STATISTICAL ANALYSIS PLAN

Prepared by:

G. MacLennan _____ 14/08/2014_

(date)

Trial Statistician

Approved by:

C. Glazener _____

_____

(date)

Chief Investigator

J. Norrie _____

_____

(date)

CHaRT Director

ISRCTN60695184

Table of Contents.

Study Design

PROSPECT is a multi-centred randomised control trial with a parallel-cohort design. The aim of the study is to investigate the safety, effectiveness and cost-effectiveness of operations for women with pelvic organ prolapse. The study includes two RCTs within a Comprehensive Cohort Study, with the following principle objectives:

In women having a primary prolapse repair, the effects of a standard repair versus the following:

1) Standard repair using a biological graft inlay
2) Standard repair using a non-absorbable or combined mesh inlay

In women having a secondary prolapse repair, the effects of a standard repair versus the following:

3) Standard repair using a non-absorbable or combined mesh inlay
4) Mesh kit procedure

Treatment allocation is minimised by age (>60/60+), type of planned prolapse surgery (anterior/posterior/both), concomitant continence procedure and concomitant prolapse procedure. Treatment allocations are summarised in Figure 1.

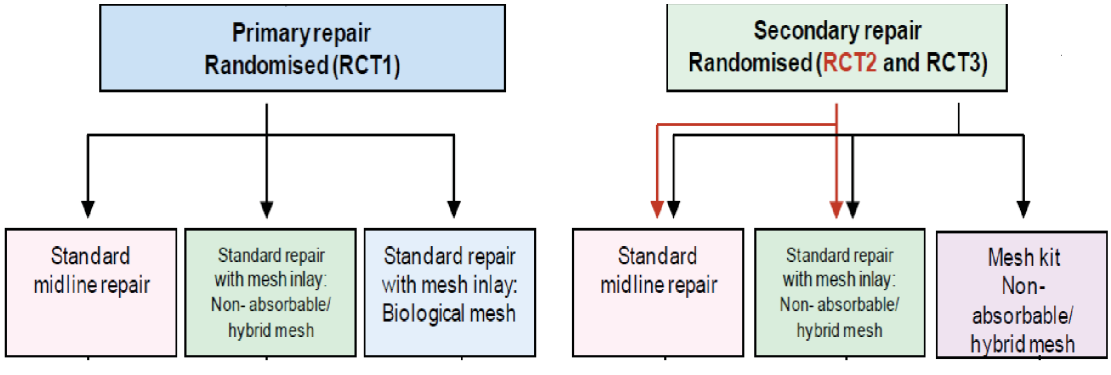

Figure 1. Treatment allocation in PROSPECT RCTs

Since recruitment began, additional randomisation menu options have been made available, partly as a result of some mesh types being unavailable on

certain days. It is possible in RCT1 to randomise just between standard repair and non-absorbable mesh (RCT1B), or between standard repair and biological mesh (RCT1C). In the secondary trial, an additional menu option of randomising between standard repair and mesh kit has been added (RCT2D).

At close of recruitment (August 2013), there were 36 participating centres throughout the UK. The centres are listed in Table 1.

Table 11– PROSPECT participating centres

Aberdeen	Cumbria	Maidstone	Rotherham
Ayrshire & Arran	Derby	Manchester	South Devon
Barnsley	Exeter	Mid Yorkshire	South Tees (Friarage)
Birmingham	Harrogate	Middlesex	South Tees (James Cook)
Bolton	Huddersfield	North Devon	Sunderland
Bradford	Hull	Nottingham	Taunton
Brighton	Imperial	Plymouth	Whipps Cross
Bristol	Leicester	Portsmouth	Wolverhampton
Chester	Luton & Dunstable	Preston	York

Outcome Measures

All outcome measures are recorded at baseline, 12 months and 24 months.

Primary Outcomes

The primary patient-reported outcomes are symptoms of prolapse, measured as:

- the number and frequency of prolapse symptoms on the Pelvic Organ Prolapse Symptom Scale (POP-SS)[1] at one year after surgery
- a quality of life outcome measured as the overall effect of prolapse symptoms on everyday life.

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.

For the primary analysis, individual items that are missing will be assumed to have a value of zero. However, this assumption will be tested in sensitivity analyses. If all seven questions are unanswered, then the POP-SS score will be treated as missing.

The primary economic outcome measure of cost effectiveness is incremental cost per QALY (QALYs based on the EQ-5D[2]). The cost effectiveness analysis is set out separately in the economic analysis plan.

Secondary Outcomes

General

- immediate and late post-operative morbidity (injury to organs, excess blood loss, blood transfusion, infection (UTI, sepsis, abscess), pain, urinary retention, constipation)
- other adverse effects or complications including mesh erosion or removal
- operating time
- blood loss
- number of nights in hospital
- time until resumption of usual activities

Prolapse outcomes

- subjective recurrence of prolapse
- subjective continuation / recurrence of prolapse symptoms
- objective residual prolapse stage (POP-Q) at original site
- development of new (*de novo*) prolapse at another site
- need for other conservative prolapse treatment (e.g. PFMT, mechanical device)
- need for further surgery for prolapse and/or for urinary incontinence
- time to further surgery
- satisfaction with surgery

Urinary outcomes

- Urinary incontinence (persistent or de novo, and types of incontinence)
- Need for alternative management for incontinence (e.g. PFMT, mechanical devices, pads, surgery, drugs, intermittent catheterisation)

Bowel outcomes

- Constipation (persistent or de novo)
- Bowel urgency (persistent or de novo)
- Faecal incontinence (persistent or de novo)

Vaginal symptoms and sexual function outcomes

- Vaginal symptoms

- Dyspareunia / apareunia / difficulty with intercourse (persistent or de novo)

Quality of life outcome measures

- Condition-specific quality of life measures (urinary, bowel, vaginal, sexual)
- General health measure (EQ-5D[2])

Missing data

Loss to follow-up

Complete loss to follow-up is defined as a participant who has no information on outcomes at any follow-up timepoint, but has not withdrawn consent. Such patients will not contribute data to any of the assessed outcomes.

Partial loss to follow-up is defined as a participant contributing some follow-up data, but no further information is known on other follow-up outcomes. Such participants will contribute to the outcomes for which there are data.

Withdrawals

If a participant prospectively withdraws consent, no further data are captured or retained on or after the date of withdrawal of consent. Depending on when the consent is withdrawn, the above rules on loss to follow-up apply.

Post-randomisation exclusions

If a participant is excluded from the trial, then their data will be excluded from analyses and will not contribute to any of the assessed outcomes.

Imputation

Imputation of missing baseline data (collected prior to randomisation) will be undertaken in order to reduce bias. Although no imputation of missing participant-level outcome data will be carried out in the main analysis of the primary outcome, imputation of instruments (e.g. POP-SS) will be undertaken at item-level according to the rules of the specific instrument.

Sensitivity analyses

It is recommended that sensitivity analyses are carried out where there are missing outcome data[3]. For the primary outcome POP-SS at data 12 months we will explore the explore the impact of missing data on the complete-case treatment estimates and confidence intervals by using multiple imputation and pattern mixture modelling methods depending on level and patterns of missing data.

Statistical Methods

General Methods

The statistical analysis of the RCTs will be based on all women as randomised, irrespective of subsequent compliance with the treatment allocated (intention to treat). The principal comparisons will be:

- In women having a primary prolapse repair,
    - a standard anterior and/or posterior repair will be compared with a standard repair using a biological graft inlay; and
    - a standard anterior and/or posterior repair will be compared with a standard repair using a non-absorbable or combined mesh inlay.
- In women having a secondary prolapse repair,
    - a standard anterior and/or posterior repair will be compared with a standard repair using a non-absorbable or combined mesh inlay; and
    - a standard anterior and/or posterior repair will be compared with a mesh kit procedure using an introducer device.

The two trials are being considered independently because different surgical options are considered to be appropriate for clinical reasons. Women who are not randomised but who are in the Comprehensive Cohort group will be analysed according to the operation actually carried out.

Descriptive statistics will be tabulated by treatment allocation for all outcomes (mean and SD for continuous data, proportions for binary data). Treatment effects will be estimated with 95% confidence intervals for all outcomes (mean differences for continuous data, odds ratios for binary data). Statistical significance will be at the 5% level and corresponding confidence intervals will be derived. Analyses will be conducted using SAS v9.3.

Primary/Secondary Outcomes

Outcomes at 12 months will be analysed using a generalised linear model which will adjust for minimisation and baseline covariates. The development of treatment effects over time will be explored using repeated measures mixed effects models that make use of available outcome data at each time point, e.g. 6, 12 and 24 months for the POP-SS (this assumes outcome data missing at random conditional on the observed covariates).

Furthermore, it is anticipated that many women may be asymptomatic one year after surgery and their POP-SS will be zero. A composite binary/linear model will be used to analyse the primary outcome (POP-SS at 12 months) so that a distribution of POP-SS with a high proportion of zero values is taken into account. The binary element will be based on a POP-SS=0, and the linear element will treat the POP-SS score as a continuous measure with possible values ranging from 0 to 28.

The menu design of the trials will be taken into account in the analyses of all outcomes. Both RCTs have 3 strata, as shown in Table 2 and Table 3.

Table 2: Number of participants randomised to each stratum in the primary RCT

Stratum	Standard repair (A)	Synthetic mesh (B)	Biological mesh (C)
RCT1	253	256	255
RCT1B	178	181	n/a
RCT1C	116	n/a	114

Table 3: Number of participants randomised to each stratum in the secondary RCT

Stratum	Standard repair (A)	Synthetic mesh (B)	Mesh kit (C)
RCT2	24	24	44
RCT2B	31	28	n/a
RCT2D	1	n/a	3

In the primary RCT, RCT1 will be analysed on its own and treatment effects for treatments B and C (compared with A) will be estimated. In addition, the RCT1 and RCT1B strata will be combined (using just data in arms A and B) in a separate model to create a further estimate of the treatment effect between A and B. Similarly, the RCT1 and RCT1C strata will be combined (using just data in arms A and C) in a separate model to create a further estimate of the treatment effect between A and C. Where strata are combined, the stratum variable will be fitted as a fixed effect in the model. The secondary trial will be similarly analysed, although RCT2 will not be combined with RCT2D due to the small number randomised to RCT2D.

Secondary outcomes will be analysed in a similar fashion to the primary outcome using appropriate link functions.

Subgroup analyses

Subgroup analyses (separately for the two populations) will explore the effect on prolapse symptoms at 12 months after surgery of:

- mesh kit versus other procedures in those that could have been randomised to mesh kits
- concomitant continence procedure or not
- concomitant hysterectomy/cervical amputation/vault procedure or not
- age (<60 or >=60 years)

- parity
- between those having one type of prolapse repair alone (anterior or posterior) versus both

Heterogeneity of treatment effects amongst subgroups will be tested for using the appropriate subgroup by treatment group interactions. Stricter levels of statistical significance (2P<0.01) will be sought, reflecting the exploratory nature of these analyses.

Non-compliance will allocated treatment

The primary analysis strategy of the trial will follow the intention-to-treat principle, i.e. participants will analysed as randomised, regardless of the intervention received. However, secondary analyses may be undertaken to investigate issues relating to compliance (e.g. mesh inlays being misidentified as mesh kits). 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.

Methodological analyses

The responses from women and their objective clinical findings will provide a rich data source for exploration of the correlation between patient-reported and clinician-observed outcomes, and between prolapse symptoms and their effect on quality of life. This methodological research is intended to advance the controversial field.

1.1. Timing of analyses

An analysis of 12 month outcomes (including the primary outcome) will be performed and published one year after recruitment closes. A final analysis of all outcomes will be conducted at the end of the trial when all follow-up has been completed (up to 24 months).

Sample Size and Power Calculation

In an average population of women having prolapse surgery, about 70% will be having a primary procedure. Two comparisons will be made:

- a standard repair versus a standard repair using a biological graft inlay; and
- a standard repair versus a standard repair using a non-absorbable or combined mesh inlay.

Pilot data have shown that a conservative estimate of the standard deviation of the primary patient-reported outcome POP-SS is 8 units. A difference in means of 2 units would represent an improvement in the response to a POP-SS question, for example, a feeling of something coming down or in the vagina, from 'Most of the Time' to 'Occasionally'. To detect a standardised difference of 0.25 with 90% power and alpha equal to 0.025 (to maintain the nominal p value at 0.05 with two tests being used), we would need to randomise 400 women to each arm of the study. Best efforts using evidence based techniques will be employed to maximise the response rate at follow up. Nevertheless, we feel it prudent to inflate the estimated sample size for 15% dropout at one year requiring approximately 1450 women having primary surgery to be recruited to the trial. Adjusting for baseline covariates and minimising the loss to follow up will potentially improve this power. A trial of this size would also be adequately powered to detect important differences in the economic and secondary outcomes.

It is estimated that the other 30% of women requiring anterior and/or posterior repair will receive a secondary or subsequent repair. Therefore, during the proposed time period required for recruiting 1450 women to the primary repair RCT above, it is anticipated approximately 620 women having secondary surgery will be eligible and will be willing to be randomised. Within the secondary RCT two comparisons will be made:

- a standard repair versus a standard repair using a non-absorbable or combined mesh inlay; and

- a standard repair versus a mesh kit procedure.

It would be possible to detect with 90% power and alpha equal to 0.025 a standardised effect size of 0.38 which equates to 3 points on the POP-SS scale (this estimated effect detectable has been calculated adjusting for potential 15% dropout at one year). The pilot data from IMPRESS indicated that women having secondary repairs have a higher level of symptoms at baseline. Therefore it is biologically plausible that these women may show a larger benefit from the options available.

Thus 2070 women will be randomised in total. Based on data from the feasibility study, we expect that in a typical centre, 200 women a year will be eligible, of whom 50% will be willing to be randomised. Of these women, 70% will be having primary surgery, 30% will have both anterior and posterior surgery, 15% may have a concomitant continence procedure and 30% a concomitant upper vaginal procedure (e.g. cervical amputation or vaginal hysterectomy). More than 15 centres are willing to take part.

If we conservatively assume 50% of the women will agree to be randomised, we calculate we will need the equivalent of 18 months full time recruitment to randomise 2070 women and will follow up 4140 women in total including those in the Comprehensive Cohort. Allowing for about another 10% who will not wish to be studied in any way, we will need to approach around 4500 women.

References

1 Hagen S, Glazener C, Sinclair L, Stark D, Bugge C. Psychometric properties of the pelvic organ prolapse symptom score. BJOG: an International Journal of Obstetrics & Gynaecology 2009; 116(1):25-31.

2 The EuroQoL - a new facility for the measurement of health-related quality of life. Health Policy 1990; 16: 199−208.

3 White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analyses in randomised trials with missing outcome data. British Medical Journal, 2011; 342: d40.