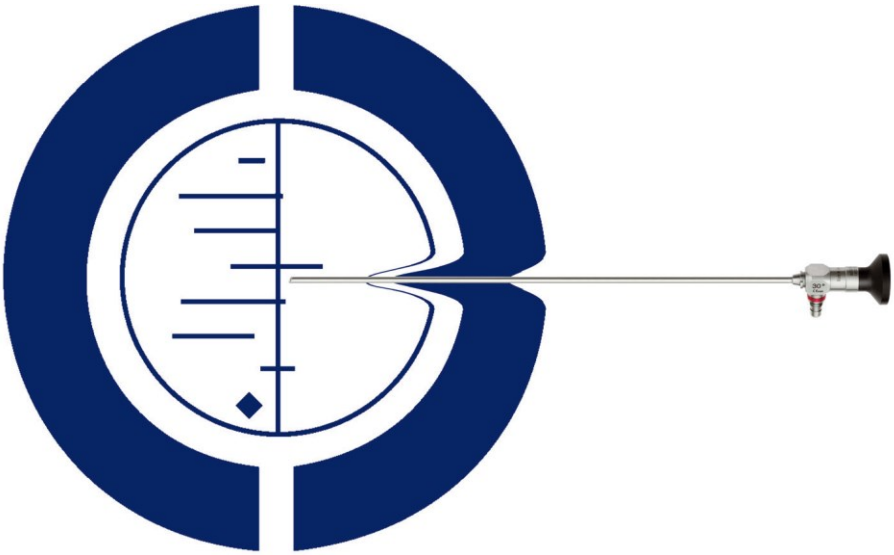
RESEARCH PROTOCOL

NOTABLE trial



(NOTes Adnexectomy for Benign pathology compared to Laparoscopic Excision)

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Independent physician	Not applicable
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Pharmacy	Not applicable

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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.

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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

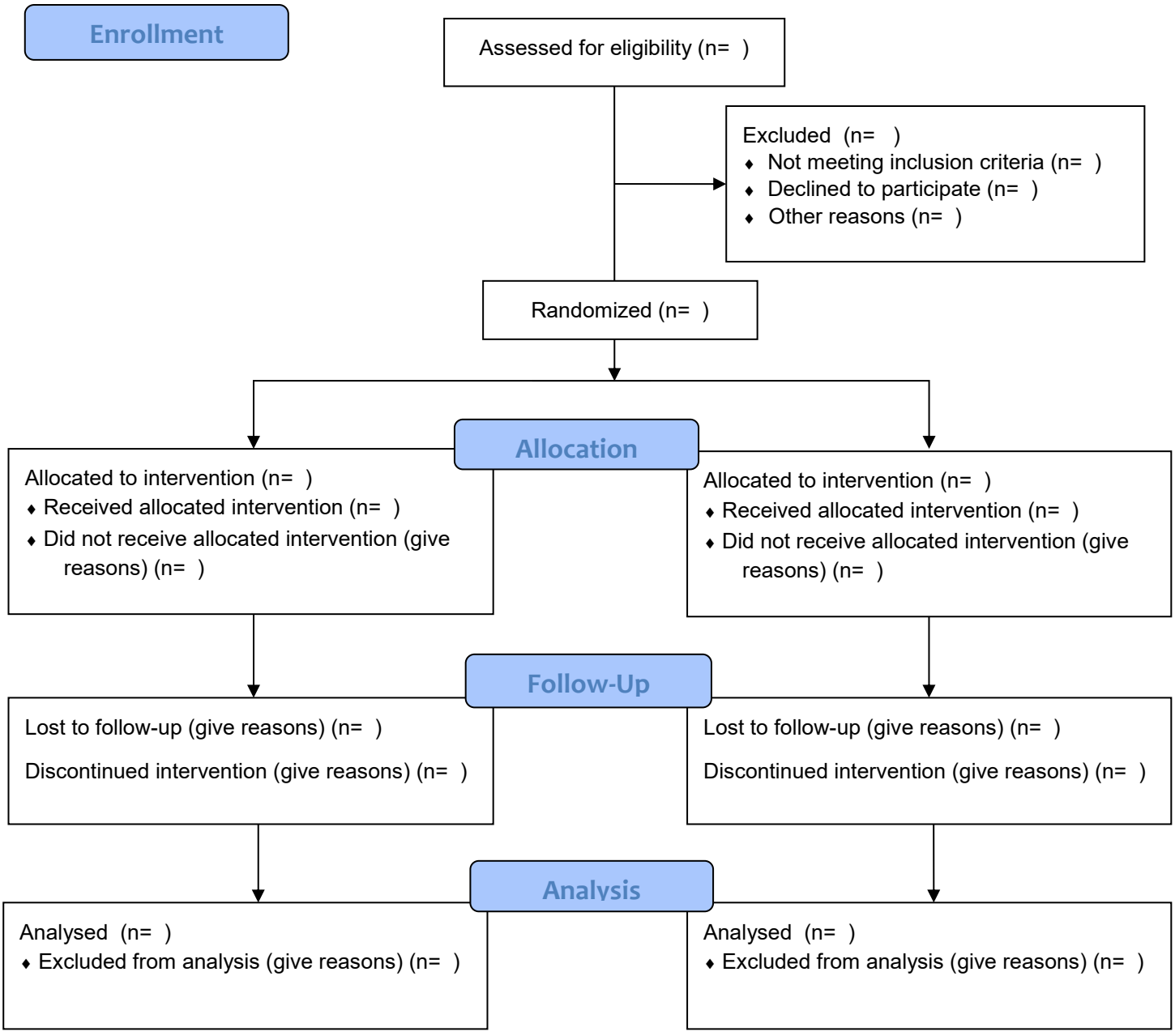
TABLE 1. Classification of Surgical Complications

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 ADNEXECTOMY – DR. BAEKELANDT

ASA I & ASA II PATIENTS

1. INDUCTION ANEASTHESIA

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

2. MAINTENANCE ANESTHESIA

- O_2/ room air 50/50
  DES 1 MAC

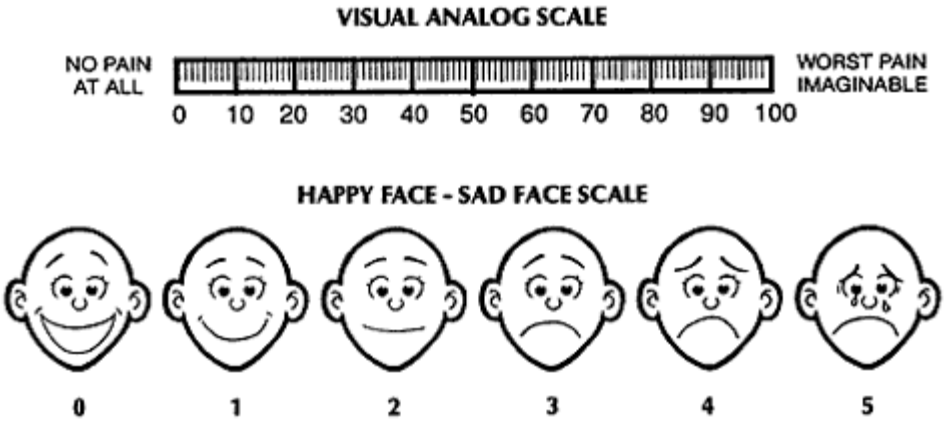
- Need be Alfentanil 5mg/kg one shot
- 30min. before end surgery IV shot
  - 1g Paracetamol
  - Ketorolac 0,5mg/kg (maximum dose 30mg)

3. POSTOPERATIVE PHASE

RECOVERY

- If VAS >4: 1g Paracetamol IV
- Reevaluation after 30min.
  - If VAS >4: 2,5mg Piritramide IV

APPENDIX VI VAS scale



APPENDIX VII: Participant's pain log book

NOTABLE trial

First & last name:	
Date of surgical procedure:	

Arrival at home:

Time of arrival at home: ……..

Pain score:

0	1	2	3	4	5	6	7	8	9	10

Pain medication:

	Dose in mg	Number of tablets	Time intake
Paracetamol			
Ibuprofen			
Other			

Day 1 after surgery:

Pain score morning:

0	1	2	3	4	5	6	7	8	9	10

Pain score evening:

0	1	2	3	4	5	6	7	8	9	10

Pain medication:

	Dose in mg	Number of tablets	Time intake
Paracetamol			
Ibuprofen			
Other			

Day 2 after surgery:

Pain score morning:

0	1	2	3	4	5	6	7	8	9	10

Pain score evening:

0	1	2	3	4	5	6	7	8	9	10

Pain medication:

	Dose in mg	Number of tablets	Time intake
Paracetamol			
Ibuprofen			
Other			

Day 3 after surgery:

Pain score morning:

0	1	2	3	4	5	6	7	8	9	10

Pain score evening:

0	1	2	3	4	5	6	7	8	9	10

Pain medication:

	Dose in mg	Number of tablets	Time intake
Paracetamol			
Ibuprofen			
Other			

Day 4 after surgery:

Pain score morning:

0	1	2	3	4	5	6	7	8	9	10

Pain score evening:

0	1	2	3	4	5	6	7	8	9	10

Pain medication:

	Dose in mg	Number of tablets	Time intake
Paracetamol			
Ibuprofen			
Other			

Day 5 after surgery:

Pain score morning:

0	1	2	3	4	5	6	7	8	9	10

Pain score evening:

0	1	2	3	4	5	6	7	8	9	10

Pain medication:

	Dose in mg	Number of tablets	Time intake
Paracetamol			
Ibuprofen			
Other			

Day 6 after surgery:

Pain score morning:

0	1	2	3	4	5	6	7	8	9	10

Pain score evening:

0	1	2	3	4	5	6	7	8	9	10

Pain medication:

	Dose in mg	Number of tablets	Time intake
Paracetamol			
Ibuprofen			
Other			

Day 7 after surgery:

Pain score morning:

0	1	2	3	4	5	6	7	8	9	10

Pain score evening:

0	1	2	3	4	5	6	7	8	9	10

Pain medication:

	Dose in mg	Number of tablets	Time intake
Paracetamol			
Ibuprofen			
Other			

APPENDIX VIII: Dyspareunia questionnaire

PAIN

LOCATION AND INTENSITY

1) Do you experience pain during sexual activity? Yes / No

2) If yes, where do you experience pain during sexual activity? Is there a specific place?

a) at the vaginal opening
b) at the *labia majora* (major lips)
c) in the vagina
d) in the pelvic or abdominal region

3) Please classify the intensity of the pain at the entrance and/or the first part of the vagina on the scale below from 0 to 10?.

0	1	2	3	4	5	6	7	8	9	10
No pain										worst pain ever

3) Please classify the intensity of the pain in the pelvic or abdominal region on the scale below from 0 to 10?

0	1	2	3	4	5	6	7	8	9	10
No pain										worst pain ever

APPENDIX IX: Short Sexual Functioning Scale

Short Sexual Functioning scale – female version

SHORT SEXUAL FUNCTION SCALE – FEMALE VERSION

We would like to know whether you experienced certain sexual difficulties over the past three months. We ask about physical reactions and feelings that may occur during sexual activity. If a sexual difficulty occurred, we also ask whether you and your partner experienced this as a problem and whether this had a negative effect on your relationship with your partner.

Please indicate for each item the degree to which you experienced difficulties during the past three months with the following aspects of sexual functioning. Sometimes it is indicated that you can skip the rest of the question; then continue to the next questions. There are no right or wrong answers. Please be careful and do not leave questions open!

1. **During the past 3 months, did you have too little desire for sex, too little desire for sexual activities, too little sexual fantasies or erotic thoughts (=too little sexual desire)?**
   0. I did not have too little desire ➔ go to question 2
   1. I had mildly too little desire
   2. I had moderately too little desire
   3. I had severely or extremely too little desire

   If I have too little desire, I experience this as:
   1. Not a problem
   2. A mild problem
   3. A moderate problem
   4. A severe or extreme problem

   If I have too little desire, my partner experiences this as:
   1. Not a problem
   2. A mild problem
   3. A moderate problem
   4. A severe or extreme problem

   If I have too little desire, I experience this in my relationship as:
   1. Not a problem
   2. A mild problem
   3. A moderate problem
   4. A severe or extreme problem

2. **During the past 3 months, if your partner initiated sex and you began the sexual encounter with no sexual desire, did you then have difficulties to get sexual desire?**
   0. I then did not have difficulties to get sexual desire ➔ go to question 3

1. I then had mild difficulties to get sexual desire
2. I then had moderate difficulties to get sexual desire
3. I then had severe or extreme difficulties to get sexual desire

If I have difficulties to get sexual desire when my partner initiates sex, I experience this as:

1. Not a problem
2. A mild problem
3. A moderate problem
4. A severe or extreme problem

If I have difficulty to get sexual desire when my partner initiates sex, my partner experiences this as:

1. Not a problem
2. A mild problem
3. A moderate problem
4. A severe or extreme problem

If I have difficulty to get sexual desire when my partner initiates sex, I experience this in my relationship as:

1. Not a problem
2. A mild problem
3. A moderate problem
4. A severe or extreme problem

3. During the past 3 months, when having pleasurable sex with your partner, did you experience difficulties with becoming lubricated (wet) during sex?

0. I did not experience difficulties becoming lubricated (wet) ➔ go to question 4
1. I had mild difficulties becoming lubricated (wet)
2. I had moderate difficulties becoming lubricated (wet)
3. I had severe or extreme difficulties becoming lubricated (wet)

If I have difficulties to become lubricated, I experience this as:

1. Not a problem
2. A mild problem
3. A moderate problem
4. A severe or extreme problem

If I have difficulties to become lubricated, my partner experiences this as:

1. Not a problem
2. A mild problem
3. A moderate problem
4. A severe or extreme problem

If I have difficulties to become lubricated, I experience this in my relationship as:

1. Not a problem
2. A mild problem

3. A moderate problem
4. A severe or extreme problem

4. During the past 3 months, when you were having pleasurable sex with your partner, did you experience little or no feelings of (emotional/subjective) arousal?

0. I did not have difficulties experiencing subjective arousal → go to question 5
1. I had mild difficulties experiencing subjective arousal
2. I had moderate difficulties experiencing subjective arousal
3. I had severe or extreme difficulties experiencing subjective arousal

If I experience little or no feelings of arousal, I experience this as:

1. Not a problem
2. A mild problem
3. A moderate problem
4. A severe or extreme problem

If I experience little or no feelings of arousal, my partner experiences this as:

1. Not a problem
2. A mild problem
3. A moderate problem
4. A severe or extreme problem

If I experience little or no feelings of arousal, I experience this in my relationship as:

1. Not a problem
2. A mild problem
3. A moderate problem
4. A severe or extreme problem

5. During the past 3 months, when you were having pleasurable sex with your partner, did you have difficulty reaching orgasm?

0. I did not have difficulties reaching orgasm → go to question 6
1. I had mild difficulties reaching orgasm
2. I had moderate difficulties reaching orgasm
3. I had extreme difficulties reaching orgasm

If I have difficulties reaching orgasm, I experience this as:

1. Not a problem
2. A mild problem
3. A moderate problem
4. A severe or extreme problem

If I have difficulties reaching orgasm, my partner experiences this as:

1. Not a problem
2. A mild problem
3. A moderate problem
4. A severe or extreme problem

If I have difficulties reaching orgasm, I experience this in my relationship as:

1. Not a problem
2. A mild problem
3. A moderate problem
4. A severe or extreme problem

6. During the past 3 months, did you have difficulty reaching orgasm during masturbation?

0. I did not masturbate over the past 3 months. ➔ go to question 7
1. I did not have difficulties reaching orgasm during masturbation
2. I had mild difficulties reaching orgasm during masturbation
3. I clearly had moderate difficulties reaching orgasm during masturbation
4. I had severe or extreme difficulties reaching orgasm during masturbation

If I have difficulties reaching orgasm during masturbation, I experience this as:

1. No or a mild problem
2. A moderate problem
3. A severe or extreme problem

7. Please select which one of the following options best reflects your experience over the past 3 months (please select only one option).

0. Vaginal penetration (= insertion of penis, finger or dildo into the vagina) was possible and not painful ➔ end of the questionnaire
1. Vaginal penetration was possible, but painful ➔ go to question 7a.
2. Vaginal penetration (with my current partner) was possible in the past, but not anymore ➔ end of the questionnaire
3. Vaginal penetration (with my current partner) has never succeeded

➔ end of the questionnaire

7a. During the past 3 months, did you have pain before, during, or after (attempting) vaginal penetration?

0. I had no pain before, during or after (attempted vaginal) penetration
1. I had mild pain before, during or after (attempting) vaginal penetration
2. I had moderate pain before, during or after (attempting) vaginal penetration
3. I had severe or extreme pain before, during or after (attempting) vaginal penetration

If I have pain before, during or after vaginal penetration, I experience this as:

1. Not a problem
2. A mild problem
3. A moderate problem
4. A severe or extreme problem

If I have pain before, during or after vaginal penetration, my partner experiences this as:

1. Not a problem
2. A mild problem
3. A moderate problem

4. A severe or extreme problem

If I have pain before, during or after vaginal penetration, I experience this in my relationship as:

1. Not a problem
2. A mild problem
3. A moderate problem
4. A severe or extreme problem

Thank you very much for completing this questionnaire !!

APPENDIX X: EQ-5D-3L Health questionnaire

Health Questionnaire

English version for the UK

(Validated for Ireland)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain / Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety / Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

2

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today