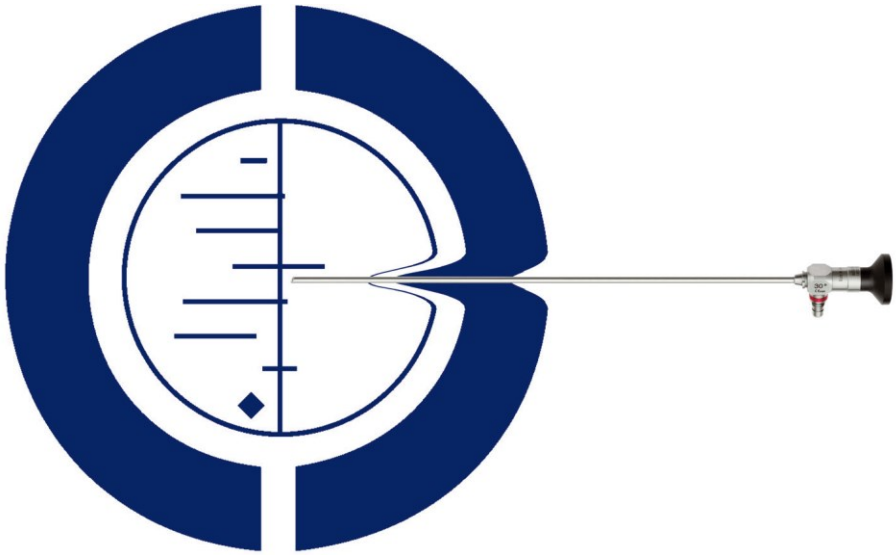
RESEARCH PROTOCOL

HALON trial



(Hysterectomy by transAbdominal Laparoscopy Or Notes)

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Independent physician	Not applicable
Laboratory sites	Clinical laboratory Imeldaziekenhuis Imeldalaan 9, 2820 Bonheiden, Belgium T: + 32 15 505460
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AH	Abdominal hysterectomy
BMI	Body Mass Index
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
DMEC	Data Monitoring and Ethics Committee
DUB	Dysfunctional uterine bleeding
EMBASE	Excerpta Medica dataBASE
EuroQoL	EQ-5D Health Questionnaire
GMT	Greenwich Mean Time
GP	General Practitioner
HTA	Health Technology Assessment
IDEAL	acronym: Idea, Development, Exploration, Assessment, Long-term follow-up
IV	Intravenous
LAVH	Laparoscopy assisted vaginal hysterectomy
LSK	Laparoscopy
MEDLINE	Medical Literature Analysis and Retrieval System Online
MeSH	Medical Subject Heading
NAVH	NOTES-assisted vaginal hysterectomy
NHS	National Health Service
NIHDI	National Institute for Health and Disability Insurance (Belgium: RIZIV/INAMI)
NOTES	natural orifice transluminal endoscopy
vNOTES	vaginal natural orifice transluminal endoscopy
OR	Odds ratio
PROM	Patient Reported Outcome Measure
RCT	Randomized Controlled Trial
SEM	Standard error of the mean
(S)AE	(Serious) Adverse Event

SD	Standard Deviation
SILS	Single Incision Laparoscopic Surgery
SSFS	Short Sexual Functioning Scale
TLH	Total laparoscopic hysterectomy
TMG	Trial management group
TSC	Trial Steering Committee
TV-NOTES	Transvaginal NOTES
tVNOTEH	Transvaginal natural orifice transluminal endoscopic hysterectomy
VAMIS	Vaginal access minimally invasive surgery
VAS	Visual analog scale
VH	Vaginal hysterectomy
QALY	Quality adjusted life year

SUMMARY

Rationale: Driven by the desire to minimize surgical morbidity, the evolution from laparotomy to laparoscopic surgery has now extended to the era of even less invasive surgery such as robotics, mini- laparoscopy, single incision laparoscopic surgery (SILS), and natural orifice transluminal endoscopy (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 procedure is performed via a natural body orifice. It has gained popularity amongst general surgeons, urologists and gastroenterologists over the past few years and its feasibility and safety has been embraced. (3)

NOTES can be performed through various entry approaches including stomach, esophagus, bladder and rectum. The vast majority of NOTES procedures in women have been performed through the vagina (4). Colpotomy has been used widely for several surgical procedures (by gynecologists but also by general surgeons for 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 introduced transvaginal pure NOTES (vNOTES) in our surgical practice since November 2013. A first case series describing the feasibility of vNOTES Hysterectomy in 16 women was published in 2012 (7). A case series of 137 women reporting the feasibility and safety of vNOTES hysterectomy was published in 2015 (8). A first case describing 10 cases of total vaginal NOTES hysterectomy in our department was published in 2015 (9). Most women reported a low postoperative pain score (range 0 to 2) measured at day 1 following surgery by a visual analogue scale (VAS).

Objective: To compare vNOTES and laparoscopic hysterectomy for successful removal of the uterus for benign gynecological pathology.

Study design: Randomized controlled/single center/single-blinded/parallel-group/non-inferiority/efficacy trial.

Study population: All women aged 18 to 70 years regardless of parity with benign indication for hysterectomy.

Randomization: After assessment of eligibility/ informed consent women will be randomly allocated to either technique before surgery by using a computer generated randomization list. We will use stratified randomization according to the estimated uterine size on clinical examination.

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 6-week period and to abstain from sexual intercourse until their 6-week booked appointment for a postoperative assessment.

Main study parameters/endpoints:

Primary study outcome parameters: successful removal of the uterus with the intended approach without conversion to an alternative approach.

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 (10) 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 up to 6 weeks 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 hysterectomy.

1. BACKGROUND

1.1. Disease: benign gynecological disease treated by hysterectomy

Hysterectomy is the most commonly performed major gynecological surgical procedure in the United States of America. Over 400,000 hysterectomies are performed annually and it is estimated that 1 in 3 women will have had a hysterectomy by age 60 years. Of the benign hysterectomies performed in the United States, 68% are done for the primary indication of abnormal uterine bleeding (AUB), uterine fibroids, and endometriosis (11). Fibroids account for approximately 30 percent of hysterectomies (12). Dysfunctional uterine bleeding accounts for approximately 20 percent of hysterectomies (12). Genital prolapse is the reason for about 15 percent of hysterectomies (12). Approximately 20 percent of hysterectomies are performed because of endometriosis and/or adenomyosis (12). Chronic pelvic pain has been the principal preoperative indication for approximately 10 percent of hysterectomies (12). Endometrial hyperplasia accounts for approximately 6 percent of hysterectomies (12).

1.1.1 Population to be studied

All women aged 18 to 70 years regardless of parity with an indication for hysterectomy for benign gynecological pathology will be eligible for inclusion provided that they have no exclusion criteria and after giving fully informed consent.

1.2. Current therapy for hysterectomy (13)

Hysterectomy is the surgical removal of the uterus. The first reported elective hysterectomy was performed by Conrad Langenbeck in 1813 who used a vaginal approach. The first elective abdominal hysterectomy, a subtotal operation (where the cervix was conserved), was performed by Charles Clay of Manchester in 1863. These approaches remained the only two options until the latter part of the 20th century. The first laparoscopic-assisted vaginal hysterectomy was performed by Harry Reich in 1989. He also reported the first total laparoscopic hysterectomy in 1993. The approaches to hysterectomy may be broadly categorized into three: abdominal hysterectomy (AH); vaginal hysterectomy (VH); laparoscopic hysterectomy where at least some of the operation is conducted laparoscopically.

The abdominal approach (AH) has traditionally been the surgical approach for gynecological malignancy, when other pelvic pathology is present such as endometriosis or adhesions, and in the context of an enlarged uterus. It remains the 'fallback option' if the uterus cannot be removed by another approach.

The vaginal approach (VH) was originally used for prolapse only, but has become more widely used for menstrual abnormalities such as dysfunctional uterine bleeding (DUB) when the uterus is fairly normal size. Compared to AH, VH was (and still is) regarded as less invasive and seemed to have the advantages of fewer blood transfusions, less febrile morbidity (fever) and less risk of injury to the ureter, but the disadvantages of more bleeding complications and greater risk of bladder injury.

The term 'laparoscopic hysterectomy' usually refers to a hysterectomy where at least part of the operation is undertaken laparoscopically and these approaches require greater surgical expertise. The proportion of hysterectomies performed by LH has gradually increased and, although the surgery tends to take longer, its proponents have argued that the main advantages are the possibility to diagnose and treat other pelvic diseases such as endometriosis, to carry out adnexal surgery including the removal of the ovaries, the ability to secure thorough intraperitoneal hemostasis (direct laparoscopic vision enables careful sealing of bleeding vessels at the end of the procedure) and a more rapid recovery time from surgery compared to AH. More recently, three sub-categorizations of LH have been described as follows.
(i) Laparoscopic assisted vaginal hysterectomy (LAVH) is where part of the hysterectomy is performed by laparoscopic surgery and part vaginally, but the laparoscopic component of the operation does not involve division of the uterine vessels.
(ii) Laparoscopic hysterectomy (LH) is where the uterine vessels are ligated laparoscopically but part of the operation is performed vaginally.
(iii) Total laparoscopic hysterectomy (TLH) is where the entire operation (including suturing of the vaginal vault) is performed laparoscopically and there is no vaginal component. This operation requires the highest degree of surgical skill and currently only a very small proportion of gynecologists are able to perform this type of surgery. It has been unclear whether TLH offers any benefit over other forms of hysterectomy.

A total hysterectomy is the removal of the entire uterus including the cervix. When the cervix is not removed, this is known as a subtotal or supracervical hysterectomy. Subtotal hysterectomies are most easily performed abdominally or laparoscopically, although it is possible to conserve the cervix in a VH or LAVH.

In common with the overall hysterectomy rate, the proportion of hysterectomies currently being performed by each of the above approaches varies markedly across countries, within the same country and even between individual surgeons working within the same unit. Women's expectations and individual surgeons' training and experience are factors underlying this. Even though VH has been widely considered to be the operation of choice for dysfunctional uterine bleeding (DUB), the

VALUE study showed that 74% of the hysterectomies performed in 1995 for this indication in the UK were AHs. The surgical approach taken at hysterectomy continues to depend upon the experience and biases of the surgeon. It was interesting to note in 1998 that there was not a single randomized controlled trial (RCT) comparing AH versus VH. The introduction of the newer approaches to hysterectomy (LAVH, LH and TLH) has stimulated a much greater interest in the proper scientific evaluation of all forms of hysterectomy.

Apart from the surgical approach to hysterectomy, other aspects of the surgical technique may have an effect on the outcome of surgery. Examples of this include total versus subtotal (where the cervix is not removed) hysterectomy; Döderlein VH or LAVH versus standard VH or LAVH; techniques to support the vaginal vault; bilateral elective oophorectomy versus ovarian conservation; other strategies, used mainly by those conducting laparoscopic surgery with the aim of reducing the likelihood of complications, including the use of vaginal delineators, rectal probes and illuminated ureteric stents.

1.3. New therapy for hysterectomy

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 randomized controlled trials of effectiveness. We conducted a comprehensive systematic review on the efficacy of NOTES for hysterectomy for benign gynecological pathology. After searching three electronic databases (MEDLINE, EMBASE and The Cochrane Library) from inception to 25 August 2015 using '*Natural Orifice Endoscopic Surgery'* and '*hysterectomy'* as MeSH terms or key words, 58 records were identified, of which a total of ten were eligible for inclusion.

DATABASE	SEARCH STRING	STUDIES
MEDLINE (PubMed) (inception to 25 August 2015)	"Natural Orifice Endoscopic Surgery" [Majr] AND "Hysterectomy"[Mesh] (8 records)	• Lee 201 • Su 2012 • Wang 2015 • Yang 2014
EMBASE (Embase.com) (inception to 25 August 2015)	'natural orifice endoscopic surgery'/exp OR 'natural orifice endoscopic surgery' AND 'hysterectomy' (50 records)	• Wang 2015 • Atallah 2015 • Wu 2014 • Yang 2014 • Lee 2013 • Su 2012 • Chen 2012 • Su 2012 abstract • Lee 2012
CDSR (The Cochrane Library) (inception to 25 August 2015)	"Natural Orifice Endoscopic Surgery" AND hysterectomy (0 records)	

After looking for duplications of study reports, seven studies including 731 study participants were identified for inclusion. None of the included studies was a randomized controlled trial. One study was a preclinical study describing the technical feasibility of transvaginal NOTES hysterectomy on a female cadaver (Atallah 2015). One study was a prospective cohort study (Lee 2013; Lee 2014; Wu 2014). Two studies were retrospective comparative studies (Wang 2015 and Yang 2014). Three studies were case series (Chen 2012; Lee 2012; Su 2012).

The main study characteristics are presented in the table below:

STUDY	N	POPULATION	INTERVENTION	COMPARISON	OUTCOME
Atallah 2015 (14)	1	Female cadaver	VAMIS[1]	None	None
Chen 2012 (15)	8 women	5 female-to-male transsexuals	TV NOTES [2] hysterectomy	None	Operating time Blood loss Complications
Lee 2012 (16)	10 women	15 women with benign adnexal/ uterine disease	TV NOTES [2] hysterectomy	None	Operating time Blood loss Complications
Lee 2013 + Lee 2014 (8) + Wu 2014	137 women	Women who were scheduled to undergo lap. hysterectomy (exclusion: virginity or suspected pelvic inflammation or cul-de-sac obliteration)	TV NOTES [2] hysterectomy	None	Successful procedure Operating time Blood loss Complications
Su 2012 (7) + Su 2012 abstr.	16 women	Women with benign disease of the uterus	TV NOTES [2] hysterectomy	None	Operating time Blood loss Hospital stay Complications
Wang 2015 (17)	512 women	Women with benign disease of the uterus and no genital prolapse	tVNOTEH [3] (n=147)	LAVH [5] (n=365)	Operating time Blood loss Hospital stay Costs Complications
Yang 2014 (18)	48 women	Women with benign disease of the uterus	NAVH [4] (n=16)	LAVH [5] (n=32)	Operating time Blood loss Pain Hospital stay Complications

(1) VAMIS: vaginal access minimally invasive surgery
(2) TV-NOTES: transvaginal natural orifice transluminal endoscopic surgery
(3) tVNOTEH: transvaginal natural orifice transluminal endoscopic hysterectomy
(4) NAVH: NOTES-assisted vaginal hysterectomy
(5) LAVH: laparoscopy-assisted vaginal hysterectomy

A summary of the evidence of the individual studies is briefly presented. We did not do a critical appraisal of the retrieved evidence by a formal risk of bias assessment: the focus was to retrieve background information before designing a RCT rather than writing a systematic review with critical appraisal.

Atallah 2015 is a preclinical study describing the technique of VAMIS (vaginal access minimally invasive surgery) in a female cadaver.

Chen 2012 is a case series describing 8 women that underwent transvaginal NOTES of hysterectomy. Five were identified as female-to-male transsexuals. The transsexuals were younger (22-45 years, median 27 years), with no parity (P0).The operating times were 70-120 minutes (median 80 minutes). Blood loss during surgery (100-650 mL, median 200 mL). There were no complications after surgery. The authors conclude that transvaginal natural orifice transluminal endoscopic surgery (NOTES) hysterectomy and bilateral salpingo- oophorectomy for female-to-male transsexuals seems a safe and feasible procedure.

Lee 2012 is a case series. Transvaginal NOTES was successfully completed in five adnexal surgeries and 10 hysterectomies without complications, an ancillary port on the abdomen, or conversion to conventional laparoscopy or laparotomy. For the 10 hysterectomies, the surgical time was 93.4 ± 6.3 minutes (mean ± standard) deviation), intraoperative estimated blood loss 245 ± 54.0 mL, uterine weight 440.1 ± 76.5 g, and the postoperative hospital stay 2.7 ± 0.3 days. No patients required intraoperative blood transfusion. The authors concluded that transvaginal NOTES for adnexal surgery and hysterectomy is feasible and safe.

Lee 2013/2014 + Wu 2014 are three published reports of a single prospective cohort study. The main study report is identified as Lee 2014. The study included 137 patients, with mean (SEM) age 46.0 (0.4) years and body mass index 24.7 (0.4). Transvaginal NOTES was successfully performed in 130 women (94.9%). Fifteen women underwent concurrent adhesiolysis and 17 underwent adnexal procedures. Mean (SEM) uterine weight was 450.0 (24.1) g; in 45 women (34.6%) the uterine weight was > 500 g, and in 7 (5.4%) it was >1000 g. Operative time was 88.2 (SEM 4.1) minutes, with blood loss of 257.7 (SEM 23.9) mL. In 2 patients there was intraoperative hemorrhage or unintended cystotomy, and in another 5 transvaginal colpotomy failed because of a narrow vagina, cul-de-sac obliteration by bowel adhesions, or mass obstruction. All complications in these seven patients (5.1%) were successfully managed via transabdominal laparoscopy. Five patients (3.6%) experienced postoperative urinary retention or febrile morbidity, and recovered uneventfully with conservative treatment. The authors concluded that transvaginal NOTES is a feasible technique for performance of hysterectomy and can be used in procedures that are difficult to complete via conventional vaginal surgery because posterior colpotomy is achievable. This procedure was not impeded by uterine volume, and had the advantage of no abdominal incision.

Su 2012 + abstract is a case series to evaluate the feasibility and safety of performing a hysterectomy using the transvaginal natural orifice transluminal endoscopic surgery (NOTES). From May through December 2010, 16 women with benign uterine disease who were eligible for laparoscopic

hysterectomy were recruited to undergo transvaginal NOTES at a tertiary referral medical center. Intraoperative and postoperative surgical outcomes were measured. All of the included hysterectomies were completed via transvaginal NOTES without conversion to conventional laparoscopy. The mean ± standard error of mean (SEM) uterine weight was 538.8 ± 102.9 g, the mean operative time was 122.7 ± 17.6 minutes, and the mean blood loss was 379.4 ± 95.4 mL. The mean postoperative hospital stay was 2.8 ± 0.2 days. No intraoperative or postoperative complications were noted in this series. The authors concluded that hysterectomy for the treatment of benign diseases can be feasibly carried out via transvaginal NOTES but prospective studies are needed to determine its full clinical application.

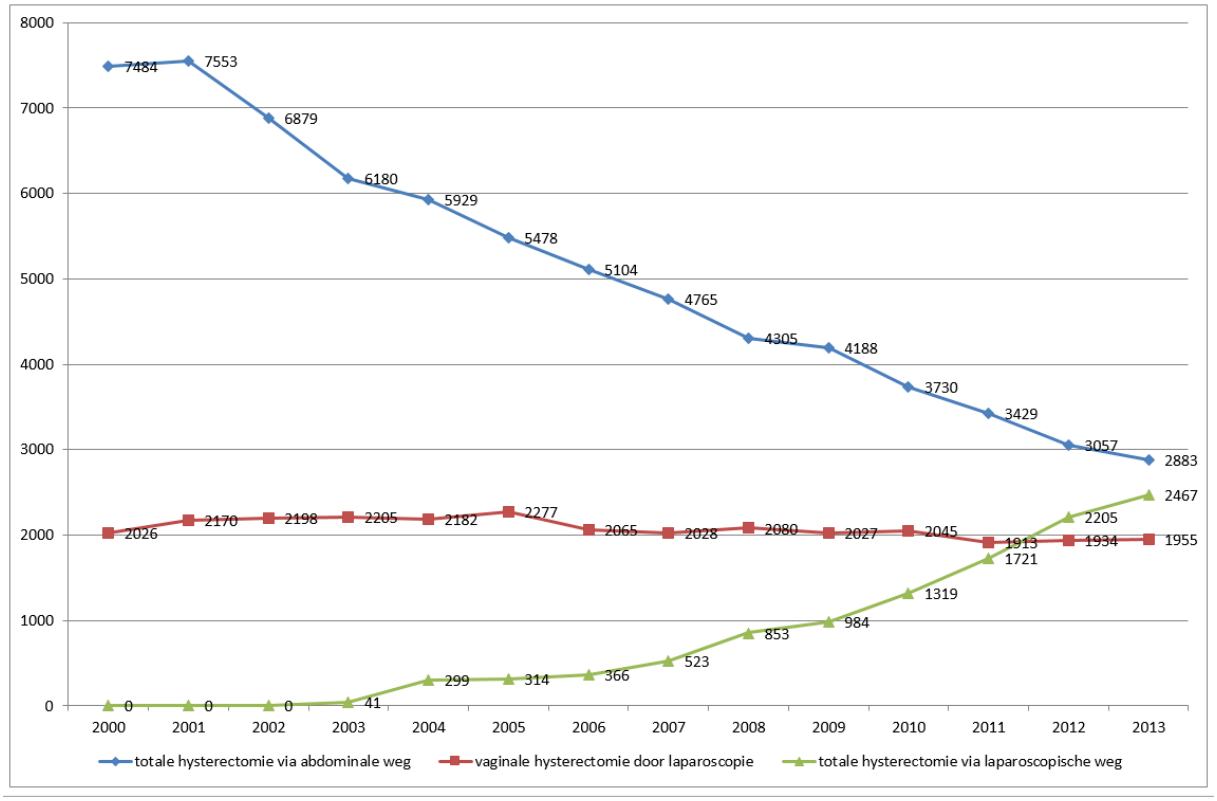
Wang 2015 is a retrospective comparative study that aimed to examine the safety and feasibility of transvaginal natural orifice transluminal endoscopic hysterectomy (tVNOTEH) for non-prolapsed uteri in the management of benign gynecological disease. Records were reviewed for the 147 consecutive tVNOTEH procedures between April 2011 and October 2013. Age, body mass index, number of vaginal deliveries, and specimen weight were used to select comparable patients who had undergone laparoscopically assisted vaginal hysterectomy (LAVH). A total of 512 women were recruited in this study (147 tVNOTEHs and 365 LAVHs, respectively). The participants were stratified into six subgroups according to the uterine weight and type of hysterectomy. There was no case of conversion to abdominal laparotomy. Length of operation, estimated blood loss (EBL), requirement of blood transfusion, and length of postoperative stay were significantly greater in the LAVH group than in the tVNOTEH group but total hospital charges were higher in the tVNOTEH group ($p<0.001$). There was no difference in overall incidence of operative complications between the two groups but more complications in LAVH for uterine weight more than 500 g (4.3 vs. 0 %, $p<0.001$); this likely reflects higher hospital charges in this subgroup. Significant linear correlations of uterine weight with operating time and EBL existed in both groups. The authors concluded that tVNOTEH can be safely performed for large and non-prolapsed uterus. Besides, as uterine weight increased, the operative efficiency of tVNOTEH increased compared with LAVH.

Yang 2014 is a retrospective comparative study for the assessment of NAVH using a novel homemade NOTES system comprised of a glove-wound retractor NOTES port versus LAVH using conventional laparoscopic instruments and an umbilical glove port. From July 2012, 16 women with benign uterine disease were treated by NAVH. Another 32 paired, AVH patients from the registered database were used to compare these two modalities of laparoscopy-assisted techniques for vaginal hysterectomy. All NAVHs were completed successfully without the need of an additional port or conversion to the standard laparoscopic approach. Intraoperative and postoperative surgical outcomes were assessed in both comparison groups. There were no significant differences between both groups in perioperative outcomes such as estimated blood loss, decrease in hemoglobin on

postoperative day 1, amount of analgesic drugs used, postoperative visual analog scale pain score, and febrile complications, except for operative time and length of postoperative hospital stay. The mean operative time was 70.6 ± 12.8 minutes for NAVH and 93.2 ± 21.4 minutes for SP-LAVH (p < 0.001). The median postoperative hospital stay was 3.5 days (range, 3–5) for NAVH and 4 days (range, 3–6) for SP-LAVH (p<0.001). The authors concluded that NAVH is a feasible and safe surgical technique and has a short operative time and postoperative hospital stay compared with LAVH. Prospective studies are needed to determine its full clinical application.

1.4.2 Current clinical practice

Based on data from 111161 hysterectomies registered between 2000 and 2013 by the Health care department of the National Institute for Health and Disability Insurance (NIHDI) of Belgium, the proportion of LAVH (RR 1.26, 95% CI 1.19 to 1.33, P<0.00001) and total laparoscopic hysterectomy has increased significantly (RR 69, 95% CI 51 to 94, P<0.00001) at the expense of the proportion of abdominal hysterectomies, which has dropped significantly (RR 0.50 , 95%CI 0.49 to 0.52, P<0.00001). There is a significant uptake in Belgium of the minimally invasive approach by laparoscopy for hysterectomy for benign gynecological disease, as reported by others (19).



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 in 2014. A first case describing 10 cases of total vaginal NOTES Hysterectomy in our department was published in 2015. (9)

The purpose of the observational case-series was to describe the present technique as well as to demonstrate the feasibility of a hysterectomy by transvaginal natural orifice transluminal endoscopic surgery (vNOTES) for the removal of benign uteri both in parous and nulliparous women. Conventional, reusable laparoscopic instruments were used, inserted through an inexpensive, self-designed single port device. All vNOTES hysterectomies were performed by a single surgeon (Jan Baekelandt).

Patients were selected based on the following criteria: no contraindication for general anesthesia, 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; no suspicion for malignancy. Obesity (BMI > 30) was not considered to be an exclusion criterion.

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 hysterectomy was performed according to the technique for standard vaginal hysterectomy but performed with laparoscopic instruments. The uterus was removed through the colpotomy incision.

The following patient and perioperative data were collected and retrospectively analyzed: patient age, body mass index (BMI), parity, history of vaginal delivery, previous pelvic surgery, type of surgery, total operating time, serum hemoglobin (Hb) drop (change between the preoperative Hb and postoperative Hb one day after surgery), peri-operative complications, and postoperative pain score. The duration of surgery was defined as the time from the insertion of the Foley catheter 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 identified to be urinary tract infection, postoperative ileus, vaginal vault bleeding or infection, or hematuria.

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 patients 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. Prophylactic intravenous antibiotic therapy, cefazoline 2 g and metronidazol 500 mg, was administrated during surgery. 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 January 2013 and March 2015, ten TVNH's were successfully performed by Poor Man's vNOTES using conventional, reusable laparoscopic instruments. No conversion to standard multi-incision laparoscopy or laparotomy was necessary. In four patients one or both adnexa were also removed; one of them had an 8 cm mucinous cystadenoma.

Table 1 (Appendix 1) presents an overview of patient and perioperative data. Individual patient details are presented in Table 2 (Appendix 2). Mean operation time was 97 minutes. Five patients had had previous pelvic surgery. There were no intraoperative complications. One patient had a postoperative cystitis for which oral antibiotic therapy was administered; and one patient had a small vault hematoma that was managed conservatively under antibiotic cover. The mean drop in hemoglobin level was 1.5 g/dl. Most patients scored a low postoperative pain score (range 1-2) 24 hours after surgery. All uteri were benign upon pathological examination (specimen weight 51-353g).

As these were the first 10 patients to be operated by a new surgical technique, we requested all patients to remain hospitalized for 72 hours for comprehensive follow up. Each patient was examined six weeks after surgery. There was no vaginal wound infection nor dehiscence, and none of the patients complained of pain during pelvic examination. All patients were in good health and were back at work.

Based on this observational case-series we concluded that total hysterectomy by vNOTES is feasible, even in nulliparous women, and even when performed with reusable, conventional laparoscopic instruments. The potential benefits with vNOTES are better cosmetics, low postoperative pain scores, and a quicker recovery. This innovative technique may enable surgeons in low resource settings to perform adnexectomies by vNOTES since no expensive devices or instruments are needed.

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

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 (20, 21, 22). The central concept is that surgeons are regularly innovating and improving their craft. 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 because the principal investigator had achieved his learning curve.

1.6. Objectives of the HALON Trial

The primary research question of this IDEAL stage 2b efficacy trial is as follows: is a vNOTES hysterectomy at least as effective compared to the standard transabdominal laparoscopic approach (LSC) for removing a uterus without the need for conversion to an alternative approach? (non-inferiority design)

Secondary research questions are:

- Do more women treated by vNOTES prefer to leave the hospital on the day of surgery compared to LSC?
- Do women treated by vNOTES suffer from less pain compared to women treated by LSC in the first postoperative week?
- Is the removal of a uterus 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 direct costs up to 6 weeks of a vNOTES compared to LSC?

2. TRIAL DESIGN

2.1. Design

A single center, single-blinded, parallel group randomized, non-inferiority efficacy trial.

2.2. Simple pilot randomized trial: minimal extra workload

This is a pilot randomized trial aiming to demonstrate that vNOTES is at least as effective compared to the classical gold standard approach of laparoscopy for successfully removing benign diseased uteri by the intended approach without conversion to an alternative approach (non-inferiority design). In this phase of HTA the trial will need the participation of only one center. 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), minimizing documentation and largely patient-based evaluation of outcome (PROM).

2.3. Time schedule

Based upon the mean number of hysterectomies performed annually for benign gynecological disease at the department of Obstetrics and Gynecology of the participating center (168) we estimate that the duration of recruitment will be 12 months. Based upon the follow up (6 months) and the period of analysis/reporting (3 months) the total study period will be 2 years.

2.4. Participating center

Department of Obstetrics and Gynecology

Imeldahospital

Imeldalaan 9

2820 Bonheiden

Belgium

3. ELIGIBILITY, CONSENT AND RANDOMIZATION

3.1. Screening and consent prior to surgery

All women aged 18 to 70 years, regardless of parity, in need of a hysterectomy for benign indication are eligible for inclusion.

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 uterus, the process of randomization and the follow-up requirements with the consultant gynecologist. 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 3 years 504 hysterectomies were performed at the department of Obstetrics and Gynecology of the participating center. The mean number of procedures per year is 168 (±SD 19). About 40 % of the eligible women should be willing to participate in the proposed study to recruit the required amount of participants within one year (see: Section 6.1. Sample size on pages 31-32).

3.2. Determining eligibility

All women aged 18 to 70 years, regardless of parity, in need of a hysterectomy for benign indication who provide consent to participation are eligible in the HALON trial and will be randomized before the procedure.

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

Inclusion criteria:

- All women aged 18 to 70 years, regardless of parity, in need of a hysterectomy for benign indication
- Written informed consent obtained prior to surgery

Exclusion criteria:

- History of rectal surgery
- Suspected rectovaginal endometriosis
- Suspected malignancy
- 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
- Failure to provide written informed consent prior to surgery

Body Mass Index or BMI > 35, age > 65, uterine weight 200-500g or uterine weight > 500 g are not considered to be an exclusion criterion per se but are characteristics that may increase the risk of conversion: the risk of conversion was increased at BMI >35 (OR 6.5, p < 0.001), age >65 years (OR 7.0, p =0.007), and uterus weight 200 to 500 g (OR 4.1, p < 0.001) and especially >500 g (OR 31, p < 0.001) based on the findings of a Dutch multicenter prospective cohort study in 42 hospitals including 1534 laparoscopic hysterectomies between 2008 and 2010 (23). We decided to stratify for uterine weight only because this is the most important variable in clinical practice and it is not practical to use four strata in this small pilot RCT.

3.3. Randomization

If the woman is eligible for the HALON trial, the trial secretary will obtain a randomized allocation the day before surgery. This will be done using a randomization list generated by a free computer software program offered by Research Randomizer (https://www.randomizer.org). The random sequence generation will be concealed using sequentially numbered opaque sealed envelopes. The envelope will be opened by the nurse assistant on the day of surgery for practical logistic reasons. We will use stratified randomization in this small pilot RCT according to the estimated uterine size on clinical examination. See 3.5 Stratification of randomization.

3.4. Patients with strong preference for treatment

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

3.5. Stratification of randomization

A blocked randomization procedure will be used to avoid chance imbalances for the parameter 'uterine size'. We preferred not to use minimization because this trial was not funded and we therefore could not afford to buy licenses for a computer-based algorithm for minimization. Although BMI and age are also prognostic parameters influencing the chances of the successful removal of the uterus, 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 only a limited number of participants. We therefore decided to stratify for uterine size only because this is the most important variable in clinical practice.

We used the following three strata:

- Stratum A: uterine size < 10 weeks
- Stratum B: uterine weight 10-16 weeks
- Stratum C: uterine size > 16 weeks

To avoid any possibility of foreknowledge, the randomized 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 non therapeutic or mock incisions in the skin 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 principal 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 minimize performance and detection bias whenever a subjective outcome is measured (24). 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 (25).

4.1.1 vNOTES hysterectomy

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 suprapubically. The small vertical intraumbilical skin incision is closed with a monocryl 3/0 intradermal suture. Wound bandages are applied to all three skin incisions.

The assessments whether the anterior and posterior colpotomy and the transection of both sacro-uterine ligaments are best performed with laparoscopic instruments (TVNH) or with classical instruments for vaginal surgery (VANH).

For VANH:

A circular incision is made around the cervix using a cold knife. The pouch of Douglas is opened using cold scissors. The vesico-uterine peritoneum is opened using cold scissors. Both sacro-uterine ligaments are transected using cold scissors and tied off using a Vicryl-1 suture. A Gelpoint (Applied Medical) is used as vNOTES port and is inserted into peritoneal cavity. 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.

For TVNH:

A Gelpoint mini (Applied Medical) is used as vNOTES port and is inserted into the vagina. CO_2 is insufflated until a maximal pressure of 15 mmHg. An optic is inserted into the pneumovagina. A circular incision is made around the cervix using a monopolar laparoscopic hook. The pouch of Douglas is opened using a laparoscopic scissors. The vesico-uterine peritoneum is opened using laparoscopic scissors. Both sacro-uterine ligaments are coagulated using a laparoscopic bipolar grasper before being cut. 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 rest of the procedure is identical for VANH and TVNH:

The ureter is identified, but not routinely dissected. It is only dissected if it cannot be identified transperitoneally. The uterine artery is coagulated using a bipolar grasper and cut. The ovarian artery is coagulated using a bipolar grasper and cut. The meso of the Falopian tube is coagulated using a bipolar grasper and cut. In patients requiring an adnexectomy, the infundibulopelvic ligament is coagulated using a bipolar grasper and is transected. Hemostasis is checked and the peritoneal cavity is rinsed. The NOTES port and the uterus are removed trans-vaginally and the pneumoperitoneum is deflated.

The colpotomy is closed using a running Vicryl-1 suture. 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.

Postoperative care

Recovery room

Analgesia: The pain management for both groups was discussed with two senior staff members of the department of anesthesiology of the hospital. The protocol will be standard for both comparison groups and is presented in appendix V.

Outpatient ward

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.

Cefazolin 2g is administered IV before discharge.

Analgesia: see appendix V.

Any additional pain medication should be reported in the nursing file which will be consulted by the outcome assessor (the coordinating investigator) who is blinded for the intervention done by the principal investigator. The assessment of whether or not additional analgesics were administered will be done on day 7 by the outcome assessor (the coordinating investigator).

VAS scores See appendix VI.

The women will be asked to use a VAS scale for measuring postoperative pain. They should place the cursor of the device 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 the nurse can measure the level of pain (range 0 to 10). The use of the VAS scale will be explained by a nurse from day care unit to ensure that women understand how the assessment of this subjective outcome is done in a clinical research setting. The measurements on the evening of the surgical procedure are noted in the patient record that will be assessed by the outcome assessor on day 7. The number to the left and right of the red line of the cursor will be recorded: e.g. pain level 0 to 1, or pain level 5 to 6.

The decision to discharge the patient 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. If the patient decides to stay in the hospital, the same procedure regarding decision to discharge will be used the following days. 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 six 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.

At home

Analgesia

The participants should note in their participant log book the name, dosage, route of administration of any additional 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. These data are assessed on day 7 by the outcome assessor (the coordinating investigator).

VAS scores

The women will be asked to measure postoperative pain using a VAS scale twice daily during 7 days. 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). They should place the cursor of the device 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.

4.1.2 LSK hysterectomy

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 reusable Hohl uterus manipulator is inserted transvaginally.

A small vertical intra-umbilical skin incision is made. A Verress needle is inserted into the peritoneal cavity; correct position 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. Three reusable 5mm trocars are placed under direct vision in the left and right iliac fossa lateral of the epigastric vessels, and in the suprapubic region. 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 meso of the Fallopian tube is coagulated from lateral to medial using a reusable bipolar grasper and is cut using cold scissors. In case of hysterectomy without ovariectomy, the ovarian ligament is coagulated and cut. In case of hysterectomy with ovariectomy, the

infundibulopelvic ligament is coagulated and cut. The round ligament is coagulated using a bipolar grasper and cut using cold scissors. The ligamentum latum is opened and the bladder is dissected from the cervix and cranial part of the vagina. The uterine artery is coagulated using a bipolar grasper and cut using cold scissors. The rest of the parametrium is coagulated using a bipolar grasper and cut using cold scissors. The same procedure is performed on the contralateral side. The vagina is then opened over the cup of the Hohl manipulator using a reusable monopolar hook. The cervix is excised circularly over the vaginal cup and the uterus is extracted transvaginally. Hemostasis is obtained using a bipolar grasper. The vaginal vault is closed laparoscopically using three figure of eight Vicryl-1 sutures.

The peritoneal cavity is rinsed and hemostasis is checked. No drains are left in the peritoneal cavity except when there might be any uncertainty concerning the hemostasis. The 5 mm trocars are removed under direct vision. The 10 mm trocar is removed. The fascia is not sutured. The umbilicus and the other incisions are disinfected with Betadine solution. The skin incisions are closed using a monocryl 3/0 intradermal suture and steri-strips. The wound sites are covered with a standard bandage. A vaginal plug (betadine gauze 10cmx5m) is placed to be removed after 3 hours together with the Foley catheter. The operating time is defined as the time from insertion of the Foley catheter until the time of placement of the vaginal plug.

Antibiotic administration:

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

Postoperative care

Recovery room

Analgesia: The pain management for both groups was discussed with two senior staff members of the department of anesthesiology of the hospital. The protocol will be standard for both comparison groups and is presented in appendix V.

Outpatient ward

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.

Cefazolin 2g is administered IV before discharge.

Analgesia: see appendix V.

Any additional pain medication should be reported in the nursing file which will be consulted by the outcome assessor (the coordinating investigator) who is blinded for the intervention done by the principal investigator. The assessment of whether or not additional analgesics were administered will be done on day 7 by the outcome assessor (the coordinating investigator).

VAS scores See appendix VI.

The women will be asked to use a VAS scale for measuring postoperative pain. They should place the cursor of the device 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 the nurse can measure the level of pain (range 0 to 10). The use of the VAS scale will be explained by a nurse from the day care unit to ensure that women understand how the assessment of this subjective outcome is done in a clinical research setting. The measurements on the evening of the surgical procedure are noted in the patient record that will be assessed by the outcome assessor on day 7. The number to the left and right of the red line of the cursor will be recorded: e.g. pain level 0 to 1, or pain level 5 to 6.

The decision to discharge the patient 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. If the patient decides to stay in the hospital, the same procedure regarding decision to discharge will be used the following days. 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 six 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.

At home

Analgesia

The participants should note in their participant log book the name, dosage, route of administration of any additional 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. These data are assessed on day 7 by the outcome assessor (the coordinating investigator).

VAS scores

The women will be asked to measure postoperative pain using a VAS scale twice daily during 7 days. 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). They should place the cursor of the device 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.

4.1.3 Failure of procedure

Occasionally, surgical removal of a benign diseased uterus 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 hysterectomy is feasible 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 anesthetic 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 HALON 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 diseased uterus will require no further intervention other than removal of the uterus with or without the adnexa. However, in some circumstances additional medical treatments may be considered necessary by the responsible clinician at the time of surgery or subsequently. This 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 HALON trial. All therapeutic interventions additional to removal of the uterus with one or both adnexa will be recorded and as the trial is randomized we anticipate that these further interventions will be symmetrically applicable.

4.3. Withdrawal from the HALON trial

All women who consent to the randomized HALON 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* randomization, 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 HALON 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 HALON Trial Office as soon as possible. This report should be followed within 2 days by a completed SAE form to be sent 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 hospitalization and have resulted from the surgical procedure, the anesthetic 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, sent at three and six months after the surgical intervention.

The postal questionnaires will be sent from the HALON Trial Office with postage paid envelopes two weeks before the due date. Reminders will be sent to patient if the questionnaire is not returned within one week of the due date and attempts will be made to contact the patient 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 uterus by the intended approach without conversion to another approach, using a dichotomous outcome measure, will be used as a measure of efficacy.

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 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 exceptional 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 analyzed 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 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 gynecological 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
- 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 utilization 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 trial centers 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 anesthesia.

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 centers participating in the trial. Published sources will include Unit Costs of Health and Social Care7 and NHS Reference costs.

Primary cost data will be collected from a representative sample of participating hospitals. In addition, the set-up costs of HALON 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 HALON 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 Gynecology 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 anonymized. All personal information obtained for the study will be held securely and treated as (strictly) confidential. All staff involved in the HALON 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. Limited data on the participants and records of any adverse events may be kept for longer if so recommended by an independent advisory board.

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 HALON 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 Dutch prospective cohort study (23). An important consideration in the approach for hysterectomy is the rate of conversion to an alternative approach: the intended technique cannot be successfully completed for technical reasons or concerns for patient safety. The literature reports a mean conversion rate for laparoscopic hysterectomy of 3.5% (range 0% to 19%); the findings of the prospective cohort study including 1534 procedures demonstrate a conversion rate of 4.6%. We calculated the sample size with a one-sided test for non-inferiority for the primary outcome. The vNOTES approach may be more convenient for women in that no scar in the abdominal wall is required. 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 conversion rates of 5% 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%.

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

6.2. Projected accrual and attrition rates

It is anticipated that recruitment of patients will take one year. Based upon the mean number of hysterectomies performed annually at the department of Obstetrics and Gynecology of the participating center (168) we estimate that the duration of recruitment will be 12 months. Based upon the follow up (6 months) and the period of analysis/reporting (3 months) the total study period will be 2 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 minimize 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 a benign diseased uterus. 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 randomization) will be explored as a secondary analysis.

Continuous measures (VAS scores) will be analyzed 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 maximizing 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 2-sided 95% confidence intervals.

Baseline characteristics of the patients enrolled in the two groups will be compared to ensure that randomization 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 HALON 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 HALON once all study entrants 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 minimize 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 patient. 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 diseased uterus, then it is likely that there can be cost implications for the health care sector. For example, as the patient can 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 hysterectomy 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 HALON 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 analyze 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 HALON 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 HALON 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 HALON will further be assessed using a qualitative methodology. Interviewing after discharge will allow the woman time to reflect on her experience, and will also minimize 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 when giving advice to family members or friends bound to undergo an hysterectomy; 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 and the Sponsor 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

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 randomized 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 HALON is a single center pilot 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 HALON 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 HALON Trial Office

The Trial Office at department of Obstetrics and Gynecology of the participating center is responsible for providing all trial materials, including the trial folders containing center specific trial documentation, standard operating procedures and training materials. Additional supplies of any printed material can be obtained on request or downloaded from the HALON 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 center.

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 (AE) 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.

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

Data	Mean	Range
Age (years)	48.4	34 - 61
BMI (kg/m^2)	25.1	19.7 – 33.3
Total operating time (min)	97	60 - 120
Serum hemoglobine drop (g/dl)	1.5	0.5 – 2.4
Postoperative pain score		
6h	2.5	1 – 6
24h	1.7	1 – 2

Table 1 Overview of patient and perioperative characteristics

APPENDIX II: TABLE II

Table 2 Patient and perioperative data

Patient no.	Age (years)	BMI (kg/m^2)	Parity	History of vaginal delivery	Previous pelvic surgery	Indication	Type of surgery	Port Type	Total operating time (min)	Serum hemo-globine drop (g/dl)	(Peri-) operative complications	Specimen Weight (grams)	Postoperative pain score	
													6h	24h
1	46	33.3	A1P1G2	yes	AE EUG	menorrhagia	TVNH	LMA	120	0.7	cystitis	83	2	1
2	46	24.8	A0P1G1	no	LLETZ CS	menorrhagia	TVNH	Wound Protector	115	1.5	3cm vault haematoma	126	2	2
3	61	22.1	A0P3G3	yes	-	Ovarian cyst	TVNH+BSO	LMA	105	1.5	-	224	2	2
4	61	24.7	A0P0G0	no	AE	PMB	TVNH+BSO	Wound Protector	120	1.9	-	107	2	2
5	34	23.8	A1P2G3	yes	LLETZ	cervical dysplasia	TVNH	LMA	65	1.0	-	39	1	1
6	36	20.3	A0P0G0	no	LLETZ LS endometriosis adhaesiolysis	dysmenorrhea	TVNH	Wound Protector	110	1.8	-	51	3	2
7	45	23.7	A0P0G0	no	-	myomatous uterus	TVNH	Wound Protector	115	2.0	-	353	2	1
8	52	31.6	A0P1G1	yes	Hemicolectomy USO	adenomyosis	TVNH+USO	LMA	70	0.5	-	62	6	2
9	52	19.7	A0P3G3	no	CS x 3 LLETZ AE	cervical dysplasia	TVNH	Wound Protector	60	1.5	-	55	3	2
10	51	26.4	A0P1G1	yes	-	myomatous uterus	TVNH+USO	LMA	90	2.4	-	223	2	2

AE = appendectomy; EUG = laparoscopic salpingectomy for ectopic pregnancy; CS = caesarean section; LLETZ = large loop excision of transformation zone; LS = laparoscopic sterilisation; endometriosis = laparoscopy for pelvic endometriosis; adhaesiolysis = laparoscopy for adhaesiolysis; USO = unilateral salpingo-oophorectomy; TVNH= total vaginal NOTES hysterectomy; BSO= bilateral salpingo-oophorectomy; LMA= self-constructed NOTES port using laryngeal mask airway ; PMB = persistent postmenopausal bleeding

APPENDIX III

CLAVIEN-DINDO CLASSIFICATION

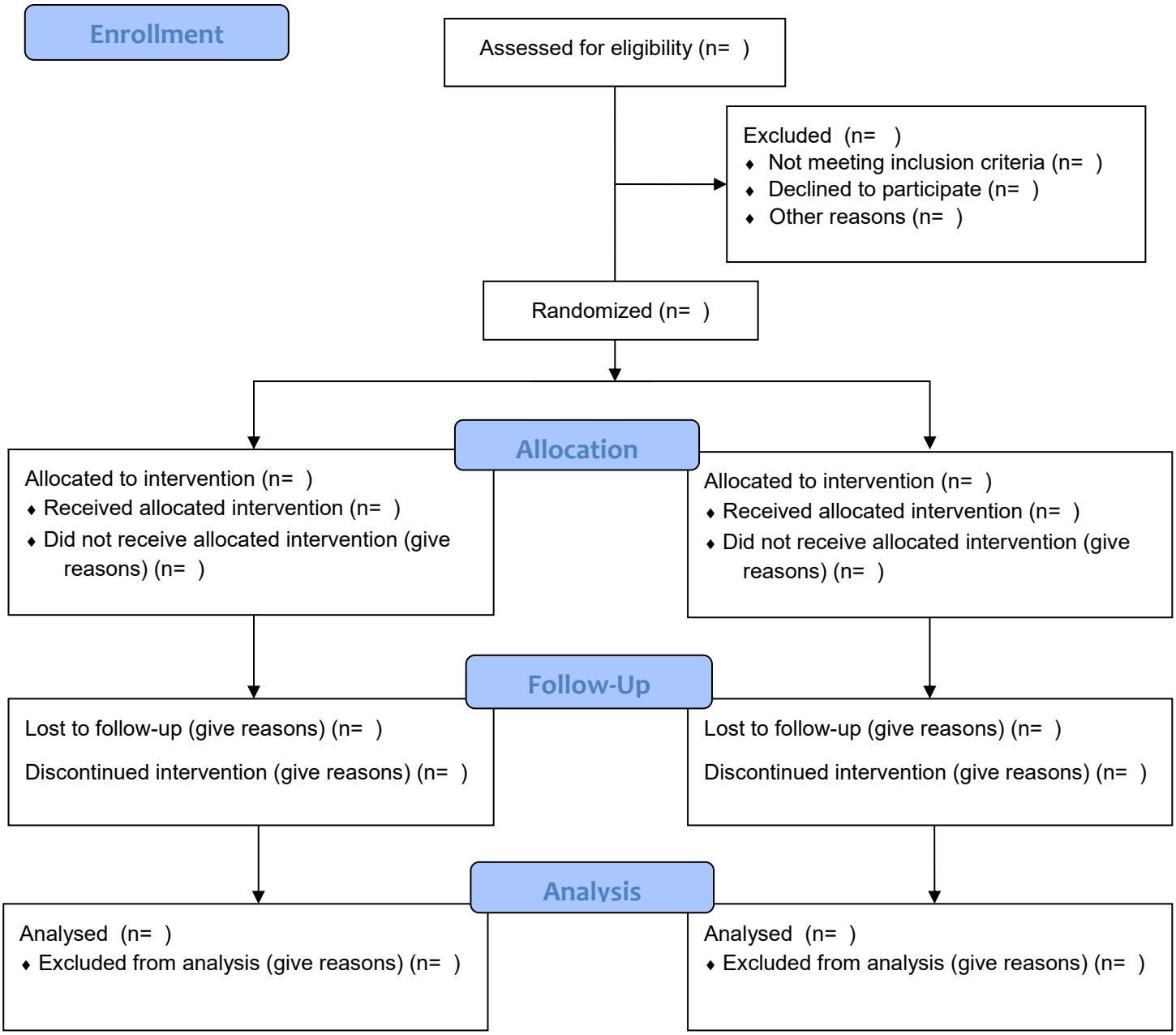
TABLE 1. Classification of Surgical Complications

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

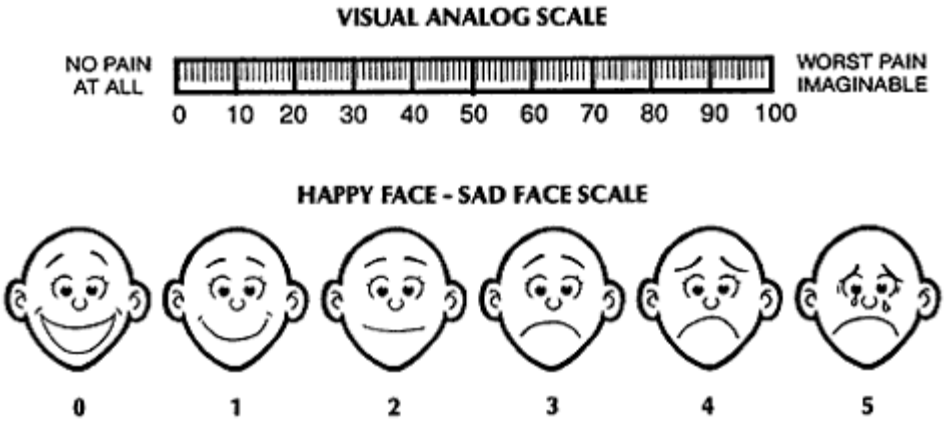
- Need be Alfentanil 5mg/kg one shot
- 30min. before end surgery IV shot
  - 1g Paracetamol
  - Ketorolac 0,5mg/kg (maximum dose 30mg)

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

HALON 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