Protocol Title

Assessment of **women's** sexual quality of life after benign adnexal surgery using vNOTES approach in comparison to conventional laparoscopy: a randomized controlled trial

Study Type:	Other Clinical Trial according to ClinO, Chapter 4
Risk Categorisation:	A
Study Registration:	Intended to be statement of study registration: ClinicalTrials.gov Registration number from the FOPH portal SNCTP (Swiss National Clinical Trial Portal): CCER 2022-00407
Sponsor:	Dr. Jean Dubuisson, MD Hôpitaux Universitaires de Genève Service de gynécologie Unité de Chirurgie Gynécologique Bd de la Cluse 30, 1205 Genève Jean.Dubuisson@hcuge.ch +41 (0)79 55 35 018
Principal Investigator:	Same as Sponsor
Investigated Intervention:	Benign adnexal surgery using vNOTES approach in comparison to conventional abdominal laparoscopy.
Protocol ID:	Study vNOTES CCER n°2022-00407
Version and Date:	Version 8.3 (dated 24.07.2022)

PROTOCOL SIGNATURE FORM

Study Title	Assessment of women's sexual quality of life after benign adnexal surgery using vNOTES approach in comparison to conventional laparoscopy: a randomized controlled trial.
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The Sponsor-Investigator has approved the protocol version 8.3 (dated 24/07/2022) and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines as well as the local legally applicable requirements.

Sponsor- Principal Investigator:

Name: *Dr Jean Dubuisson*

Date: 21/07/22.

Signature:

Dr Jean Dubuisson
Médecin adjoint agrégé
Unité de chirurgie
gynécologique - HUG

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GLOSSARY OF ABBREVATIONS

AE	Adverse Event
ASR	Annual Safet Repot
BASEC	Business Administration S stem for Ethical Committees
CAL	Conventional Abdominal Laparoscop
ClinO	Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)
CRF	Case Report Form
CTCAE	Common Terminolog Criteria for Adverse Events
eCRF	electronic Case Report Form
FADP	Federal Act on Data Protection (in German: DSG, in French: LPD, in Italian: LPD)
FOPH	Federal Office of Public Health
GCP	Good Clinical Practice
HRA	Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)
ICH	International Conference on Harmonisation
POD	Pouch Of Douglas
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
vNOTES	Transvaginal Natural Orifice Transluminal Endoscopic Surger

1 STUDY SYNOPSIS

Sponsor-Investigator	Dr. Jean Dubuisson, MD Hôpitaux Universitaires de Genève Service de gynécologie Unité de Chirurgie Gynécologique Bd de la Cluse 30, 1205 Genève Jean.Dubuisson@hcuge.ch +41 (0)79 55 35 018
Study Title	Assessment of women's sexual quality of life after benign adnexal surgery using vNOTES approach in comparison to conventional laparoscopy: a randomized controlled trial.
Short Title / Study ID	Study vNOTES CCER n°2022-00407
Protocol Version and Date	Version 8.3 (dated 24/07/2022)
Study Registration	Intended to be statement of study registration: ClinicalTrials.gov
Study Category and Rationale	A, used in accordance with the prescribing information.
Background and Rationale	Transvaginal Natural Orifice Transluminal Endoscopic Surgery (vNOTES), a recent innovation in minimally invasive surgery, has already demonstrated its potential superiority to conventional abdominal laparoscopy (CAL) for hysterectomy in terms of effectiveness and safety and its absence of impairment on women's sexuality. However, we note a lack of medical literature and no specific randomized controlled trial (RCT) assessing women's sexual function after vNOTES for benign adnexal surgery.
Risk / Benefit Assessment	Risk: any. Both surgical techniques are used in routine and have proven their effectiveness and safety for benign adnexal surgery. Benefit: by contributing to the general and sexual well-being research and by aiming to promote a more effective and safer surgical technique.
Objective(s)	Primary objective: confirm non-inferiority of vNOTES on women's sexual function. Secondary objective: confirm vNOTES technique's equivalency in terms of efficiency, morbidity and complications compared to CAL.
Endpoint(s)	Primary outcome: women's quality of sexual life evaluation after benign adnexal surgery by vNOTES compared to CAL using FSFI, CSI-16 questionnaires and a self-reported questionnaire on dyspareunia. Secondary outcomes: compare vNOTES with CAL in terms of effectiveness (operation duration and length of stay, need to specimen morcellation for extraction), recovery (postoperative pain and pain medication consumption) and complications up to 30 days postoperative (rate of entry failure, complications during laparoscopic entry, vaginal or parietal complications, re-hospitalization and reoperation).
Study Design	Open label; randomized (1:1 ratio); active control; parallel groups.
Statistical Considerations	Analyses will be carried out according to the intention-to-treat principle. Sensitivity analyses will be conducted to verify whether the exclusion of participants who no longer conform to the protocol may alter the study's final results. Sample size was calculated considering truly no difference in the preoperative and postoperative FSFI score between women treated with laparoscopy and with the vNOTES approach. 80% sure that the lower limit of a one-sided 95% confidence interval will be above the non-inferiority limit of -2, with a significance level of 5%. Standard deviation of the outcome equal to 3.

Inclusion- / Exclusion Criteria	Inclusion criteria: Women aged from 18 to 70 years; Discernment capacity with oral and written consent signed; Heterosexual intercourse (with vaginal penetration) within four weeks prior to inclusion in the study. Exclusion criteria: History of rectal surgery; Suspected rectovaginal/retrocervical endometriosis; History of brachytherapy or pelvic radiation; Suspected ovarian malignancy; History of severe pelvic inflammatory disease; Active lower genital tract infection; Pregnancy; Women who do not speak fluent French or English (language of surveys); Patients under tutelage.
Number of Participants with Rationale	Total of participants: 62. 31 participants per treatment group.
Study Intervention	Benign adnexal surgery using transvaginal Natural Orifice Transluminal Endoscopic Surgery
Control Intervention	Benign adnexal surgery using Conventional Abdominal Laparoscopy.
Study procedures	Women aged 18–70 years with a benign adnexal surgery planed (elective cystectomy/oophorectomy for presumed benign adnexal pathology, elective salpingectomy or tubal sterilization) at Geneva University Hospitals will be eligible and randomized to one of the two intervention groups. Participants will complete the FSFI, the CSI-16 and a self-reported questionnaire on dyspareunia within 4 weeks prior to randomization and at 3 + 6 months after surgery. General and clinical data will be collected when the patient is enrolled in the study, during hospitalization and at 1 month postoperative to assess secondary outcomes.
Study Duration and Schedule	Pilot phase: 6 months Total estimated duration: 2 years First-Participant-In: 10.2022 Last-Participant-Out: 04.2023 (pilot phase) / 10.2024
Investigator(s)	Doctorate- Co-Investigator: Med. Pract. Eloïse Krull Université de Genève, Faculté de Médecine eloise.krull@bluewin.ch Co-Investigator: Dr. Shahzia Lambat Emery Hôpitaux universitaires de Genève Services de gynécologie et obstétrique Shahzia.LambatEmery@hcuge.ch Statistician: Dr. Manuela Viviano Hôpitaux universitaires de Genève Services de gynécologie et obstétrique Manuela.Viviano@hcuge.ch Co-Investigator: Dr. Leen Aerts Hôpitaux universitaires de Genève Service de gynécologie Leen.Aerts@hcuge.ch Co-Investigator: Prof. Patrick Petignat Hôpitaux universitaires de Genève Service de gynécologie Patrick.Petignat@hcuge.ch Research nurse : not yet known

Study Centre(s)	Hôpitaux Universitaires de Genève Service de gynécologie 30 Bd de la Cluse 1211 Genève
Data privacy	Access to data by authorised persons only; Anonymization by using study numbers; Documents locked in a secure place; Care maps for traceability; Use of secure generated computer program and online research platform; Use of opaque envelope.
Ethical consideration	Contribution to clinical research; Improvement of women's quality of life; Safety of care; Valid clinical and scientific results; Favourable Risk-Benefit ratio; Fair study; Voluntary consent; Respect for participants.
GCP Statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA as well as other locally relevant legal and regulatory requirements.

2 BACKGROUND AND RATIONALE

By the end of the twentieth century, conventional abdominal laparoscopy (CAL) has become the gold standard and the technique of choice for minimally invasive surgery in many gynaecological indications, especially to treat benign adnexal pathologies. Nevertheless, surgical techniques are constantly evolving with the aim of being ever less invasive and improving surgical efficiency. NOTES (Natural Orifice Transluminal Endoscopic Surgery) is the latest evolution in minimally invasive surgery. This surgical technique uses natural orifices of the human body for surgical approach (for instance oropharynx, rectum or vagina).

vNOTES is a surgical technique in full expansion in Switzerland. Its use requires specific and additional training compared to CAL. This explains why vNOTES is currently only used in certain centres and more widely in university hospitals.

Vagina as a surgical route has a long medical history. It has been described and spread since the 19th century for hysterectomy (1). Today vaginal route is recommended by international societies as the approach of choice for hysterectomy when feasible (2). As demonstrated by two medical literature reviews of randomized trials comparing surgical approaches to hysterectomy for benign pathology, vaginal hysterectomy has proven its superiority and should be preferred to abdominal open hysterectomy for its lower rate of pain and complications, its shorter procedure duration and its shorter recovery time (3,4).

The first randomized clinical trial available in the medical literature compares transvaginal NOTES (vNOTES) and CAL hysterectomy for a benign pathology (5). Not only does this study prove that vNOTES is not inferior to CAL in achieving a successful hysterectomy, without the need for conversion, but it also proves that vNOTES is superior to CAL with a shorter procedure duration and length of stay, a lower pain Visual Analog Scale (VAS), a diminished use of pain medication the week following surgery and a lower rate of postoperative complications.

Although vNOTES for adnexal surgery is also considered effective in the medical literature (shorter procedure and length of stay, lower rate of conversion to CAL) and safe (lower rate of postoperative complications) (6–12), there is little evidence available. Up to now, there is only one recent randomized controlled clinical trial comparing the effectiveness and safety of vNOTES technique to CAL for benign adnexal surgery in the medical literature (13). This NOTABLE trial demonstrates non-inferiority of vNOTES approach in terms of effectiveness (success of the allocated intervention without the need for conversion to another technique). It also demonstrates shorter procedure time, lower pain VAS and diminished use of pain medication during the first postoperative week with the vNOTES approach. However, the study shows a trend for more adverse effects with vNOTES approach (one case of intraperitoneal spilling, four cases of postoperative bleeding) but no statistically significance between the two approaches for intraoperative and postoperative complications.

vNOTES adnexal surgery is particularity attractive to women (14,15) because it does not involve any parietal scarring and thus represents a reduced risk of parietal complications. These complications include trocar-site hematoma (mainly due to injury of the lower epigastric vessels), trocar-site infection, trocar-site neuralgia (due to iliohypogastric or iliolinguinal nerves injury during fascial closure of the trocar incisions), trocar-site dehiscence, trocar-site hernia, leading to re-hospitalization and re-operation (14–17). Intraoperatively, the laparoscopic entry and the creation of the pneumoperitoneum during CAL can lead to vessel or bowel injuries as well as failure to enter the peritoneal cavity, particularly in case of severe intraabdominal adhesions. The transvaginal approach bypasses these intraabdominal adhesions by using a direct route and thus represents less risk.

vNOTES for adnexal pathology seems to be a promising technique but the consequences of a transvaginal approach, including a vaginal scar, on women's sexual quality of life are not well established yet.
Studies looking at women's perceptions towards vNOTES showed that young nulliparous women, although more concerned than older women about vNOTES's cosmetic benefits, were less likely to accept it because they feared for their future sexual function (including dyspareunia) and fertility (14,15,18). Bucher et al. detailed patients fears and showed that 76% of their participants had concerns regarding postoperative intercourse abstinence after vNOTES, including: feeling less attractive (40%), less feminine (40%), tension with their intimate (35%), lover non-acceptation (20%), possible abortion of new relationship (26%) and feeling less comfortable socially (16%).

Assessment of women's sexual function before and after vNOTES has already been studied for non-gynaecological surgical procedures (cholecystectomy, anterior gastrointestinal resection, appendectomy, bariatric surgery, adrenalectomy and nephrectomy with or without renal transplantation). Although a 2016 review of the medical literature (19) concluded that there was no risk of sexual dysfunction after vNOTES gynaecological surgeries, we note a lack of data assessing women's sexual function.

Therefore, we propose a randomized controlled trial comparing vNOTES with CAL for benign adnexal surgery (risk category: A, used in accordance with indication). The primary objective of this study is to confirm non-inferiority of vNOTES on women's sexual function. The secondary objective is to compare vNOTES with CAL in terms of effectiveness (operation duration and length of stay, need to specimen morcellation for extraction), recovery (postoperative pain and pain medication consumption) and complications (rate of entry failure, complications during laparoscopic entry, vaginal or parietal complications, re-hospitalization and reoperation).

By proving the absence of statistically significant alteration of the vNOTES technique on women's sexual quality of life compared to CAL, associated with the confirmation of this technique's equivalency in terms of its efficiency, we hope to increase the acceptance of the vNOTES technique for benign adnexal surgery in the female general population and more specifically in the younger women, who are presently more reticent to this technique.

3 STUDY OBJECTIVES AND DESIGN

3.1 Hypothesis and primary objective

The primary objective of this study is women's quality of sexual life evaluation after benign adnexal surgery (cystectomy, oophorectomy, tubal sterilization, salpingectomy) by vNOTES compared to CAL using FSFI, CSI-16 questionnaires and a self-reported questionnaire on dyspareunia.

Based on the data available, our hypothesis is that vNOTES does not alter women's sexual function after benign adnexal surgery, with similar outcomes to CAL.

The secondary objective of this study is to confirm the vNOTES technique's equivalency in terms of efficiency, morbidity and complications compared to CAL.

3.2 Primary and secondary endpoints

Primary outcome:

Sexual function is a complex and multidimensional issue. It interacts closely with emotional well-being, quality of life, relationship with partner and health status (20). In order to evaluate sexual quality of life of patients after benign adnexal surgery, it is important to consider these close links. In our study, emotional well-being is assessed asking the presence of any anxiety or depressive disorder during the medical preoperative consultation. No specific questionnaire to identify the anxiety-depressive state is added in order to avoid overloading patients with questions. Information about the patient's health status will also be collected during the preoperative medical consultation. The FSFI questionnaire precisely assesses each domain of sexuality and includes questions about the intimate relationship with the partner. CSI-16 asks questions related more generally to the love relationship with the partner. We added a self-developed questionnaire on dyspareunia. The presence of superficial and/or deep dyspareunia will be assessed together with pain intensity.

FSFI

The FSFI questionnaire, created in 2000 by Raymond Rosen, is a reliable and complete multidimensional self-reported instrument for the measurement of female sexual function. It is validated in English and assesses 19 items divided into six domains of sexual function: (a) desire (2 items), (b) subjective arousal (4 items), (c) lubrication (4 items), (d) orgasm (3 items), (e) satisfaction (3 items) and (f) pain/discomfort (3 items). Each item focuses on the situation during the last 4 weeks. FSFI is a good instrument as it addresses both cognitive and functional dimensions of sexual function (21). Moreover, it is available in a validated French version (22).
The total score is the sum of answers provided for each of the 6 domains. The scores for items 1, 2, 15 and 16 range from 1 to 5 while the others range from 0 to 5. Lower is the score, worse is the patient's sexual function. A total score below 26 defines impaired sexual function (23).

CSI-16

The Couple Satisfaction Index (CSI) is a precise, consistent and validated scale that evaluates the quality of a couple's relationship satisfaction (24). A longer version (CSI-32) and a shorter version exist (CSI-4). We chose the 16-items version because it provides enough information for the assessment of relationship satisfaction (24) and reduces the number of questions to be answered, a significant aspect in our study, which includes several questionnaires for a multidimensional assessment. Limitation of this questionnaire is the insufficient evidence of good reliability over short periods of time (25). Each item is scored from 0 to 5 with different answer formats. The total score can range from 0 to 81. Higher is the total score, better is the relationship satisfaction. A relationship dissatisfaction is suggested when the total score is bellow 51,5 (25).

The French available version of CSI-16 has unfortunately not been translated and validated by the developers.

Primar Outcome: Sexual Function

The primary outcome regarding the absence of impairment on sexual function, after elective benign adnexal surgery by vNOTES in comparison with CAL, refers to the stability or improvement of FSFI total scores in each group at 3 and 6 months after surgery compared with the preoperative score and the absence of a statistically significant difference in FSFI total postoperative scores between the two groups.

The results of preoperative CSI-16 and self-reported questionnaire on dyspareunia provide an indication of the patient's baseline status. Results and evolution of these questionnaires scores at 3 and 6 months postoperatively allow us to specify, in the case of a de novo postoperative sexual dysfunction, whether it is solely related to the surgical technique used, in which case CSI-16 and self-reported questionnaire on superficial dyspareunia scores are the same as baseline values or below the diagnostic cut-off point, or whether it is associated with a relationship issue or superficial dyspareunia, in which case such scores are statistically increased in comparison with baseline values.

Secondary outcomes:

Comparison on effectiveness, morbidity, complications rate

Evaluation of the success rate (removal of the specimen without the need of conversion to laparoscopy or open-surgery), the procedure duration including the need for adhesiolysis, recovery (length of stay, pain scores) and perioperative complications up to 30 days postoperatively:

- Intraoperative complications: failure to enter the peritoneal cavity, need for conversion, intraoperative complication during peritoneal cavity access, intraoperative blood loss, bowel or vessel injury.
- Postoperative complications: delayed vaginal or parietal healing (abscess, hematoma, dehiscence), trocar-site hernia, trocar-site nerve injury, re-hospitalization and re-operation.

Morcellation/aspiration and histological analysis

Although our study focuses on presumed benign adnexal masses, the risk of unexpected malignancy needs to be taken into consideration during the specimen extraction in order to avoid any tumoral cell spillage. Only postoperative histological analysis can determine the definitive diagnosis. The Swiss Society of Gynaecology and Obstetrics practice guide for the discovery of an adnexal mass recommends that a suspicious diagnosis of a mass should be established on the basis of the information provided by clinical and paraclinical examinations, including mass size and ultrasound morphological criteria (26). This type of information allows scoring and facilitates the distinction between benignity and malignancy and thus the subsequent management (26).

Morcellation or aspiration of an adnexal mass is not recommended (26). However, it is performed in case of a large mass to provide its extraction during CAL in order to limit the cosmetic sequelae and possible parietal consequences of enlarging the incision. If morcellation or aspiration is required, it is done in an endoscopic bag in order to limit cell spillage.

To the best of our knowledge, there is no data in the literature investigating the relationship between adnexal mass morcellation/aspiration and histological analysis quality of the surgical specimen. In fact, histological analysis is always possible even on a fragmented specimen. However, the ability to obtain an accurate malignancy diagnosis seems to be compromised since TNM Classification of malignant tumors requires macroscopic information such as ovary's surface invasion for instance.

We believe that the elastic vaginal incision offered by vNOTES reduces the need for operative morcellation or aspiration during the specimen extraction in comparison with transparietal removal.

3.3 Study design

This is a single-centre, parallel-group, unblinded, balanced randomization study (1:1 matching for vNOTES and CAL) conducted in the Department of Paediatrics, Gynaecology and Obstetrics at the Geneva University Hospitals, Switzerland. We will be using a non-inferiority study design to address primary outcome of vNOTES versus CAL for elective benign adnexal surgery.

Methods of minimising bias include: randomisation and use of validated questionnaires.

3.4. Study intervention

Intervention description: vNOTES interventional group

First common steps:
General anaesthesia, prophylactic antibiotic, 0° Trendelenburg position. Bladder catheterization. The bladder is catheterized during the whole procedure.

1. **Clinical examination**
   A pelvic examination is performed to confirm the absence of nodularity infiltrating the rectouterine (RU) pouch, to assess the mobility of the uterus.
   Vaginal retractors help to well expose the operative field.

2. **Vaginal infiltration**
   Vaginal mucosa in the posterior fornix is infiltrated with diluted adrenaline solution according to patient comorbidities.

3. **Posterior colpotomy**
   A cold scalpel is used for the colpotomy.
   A 2.5 – 3 cm «smile-like» incision is performed, 2cm away from the cervix.
   Dissection is then performed with scissors, pushing away dorsally the rectal fibres until seeing the pouch of Douglas (POD) by transparency.
   Peritoneal incision is performed to access to the entire POD, stretching the opened peritoneum.

4. **Insertion of the Alexis wound retractor**
   The Alexis retractor-protector is inserted into the created spaces by squeezing the inner ring.
   The tenaculum is removed.

   The outer ring of the Alexis is then rolled up

5. **Attachment of the GelPoint cap**
   The GelPOINT access platform is connected to the Alexis retractor.
   A 7cm vNOTES port is chosen.
   The GelPOINT has 3 port access: 1 for the endoscope and two for the accessory trocars.
   Concerning the trocar placement, the optic trocar is placed at 6 o'clock and 2 accessory trocars at 10 and 2 o'clock.

6. **CO2 insufflation**
   A pneumoperitoneum is created with CO2 insufflation as in conventional abdominal laparoscopic surgery. Low intraabdominal pressures are used (10-12 mmHg).
7. **Endoscopic part of the vNOTES procedure:**
   The patient is then put in a 20° Trendelenburg position.
   A 0° or 30° 10mm endoscope is inserted with standard laparoscopic instruments.
   The entire abdominal cavity is inspected.

Peritoneal washing is performed at this time.
The specific procedures include the same steps as during CAL.

An endoscopic bag is inserted to remove the specimen.

Common final steps:
the vNOTES GelPoint platform and the Alexis retractor are removed
The posterior colpotomy, including vaginal mucosa and peritoneum, is closed using a running absorbable suture.

No packing, no Foley catheter is needed in the postoperative period, following the principles of FAST TRACK surgery

Intervention description: CAL control group

First common steps:
General anaesthesia, prophylactic antibiotic, 0° Trendelenburg position. Bladder catheterization. The bladder is catheterized during the whole procedure.
Clinical examination.

1. Laparoscopic entry using a Veres needle, either at the Palmer point or in the umbilicus.
2. 3 or 4 trocars are inserted with a high pressure pneumoperitoneum (20 mmHg). In a second step the pressure is decreased to 12 mmHg after the trocar placement. A 0° 5mm or 10mm endoscope is used.
3. 20 to 25° Trendelenburg position.
4. Inspection of the entire abdominal cavity
5. Peritoneal washing. Identify the ureters. Inspect the entire abdominal cavity (liver, stomach, peritoneum).

The specific procedures include the same steps as during vNOTES.

An endoscopic bag is inserted for the removal of the specimen.
Most of time, the parietal incision of the left accessory trocar is enlarged to remove the specimen. Depending on its size and its components, using in-bag cold morcellation and/or intracystic liquid aspiration may be necessary.

The Foley catheter is removed at the end of the surgery.

4 STUDY POPULATION AND STUDY PROCEDURES

4.1 Inclusion and exclusion criteria, justification of study population

All women aged from 18 to 70 years regardless of parity in whom a benign adnexal surgery (elective cystectomy/oophorectomy for presumed benign adnexal pathology, elective salpingectomy or tubal sterilization) is planned in the division of Gynaecology of the Geneva University Hospitals will be proposed this study, if they do not meet exclusion criteria.

The study needs a total number of participants of 62 (31 in each group) to achieve sufficient power.

Inclusion criteria are the following:

1. Women aged from 18 to 70 years.
2. Discernment capacity with oral and written consent signed.
3. Heterosexual intercourse (with vaginal penetration) within four weeks prior to inclusion in the study.

Exclusion criteria are the following:

- History of rectal surgery
- Suspected rectovaginal/retrocervical endometriosis
- History of brachytherapy or pelvic radiation
- Suspected ovarian malignancy
- History of severe pelvic inflammatory disease
- Active lower genital tract infection
- Pregnancy
- Women who do not speak fluent French or English
- Patients under tutelage

Patients under tutelage, with or without capacity of judgement, will be excluded from the study because of assessment modalities including the intrusive nature of the questionnaires.

4.2 Recruitment, screening and informed consent procedure

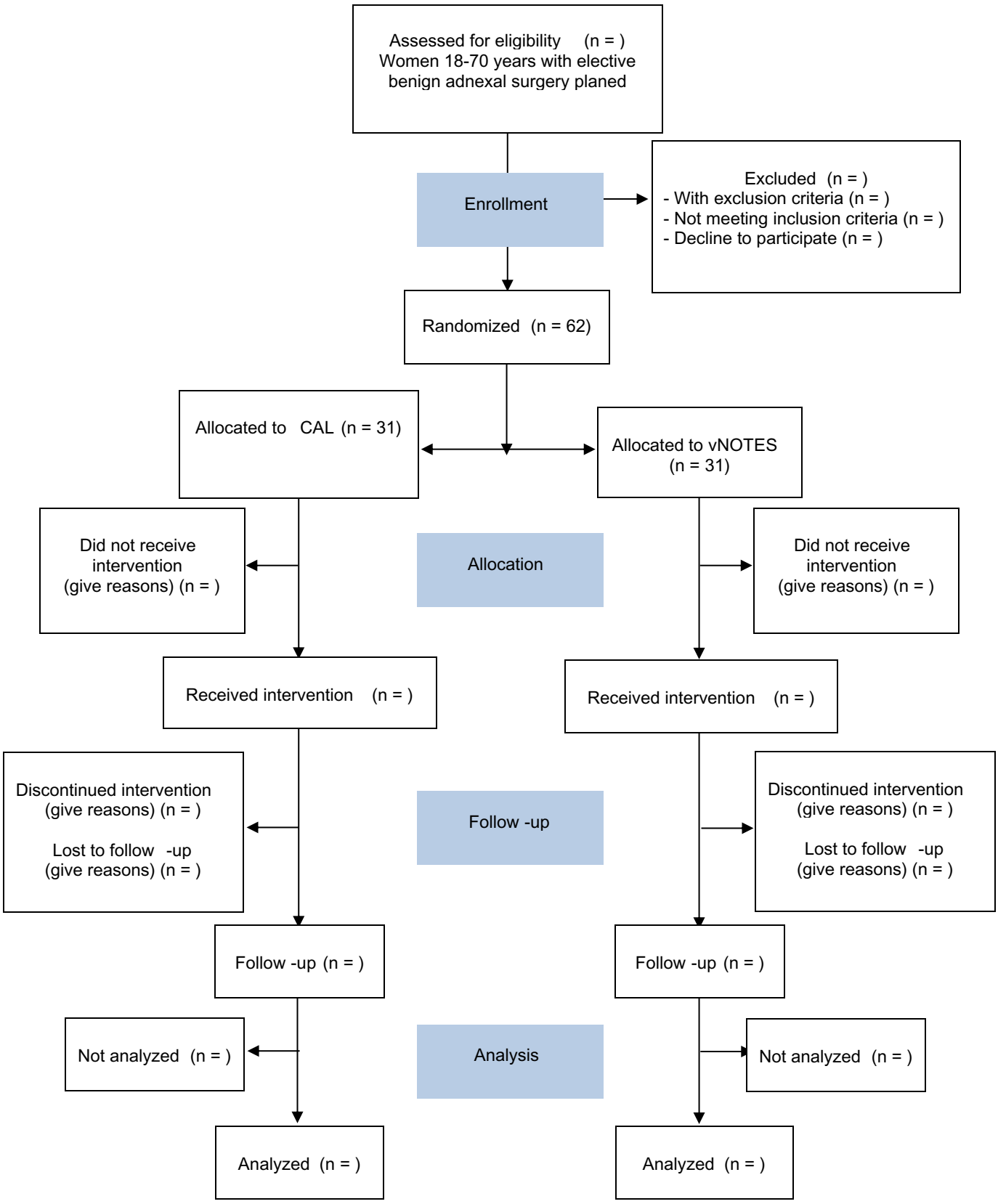
The surgeon will give eligible patients who agree to participate all the information specific to the two surgery approaches in order to have the surgical consent form signed in a free and informed manner during the medical preoperative consultation.

Right after the medical preoperative consultation, the research nurse will give to those patients all the information (nature, purpose, procedures, expected duration, potential risks and benefits and any discomfort it may entail) about the study to get the information sheet and consent form describing the study signed in a free and informed manner. Each patient is informed that the participation is voluntary and that she may withdraw from the study at any time and that withdrawal of consent will not affect her subsequent medical assistance and treatment. The patient is also informed that authorised individuals other than their treating physician may examine their medical records. The patient is informed that she can ask any question, and consult with family members, friends, their treating physicians or other experts before deciding about their participation in the study. Enough time is given to the subjects. A subsequent consultation appointment with the research nurse can be arranged few days to one week later if necessary.

If the patient agrees to participate in the study, a copy of the consent form signed by the patient, the surgeon and/or the research nurse will be given to the patient and the original will be kept as part of the survey records. The informed consent process will be documented in the patient file and any discrepancy to the process described in the protocol will be explained.

The formal consent of a participant, using the approved consent form, will be obtained before the participant is submitted to any study procedure.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) 2010 flowchart



4.3 Study procedures

If the patient accepts to participate in the study, the surgeon will get the surgery informed consent form signed and collect clinical and demographic information on the medical-logbook during the preoperative medical consultation. Right after, the research nurse will complete general information and will get the study informed consent form signed.

The FSFI and CSI-16 questionnaires will be provided in French or English depending on the patient's preference and self-completed by the patient within 4 weeks prior to randomization and 3 + 6 months postoperatively on a secure online platform. If patients do not respond on time, the online response platform will send them up to three reminders.

Patients with pre-existing sexual dysfunction can be included in the study. The type of sexual dysfunction must be documented and the evolution of sexual function can still be assessed by comparing preoperative and postoperative questionnaires scores.

The diagnosis of rectovaginal or retrocervical endometriosis is strong anatomical exclusion criteria for vNOTES approach.

We have deliberately not given a latency postoperative period before resuming sexual activity to avoid biasing women according to the surgical technique used. We trust that they will resume sexual activity based on the sensations of their body. We do not fear more vaginal infectious complications or vaginal cuff dehiscence when resuming sexual activity early after using the vNOTES approach.

Instruments:

1) Care maps will be used as a step-by-step procedure for all medical providers (surgeons, residents, anaesthetists, nurses and the research nurse) for each group.
2) A medical-logbook containing general and clinical information will follow the patient at each stage of her medical pathway (preoperative, intraoperative, during hospitalization and at 1 month postoperatively) and will be filled in by each medical provider.
3) All three questionnaires will be self-completed by the patient within 4 weeks prior to randomization and at 3 + 6 months postoperative on a secure online platform. A satisfaction enquiry will be self-completed by the patient on the last day of her hospitalization.

General information collected preoperatively are the following:

1) Age
2) BMI
3) Parity/gestity
4) Number of vaginal deliveries
5) Menopausal status (pre-menopause, post-menopause)
6) Marital status (single, in couple)
7) Employment status (employed part-time, employed full-time, unemployed but looking for work, unemployed and not looking for work, self-employed, student)
8) Level of education (high school, college or equivalent, university or other higher studies)
9) Habits (smoking, alcohol, drugs)
10) Infertility: primary or secondary
11) Non-gynaecological comorbidities
12) Gynaecological comorbidities
13) Active follow-up for sexual function disorder: if yes, which type?
14) History of abdominal or pelvic surgery
15) History of pelvic radiation
16) Diagnosis of anxiety-depressive disorder
17) History of sexual abuse
18) Treatments (hormonal, potentially sexual impacting drugs such as antidepressants or antipsychotics)

The research nurse will be trained by the HUG's UIMPV (Interdisciplinary Unit for Medicine and Prevention of Violence) to ask about a history of sexual abuse. In this way, she will be able to receive the information and to refer the patient to the HUG's UIMPV in a more or less urgent manner depending on the situation. If the patient refuses help, the research nurse will give her contact details in case she changes her mind, as well as emergency numbers and places for help in case such a situation occurs again. The research nurse will obviously explain to the patient how this information will be used to interpret the data.

Clinical information collected include:

1) Preoperative:
   a) Clinical examination:
      i) Pain (0-1), intensity (VAS scale 0-10), location of the pain
   b) Paraclinical examination: ultrasound +/- MRI
      i) Uterus: size, morphology (anteverted/ retroverted/ lateralized)
      ii) Ovaries and adnexal mass: size, type (cystic (functional, organic), solid, mix), O-RADS and/or IOTA classification.
      iii) Other findings
   c) Tumoral markers: CA 125, others
   d) Urine pregnancy test

2) Intraoperative:
   a) Surgery:
      i) Type: unilateral cystectomy (1), bilateral cystectomy (2) unilateral oophorectomy (3), bilateral oophorectomy (4), tubal sterilization (5), unilateral salpingectomy (6), bilateral salpingectomy (7)
      ii) Interventional group: vNOTES arm vs CAL arm
      iii) vNOTES intraoperative complications:
         (1) Entry failure
         (2) Need for CAL/open surgery conversion
         (3) Blood loss (ml), localization (vessel injured) need for blood transfusion (number of erythrocyte concentrate (EC))
         (4) Bowel injury
         (5) Other
      iv) CAL intraoperative complications:
         (1) Entry failure
         (2) Need for conversion to open surgery
         (3) Bleeding at trocar site
         (4) Blood loss (ml), localization (vessel injured), need for blood transfusion (number of EC)
         (5) Bowel injury
         (6) Other
      v) Intraabdominal parietal adhesions: yes/no, Need for adhesiolysis: yes/no
      vi) Procedure duration
   b) Surgical specimen extraction method:
      i) Transvaginal / transparietal
      ii) Use of endoscopic bag: yes/no
      iii) Need to enlarge the incision: yes/no, if yes how many millimetres (mm) more?
      iv) Need for morcellation or aspiration: yes/no, if morcellation: number of fragments (1-5; 5-10; >10)

3) <u>During hospital stay</u>:
   a) Postoperative complications during hospital stay: type according to Clavien-Dindo classification
      i) Vaginal hematoma (hematic collection confirmed on ultrasound or CT scan associated with clinical signs (pelvic or vaginal pain)).
      ii) Parietal hematoma (hematic collection confirmed on ultrasound or CT scan associated with clinical signs (pain at the site of the hematoma).
      iii) Vaginal bleeding (ml).
      iv) Intraperitoneal haemorrhage (hematic fluid confirmed on ultrasound or CT scan associated with abdominal pain and or hypotension / tachycardia).
      v) Need for blood transfusion (number of EC)
      vi) Other
   b) Need for an intervention procedure/ reoperation: rate and reason
   c) Length of stay in hours
   d) Postoperative pain:
      i) Mean VAS
      ii) Pain relief: total number and level

4) <u>At 1 month postoperative</u>:
   a) Surgery recommendation to surroundings (reasons)
   b) Pain
      i) Mean VAS
      ii) Location
      iii) Pain relief: level

   c) Complications: type, Clavien-Dindo classification
      i) Delayed vaginal healing
         Secondary to:
         (1) Abscess: a fluid-like collection seen on ultrasound or CT scan with clinical (pain, leucorrhoea, fever) and/or biological (leucocytosis, increased CRP) infectious signs +/- presence of a germ on culture.
         (2) Hematoma: a hematic collection seen on ultrasound or CT scan with clinical signs (pelvic or vaginal pain).

      ii) Delayed parietal healing
         Secondary to:
         (1) Abscess: a fluid-like collection seen on ultrasound or CT scan with clinical (pain at the site of the hematoma, fever) and/or biological (leucocytosis, increased CRP) infectious signs +/- presence of a germ on culture.
         (2) Hematoma: a hematic collection seen on ultrasound or CT scan with clinical signs (parietal pain).

      iii) Trocar-site dehiscence
         (1) Superficial dehiscence limited to the skin and clinically evident.
         (2) Incisional hernia including peritoneal tissue which must be confirmed on ultrasound or CT scan.

      iv) Vaginal scar dehiscence: opening of the vaginal mucosa confirmed at the clinical examination

v) Trocar-site neuralgia: iliohypogastric or iliolinguinal nerves injury during fascial closure of the trocar incisions or introduction of the trocars. It is characterized by a persistent pain at 4 weeks postoperative or appearing after surgery, such as electric discharge/burning or painful cold sensation, respecting the territory of the nerve affected (with irradiation towards the pubis for the iliohypogastric nerve and towards the labia majora with or without presence of dyspareunia for the ilioinguinal nerve) and which may be associated with dysesthesia (tingling, prickling, itchiness, numbing)(27).

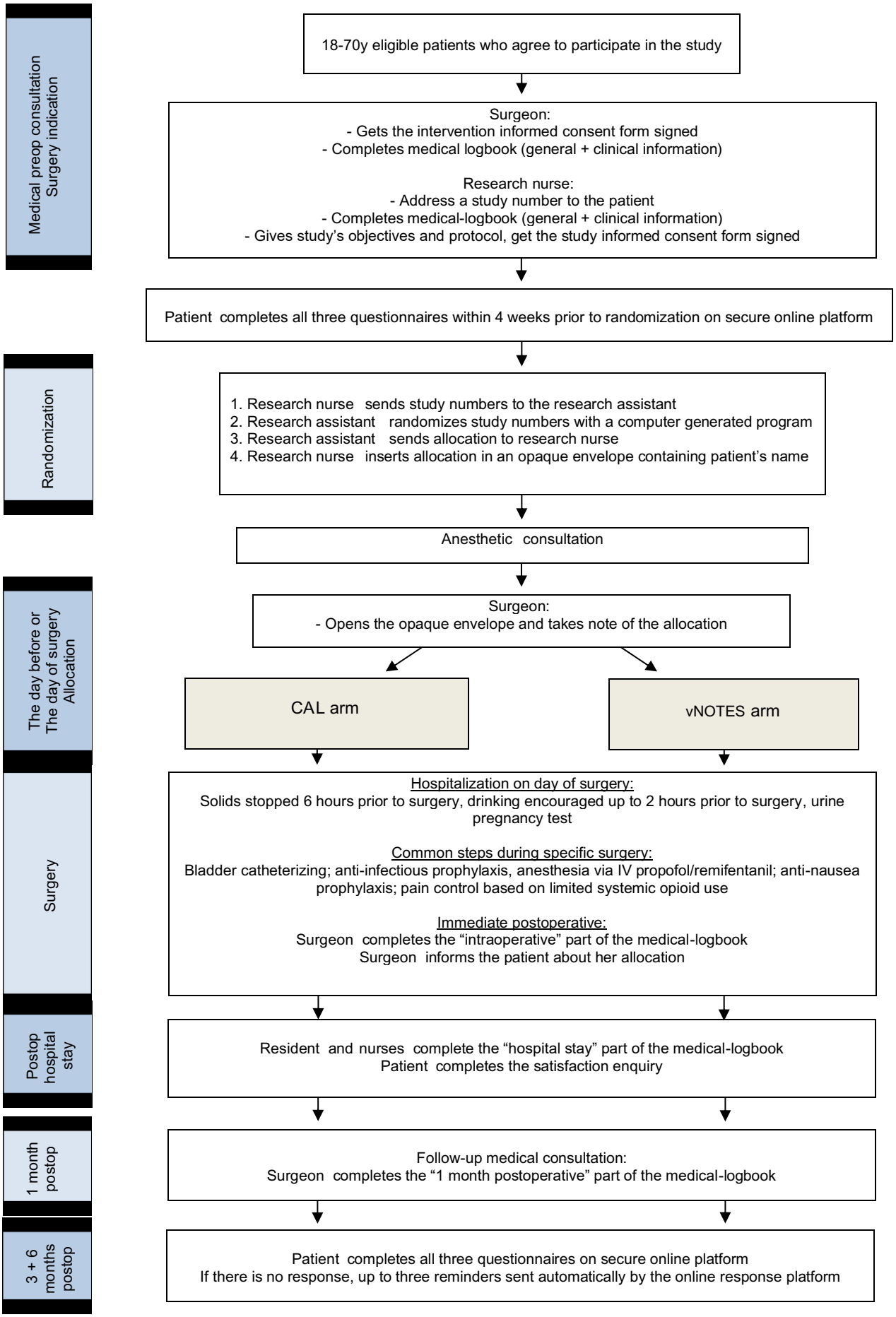
vi) Others

d) Rehospitalisation: rate and reason
e) Need for an interventional procedure/ reoperation: rate and reason

f) Sexuality:
   i) Latency to resume sexual activity (vaginal penetration)
   ii) Frequency of sexual intercourse in the last month (vaginal penetration)

g) Histology: complete/limited, diagnosis

Figure 2. Study protocol; preop = preoperative; postop = postoperative



4.4 Withdrawal and discontinuation

The participant is withdrawn from the study if she requests it, if exclusion criteria are identified during the course of the study, if the disease progresses and requires different medical management. Upon premature patient withdrawal from the study, all patient data collected up until her drop out will be analysed. Data will be kept anonymous. Reasons for patient drop-out will be explained in the final manuscript.

5 STATISTICS AND METHODOLOGY

5.1. Statistical analysis plan and sample si e calculation

Statistician: Dr Manuela Viviano, Hôpitaux Universitaires de Genève, Services de Gynécologie et Obstétrique

Role: Participation in the creation of the study design, creation of the statistical analysis plan, calculation of the sample size, help with analysis of the statistical data.

Sample size

Sample size was calculated considering the mean difference in the preoperative and postoperative FSFI score, and comparing such difference between women treated with abdominal laparoscopy and with the vNOTES approach. If there is truly no difference between abdominal laparoscopy and vNOTES in terms of FSFI score, then a sample size of 56 patients, corresponding to 28 women in each of the two groups, is needed to be 80% sure that the lower limit of a one-sided 95% confidence interval will be above the non-inferiority limit of -2, with a significance level of 5%. We considered a standard deviation of the outcome to be equal to 3. We selected the non-inferiority margin based on previously published literature, according to which a mean difference of FSFI score by as much as 2 was not statistically significant between the abdominal laparoscopic and vaginal approach for hysterectomy (28). Similarly, a study evaluating the FSFI after surgery for endometriosis found a statistically significant difference between the pre-operative score of 19.1 and the post-operative score of 22.7 (29). Sample size was calculated using the online software available at www.sealedenvelope.com.
We expect a drop-out rate of 10% over the study period, which makes it reasonable to increase the total sample size to 62 patients, corresponding to 31 patients per group. Analyses will be carried out according to the intention-to-treat principle. Sensitivity analyses will be conducted to verify whether the exclusion of participants who no longer conform to the protocol may alter the study's final results, so as to show non-inferiority in both the intention-to-treat and the per-protocol populations (30). Reasons of non-conformity may include, among others, the patient's personal decision to drop out of the study after initial inclusion and surgical complications affecting the woman's intra- and post-operative course.

The Department of Paediatrics, Gynaecology and Obstetrics at the Geneva University Hospitals surgically treat an average of 100 benign adnexal surgeries per year. We expect a recruitment rate of 31%. Thus, we believe that our study will take two years to be completed. This recruitment rate may seem high. To test our recruitment rate. We will conduct a 6-month pilot phase. In case the recruitment is lower than expected, the study duration will be extended proportionally to obtain the desired sample size. If recruitment at 6 months is greater than or equal to 16 patients, then the study will continue for a total duration of 2 years.

Randomization

Randomization of included patients will be computer-generated with a 1 to 1 ratio, in randomly alternating blocks of 4, 6 and 8. After having signed the study and intervention informed consent form, patients will be allocated to one of the two treatment arms (vNOTES vs CAL) by means of consecutive, numbered, sealed and opaque envelopes.

Randomization will be performed using an automatically-generated computer program (www.randomization.com).

Sequence design

A research nurse will be responsible of inserting the randomized pairing choice into a sequentially numbered opaque envelope. To avoid the risk of switching the allocation sequence, the participant's name and date of birth will be written on the envelope in addition to the allocated number. To avoid selection bias, the research assistant will not be allowed to see the patient's file and will not be involved in the data collection. The research nurse will place the sealed envelope in the patient's file.

The surgeon will open the opaque envelope and read the patients assignment to one of the two treatment arms on the day before surgery or on the day of surgery and inform the patient about her allocation after the surgery. In case the patient decides to withdraw from the study, it should be documented in the patient's record.

Blinding

This is an unblinded study where neither the surgeon, nor the patient is blinded to treatment arm assignment.

Statistical analysis

As recommended by the Consolidated Standards of Reporting Trials (CONSORT) statement, analysis will be performed in an intention-to-treat principle. Continuous variables will be reported as means with the relative standard deviation (SD). Non-normally distributed continuous variables will be reported as medians with the relative inter-quartile range (IQR). Categorical variables will be reported as absolute numbers and percentages. The Student T-test will be used to compare continuous variables when reported as means, whereas the $\chi 2$ test will be used to compare categorical variables. The alfa value will be set at 5%, with a probability (p) less than 0.05 to be considered as statistically significant.

5.2. Handling of missing data and drop-outs

Patient's data will be analysed until their withdrawal from the study, as in the intention-to-treat principle. Reasons for dropping out from the study will be explained in the study's final manuscript. Sensitivity analyses will be carried out in order to evaluate whether the participants who have dropped out of the study may alter its final results. The handling of drop-outs is further explained in the paragraph "Sample size".

6 REGULATORY ASPECTS AND SAFETY

6.1 Local regulations / Declaration of Helsinki

This study is conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA as well as other locally relevant legal and regulatory requirements.

6.2 (Serious) Adverse Events and notification of safety and protective measures

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation subject which does not necessarily have a causal relationship with the trial procedure. An AE can therefore be any unfavourable or unintended finding, symptom, or disease temporally associated with a trial procedure, whether or not related to it.

A Serious Adverse Event (SAE) (ClinO, Art. 63) is any untoward medical occurrence that

- Results in death or is life-threatening,
- Requires in-patient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity, or
- Causes a congenital anomaly or birth defect

Adverse effects are reported by the operators themselves. Indeed, as with many surgical specialties, the surgeon must be able to identify and manage such complications.

In order to reduce the risk of measurement bias as much as possible, we will include in our database the diagnoses and management of perioperative complications carried out by the gynaecological emergency service at the HUG or at other external hospital centres.

Both Investigator and Sponsor-Investigator make a causality assessment of the event to the trial intervention, (see table below based on the terms given in ICH E2A guidelines). Any event assessed as possibly, probably or definitely related is classified as related to the trial intervention.

Relationship	**Description**
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Both Investigator and Sponsor-Investigator make a severity assessment of the event as mild, moderate or severe. Mild means the complication is tolerable, moderate means it interferes with daily activities and severe means it renders daily activities impossible.

Reporting of SAEs (see ClinO, Art. 63)

All SAEs are documented and reported immediately (within a maximum of 24 hours) to the Sponsor-Investigator of the study.

If it cannot be excluded that the SAE occurring in Switzerland is attributable to the intervention under investigation, the Investigator reports it to the Ethics Committee via BASEC within 15 days.

Follow up of (Serious) Adverse Events

Participants terminating the study with reported ongoing (S)AEs will be followed up in specialized medical consultations respecting the general guidelines of the gynaecology department until resolution or stabilisation.

Notification of safety and protective measures (see ClinO, Art 62, b)

If immediate safety and protective measures have to be taken during the conduct of the study, the investigator notifies the Ethics committee of these measures, and of the circumstances necessitating them, within 7 days.

6.3 (Periodic) safety reporting

An annual safety report (ASR) is submitted once a year to the local Ethics Committee by the Investigator (ClinO, Art. 43 Abs 1).

6.4 Radiation

Not applicable.

6.5 Pregnancy

Not applicable.

6.6 Amendments

Substantial changes to the study setup and study organization, the protocol and relevant study documents are submitted to the Ethics Committee for approval before implementation. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Ethics Committee. Such deviations shall be documented and reported to the Ethics Committee as soon as possible.

Substantial amendments are changes that affect the safety, health, rights and obligations of participants, changes in the protocol that affect study objective(s) or central research topic, changes of study site(s) or of study leader and sponsor (ClinO, Art. 29).

A list of substantial changes is also available on www.swissethics.ch.

A list of all non-substantial amendments will be submitted once a year to the competent EC together with the ASR.

6.7 Notification and reporting upon completion, discontinuation or interruption of the study

Upon regular study completion, the Ethics Committee is notified via BASEC within 90 days (ClinO, Art. 38).

Provide a statement that the Sponsor-Investigator and any other competent authority may terminate the study prematurely according to certain circumstances, e.g.:

- Ethical concerns,
- Insufficient participant recruitment,

- When the safety of the participants is doubtful or at risk (e.g. when the benefit-risk assessment is no longer positive),
- Alterations in accepted clinical practice that make the continuation of the study unwise, or
- Early evidence of harm or benefit of the experimental intervention

Upon premature study termination or study interruption, the Ethics Committee is notified via BASEC within 15 days (ClinO, Art. 38).

A final report is submitted to the Ethics Committee via BASEC within a year after completion or discontinuation of the study, unless a longer period is specified in the protocol (ClinO, Art. 38).

6.8 Insurance

In the event of study-related damage or injuries, the liability of the institution Hôpitaux Universitaires de Genève; Département de la Femme, de L'Enfant et de l'Adolescent; Service de Gynécologie provides compensation, except for claims that arise from misconduct or gross negligence.

7 FURTHER ASPECTS

7.1 Overall ethical considerations

By providing new knowledge, this study contributes to clinical research. Improving the quality of life of women in gynaecological surgery, while ensuring safety of care, is our priority. The rigorous methodology of this study, and the resulting valid clinical and scientific evidence, could lead to a change in recommendations for a better surgical experience for the patient.

By using two types of surgery already used routinely and considered safe and valid for the indication of benign adnexal disease, this study represents potential benefits to society that outweigh the risks involved.

The study is designed to be as fair as possible. The target population for this study is chosen to correspond to the population most commonly affected by benign adnexal disease that may require surgical management. The exclusion criteria for this study correspond mainly to the exclusion criteria for the vNOTES surgical technique. The limitation of this study to the French or English speaking population only, thus excluding a major part of the Geneva foreign population, is explained by the limited availability of the questionnaires in a validated translated version. Indeed, the validity of a randomized controlled trial study depends on the validity of its measurement instruments. The validity of the study also relies on the review of non-affiliated parties.

Participation is voluntary and withdrawal from the study can be made at any time, without justification. The free and informed signature of the consent form, after having received all the necessary information and having benefited from a period of reflection if needed, is mandatory.

Respect for the participant is a key point of the study and this is reflected in the respect for privacy, attention to the participant's well-being and absence of judgment.

7.2 Risk-benefit assessment

This study does not present any risk for patients who will undergo elective adnexal surgery for benign pathology by CAL or by vNOTES. Both surgical techniques are used in routine and have proven their effectiveness and safety for benign adnexal surgery. The objectives of this study are in accordance with the principle of beneficence for the patients by contributing to their general and sexual well-being and by aiming to promote a more effective and safer surgical technique.

As the study progresses, patients will be informed of new findings, which may influence their decision to participate or not. A patient who presents more risks than benefits from such a randomized allocation will be withdrawn from the study for safety reasons. Adverse effects will be managed by following the standard protocols of the Geneva University Hospitals. In the event that significant side effects are observed and attributed to the study, the study will be stopped. The results will be shared with the patients at the end of the study.

8 QUALITY CONTROL AND DATA PROTECTION

8.1 Quality measures

Measures taken for quality assurance and quality control: double data entry, study personnel trained on all important study related aspects, planned quality visits, data management from a specialized team.

For quality assurance the sponsor, the Ethics Committee or an independent trial monitor may visit the research sites. Direct access to the source data and all study related files is granted on such occasions. All involved parties keep the participant data strictly confidential.

8.2 Data recording and source data

Clinical data management will be carried out with the help of the Geneva University Hospitals Clinical Research Centre (CRC) in accordance with all laws and regulations relating to Good Clinical Trial Practice. We have chosen the REDCap® platform as our data collection (CRF) and online questionnaire response platform. It is a platform that provides secure and anonymous data collection, analysis and storage. Patients will receive an invitation to complete the questionnaires by email or SMS. They will register to the online questionnaire platform using their study number. The platform will automatically send them up to 3 reminders if they do not respond in time.

The source data used in the study are listed under the following headings above: general and clinical information which will be found in the patient's file (personal information, medical history, laboratory and radiological results) and transferred to the patient's CRF. More detailed clinical information designed specifically for the study will be collected directly from the CRFs. The same applies to the response to the questionnaires.

8.3 Confidentiality and coding

Trial and participant data will be handled with uttermost discretion and is only accessible to authorised personnel who require the data to fulfil their duties within the scope of the study. On the CRFs and other study specific documents, participants are only identified by a unique participant number.

To ensure patient confidentiality, all patient data will be anonymized. Patients included in the study will immediately receive a study number on a first-come, first-served basis, which will follow them on all study documents (care maps and logbooks) according to the "main courante" principle. For instance, the third participant included in the study will be known under patient 3 and she will keep this number throughout the study, regardless of the allocation.

Only the investigators and the research nurse will have access to patient's names assigned to the study numbers. All study documents will be locked in the Gynaecology division of the Geneva University Hospitals. The person responsible for data analysis (statistician) will only have access to the study numbers and data will be collected in a computerized file. Care maps will be used as a step-by-step procedure for all medical providers but also to ensure traceability.

Study numbers will be randomized to one of the two interventional arms using an automatically-generated computer program. The allocation of the study number to the intervention arm will be inserted in an opaque envelope and place in the patient's file by the research nurse. This envelope will also include the patient's name to avoid the risk of exchange.

The surgeon will open the envelope on the day before or on the day of surgery and informs the patient about her allocation after the surgery.

Access to the Geneva University Hospital's computerised medical file is limited to persons authorised by an identifier and a password. The history of the individuals who opened the file is recorded. The same applies to access to the online research platform REDCap®.

Only non-genetic data are used.

8.4 Retention and destruction of study data

All study data are archived in Geneva University Hospitals for 10 years after study termination or premature termination of the study.

9 MONITORING AND REGISTRATION

The Sponsor-Principal Investigator is fulfilling the monitoring duties. The monitoring visits will take place on site, in the gynaecology department of the Geneva University Hospital. The visits will involve the Sponsor-Principal investigator, the research nurse and the principal co-investigators. The monitor must ensure that the clinical study is being conducted in accordance with the protocol and that data are being collected and processed correctly. The monitor will also ensure that the study is conducted in accordance with standard operating procedures, good clinical practice and the legislative and regulatory provisions in force. The monitoring will include the 4 key stages: pre-visit, study initiation visit, intermediate visits (per semester), closing visit.

As the monitor is the principal investigator, he has access to all the data of the study and can communicate with his working team through a professional email address.

The study is intended to be registered on ClinicalTrials.gov (database of privately and publicly funded clinical studies conducted around the world). The study is already registered on SNCTP vis BASEC.

10. FUNDING / PUBLICATION / DECLARATION OF INTEREST

Funds were allocated as follows:

- A research nurse at 20% for 6 months (pilot phase), statistical analysis, data management through Geneva University Hospitals Clinical Research Centre, and spell checking will be covered by the medical direction, Geneva University Hospitals (Public, 50'000 CHF, 83,3%).
- Computing resources, office equipment, premises, request to the ethics committee and publication costs will be covered by the Geneva University Hospitals (Public, 10’000CHF, 16,7%).

A request for additional funds will be applied to continue the study after the pilot phase.

The members of the study intend to publish the study protocol, as well as the study results, once obtained. Each investigator and co-investigator, including the statistician, will be included in the list of authors. This study is also part of a MD thesis under the direction of the Principal-Investigator and will be presented to a jury for validation. In any case, no personal data identifying any of the participants of the study will be revealed. The principles of confidentiality and anonymity will always be respected.

The authors declare no conflict of interest.

11. ETHICAL REFERENCES

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- International Conference on Harmonization (ICH) E6(R2) Guideline for Good Clinical Practice http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf
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