worden ➔ ***ga naar vraag 4***
2. ik had in lichte mate moeilijkheden om vochtig/nat te worden
3. ik had duidelijk moeilijkheden om vochtig/nat te worden
4. ik had in extreme mate moeilijkheden om vochtig/nat te worden

a) Indien ik minder vochtig/nat word, is dit <u>voor mij</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

b) Indien ik minder vochtig/nat word, is dit <u>voor mijn partner</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

c) Indien ik minder vochtig/nat word, is dit <u>voor onze relatie</u> in het algemeen:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem

4. een ernstig probleem

4. Had je - de voorbije 3 maanden - wanneer je partner fijn met jou vrijde, geen of weinig gevoel van opwinding (emotioneel)?

1. ik had geen moeilijkheden met het krijgen van een gevoel van opwinding (emotioneel) ➔ ***ga naar vraag 5***
2. ik had in lichte mate moeilijkheden met het krijgen van een gevoel van opwinding (emotioneel)
3. ik had duidelijk moeilijkheden met het krijgen van een gevoel van opwinding (emotioneel)
4. ik had in extreme mate moeilijkheden met het krijgen van een gevoel van opwinding (emotioneel)

a) Indien ik geen of weinig gevoel van opwinding ervaar, is dit voor mij:
1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

b) Indien ik geen of weinig gevoel van opwinding ervaar, is dit voor mijn partner:
1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

c) Indien ik geen of weinig gevoel van opwinding ervaar, is dit voor onze relatie in het algemeen:
1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

5. Had je - de voorbije 3 maanden - wanneer jouw partner fijn met jou vrijde, moeilijkheden om klaar te komen (een orgasme te bereiken) ?

1. ik had geen moeite om klaar te komen of een orgasme te bereiken ➔ ***ga naar vraag 6***
2. ik had in lichte mate moeite om klaar te komen of een orgasme te bereiken
3. ik had duidelijk moeite om klaar te komen of een orgasme te bereiken
4. ik had in extreme mate moeite om klaar te komen of een orgasme te bereiken

a) Indien ik moeite heb om een orgasme te bereiken, is dit voor mij:
1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

b) Indien ik moeite heb om een orgasme te bereiken, is dit <u>voor mijn partner</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

c) Indien ik moeite heb om een orgasme te bereiken, is dit <u>voor onze relatie</u> in het algemeen:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

6. Had je - de voorbije 3 maanden - wanneer je met jezelf vrijde of masturbeerde, moeilijkheden om een orgasme te bereiken?

0. ik heb niet gemasturbeerd de laatste 4 weken ➔ ***ga naar vraag 7***

1. ik had geen moeite om bij masturbatie een orgasme te bereiken ➔ ***ga naar vraag 7***
2. ik had in lichte mate moeite om bij masturbatie een orgasme te bereiken
3. ik had duidelijk moeite om bij masturbatie een orgasme te bereiken
4. ik had in extreme mate moeite om bij masturbatie een orgasme te bereiken

a) Indien ik moeilijk kan klaarkomen bij masturbatie, is dit <u>voor mij</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

7. Kan je in de volgende lijst aangeven wat voor jou de voorbije 3 maanden van toepassing was? Je kan slechts één antwoord aanduiden.

1. vaginale penetratie (= het inbrengen van penis of vinger in de vagina) was mogelijk en niet pijnlijk ➔ ***einde van de vragenlijst***
2. vaginale penetratie was mogelijk, maar was pijnlijk
3. ➔ ***ga naar vraag 7a***
4. vaginale penetratie is (met mijn huidige partner) nog nooit gelukt ➔ ***einde van de vragenlijst***
5. vaginale penetratie was (met mijn huidige partner) vroeger mogelijk, maar nu niet meer ➔ ***einde van de vragenlijst***

7a. Had je - de voorbije 3 maanden - pijn voor, tijdens of na vaginale penetratie?

1. Ik had geen pijn voor, tijdens of na penetratie
2. Ik had een lichte pijn voor, tijdens of na penetratie
3. Ik had een duidelijke pijn voor, tijdens of na penetratie
4. Ik had een extreme pijn voor, tijdens of na penetratie

a) Indien ik pijn heb voor, tijdens of na vaginale penetratie, is dit <u>voor mij</u>:

1. geen probleem

2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

b) Indien ik pijn heb voor, tijdens of na vaginale penetratie, is dit <u>voor mijn partner</u>:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

c) Indien ik pijn heb voor, tijdens of na penetratie, is dit <u>voor onze relatie</u> in het algemeen:

1. geen probleem
2. een licht probleem
3. een duidelijk probleem
4. een ernstig probleem

Hartelijk dank voor het invullen van deze vragenlijst !

APPENDIX X: EQ-5D Health questionnaire

Gezondheidsvragenlijst

Nederlandse versie voor België

(Dutch version for Belgium)

Zet bij iedere hieronder vermelde groep een kruisje in één hokje achter de zin die het best uw gezondheidstoestand van vandaag weergeeft.

Mobiliteit

Ik heb geen problemen met rondwandelen ❑

Ik heb enige problemen met rondwandelen ❑

Ik ben bedlegerig ❑

Zelfzorg

Ik heb geen problemen om voor mezelf te zorgen ❑

Ik heb enige problemen om mezelf te wassen of aan te kleden ❑

Ik ben niet in staat mezelf te wassen of aan te kleden ❑

Dagelijkse activiteiten *(bijv. werk, studie, huishouden, gezins- of vrijetijdsactiviteiten)*

Ik heb geen problemen met mijn dagelijkse activiteiten ❑

Ik heb enige problemen met mijn dagelijkse activiteiten ❑

Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren ❑

Pijn/klachten

Ik heb geen pijn of andere klachten ❑

Ik heb matige pijn of andere klachten ❑

Ik heb zeer ernstige pijn of andere klachten ❑

Angst/depressie

Ik ben niet angstig of depressief ❑

Ik ben matig angstig of depressief ❑

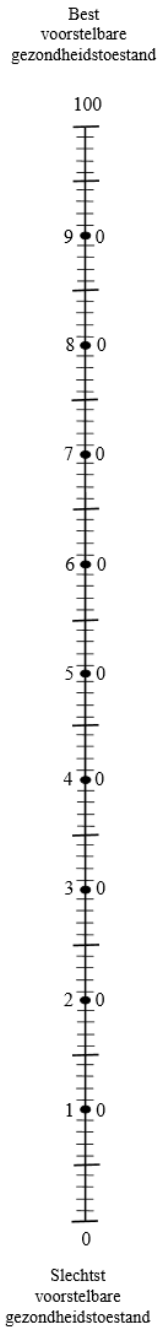
Ik ben erg angstig of depressief ❑

 2

Om mensen te helpen bij het aangeven hoe goed of hoe slecht een gezondheidstoestand is, hebben we een meetschaal (te vergelijken met een thermometer) gemaakt. Op de meetschaal hiernaast betekent "100" de beste gezondheidstoestand die u zich kunt voorstellen, en "0" de slechtste gezondheidstoestand die u zich kunt voorstellen.

We willen u vragen op deze meetschaal aan te geven hoe goed of hoe slecht volgens u uw eigen gezondheidstoestand vandaag is. Trek een lijn van het hokje hieronder naar het punt op de meetschaal dat volgens u aangeeft hoe goed of hoe slecht uw gezondheidstoestand vandaag is.

Uw gezondheidstoestand vandaag



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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_4_____
	2b	All items from the World Health Organization Trial Registration Data Set	_Appendix 1 ___
Protocol version	3	Date and version identifier	_4_____
Funding	4	Sources and types of financial, material, and other support	_24_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_1,2, 26_____
	5b	Name and contact information for the trial sponsor	_Not applicable__
	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	_Not applicable__
	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)	_Not applicable _____

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	__6,7_____
	6b	Explanation for choice of comparators	__6,7,22_____
Objectives	7	Specific objectives or hypotheses	__6,7_____
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)	___8_____

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	___8_____
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)	__8,9_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	___9,10,11,12
	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)	_11,12_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_11,12_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_9,10,11,12_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_12,13,14_____

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)	__Table 1_____
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_15_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__8_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__14_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	__14_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__14_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__14_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	__14_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__20_____

	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	__21_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__Appendix 3 protocol_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___16-19_____
-	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___16-19_____
	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)	___16-19_____
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	_19_____
	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	__19_____
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	__19_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__19_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__24_____

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)	___24_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	__24_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_Not applicable__
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	_24,25_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__26_____
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	_25_____
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	__25_____
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	__25_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__25_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_24_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Appendix 2____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable__

*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.