VUE STUDY

Two parallel randomised controlled trials of surgical options for upper compartment (vault or uterine) pelvic organ prolapse.

SAP Date: September 29, 2017

ISRCTN: 86784244

Senior Statistician: _____

(Andy Elders)

Chief Investigator: _____

(Christine Hemming)

CHaRT Director: _____

(Graeme MacLennan)

Contents

List of Tables

1 Introduction

2 Study Design

VUE is a study with two randomised controlled trials running in parallel in 46 hospitals in the UK. Both RCTs are two-arm superiority trials, one for women with uterine prolapse and the other for vault repairs.

We will randomise women having surgery for uterine or vault prolapse to one of two trials:

- Uterine trial: vaginal hysterectomy compared with an operation to suspend the uterus without removing it, and
- Vault trial: suspending the vault from below (the vaginal route) compared with suspending it via the abdomen.

2.1 Primary research question

The aim of the study is to investigate the safety, effectiveness and cost-effectiveness of operations for women with upper compartment pelvic organ prolapse.

2.2 Randomisation and blinding

Randomisation will be computer-allocated separately for each trial and minimised on:

- need for a concomitant anterior and/or posterior POP operation or none,
- need for a concomitant incontinence procedure (e.g. TVT) or not,
- previous vault repair or not (for vault trial only),
- age (less than 60 years or 60 and over), and
- surgeon.

3 Outcome measures

3.1 Primary outcome

The primary clinical outcome is womens prolapse symptoms measured using the Pelvic Organ Prolapse Symptom Scale (POP-SS), at one year after randomisation. The primary quality of life outcome is the overall effect of prolapse symptoms on everyday life. The primary economic outcome measure of cost effectiveness is incremental cost per QALY.

The POP-SS is a composite outcome measure comprising seven patient recorded items each relating to a different symptom. Each item has an ordinal response schedule with five levels of response based on frequency of the

symptom (never, occasionally, sometimes, most of the time and all of the time) and is scored from 0 to 4 respectively. The overall POP-SS score is the sum of each item score and can range from zero to 28.

Item-level missing data
For the primary analysis, if only one item from the seven item scale is missing, we will impute it as zero. If more than one item is missing from the scale, we will consider the whole scale to be missing. Our approach will be tested in a sensitivity analysis where we will use different assumptions regarding the item-level missing data.

3.2 Secondary outcomes

General

- immediate and late post-operative morbidity (complications collected at the post-surgery time point);
- adverse events;
- operating time;
- blood loss;
- number of nights in hospital;
- number of readmissions to hospital;
- need for further surgery for prolapse or for urinary incontinence;
- time to further surgery;
- recommendation to a friend; and
- satisfaction with surgery.

Prolapse outcomes

- subjective recurrence of prolapse;
- objective residual prolapse stage (POP-Q) at original site;
- development of new (de novo) prolapse at another site; and
- need for other conservative prolapse treatment (e.g. PFMT, mechanical device).

Urinary outcomes

- Any incontinence
- ICIQ-SF score

- Severe incontinence
- Persitent incontincence
- De novo incontinence
- Incontinence-related QoL score
- Stress UI
- Urgency UI
- Overactive bladder
- FLUTS filling score
- FLUTS voiding score
- FLUTS incontinence score

Bowel outcomes

- Bowel frequency
- Constipation (including persistent and de novo)
- Bowel urgency
- Any faecal incontinence (including persistent and de novo)
- Faecal incontinence (severe)
- Bowel symptoms QoL score

Sexual function outcomes

- ICI Vaginal Symptoms Score
- Vaginal symptoms QoL score
- Vagina too tight
- Dyspareunia (In PROSPECT, we only included data for sexually active women, and women who were sexually inactive due to prolapse symptoms)
- ICI Sexual Matters Score
- Sex life QoL score

Quality of life outcome measures

- condition-specific quality of life measures; and
- general health measures (EQ-5D).

Adverse effects and complications Complications related to mesh or native tissue will be recorded.

3.3 Timing of outcome measurements

Women will be followed up at 6 months post-surgery and 12 months after randomisation. They will also be invited to attend a clinical appointment at 12 months post-surgery. They will be asked to consent to long term follow-up although this is not to be funded by this application. A single main analysis will be performed at the end of the trial when all 12-month follow-up has been completed. An independent DMC will review confidential interim analyses of accumulating data at its discretion but at least annually.

3.4 Adverse events

Adverse events will be reported in line with National Research Ethics Committee (NREC) guidance. Any of the following events will be reported as a serious adverse event:

- results in death;
- is life threatening;
- prolongs inpatient hospitalisation;
- results in persistent/significant disability/incapacity;
- is otherwise considered medically significant by the investigator.

Serious and not serious adverse events will be reported and analysed separately.

4 Sample size and power calculation

4.1 Original sample size

In the Uterine Trial, 268 women in each arm would be required to achieve 90 % power to detect a difference in the primary outcome measure (i.e. POP-SS at 1 year following randomisation) of 0.28 of a standard deviation at a significance level of 5 % (two-sided alpha). Allowing for 15 % loss to follow-up at 1 year would require 315 to be recruited to each arm (630 in total). The accumulating PROSPECT data indicate that a conservative estimate of the standard deviation of the primary outcome is 7 units and a difference in means of 2 units would represent a clinically important difference in POP-SS. Therefore, a standardised effect size of $2/7 = 0.28$ standard deviations (SDs) is used.
A smaller number of women would be expected to be recruited to the Vault Trial. Using data from the women recruited to PROSPECT to date with vault or uterine prolapse, the expected number of recruits to the Vault Trial can be estimated at 27 % of that recruited to the Uterine Trial. Therefore, in the time that 630 women could be recruited to the Uterine Trial, an expected 85 women would be recruited to each arm of the Vault Trial (170 in total). A trial of 170 would have 80 % power to detect a difference of 0.43 SDs at a 5 % significance

level (two-sided alpha). A standardised effect size of 0.43 equates to a difference in means of 3 units in the POP-SS measure. In total, based on these assumptions, the number of recruits required across both trials would be 800 women.

4.2 Recruitment extension and increase in Vault Trial sample size

At steady state, recruitment rate of the Uterine Trial was assumed to be approximately 29 women per month. Recruitment has been slower than anticipated, and is currently averaging 15 per month. Reasons for lower recruitment include womens preference (particularly for a hysterectomy) and lower than anticipated consent rates (around 30 % of those approached to participate in the Uterine Trial consent to do so, compared to the 50 % anticipated). As a result, an extension to the recruitment phase (an additional 15 months) is necessary to achieve the original target sample size (630). PROSPECT data showed that the number of women requiring vault repair is approximately 27 % of the number presenting with uterine prolapse. Therefore, during the original time period for randomising 630 women to the Uterine Trial, it was anticipated that a further 170 women requiring vault repair would also be randomised to the Vault Trial. Recruitment rates to the Vault Trial are in line with original predictions. With an additional 15 months of recruitment, the Vault Trial will continue to recruit beyond the original sample size of 170. Conservatively assuming an average of 7 women randomised per month, we project a revised total of 280 Vault Trial participants may be recruited, which is 140 per arm or 119 allowing for 15 % loss to follow-up. This would give 80 % power to detect a difference of 0.36 SDs at 5 % significance level (two-sided alpha). A standardised effect size of 0.36 SDs equates to a difference in means of 2.5 units in the primary outcome (POP-SS), considering a SD of 7. This is a smaller difference than originally calculated (i.e. 3 units, with 80 % power). This also equates to a relative reduction in the width of the confidence interval of 22 % when compared to the precision without the extension. As the POP-SS at baseline is higher in women with vault prolapse (15.2 versus 12.0 in women with a uterine prolapse, data from PROSPECT) we could reasonably expect a greater difference after surgery.

5 Statistical methods

These methods will apply to both uterine and vault and each trial will be reported and analysed separately.
A single principal analysis is anticipated at 12 months after the last woman was randomised.
All analyses will be based on the intention-to-treat principle. All outcomes in both trials will be described with the appropriate descriptive statistics where relevant: mean and standard deviation for continuous and count outcomes, or medians and interquartile range if required for skewed data, numbers and per-

centages for dichotomous and categorical outcomes.
Analysis of the primary outcome POP-SS will estimate the mean difference (and 95 % confidence interval) between intervention and control groups at 12 months after randomisation using a linear mixed model with surgeon fitted as a random effect that adjusts for the minimisation covariates and the baseline score. A similar analysis will be used to analyse the primary outcome at 6 months after surgery.
All secondary outcomes will be analysed in a similar manner but using the appropriate generalised linear model (e.g. logistic regression for dichotomous data such as subjective prolapse failure, Poisson or negative binomial regression for count data such as number of nights in hospital) or time to event methods (e.g. Cox regression on time to further surgery) where required. We will explore analysing outcomes at all time points simultaneously using, for example, generalised estimating equations or generalised linear latent and mixed models with relevant link functions.

5.1 Planned subgroup analyses

Subgroup analyses will be carried out within the following groups:

- Concomitant anterior and/or posterior repair or none
- Concomitant continence procedure or not
- Age (below 60 years or 60 years and older)

5.2 Non-compliance with allocated treatment

The primary analysis strategy of the trial will follow the intention-to-treat principle, i.e. participants will be analysed as randomised, regardless of the intervention received. However, secondary analyses may be undertaken to investigate issues relating to compliance. Depending on levels and patterns of non-compliance analyses methods other than intention-to-treat may be used, for example per-protocol analyses or estimation of complier average treatment effects.

5.3 Missing data

The primary analysis will be done using the observed outcome data for the participants. If participants do not have the outcome data they will be excluded from the primary analysis, however sensitivity analyses considering different assumptions will be run.

5.3.1 Missing outcome data

Missing data mechanisms will be explored but an underlying assumption of missing at random will be made, unless there is reason to consider a missing

not at random pattern. For the primary outcome POP-SS at 12 months we will explore the impact of missing data on the available data treatment estimates and confidence intervals by using multiple imputation and pattern mixture modelling methods depending on level and patterns of missing data.
Although no imputation of missing participant-level outcome data will be carried out in the main analysis of the primary outcome, imputation of instruments will be undertaken at item-level according to the rules of the specific instrument. All randomised participants will be included in the analysis. Participants deemed ineligible after randomisation will be considered post-randomisation exclusions and will be excluded from the analysis.

5.3.2 Missing outcome baseline data

Centre mean imputation of missing baseline data for continuous variables will be undertaken in order to reduce bias. For categorical variables, an additional category for the missing data will be created.

6 CONSORT diagram

See Protocol.

7 Dummy tables

Variable	Hysterectomy (N=)	Preservation (N=)
Age		
Parity		
BMI		
Delivery mode history		
Prolapse symptoms		
EQ5-D		
Previous conservative treatment		
Previous surgery		

Table 1: Baseline