STUDY TITLE: Hysterectomy by trans Abdominal Laparoscopy Or Notes

SHORT TITLE: HALON study

STUDY ID: ClinicalTrials.gov ID: NCT02631837

SAP VERSION: version 1.1. Date:14/01/2016

PROTOCOL VERSION: version 1.5. Date: 28/12/2015

STUDY OBJECTIVE: To compare v-NOTES and laparoscopic hysterectomy for successful removal of the uterus for benign gynecological pathology.

STUDY DESIGN: Randomized clinical trial (RCT)

KEY DATES:

- Start of recruitment: December 2015
- Anticipated completion recruitment: December 2016

STUDY SETTING: single centre study, non- university general hospital

SOURCE POPULATION: All women aged 18 to 70 years regardless of parity with benign indication for hysterectomy, presenting at the department of Obstetrics and Gynecology of the Imelda hospital Bonheiden, Belgium.

INTERVENTION/COMPARISON: Hysterectomy by NOTES (Natural orifice transluminal endoscopic surgery) versus classical laparoscopy.

OUTCOMES:

Primary: The proportion of women successfully treated by removing the uterus by the intended technique (NOTES versus laparoscopy) without conversion to another approach.

Secondary:

- The proportion of women discharged the same day based on their own preference

- Postoperative pain scores, measured using a VAS scale twice daily from day 1 till 7 self-reported by the study participants
- The total dose analgesics used during the first week following surgery
- Postoperative infection during the first six weeks of surgery
- Intra- operative complications
- Postoperative complications during the first six weeks of surgery
- Hospital readmission during the first six weeks of surgery
- The incidence of dyspareunia recorded by the participants at baseline, 3 and 6 months by self-reporting using a simple questionnaire and VAS scale
- The severity of dyspareunia recorded by the participants at baseline, 3 and 6 months by self-reporting using a simple questionnaire and VAS scale
- Sexual wellbeing at baseline, at 3 and 6 months by self-reporting the SSFS questionnaire
- Quality of life at baseline, at 3 and 6 months by self-reporting the EQ-5D-3L questionnaire
- Duration of surgery
- The total costs of both surgical techniques

SAMPLE SIZE CALCULATION:

We assumed a conversion rate of 5 % based on the findings of a prospective cohort study identified after a systematic review of the literature. The NOTES approach may be more convenient for women in that no scar in the abdominal wall is required. We assumed in our hypothesis that the NOTES technique is not inferior to the classical laparoscopic approach for successfully removing the uterus without conversion to another technique. We assumed that women would prefer the NOTES technique because in pure NOTES there are no scars. Non inferiority will be concluded when 15% lies above the upper limit of the 95% confidence interval calculated for the difference in the proportion of women successfully treated with either of both techniques. We calculated the sample size with a one-sided test for non-inferiority for the primary outcome: 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%.

SAP OBJECTIVE

The objective of this SAP is to describe the statistical analyses to be carried out for the final analysis of the HALON study.

GENERAL PRINCIPLES

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

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

Comparisons between the two arms will be done by applying Chi-square testing for the primary and other dichotomous outcome measures. Differences in outcomes between the groups will be expressed as relative risks (RR) with 95% confidence intervals.

Continuous outcomes will be analysed using an independent T-test or Mann–Whitney U- Test as appropriate.

Time-to-event analyses will be conducted to compare time to reach 0 VAS scale pain scores.

Follow-up will start at date of randomization and ends when the last three of the Pain, SSFS and EQ-5D-3L questionnaires at a follow-up of six months have been received at the trial centre.

(Which type) of curves will be constructed to account for time to reach a 0 VAS pain score after surgery. The (which?) test will be used to test for significance between the (?) curves.

SOFTWARE

The IBM Statistical Package for Social Sciences (SPSS) will be used for all statistical analyses (IBM Corp., USA).

ANALYSES

Study population – baseline characteristics

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

STUDY ENDPOINTS

Main study parameter/endpoint

Differences in the proportions of women successfully treated by removing the uterus by the intended technique without conversion to another approach will be expressed as relative risks (RR) with 95% confidence intervals (CI). These data will be reported as NOTES versus laparoscopy.

Secondary study parameters/endpoints

- Differences in the proportions of women discharged the same day based on their own preference will be expressed as relative risks (RR) with 95% CI.

- Differences in the postoperative pain scores, measured using a VAS scale twice daily from day 1 till 7 self-reported by the study participants will be expressed as mean differences (MD) with 95% CI.
- Differences in the time to reach VAS scores 0 will be expressed as (….)
- Differences in the the total dose analgesics used during the first week following surgery will be expressed as mean differences (MD) with 95% CI.
- Differences in the incidence of postoperative infection during the first six weeks of surgery will be expressed as relative risks (RR) with 95% CI.
- Differences in the incidence of intra-operative complications will be expressed as relative risks (RR) with 95% CI.
- Differences in the incidence of postoperative complications during the first 6 weeks following surgery will be expressed as relative risks (RR) with 95% CI.
- Differences in the incidence of readmission during the first six weeks of surgery will be expressed as relative risks (RR) with 95% CI.
- Differences in the incidence of dyspareunia recorded by the participants at baseline, 3 and 6 months by self-reporting using a simple questionnaire will be expressed as relative risks (RR) with 95% CI.
- Differences in the severity of dyspareunia recorded by the participants at baseline, 3 and 6 months by self-reporting using a VAS scale will be expressed as mean differences (MD) with 95% CI.
- Differences in sexual wellbeing at baseline, at 3 and 6 months by self-reporting the SSFS will be expressed as mean differences (MD) with 95% CI.
- Difference is the quality of life (QoL) at baseline, at 3 and 6 months by self-reporting the EQ-5D-3L questionnaire will be expressed as mean differences (MD) with 95% CI.
- Differences in the duration of surgery will be expressed as mean differences (MD) with 95% CI.

- Differences in the total costs of both interventions surgery will be expressed as mean differences (MD) with 95% CI.

STATISTICAL ANALYSIS

For the manuscript all above listed secondary outcomes will be compared between the two groups. These data will be reported as NOTES versus laparoscopy. All data will be analysed according to the intention to treat principle (ITT).

We will calculate Relative Risks (RR) and 95% confidence intervals for the primary and other binary outcome measures. We will use Chi-square test to assess statistical significance. Continuous outcomes will be analysed using an independent T-test or Mann–Whitney U- Test as appropriate.

We will construct Kaplan-Meier curves to express time to achieve 0 VAS score for pain after surgery. A log rank test will be used to compare time to achieve 0 VAS score for pain in the first week after surgery between both comparison groups.

SUMMARY OF SAP CHANGES

No changes were made in the statistical analysis plan. SAP version 1. Date: 14-01-2016 is the original version of the planned statistical analysis of the HALON trial.