PROSPECT STUDY

PROSPECT: PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials

Clinical and cost-effectiveness of surgical options for the management of anterior and/or posterior vaginal wall prolapse: two randomised controlled trials within a Comprehensive Cohort Study.

PROTOCOL

A UK Collaborative Study funded by the
NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC),
Health Technology Assessment (HTA) Programme

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PROTOCOL SUMMARY

QUESTION ADDRESSED	Which prolapse operations are the safest and most effective and cost-effective for women with pelvic organ prolapse?
CONSIDERED FOR ENTRY	Women who are going to have prolapse surgery
POPULATIONS	1. Primary (first) prolapse operation 2. Second or subsequent prolapse operation
STUDY ENTRY	All women having prolapse surgery will be studied. Consent will be obtained from women after written and oral information has been provided.
INTERVENTIONS	1. Standard anterior and/or posterior repair 2. Standard repair with biological mesh inlay 3. Standard repair with combined or non-absorbable mesh inlay 4. Mesh procedure using an introducer kit
OUTCOME ASSESSMENT	Postal questionnaires at 6, 12 and 24 months after the date of their prolapse operation POP-Q and clinical examination at 12 months following surgery Health care utilisation questions at 12 and 24 months Participant time and travel cost questionnaire at 18 months only
CO-ORDINATION	**Local**: by local lead Gynaecologist and Recruitment Officer. **Central**: by Study Office in Aberdeen (Telephone 01224 438197). **Overall**: by the Project Management Group and overseen by the Steering Committee and the Data Monitoring Committee.
FUNDING	National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre, Health Technology Assessment (NETSCC HTA) Programme
Start date:	September 2009
Current funding end date:	April 2020

GLOSSARY OF ABBREVIATIONS

CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
DMC	Data Monitoring Committee
ISRCTN	International Standard Randomised Controlled Trial Number
POP	Pelvic Organ Prolapse
PROSPECT: PROlapse Surgery: Pragmatic Evaluation and Randomised Controlled Trials	
REC	Research Ethics Committee
NETSCC	NIHR Evaluation, Trials and Studies Coordinating Centre
HTA	Health Technology Assessment
SAE	Serious Adverse Event
TSC	Trial Steering Committee
PFMT	pelvic floor muscle training
IP	Interventional Procedure

Summary in Plain English

Around 1 in 10 women will need prolapse surgery at some point in their lives. Prolapse occurs when the pelvic organs (such as the bladder, the bowel or the womb) come down into, or out of, the vagina. This is caused either by weakness of the connective tissues which normally support these organs or by weak pelvic floor muscles. It is most common in women who have had children, although there has been surprisingly little research into its causes and treatment.

There are many different operations for prolapse, depending on the type of prolapse, whether the woman is having her first or a secondary repair and the preference of the gynaecological surgeon. To date, there is a high failure rate after surgery: three in ten women who have an operation will have further surgery. This study will address prolapse of the front wall of the vagina (anterior prolapse, the bladder is often involved with this type) and the back wall (posterior prolapse, which often involves the bowel). Some women may need an extra procedure if the womb is also coming down or for leaking urine (incontinence). If necessary, the extra procedures can be carried out at the same time.

There is not enough evidence from research to identify which operation is best. New techniques have been introduced which use mesh to reinforce the surgery, but these have not been properly evaluated, especially in terms of how well they improve prolapse symptoms. In particular, a recent review by NICE (the National Institute for Clinical Excellence) has found that there is insufficient information on the efficacy and safety of mesh used in prolapse surgery in women.

The study will be carried out in at least 15 hospitals in the UK. We will randomise women having an anterior and/or posterior vaginal wall prolapse operation to one of two trials:

(1) A woman who is having her first repair operation will be randomised to one of: a) a standard anterior or posterior prolapse repair, b) a standard repair with a biological graft inlay to support the stitches; or c) a standard repair with a non-absorbable mesh inlay to support the stitches.
(2) A woman who is having a second or subsequent repair will be randomised to: d) a standard anterior or posterior prolapse repair, e) a standard repair with a non-absorbable mesh inlay to support the stitches, or f) a new mesh repair in which the whole prolapse is held up with a large piece of mesh threaded into surrounding tissues using an introducer (mesh kit). This last option will only be available for women having a secondary operation for prolapse as it is thought that it is a more invasive operation than the other options and so should be reserved for such women, who have a higher risk of failure.

It is likely that there will be mixed costs and benefits for these operations. For example there may be better cure rates with some operations although with a higher chance of complications especially related to mesh or at a higher cost to both the NHS and patients.

All women having prolapse operations will be eligible for our study. They will be given information about the study before they are admitted to hospital. After discussion with their gynaecologist, women will be able to choose whether or not they are willing to be randomised to one of the specified operations. They will sign a consent form approved by the Ethics Committee. Those women who do not wish to be randomised to a particular procedure but are happy for their outcomes to be monitored, will be examined and will complete the questionnaires in the same way as the randomised groups.

Women will have a routine physical examination before surgery and they will complete questionnaires both before and after their operation. Further symptom questionnaires will also be filled in 6, 12 and 24 months later. The women will be examined and reviewed in outpatients at 12 months after surgery. Our main interest is in the cure or improvement of prolapse symptoms, as reported by the women themselves. We have carried out feasibility studies using these questionnaires and examination methods to show that we will be able to measure differences.

Ethical approval has been sought for this study. We consider that it is ethical to study this problem using randomisation as this is the gold-standard method most likely to provide an unbiased answer. The procedures used in the study will be standardised and agreed with a team of experienced gynaecologists from the British Society of Urogynaecology.

Within the next 10 years, an extra 1 million women will reach the age when they are most likely to need prolapse surgery. This study will show which prolapse operations are the safest and most effective for all women.

PROSPECT PERSONNEL

Grant Holders

1	Cathryn Glazener	8	Suzanne Hagen
2	Anthony Smith	9	Mary Kilonzo[b]
3	Robert Freeman	10	Graeme MacLennan
4	Christine Bain	11	Alison McDonald
5	Kevin Cooper	12	Gladys McPherson
6	Adrian Grant	13	Isobel Montgomery
7	John Norrie[a]		

[a]John Norrie replaced Jennifer Burr in September 2011
[b]Mary Kilonzo replaced Luke Vale in February 2011

Project Management Group:

This group is comprised of all grant holders along with representatives from the PROSPECT study team.

Key PROSPECT study team invited members:

1	Suzanne Breeman	4	Mary Kilonzo
2	Margaret MacNeil	5	Dwayne Boyers
3	Fiona Reid		

Trial Steering Committee:

This committee is comprised of four independent members along with the Chief Investigator (Cathryn Glazener), the other PROSPECT grant-holders and key members of the central office (eg the trial manager). The funders will be notified in advance of meetings and a representative invited to attend. Other relevant experts may be invited to attend as appropriate.

Independent members:

1	Henry Kitchener (Chair)	3	Ranee Thakar
2	Pamela Warner	4	Trish Emerson

Members:

1	Cathryn Glazener	3	Trialist grant holder[b]
2	Clinical grant holder[a]	4	Senior CHaRT representative[c]

[a] A representative from Anthony Smith, Robert Freeman, Christine Bain and Kevin Cooper
[b] A representative from Adrian Grant, Graeme MacLennan and Mary Kilonzo
[c] A representative from John Norrie, Alison McDonald and Gladys McPherson

Data Monitoring Committee members:

1	Jim Neilson (Chair)	3	Lucia Dolan
2	Paula Williamson	4	Gill Gyte

PROSPECT Study Office Team in Aberdeen:

This team is comprised of the Aberdeen-based grant holders along with the Aberdeen-based study team members.

Other Information

International Standard Randomised Controlled Trial Number (ISRCTN)	ISRCTN60695184
REC Reference Number	09/SO802/56
HTA Project Number	07/60/18
The NETSCC, HTA Programme website	http://www.nets.nihr.ac.uk/projects/hta/076018
CHaRT website:	http://www.charttrials.abdn.ac.uk/prospect

SURGERY FOR WOMEN WITH PELVIC ORGAN PROLAPSE

Known as PROSPECT
PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials

Title of trial: Clinical and cost-effectiveness of surgical options for the management of anterior and/or posterior vaginal wall prolapse: two randomised controlled trials within a Comprehensive Cohort study

This protocol describes a major multicentre UK trial to establish which type of prolapse surgery results in better prolapse and other outcomes in women who are having prolapse surgery. The study is designed to be as simple as possible both for those participating and for those involved in clinical care.

Recruitment officers in each centre will identify and recruit women undergoing prolapse surgery and collect descriptive information and baseline prolapse measurements (POP-Q). Those who are eligible will also be invited to enter a randomised trial of different types of prolapse surgery. All women (whether randomised or not) will be followed up at 6, 12, 18 and 24 months.

1. THE REASONS FOR THE TRIAL (see Appendix I for background)

1.1 The decision to test alternative forms of surgery

There is little evidence available from randomised controlled trials (RCTs) to guide management for women with prolapse. Three Cochrane reviews cover the main options: surgical management;[1] and conservative management including: mechanical devices;[2] and physical treatment such as pelvic floor muscle training (PFMT).[3] A new Interventional Procedures (IP) Review has also just been published on the use of mesh in anterior and posterior prolapse surgery.[4] The conclusion from these publications is that there is insufficient information about any of the surgical options to guide management of any type of pelvic organ prolapse in any population of women with prolapse.

We have identified that the largest group of women are those with anterior and/or posterior prolapse, who comprise around 90% of those having prolapse surgery (including those having a concomitant hysterectomy). The evidence base for treating these women is clearly inadequate, with very little evidence regarding subjective prolapse symptoms, effect on quality of life and safety. In particular, the routine use in the NHS of mesh for prolapse surgery should be informed by well designed RCTs.

Both the Cochrane Review[1] and the IP review[4] identified a need for adequately powered RCTs of the use of mesh in prolapse surgery. This study comprises the largest, only adequately powered, and independent RCT comparing traditional prolapse operations with new methods incorporating mesh as an inlay or mesh inserted using an introducer system. The different clinical characteristics of women having primary as opposed to secondary surgery will be considered and confounding factors which may predict outcomes identified.

1.2 The questions which this study will address

Principal Objectives

To determine the effectiveness (including safety) and cost-effectiveness of surgical treatment, primarily in terms of improvement in prolapse symptoms, in women having anterior and/or posterior vaginal wall pelvic organ prolapse surgery, in two groups:

(A) In women having a primary prolapse repair, the effects of:

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

(B) In women having a secondary prolapse repair, the effects of:

3) a standard repair versus a standard repair using a non-absorbable or combined mesh inlay; and
4) a standard repair versus a mesh kit procedure.

The two groups are being considered independently because different surgical options are considered to be appropriate for clinical reasons.

Secondary Objectives

5) to determine the differential effects on other outcomes such as urinary, sexual and bowel function, quality of life, general health, need for secondary surgery and adverse effects;
6) to identify possible effect modifiers (eg different types of mesh, concomitant procedures, age, complex prolapse types);
7) to establish if the findings of the research, including implications for service delivery, training and introduction of mesh, are generalisable to the NHS.

2 TRIAL RECRUITMENT AND ALLOCATION

2.1 Women considered for trial entry

The study will involve women who are having pelvic organ prolapse surgery. Two parallel but separate trials will be conducted, amongst:

(A) Women having a primary prolapse repair; and
(B) Women having a secondary prolapse repair.

In addition, women who do not consent to randomisation, or whose gynaecologists consider one surgery type is more appropriate will be followed-up within the non-randomised cohort.

Secondary prolapse is defined as a recurrence of prolapse after a primary procedure, when the recurrence is in the same compartment. If the prolapse is in a different compartment and the original site does not require revision surgery, the woman will be classed as having a primary repair of the de novo prolapse.

Inclusion criteria:

1. All women having primary or secondary pelvic organ prolapse surgery for anterior and/or posterior vaginal wall prolapse who are eligible and willing to be randomised.
2. Women undergoing concurrent hysterectomy/cervical amputation, vault surgery or continence procedures are also eligible.
3. Women who are unwilling or unsuitable for randomisation will be eligible to be followed up using the same protocol as part of the Comprehensive Cohort.

Exclusion criteria:

1. Women undergoing prolapse surgery who are unwilling or unable to participate in the study.
2. Women who are unable or unwilling to give competent informed consent, or are unable to complete study questionnaires.

2.2 Identification and enrolment of potential participants

All women who require pelvic organ prolapse (POP) surgery will be identified by a dedicated Recruitment Officer in each centre. A log will be maintained of all women meeting the eligibility criterion (admission for prolapse surgery), describing reasons if

they do not agree to enter the study or be randomised. Every woman will be allocated a unique Study Number.

Every eligible woman will be given a flyer containing a brief summary of the study when they attend their initial clinic appointment. She will then be given the Patient Information Sheet with her admission documents (which may be during the initial clinic appointment) or by separate mail if the woman agrees. Women will have the opportunity to discuss all aspects of the study with their GP and/or family members before admission, and their gynaecologist, the Recruitment Officer, and staff at pre-admission clinics and/or when admitted to hospital. In addition, all documentation will have the PROSPECT Study Office contact details to enable women to obtain information from the study organisers. Signed consent will be obtained from each woman to participate (and, if suitable, to be randomised) and followed up after her prolapse surgery by questionnaires and an examination in Gynaecology Outpatients. The Patient Information Sheet and the Consent Form both refer to the possibility of long-term follow-up, being contacted about other prolapse research and access to their NHS records for these purposes.

Women who do not wish to be randomised, or are not suitable for randomisation, will still be eligible to be followed-up using the same Study Protocol as part of the Comprehensive Cohort. They will complete all the study procedures and documents including follow-up, except for the examination at 12 months.

Women who consent to participate in the study will complete a Baseline Questionnaire before surgery. The woman will keep a copy of the Patient Information Sheet and the consent form (one copy will be filed in the notes, one kept in the local recruitment office and the top copy returned to the PROSPECT Study Office in Aberdeen). Women who initially agree to enter the study but later decide to withdraw or become unable to continue will be asked for verbal consent to enable us to maintain their existing data and access relevant NHS data. A letter and GP Information Sheet will be sent to the woman's GP. A copy of the consent form, together with a summary of the study, will be filed in the woman's hospital notes.

Women who do not agree to participate in the study in any way will be logged anonymously along with a minimum dataset of age, type of prolapse (anterior, posterior, uterine, vault; primary or secondary procedure) and parity.

The Baseline Questionnaire completed by participants before surgery includes subjective quantification of prolapse, bowel, urinary and sexual symptoms (see Section 5.1 below), and an objective prolapse assessment (Pelvic Organ Prolapse – Quantification, POP-Q[5]) carried out by the Recruitment Officer. Consenting women who are deemed eligible for randomisation by their gynaecological surgeon will be randomised into one of the trial arms appropriate for her type of prolapse.

The PROSPECT Patient Information Sheet gives patients information about the study and the randomised controlled trials. Our counselling protocols will ensure that women are aware that there is little evidence regarding outcomes and complications after prolapse surgery, especially when mesh is used, in accordance with the guidance from the NICE IPAC recommendations.[4] In addition, a generic Consent and Information Form for Prolapse Surgery will be used by all centres. This will include patient information regarding what to expect from surgery with particular emphasis on expected adverse effects.

Hospital staff will be informed about the study by the local Principal Investigator (PI) and the Recruitment Officer so that they can answer queries from participants and their relatives.

All randomised participants will have a review appointment with an appropriately qualified Recruitment Officer and, if necessary, their gynaecologist, at 12 months to evaluate the results of surgery and identify problems or a need for other treatment. In some sites, this amounts to more postoperative surveillance than is available routinely in the NHS, and should ensure that women receive optimum care.

2.3 Randomisation and allocation to management group for women who consent to be randomised (avoiding selection bias)

When contact details, essential baseline information and confirmation of signed consent are entered into the internet based PROSPECT database, the local researcher will be able to randomise the woman (if appropriate) to one of the groups for which she is eligible (see Flow Diagram, Appendix II). Randomisation will be carried out as close to the time of surgery as is practical (either on the morning of the operation or the previous afternoon), taking into account the hospital routines and time needed for setting up the operating theatre.

Randomisation will utilise the existing proven remote automated computer randomisation application at the study adminstrative centre in the Centre for Healthcare Randomised Trials (CHaRT, a fully registered UK CRN clinical trials unit) in the Health Services Research Unit, University of Aberdeen. This randomisation application will be available both as a telephone-based IVR system and as an internet based service.

Randomisation will be computer-allocated and stratified depending on whether a woman is having a primary or secondary repair.

Primary prolapse (de novo) is defined as a prolapse in a compartment that has not previously been repaired. If the woman is having two primary procedures (i.e. both anterior and posterior vaginal wall prolapses require repair), the randomised allocation will be applied to both prolapse repairs.

Secondary prolapse is defined as a recurrence of prolapse after a previous procedure, when the recurrence is in the **same** compartment. If the woman also needs a concomitant primary repair of a de novo prolapse in a different compartment, this procedure will be chosen on clinical grounds (i.e. not dictated by the randomisation allocation for the secondary procedure).

If the new prolapse is in a different compartment (de novo) and the original site does not require revision surgery, the woman will be classed as having a **primary** repair of the de novo prolapse and randomised in the primary trial.

Randomisation will be minimised on:

- age (less than 60 years or 60 and over);
- type of prolapse being randomised (anterior, posterior or both);
- need for a concomitant incontinence procedure (e.g. TVT) or not;
- need for a concomitant upper vaginal prolapse procedure (e.g. hysterectomy, cervical amputation, vault repair) or not;
- surgeon.

2.4 Ensuring standardisation of intervention and outcome measurement (avoiding performance bias)

All gynaecologists will agree to perform the prolapse surgery using the agreed and standardised methods, materials and procedures as detailed in the Standard Operating Procedures. Both specialist urogynaecologists and general gynaecologists will be eligible for recruiting and randomising women, thus extending the generalisability of the trial and facilitating the future transfer of skills. All the staff delivering the surgical intervention and measuring the objective outcomes will receive

training to ensure standardisation and consistency of their surgical techniques and measurement of pre-operative and post-operative prolapse parameters.

All staff will be proficient in performing the POP-Q[5] method of objective quantification of prolapse descent used pre- and post-operatively. Suitably qualified and trained research Recruitment Officers (rather than clinical staff with direct responsibility for patient care) will be responsible for ensuring that these are carried out and recorded independently before and, for randomised women, at 12 months after surgery. The POP-Q assessments will be recorded on standard study forms or using the POP-Q grid (Appendix III). Data from these forms will be entered using the internet based PROSPECT database and paper copies collected and stored centrally at the Study Office in Aberdeen.

Training and standardisation of surgical techniques will be the responsibility of the four grant applicants in active clinical practice (CB, KC, RF, AS). However, the gynaecological surgeons who agree to participate in the study will have extensive experience and training in urogynaecological reconstructive surgery. Any additional training required will be conducted by the clinical grant applicants and will be directed mainly towards ensuring standardisation of their existing techniques and outcome measurements.

The standard repair and the mesh inlay repair for anterior and posterior prolapse are within the skill capacity of all gynaecologists. The mesh kit repair can be carried out by the PIs and other suitably qualified gynaecologists at each site and capacity is increasing across the UK due to active marketing by the commercial companies introducing these new systems. However, our trial procedures will ensure that only gynaecologists who are trained, experienced (beyond the learning curve) and uncertain about its value will randomise women having secondary surgery to this option.

Compliance
The non-compliance rate amongst gynaecologists is expected to be low because gynaecologists who are uncertain about which operation to choose for their patients, and who are motivated to help with research to establish the answer are expected to collaborate. Several non-specialist gynaecologists in Aberdeen also participated enthusiastically in the pilot study, IMPRESS[6], despite initial unfamiliarity with the use of mesh inlays. The results of the IMPRESS trial indicated that women were particularly well motivated to participate in the study: only 7% declined to be randomised; 88% of women attended for Outpatient Review; and there was a 94% response rate to a follow-up questionnaire 6 months after surgery.[6] An 82% response at 2 years after surgery was achieved without instigating intensive tracing measures.

Completeness of baseline data collection
The surgeons and/or the Recruitment Officers will in conjunction with the British Society of Urogynaecologists (BSUG) Database, complete a Theatre Questionnaire at the time of surgery to ensure a complete record of all surgical techniques and materials used, and any intra-operative difficulties or complications. The Recruitment Officers in each centre will ensure completeness and accuracy of data entry using remote data capture via the study internet based portal at the Study Office in Aberdeen, authored and managed by the UK CRN registered trials unit in Aberdeen (CHaRT). Reciprocal arrangements will be made so that data from PROSPECT study women can be transferred between this and the BSUG database thus reducing duplication of data entry and simplifying the collection of follow up data available to individual gynaecologists via BSUG.

Routine clinical care in hospital
Postoperative care will be standardised as far as possible within each centre and between centres to ensure that differences can be attributed directly to the randomised operative procedures.

2.5 Loss to follow up (avoiding attrition bias)

We obtained over 90% response rates to the 6-month follow-up questionnaires in the feasibility study, IMPRESS.[6] However, a more conservative estimate of 15% loss to follow up has been used in the power calculations: this is in line with the 82% follow up at two years achieved recently in IMPRESS. Active measures to minimise such loss, such as telephoning the women, obtaining back-up 'best contact' addresses, using evidence-based retention measures and checks with their GPs will be undertaken.

In addition we will obtain consent from the women to enable us to access centrally-held NHS data for example via the NHS Summary Care Record in England and Wales, and using CHI numbers from the Information Services Division in Scotland.

2.6 Other sources of bias (avoiding detection bias)

Group allocation will be concealed from the woman and the ward staff, although blinding in theatre is not possible given this is a surgical trial. Women will not be informed after their surgery of the procedure actually carried out unless they specially request this information. Outcome assessment is largely by participant self-completed questionnaire, so avoiding interviewer bias. The clinical review at 12 months in Outpatients will be conducted by research staff blinded to allocation rather than the clinical staff caring for the woman. Randomised participants will undergo an objective vaginal POP-Q assessment without the operator having knowledge of the group allocation. Women and research staff will not be explicitly informed of which operation was randomly selected, although examination may reveal which operation was actually carried out.

A researcher who is blinded to allocation will conduct the data collection, data entry and analysis, using Study Numbers only to identify women and questionnaires. In the RCTs, all women will be actively followed up with analysis based on the intention-to-treat principle. All analyses will be clearly predefined to avoid bias.

2.7 Sample size and feasibility

2.7.1 Feasibility study

In 2006 a pilot RCT was carried out in one centre (Aberdeen) to test the methods, practical arrangements and feasibility of use of mesh in women having prolapse surgery. IMPRESS (Insertion of Mesh or sutures for PRolapsE Surgery Success) was a 2x2 factorial design RCT of mesh versus no mesh, and polydioxanone versus polyglactin sutures.[6] We have now carried out a two-year follow up (IMPRESS). We found that the primary outcome, the patient-reported Pelvic Organ Prolapse-Symptom Scale (POP-SS) improved by 9 units from baseline to 6 months after surgery (94% response), and this was largely maintained at 2 years (83% response).

This trial forms the template for this study. Very few women were unwilling or unsuitable to be randomised (7%) in the pilot but we have used a much more conservative estimate of 50% in the sample size calculations because the proposed trial includes a more radical mesh option (which women and gynaecologists may not wish to choose) and because in a UK-wide multicentre trial, there may be more variation in uptake between centres.

Women who are not suitable or who do not wish to be randomised will be followed up in the same manner as the randomised women, with supplementary information on the reasons for non-randomisation, in the Comprehensive Cohort Study design.

2.7.2 Sample size sought

In an average population of women having prolapse surgery, about 70% will be having a primary procedure. In the current RCT amongst these women, two comparisons will be made:

1. a standard repair versus a standard repair using a biological graft inlay; and
2. 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:

1. a standard repair versus a standard repair using a non-absorbable or combined mesh inlay; and
2. 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.

Allowing for a staggered start, with the inception of the trial in the three centres led by the co-applicants, then rolling out to the other centres, this recruitment will take place over 30 calendar months. We have collected recent information from the

participating centres to give robust reassurance of the feasibility of these recruitment estimates and their willingness to participate. The centres are in: Aberdeen, Manchester, Plymouth, Liverpool, Croydon, Basingstoke, London (Homerton), Leeds, Glasgow (Southern General, Victoria), Stirling, Rotherham, Leicester, Birmingham, York, Hull, Nottingham, Gwent, Bradford, Blackburn, Dundee, Middlesborough and Bristol.

Table 1 Recruitment numbers expected

	Primary procedure (randomised) N=1450	Secondary procedure (randomised) N=620	Non-randomised cohort N=2070
Women needed per arm (minimum)	400	175	
Allowing for 15% dropout	483	206	
Total N of women	1450	620	2070
Assuming 50% willing to enter RCT, N. women having prolapse surgery needed	2900	1240	2070
No. of operations per year per typical centre	70	30	100
No. of typical centres needed for approx 18 months		15	

Allowing for 10% of women who will not wish to take part in the study at all, it is anticipated that 4500 women will need to be screened in order to achieve the recruitment rates required.

2.7.3 Recruitment extension

Various issues caused delays in establishing the study at many participating sites, with the supply of mesh, delay in establishing research nurse support and the waiting time for surgery being the main issues. Therefore an extension to the recruitment phase of the trial is necessary to achieve the required recruitment targets.

1. *Primary repair RCT*

At steady state, the recruitment rate was assumed to be approximately 84 primary repair women per month. However recruitment to the primary repair trial has been slower than anticipated.

The revised projections for the extension period are based on a moving average from the previous two months (October and November 2011), resulting in an expected mean recruitment figure of 70 primary repair women per month (1.9 women per centre per month). Allowing for a staggered start for the remaining centres (37 in total), a 12 month extension will be required to reach the originally specified sample size.

2. *Secondary repair RCT*

It was estimated that 30% of the women screened during PROSPECT would be having a secondary or subsequent repair. Therefore, during the proposed time period for randomising 1450 women to the primary repair trial, it was anticipated that approximately 620 women having secondary surgery would also be randomised. However recruitment to the secondary repair arm has been lower than expected. The main reason for this is that a secondary repair in PROSPECT is defined as a

recurrence of prolapse after a previous procedure, when the recurrence is in the **same** compartment. An analysis of the first 1000 women recruited to PROSPECT indicated that approximately 16% of women meet this criterion. As a result there are fewer women than expected who are eligible for the secondary repair trial (16% compared with the anticipated 30%).

Although a 12 month extension will not be sufficient in terms of achieving the original recruitment target for this RCT, it is anticipated that 174 women will be randomised.

3 TRIAL INTERVENTIONS (Operations and Standard Operating procedures)

3.1 Planned interventions

Women will be randomised to an operation (see Appendix I, Section 1.3) according to their surgical history (previous prolapse repair or not), the availability of the mesh (non-absorbable and/or biological) and the skill capacity of their operating gynaecologist (trained in mesh kit use or not). The study design is shown in the Flow Diagram (Appendix II).

If the non-absorbable mesh inlay or the biological mesh graft is temporarily or permanently (due to financial constraints) unavailable then the women can be randomised to one of the other two arms.

In addition, the expectation is that mesh kits would normally only be used for women who had been randomised to this option. If the operating gynaecologist is not trained in the use of mesh kits the women under their care will be randomised to one of the other two arms. Furthermore, in view of the scarcity of data about its safety and efficacy, we propose to use it only for women who are having a secondary procedure, who have a more complex prolapse problem.

Therefore, women having a primary repair may be randomised to:

- standard anterior and/or posterior repair (central plication) (reference technique);
- standard anterior and/or posterior repair with biological mesh inlay; or
- standard anterior and/or posterior repair with a non-absorbable or hybrid mesh inlay.

Women having a secondary repair may be randomised to:

- standard anterior and/or posterior repair (central plication) (reference technique);
- standard anterior and/or posterior repair with a non-absorbable or hybrid mesh inlay; or
- a mesh kit (using an introducer device) with a non-absorbable or hybrid mesh.

As different mesh types and materials are being introduced, surgeon preference, ability and availability may influence the technologies chosen. However, choices will be limited to mesh from two classes: biological mesh (primary surgery only) or non-absorbable / hybrid mesh. Mesh type and divergence from pre-specified choices will be documented with reasons. All other operative variables will be recorded or standardised using agreed protocols.

The exact operative protocols, including permitted types of mesh, will be agreed and standardised by consensus with the Research Committee of BSUG before the trial begins.

Control interventions

The women in different arms of the surgical trials will act as controls for each other (within each trial). However, the first option (standard anterior and/or posterior

repair) will be regarded as the reference technique for each of the randomised alternatives.

4 SUBSEQUENT ARRANGEMENTS

4.1 Informing key people

Following formal trial entry:

The Study Office will:

i) inform the woman's General Practitioner (by letter enclosing information about PROSPECT and Study Office contact details.

The local Recruitment Officer will:

i) file the Hospital Copy of the Consent form in the hospital notes along with information about PROSPECT and the POP-Q measurements.
ii) inform the ward and theatre staff as appropriate of the woman's entry to the study and details of the intervention allocation (theatre only).
iii) use the PROSPECT internet database to enter data regarding the participant, including data required to complete randomisation; and intra-operative and postoperative information abstracted from local medical records.
iii) return all study documentation to the Study Office in Aberdeen after database entry of essential data.

4.2 Monitoring the women

Women will be contacted by phone, post or email as appropriate. In case of non-return of questionnaires, or non-attendance at outpatient appointments, attempts will be made by staff at the Study Office to trace the women directly using these means or indirectly by contacting the GP or the Best Contact.

Notification by GPs

GPs are asked to contact the Study Office if one of the participants moves, becomes too ill to continue or dies, or any other notifiable event or possible serious adverse event occurs. Alternatively, staff at the Study Office may contact the GP.

Notification by 'Best Contact'

If the PROSPECT Study Office loses touch with a participant (eg questionnaires), we will try to establish why via the 'Best Contact'. Women will be asked when they join the study to nominate a family member or close friend, who will be asked to agree to this nomination.

Offices for National Statistics (HES data in England, ISD data in Scotland)

Consent will be sought from all women to trace their medical records and addresses from centrally held computerised databases. This should facilitate longterm follow up.

5. DATA COLLECTION AND PROCESSING

Follow up will continue for 24 months from the date of operation. It is not part of this protocol or the current study to follow up the women beyond this time. However, consent will be sought to make this possible in the future, and long term follow up is planned (Appendix IV).

5.1 Questionnaires

Women will be asked to complete a baseline questionnaire before surgery. Follow up questionnaires will be sent by post at 6, 12, 18 and 24 months after surgery. Content will include:

i) Prolapse symptoms (POP-SS,[7])

ii) Urinary outcome questions (urinary symptoms and urinary leakage, effect on QOL, http://www.iciq.net/), pad use, catheter use)
iii) Bowel function outcome questions and effect on QoL
iv) Sexual function and vaginal symptoms, effect on QoL (http://www.iciq.net)
v) Health care utilisation questions
vi) Exercise, weight and height, including pelvic floor exercises
vii) EQ 5D[12]

and additionally at baseline only:
i) Obstetric history
ii) GP address and phone number
iii) 'Best Contact' at another address for follow up (not wife or partner)
iv) Other medical problems
v) Date of operation

Postoperatively within a week of surgery:
i) infection / pyrexia
ii) pain and pain relief
iii) blood transfusion
iv) vaginal pack
v) urinary catheter and recatheterisation
vi) bowel function (need for laxatives)
vii) complications and return to theatre
viii) length of stay

At 12 months after surgery (randomised women only):
ii) clinical findings

At 18 months only:
i) Participant Unit Cost Questionnaire

At 6, 12 and 24 months:
i) Complications
ii) Need for further treatment for prolapse
iii) Further treatment for prolapse received or planned, use of health services

Theatre findings and procedures will be recorded in the BSUG database, using a questionnaire designed to be compatible with the requirements of both BSUG and PROSPECT.

5.2 HES and ISD Data

Approximately 24 months after the last woman has been recruited we will run a check for operations, diagnoses and hospital admissions with centrally collected data, to supplement and validate data collected from the participants, and to set up mechanisms for long-term follow up.

5.3 Data processing

Data from the various sources outlined above will be sent to the Study Office in Aberdeen for processing. Staff in the Study Office will work closely with local Recruitment Officers to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks will further enhance the quality of the data.

6. ANALYSIS PLANS

6.1 Ground rules for the statistical analysis

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

(A) In women having a primary prolapse repair,
1) a standard anterior and/or posterior repair will be compared with a standard repair using a biological graft inlay; and
2) a standard anterior and/or posterior repair will be compared with a standard repair using a non-absorbable or combined mesh inlay.

(B) In women having a secondary prolapse repair,
3) a standard anterior and/or posterior repair will be compared with a standard repair using a non-absorbable or combined mesh inlay; and
4) 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.

It is anticipated that the data generated by the study, along with other focused data collection sets, may be used as a basis for exploratory or epidemiological research, but these will be described in separate protocols.

6.2 Measures of outcomes

Primary outcomes

1. The primary patient-reported outcome is symptoms of prolapse, measured as (i) the number and frequency of prolapse symptoms on the Pelvic Organ Prolapse Symptom Scale (POP-SS), (POP-SS questions A1-A7[7]) at one year after surgery and (ii) a quality of life outcome measured as the overall effect of prolapse symptoms on everyday life.
2. The primary economic outcome measure of cost effectiveness is incremental cost per QALY (QALYs based on the EQ-5D[8])

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; and
- 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; and
- satisfaction with surgery.

Urinary outcomes

- Urinary incontinence (persistent or de novo, and types of incontinence); and
- 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); and
- Faecal incontinence (persistent or de novo).

Vaginal symptoms and sexual function outcomes

- Vaginal symptoms ; and
- 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[8])

Economic outcome measures

- Cost and use of NHS services;
- Cost to the women and their families/carers;
- QALYs estimated from the responses to the EQ-5D[8];
- The incremental costs, QALYs and incremental cost per QALY derived by the economic model.

Woman-reported outcomes will be assessed by participant-completed questionnaires in hospital after surgery and at home at 6, 12, 18 and 24 months. Gynaecologists, supported by Recruitment Officers, will complete a questionnaire at the time of surgery providing details of the operative procedures, complications and resource use, and a short clinical questionnaire at the 12 month outpatient review appointment including a POP-Q measurement.

Economic outcomes will be assessed using standard economic methods plus study-specific data collection described earlier. The standardised outcome instruments developed by the International Consultation on Incontinence (ICI)[9] for urinary and bowel function will be used. We will use the International Continence Society (ICS) recommendations for terminology and standard techniques.[10] Consumer groups and our Consumer Advisor will contribute to ensuring that all relevant issues are covered, the patient information and survey instruments are acceptable to the women and the outcome measures relevant.

The ways in which these data will be analysed are set out in the PROSPECT Statistical Analysis Plan and Dummy Tabulations.

It is anticipated that the data generated by the study, along with other focused data collection sets, may be used as a basis for exploratory or epidemiological research, but these will be described in separate protocols.

6.3 Statistical analysis

A single principal analysis is anticipated at 12 months after the last woman is recruited. The Data Monitoring Committee will determine the frequency of confidential interim analyses, but at present these are planned on four occasions during the data collection period.

All analyses within the RCT 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 inter-quartile range if required for skewed data, numbers and

percentages for dichotomous and categorical outcomes (for example subjective recurrence of prolapse).

Analysis of the primary outcome (POP-SS) will estimate the mean differences (and 95% confidence interval) between the intervention and control groups using a general linear model that adjusts for the minimisation covariates and other important prognostic covariates, including the baseline symptom score, at 12 months after surgery. A similar analysis will be used to analyse the primary outcome at 6 and 24 months.

All secondary analyses will be analysed in a similar manner but using the appropriate generalised linear model (for example 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, and relevant link functions, to explore changes in outcome over time.

Within the non-randomised women included in the Comprehensive Cohort Study, efficacy and safety outcomes will be described using the same descriptive statistics as above. Randomised and non randomised cohorts will be compared on baseline characteristics initially. An exploratory analysis will replicate the analysis of the randomised trials as stated above on the non-randomised cohort. A further exploratory analysis will assess any potential differential treatment effects between randomised and non-randomised cohorts. This will allow us to provide potentially more precise estimates of effects and to place the findings of the RCT in the context of the Comprehensive Cohort evidence, thus increasing the generalisability of findings.

Proposed frequency of analyses
Women will be followed up at 6, 12, 18 and 24 months after their prolapse operation. They will be asked to consent to long-term follow up although this is not to be funded by this application.

6.4 Planned secondary subgroup analyses

The two populations of women (having primary or secondary prolapse surgery) will be analysed as separate trials as shown above in section 6.1.

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

1. mesh kit versus other procedures in those that could have been randomised to mesh kits;
2. concomitant continence procedure or not;
3. concomitant hysterectomy/cervical amputation/vault procedure or not;
4. age (<60 or >=60 years);
5. parity; and
6. 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.[11] Stricter levels of statistical significance (2P<0.01) will be sought, reflecting the exploratory nature of these analyses. All study analyses will be according to a statistical analysis plan that will be agreed in advance by the PROSPECT Steering Committee.

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 of prolapse outcome measurement, and build upon our existing work in this area.

6.5 Economic issues

The trial will include a formal economic evaluation assessing the costs and cost-effectiveness of the interventions from the perspective of the NHS and from the women and their families. NHS and patient costs will be presented separately. In the base case analysis relative cost-effectiveness will be based upon NHS costs only, as it is the appropriate use of the NHS's budget that the economic evaluation seeks to inform. Nevertheless, the effect of incorporating patient costs will be considered in sensitivity analysis. This wider perspective will also identify the effect of any shifts in the balance of care between the NHS and patients and their families.

6.5.1 Collection of NHS resource utilization data and costs

Resource utilization
Data collected will include the resources used for the intervention and the use of primary and secondary NHS services by the women including referral for specialist management. Resource use will be recorded prospectively for every patient within the study.

For the surgical interventions operative details will be recorded at the time of surgery (e.g. time the surgery takes, the time spent in recovery, grade of surgeon and assistant, grade of anaesthetist). These details will be recorded on the theatre form.

A parallel exercise will establish resources used immediately before, during and after (i.e. in recovery) the operation e.g. other staff, consumables (surgical requisites, mesh) and capital (costs associated with using the theatre facilities, costs of using reusable equipment).

The use of secondary care services (e.g. length of hospital stay, outpatient appointments and readmissions) will be recorded on the CRF.
The use of primary care services, including medications will be collected using a health service utilisation patient questionnaire. This questionnaire (the health care utilisation questionnaire) will be organised centrally at the Study Office in Aberdeen and will be administered at baseline, 12, and 24 months post randomisation. This approach will also facilitate long-term follow up, even if participants move.

Costs of intervention
Health service costs incurred as the consequence of the prolapse surgery will be estimated prospectively for every participant in the study. Main areas of costs will be: staffing (gynaecologists and nurses), theatre and hospital resource use, capital costs (buildings and equipment), and consumables (mesh inlays, sutures, mesh kits, catheters, packs etc). NHS costs of other health services used will include:

- Consumables (drugs, pads etc)
- Staff time (GP, nurse, consultants)
- Outpatient visits
- Further hospital admissions (operations for complications, other treatment for complications, repeat prolapse surgery)

Unit costs/prices will be obtained using study specific and published estimates for health care services and/or interventions.

6.5.2 Collection of participant resource utilisation and costs

Resource use utilisation data

Participant resource utilisation will comprise three main elements: self purchased healthcare; travel costs for making return visit(s) to NHS health care; and time costs of travelling and attending NHS health care.

- Self-purchased health care is likely to include items such as pads bought by the participant, prescription costs and over the counter medications. Information about these will be collected through the health care utilisation questions (see 6.5.1 above).
- Estimation of travel costs requires information from participants about the number of visits to, for example, their GP or physiotherapist (estimated from the health care utilisation questions) and the unit cost of making a return journey to each type of health care provider (from the Participant Time and Travel Cost Questionnaire).
- The cost of participant time will be estimated in a similar manner. The participant will be asked, in the Participant Time and Travel Cost Questionnaire, how long they spent travelling to and attending their last visit to each type of health care provider. Participants will also be asked what activity they would have been undertaking (e.g. paid work, leisure, housework) had they not attended the health care provider. These data will be presented in their natural units, e.g. hours, and also costed using standard economic conventions, e.g. the Department of Transport estimates for the value of leisure time. These unit time costs, measured in terms of their natural and monetary terms will then be combined with estimates of number of health care contacts derived from the health care utilisation questions.

Administration of time and travel cost questionnaire

The questionnaire eliciting women's time and travel costs associated with accessing and using care will be administered once, at 18 months.

As described above its purpose is to estimate study-specific unit estimates of time and travel costs for individual types of NHS contacts (e.g. outpatient attendances and GP attendances, etc). These unit estimates will then be multiplied by the number of contacts (obtained from the health service utilisation questionnaire) to obtain a total cost for time or travel for that contact. This approach avoids overburdening participants and has been used successfully in many other studies.

6.5.3 Quality of life

A generic instrument (the EQ-5D[26]) will be used to measure health outcomes. Trial participants will be asked to complete the EQ-5D at baseline and at 6, 12 and 24 months after their prolapse operation. This instrument will provide the quality of life weights to compute the QALYs.

6.5. 4 Cost effectiveness

Effectiveness within the trials will be measured in terms of quality adjusted life years (QALYs) and the subjective prolapse symptom score at 12 months (assessed using data from the POP-SS questions). QALYs will be estimated by combining estimated quantity of life, with quality of life derived from the EQ 5D questionnaire (administered at baseline, 6 and 12 months) and UK tariffs. The estimation of QALYs will take account of the mortality of study participants. Participants who die within the study follow-up will be assigned a zero utility weight from their death until the end of the study follow up. QALYs before death will be estimated using linear extrapolation between the QALY scores at baseline and all available EQ 5D scores up to death. The method of eliciting QALYs described is one commonly adopted in economic evaluation.

The primary analysis is based on the one-year follow-up of the trial and two outcomes have been specified. These are incremental cost per additional woman

cured and incremental cost per QALY. The former outcome has been chosen to facilitate understanding of the findings amongst health care professionals while the second measure, the primary economic outcome, has been chosen to reflect a societal decision-making perspective. The results will be presented as point estimates of mean incremental costs, per QALYs and cost per woman cured or per QALY.. Measures of variance for these outcomes are likely to involve bootstrapping estimates of costs, proportion of women cured, QALYs, and incremental cost per additional woman cured and per QALY. Incremental cost-effectiveness data will be presented in terms of cost-effectiveness acceptability curves (CEACs).

Other forms of uncertainty, e.g. concerning the unit cost of a resource, will be addressed using standard deterministic sensitivity analysis. The results of the sensitivity analyses will also be presented as CEACs. Further sensitivity analysis will be conducted to consider the effect of differential timing over which treatments may be given. These data are likely to prove useful for the economic model.

6.5.5 Modelling

While the within study results will prove useful it is important to note that prolapse is a chronic condition and the effects of treatment on costs and outcomes may persist into the future. Therefore, assuming that one intervention is not dominant (less costly but more effective at 12 months), additional useful information for policy makers will be derived from an economic model that considers a longer time horizon. In the model, the findings of the trial will be extrapolated to the patient's lifetime. The model will describe the change in levels of incontinence over the patient's lifetime following the start of treatment. The structure of the model will be developed in collaboration with clinicians and trial collaborators, and parameter estimates for costs and utilities will be derived from the trial data.

In order to extrapolate estimates of cost-effectiveness to a longer time horizon (eg the participant's lifetime) than that considered by the trial, a modelling exercise will be performed. The model will be populated using individual patient data from the study as well as both published and unpublished evidence in the field. The methods used to assemble additional data will follow recognised methodology, which will vary according to the type of parameter, extent of uncertainty and role within the model. Therefore, comprehensive systematic searching will be limited to those parameters to which the results of the model are likely to be particularly sensitive. The modelling exercise will comply with recent recommendations on good practice for modelling[12] and the results will be presented in terms of incremental cost per symptom-free woman and incremental cost per QALY gained.

Estimates of mortality will be based on data from life tables. As the model will be constructed to estimate outcomes both for women having their first prolapse operation, and those having a repeat operation, who are on average 12 years older, mortality rates will be adjusted, where necessary, using relative risks of mortality after prolapse surgery. These data will be obtained from the literature.

Outcomes in the model will be expressed in terms of an incremental cost per QALY. Parameter uncertainty will be integrated by the incorporation of probability distributions into the model and involving Monte Carlo simulation. Other forms of uncertainty such as that associated with choices made about the structure of the model, discount rate, etc., will be addressed though sensitivity analysis. The base case and sensitivity analyses will be presented as CEACs.

Where data allow, the model will be re-estimated for the sub-groups identified above for the within trial analysis. Outcomes in the model will be expressed in terms of an incremental cost per QALY. Parameter uncertainty will be integrated by the incorporation of probability distributions into the model and involve Monte Carlo simulation. Other forms of uncertainty such as that associated with choices made

about the structure of the model, discount rate, etc will be addressed through deterministic sensitivity analysis. The base case, sub-group and sensitivity analyses will be presented as cost and effectiveness plots and, using the net benefit statistic, as CEACs. The model will also be used to identify priorities for further research by identifying threshold values for key parameters (e.g. failure rates) and by investigating the expected value of information.

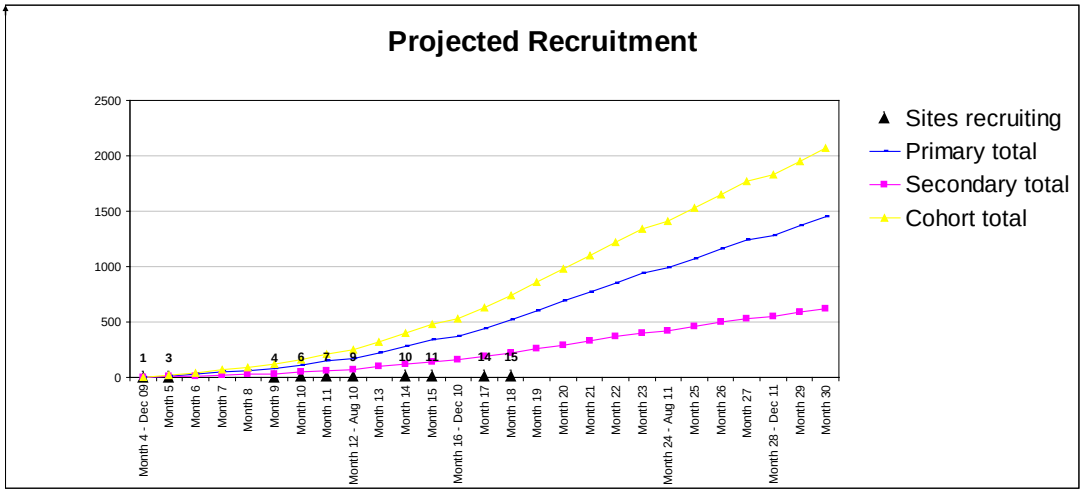
All study analyses, including the within trial, and modeling analyses will be conducted according to an economic analysis plan that will be agreed in advance by the PROSPECT Steering Committee.

7. RECRUITMENT RATES AND MILESTONES

7.1 Recruitment rates

Figure 1 shows the projected recruitment of centres and participants, and projected number of women to be approached. Three centres will be established relatively early in the project (by three months) followed by roll out to the others over the subsequent 15 months.

The participant recruitment graph in Figure 1 has been modelled to take into account: the phased rollout to the centres over the first 18 months; that there will be lags between the approach to women when they are in hospital for pre-assessment and their admission for operation; and that there are likely to be fewer operations around August and over Christmas (due to holidays). Randomisation continues after the final recruitment because of these 'lags'.

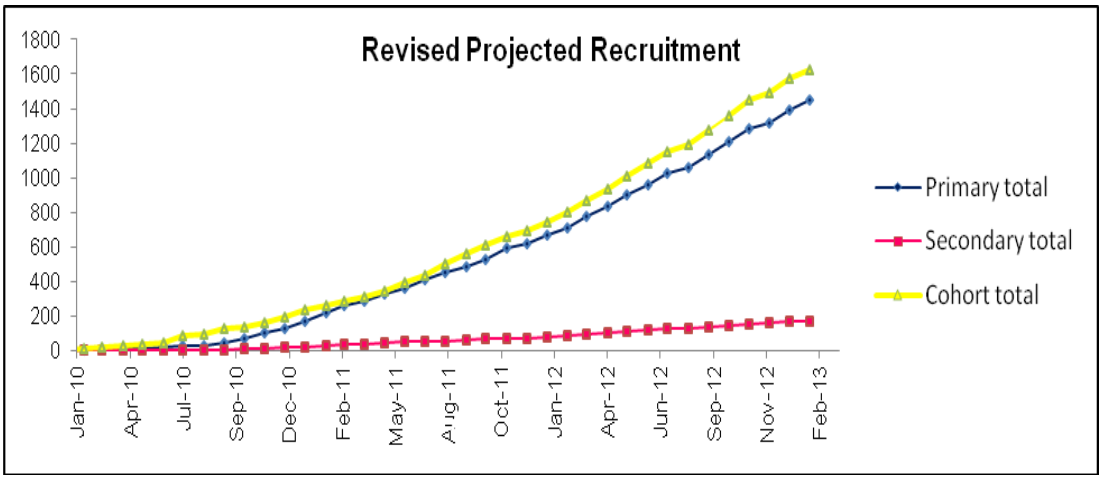


In summary, we aim to recruit around 2250 women to the randomised trials, and a further 2250 to the non-randomised Comprehensive Cohort. This amounts to 300 women per centre (15 sites) over an average recruitment period of 18 months, half of whom will be randomised.

7.2 Revised recruitment rates with extension

Due to the lower than expected recruitment rates, a 12 month extension to the recruitment phase has been approved by the TSC and DMC oversight groups and Funder (December 2011). A revised recruitment graph detailing changes to the primary RCT, secondary RCT and comprehensive cohort is shown in Figure 1a.

Figure 1a Revised projected recruitment chart



In summary, we aim to randomise 1450 woman to the primary repair RCT, 174 women to the secondary repair RCT and enter 1624 into the non-randomised Comprehensive Cohort.

7.3 Project timetable and milestones

Before Start	Agree surgical protocols, standardisation of surgical procedures and mesh options by consensus between Research Committee of BSUG and grant holders.

Year One	
By month 1	NRES approval
By month 3	Set up office and administrative base Construct customised web-based database, including randomisation program and link to BSUG Database
By month 5	Establish first three centres (NRES approval, R&D negotiations, train and appoint local Recruitment Officers)
By month 6	First Steering Committee Meeting Finalise study documentation, training and teaching materials, questionnaires
By month 12	First Data Monitoring Committee meeting Roll out to further 6 centres (R&D approvals, appoint local Recruitment Officers)

Year Two	
By month 15	First 3 centres fully active, next 8 centres initiated, 610 women recruited to RCTs, 610 to non-randomised Comprehensive Cohort Second Steering Committee meeting
By month 18	Establish last 4 centres (R&D approvals, appoint local Recruitment Officers) Collaborators' Meeting
By month 24	1598 women recruited to RCTs, 1598 to non-randomised Comprehensive Cohort Second Data Monitoring Committee meeting

Year Three

By month 30	Recruitment complete, 2070 women recruited to RCTs, 2070 to non-randomised cohort) Third Steering Committee meeting
By month 36	Third Data Monitoring Committee meeting

Year Four

By month 42	Follow up of women at 12 months after randomisation completed (primary end point) Fourth Steering Committee meeting

Year Five

By month 54	Follow up at 24 months after randomisation completed (secondary end point) Data collection completed, data cleaning finished Final Steering Committee meeting
By month 56	Data analysis completed
By month 60	Data archiving, arrangements for long term follow up Final Collaborators' Meeting Submit Final Report and dissemination via main papers describing the study

7.4 Revised timetable and milestones with extension

Year Three

By month 28	All centres fully active
By month 33	Sixth Steering Committee meeting
By month 36	1104 women recruited to the primary repair arm, 132 to the secondary repair arm and 1236 in the non-randomised cohort. Third Data Monitoring Committee meeting

Year Four

By month 42	Recruitment complete, 1450 women recruited to the primary repair arm, 174 to the secondary repair arm and 1624 in the non-randomised cohort. Seventh Steering Committee meeting
By month 48	Fourth Data Monitoring Committee meeting

Year Five

By month 54	Follow up of women at 12 months after randomisation completed (primary end point) Eighth Steering Committee meeting

Year Six

By month 66	Follow up at 24 months after randomisation completed (secondary end point) Data collection completed, data cleaning finished Final Steering Committee meeting

By month 68	Data analysis completed
By month 72	Data archiving, arrangements for long term follow up Final Collaborators' Meeting Submit Final Report and dissemination via main papers describing the trials

8 ORGANISATION

A detailed plan and timetable of study organisation is given in the Gantt chart (Appendix V).

The Gantt chart indicates when it is anticipated that the major study events will occur, including recruitment, study progress and meetings. There will be 3-monthly project management meetings, nine meetings of the Steering Committee and four of the Data Monitoring Committee. Two meetings are planned for collaborators (including gynaecologists, local recruitment officers, consumer participants and members of BSUG), the first timed to occur when all the sites have been identified and the second when results are available.

These time-related milestones will be used to enable close monitoring of progress.

8.1 Local organisation in centres

i) Lead Gynaecologist (Local Principal Investigator)

Each collaborating centre will identify a Lead Gynaecologist who will be the point of contact for that centre. The responsibilities of this person will be to:

- establish the study locally (for example, by getting agreement from clinical colleagues; facilitate local regulatory approvals; identify, appoint and train a local Recruitment Officer; and inform all relevant local staff about the study (eg other consultant gynaecologists, junior medical staff, secretaries, ward staff))
- take responsibility for clinical aspects of the study locally (for example if any particular concerns occur)
- explain the different surgery options to women and ensure informed consent to randomisation or (if not suitable) follow up in the Comprehensive Cohort study has been obtained
- notify the Study Office of any unexpected clinical events which might be related to study participation
- provide support, training and supervision for the local Recruitment Officer(s)
- represent the centre at the collaborators' meetings.

ii) Local Recruitment Officer

Each collaborating centre will appoint a local Recruitment Officer to organise the day to day recruitment of women to the study. The responsibilities of this person will be to:

- keep regular contact with the local Lead Gynaecologist, with notification of any problem or unexpected development
- maintain regular contact with the Study Office
- keep local staff informed of progress in the study
- contact potential participants by: mailing out the Patient Information Sheet to women being admitted electively for prolapse surgery; identifying all eligible women at pre-assessment clinics or on the ward while they are in hospital for their prolapse surgery; explain the study and the potential for participation in a trial if they are eligible; explaining what is intended by research access to their NHS data; and describing the possibility of long-term follow up and participation in other research
- obtain the woman's written consent to participation (and randomisation as appropriate)

- keep a log of whether eligible women are recruited or not (with reasons for non-participation and non-randomisation)
- collect baseline data describing the women, log this information in the web-based PROSPECT database and send paper copies to the Study Office along with the original signed consent forms
- use this information to randomise the women using the web-based PROSPECT database or the linked telephone randomisation service
- ensure operative and postoperative data are collected and recorded in the web-based PROSPECT database or the BSUG database as appropriate, and send paper copies to the Study Office
- file relevant study documentation (eg consent forms, POP-Q results) in the woman's medical records
- organise and supervise alternative recruiters in case of holiday or absence
- represent the centre at the collaborators' meetings.

8.2 Study co-ordination in Aberdeen

i) The Study Office Team

The Study Office is in CHaRT, Health Services Research Unit in Aberdeen and provides day to day support for the clinical centres. It is responsible for all data collection (such as mailing questionnaires), follow-up, data processing and analysis. It is also responsible for randomisation, and communicating with the sites about PROSPECT specific issues. We will produce a yearly PROSPECT Newsletter for participants and collaborators to inform everyone of progress and maintain enthusiasm.

The PROSPECT Study Office Team (Aberdeen-based grant holders and study office members) will meet formally at least monthly during the course of the study to ensure smooth running and trouble-shooting.

ii) The Project Management Group (PMG)

The study is supervised by its Project Management Group. This consists of the grant holders and representatives from the Study Office. Observers may be invited to attend at the discretion of the Project Management Group. We plan to meet or hold a teleconference every three months on average.

iii) The Trial Steering Committee (TSC)

The study is overseen by an independent Steering Committee. The membership comprises of the four independent members (including the Chairman), the CI and grantholders. Observers or members of the host university (Aberdeen) and the funders (the HTA) may also attend, as may other members of the PROSPECT Study Office or members of other professional bodies at the invitation of the Chair. It is anticipated the TSC will meet on nine occasions.

8.3 Research Governance, Data Protection and Sponsorship

8.3.1 Research Governance

The trial will be run under the auspices of CHaRT based at the Health Services Research Unit, University of Aberdeen. CHaRT is a registered Clinical Trials Unit with particular expertise in running multicentre RCTs of complex and surgical interventions. The study will be conducted in line with local implementation of Research Governance to at least the standard of the Aberdeen University policy on Research Governance
(http://www.abdn.ac.uk/iahs/research-governance/index.shtml).
CHaRT will provide centralised trial administration, database support and economic and statistical analyses.

8.3.2 *Data Protection*

The trial will comply with the Data Protection Act 1998 and regular checks and monitoring are in place to ensure compliance. Data are stored securely in

accordance with the Act and archived to a secure data storage facility. The consent form will state that other researchers may wish to access (anonymised) data in the future. The trial statistician (in collaboration with the Chief Investigator) will manage access rights to the data set. Prospective new users must demonstrate compliance with legal, data protection and ethical guidelines before any data are released. We anticipate that anonymised trial data will be shared with other researchers to enable international prospective meta-analyses.

8.3.3 Sponsorship

The study is sponsored by the University of Aberdeen.

The CI will ensure, through the TSC, that adequate systems are in place for monitoring the quality of the study (compliance with GCP) and appropriate expedited and routine reports of adverse effects, to a level appropriate to the risk assessment of the study.

8.3.4 Retention of data

It is intended to follow up the whole cohort of women for at least 10 years, and data will be retained as long as necessary for this purpose. Permissions will be sought from the relevant Research Governance bodies and the Ethics Committee. Attention has recently been drawn to the importance of long-term follow up, especially in the study of pelvic floor dysfunction.[13]

8.4 Data and safety monitoring

8.4.1 Data Monitoring Committee

A separate and independent Data Monitoring Committee (DMC) will be convened. It is anticipated the members will meet once to agree terms of reference and on at least three further occasions to monitor accumulating data and oversee safety issues. This Committee will be independent of the study organisers and the TSC. During the period of recruitment to the study, interim analyses will be supplied, in strict confidence, to the DMC, together with any other analyses that the committee may request. This may include analyses of data from other comparable trials. In the light of these interim analyses, the DMC will advise the Steering Committee if, in its view:

a) one of the methods of prolapse surgery has been proved, beyond reasonable doubt[*], to be different from the control (standard management) for all or some types of women (in respect of either effectiveness or unacceptable safety concerns), and
b) the evidence on the economic outcomes is sufficient to guide a decision from health care providers regarding recommendation of which operation to choose.

The TSC can then decide whether or not to modify intake to the trial. Unless this happens, however, the TSC, PMG, clinical collaborators and study office staff (except those who supply the confidential analyses) will remain ignorant of the interim results.

The frequency of interim analyses will depend on the judgement of the Chairman of the DMC. However, we anticipate that there might be two interim analyses and one final analysis.

The Chairman and the other independent members are to be appointed after confirmation by the HTA.

[*] Appropriate criteria for proof beyond reasonable doubt cannot be specified precisely. A difference of at least three standard deviation in the interim analysis of a major endpoint may be needed to justify halting, or modifying, such a study prematurely (Peto R et al, *Br J Cancer* 1976;34:548-612).

8.4.2 Safety concerns

The PROSPECT trial involves surgical operations for prolapse which are well established in clinical practice, and others which have been developed in response to the poor success rates for standard primary surgery (30% of women will require a further operation). New operations involve the use of mesh. Their effectiveness is largely unproven and adverse effects may include pain, haemorrhage, infection, dyspareunia and mesh erosion, as well as damage to pelvic organs. However, these adverse effects may also occur after 'standard' prolapse surgery. The relevant guidelines for reporting serious adverse events will be followed.

Possible expected occurrences

In this study the following occurrences are potentially expected:

- Possible (expected) intraoperative occurrences associated with surgery are: injury to organs or blood vessels, excess blood loss, blood transfusion, anaesthetic complications, death.

- Possible (expected) occurrences following surgery are: thrombosis, infection (UTI, sepsis, abscess), pain, urinary retention, bowel obstruction, constipation, mesh erosion, excess blood loss, haematoma, vaginal adhesions, skin tags, granulation tissue, new or persistent urinary tract symptoms, death.

Details of any of the occurrences listed above will be recorded on the case report forms (CRFs) and reported to the DMC.

8.4.3 Procedure for reporting untoward and related SAEs in this study

A Serious Adverse Event (SAE) in PROSPECT is defined as an event occurring to a research participant that is both:

- related (resulted from administration of any of the research procedures) and
- unexpected (ie the type of event that is not listed above as an expected serious occurrence) that causes death, is life threatening, requires hospitalisation or prolongation of an existing hospital admission, or results in significant incapacity/disability.

All SAEs will be recorded on the Serious Adverse Event Report form. In addition, SAE forms will record all deaths for any cause during the course of the study.

8.4.4 Reporting responsibilities of the CI

The CI will be automatically notified of any potential related and unexpected SAEs. If, in the opinion of the local PI and the CI, the event is confirmed as being related and unexpected, the CI will submit a report to the main REC, the study sponsor and the DMC within 15 days of the CI becoming aware of it.

Collaborators and participants may contact the chairman of the TSC through the Study Office about any concerns they may have about the study. If concerns arise about procedures, participants or clinical or research staff (including risks to staff) these will be relayed to the Chairman of the DMC.

As the trial arm to which women are allocated cannot be blind to the gynaecologist or theatre staff after randomisation has occurred, unblinding is not an issue in this trial. A record of the operative procedures actually carried out will be available in the medical notes if required clinically.

8.5 Ethical issues and arrangements

The North of Scotland Ethics Committee (NOSRES) has reviewed this study. The study will be conducted according to the principles of good practice provided by Research Governance Guidelines.

We believe this study does not pose any specific risks to individual participants beyond those of any surgery, nor does it raise any extraordinary ethical issues. It is possible that cultural or religious factors may affect the choice of graft material, as some biological grafts are of porcine origin (which may be inappropriate for certain religious groups). This will be taken into account in choosing appropriate materials for particular groups.

8.5.1 Risks and benefits

The benefit to the women participating in the trial is the chance of receiving the optimum treatment for their prolapse, although we do not know what that treatment is. The risks are that they may have a sub-optimal operation but any operation carries a risk, and it is not known which is optimal or more risky. The benefit to society is that, at the end of the trial, it will be known which operations are most effective and cost-effective. Extra information will be available on safety and efficacy outcomes through analysis of data from the non-randomised women included in the Comprehensive Cohort.

8.5.2 Information about risks and benefits and informed consent

Women will be informed of possible benefits and known risks by means of a generic prolapse surgery consent form, discussion with the local Recruitment Officers and their own gynaecologist. Women who are not able or not willing to give informed consent to be studied will not be recruited.

9. FINANCE

The study is supported by a grant from the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), Health Technology Assessment (HTA) Programme (ref 07/60/18).

10. EXPLANATORY STUDIES

The funds provided by the NETSCC HTA are to conduct the randomised controlled trials and Comprehensive Cohort study as described in this protocol. It is recognised, however, that the value of the study will be enhanced by ancillary studies of specific aspects. Plans for some of these may be submitted to other grant funding bodies. Suggestions will be discussed and agreed in advance with the TSC and also agreed with the NETSCC HTA. Appropriate legislative approvals will be sought for any new proposals.

11. INDEMNITY

The Patient Information Sheet provides the following statement regarding indemnity for negligent and non-negligent harm:

> 'We do not expect any harm to come to you by taking part in this study. All the materials and techniques are already being used in the NHS for prolapse surgery. Your participation in the study is therefore only to help us evaluate these procedures and should not involve any additional risk to you. Taking part in this study does not affect your normal legal rights. Whether or not you do take part, you will retain the same legal rights as any other patient in the NHS (which include professional indemnity insurance for negligence). If you wish to complain about your health care or any aspects of this study, the normal NHS mechanisms will be available to you.

In addition, the universities involved with this study hold and maintain a 'no fault' insurance policy. This policy covers all employees of the universities and those working under their direction.

12. PUBLICATION

The success of the study depends entirely on the wholehearted collaboration of a large number of women undergoing prolapse surgery, as well as their nurses and doctors. For this reason, chief credit for the study will be given, not to the

committees or central organisers, but to all those who have collaborated in the study. The study's publication policy is described in detail in Appendix VI. The results of the study will be reported first to study collaborators. The main report will be drafted by the Project Management Group and circulated to all clinical collaborators for comment. The final version will be agreed by the Steering Committee before submission for publication, on behalf of all the PROSPECT collaborators.

To safeguard the integrity of the main trial, reports of explanatory or satellite studies will not be submitted for publication without prior agreement from the Project Management Group.

We intend to maintain interest in the study by publication of PROSPECT newsletters at intervals for participants, staff and collaborators. Once the main report has been published, a lay summary of the findings will be sent in a final PROSPECT Newsletter to all involved in the trial.

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APPENDIX I BACKGROUND TO THE STUDY

1. THE REASONS FOR THE TRIAL

Introduction

Gynaecologists have recognised for some time that both anatomical failure of supporting pelvic structures and recurrence of prolapse after surgery are common. More recently, it has also been recognised that surgery can be followed by a greater impairment of quality of life than the original prolapse itself (for example new urinary incontinence after surgery or new prolapse at a different site). Furthermore, additional surgical support materials are being actively promoted and introduced to clinical practice (including many types of mesh with different properties), without robust evidence of their value or clear analysis of the risks (such as infection, erosion or dyspareunia) from rigorous independently-managed RCTs.

This study will definitively assess which of the most frequently employed techniques for the most common types of prolapse (anterior and posterior vaginal wall prolapse) produce the optimal symptomatic result. This will guide gynaecologists in their surgical practice and purchasers in their choice of provision of health care. The study will also identify which procedures are not only less clinically effective but also not cost effective. Given the number of prolapse procedures currently performed (28,000 annually in the UK)[14] and the anticipated rise in need for such surgery with an ageing population (a two fold increase in the age group at risk in the next thirty years is predicted)[15] the potential cost implications for the health service are considerable.

1.1 Scale of the problem in the UK and use of NHS resources

Pelvic organ prolapse (POP) is the descent from its normal anatomical position of some of the female genital organs. POP is caused by herniation through deficient pelvic fascia, or due to weaknesses or deficiencies in the ligaments or muscles which should support the pelvic organs. There is little epidemiological research into this condition because it has a variety of presentations and they do not all cause symptoms, particularly in the early stages.[16] Estimates of the prevalence of prolapse vary from 41%[17] to 50%[18] of women over the age of 40 years.

It has been estimated that women have a lifetime risk of 11% of undergoing surgery for urinary incontinence or prolapse and 7% for prolapse alone.[19] The annual incidence of surgery for POP is within the range 15 to 49 cases per 10,000 women years[16], and it is likely to double in the next 30 years.[20] Little is known about the prevalence and effectiveness of different types of operations, but it is notoriously prone to failure: around 30% of women undergo further operations, the mean time interval to the first secondary operation is about 12 years, and the time interval between subsequent procedures decreases with each successive repair.[19] In addition, repair of one type of prolapse may predispose the women to the development of a different type of prolapse (a new, or de novo prolapse) in another compartment of the vagina due to alteration in the dynamic forces within the pelvis.[19]

Surgery is common. In England and Wales in 2004-2005, 26,947 women were admitted to hospital with a main diagnosis of female genital prolapse, and 28,297 operations were performed (some women had more than one type of prolapse operation).[14] The majority of the operations (93%) were in women having anterior repair (n=8,560), posterior repair (5,406), or both operations (5,654), or with a concomitant uterine prolapse (6,837). Only 7% were in women with vault prolapse (1,840). Assuming a population of about 20 million women in the age group at risk for prolapse surgery (50 to 85 years), the UK operation rate is currently around 14[14] to 16[20] women having prolapse operations per 10,000 per year.

The need is likely to increase due to the rising number of elderly women. It has been projected that the number of women in the age group 50 to 85 years (those most likely to need prolapse surgery) will increase by 1.14 million between 2004 and 2014.[15]

1.2 The decision to test alternative forms of surgery

Existing research

There is little evidence available from RCTs to guide management for women with prolapse. Three Cochrane reviews cover the main options: surgical management;[1] and conservative management including: mechanical devices;[2] and physical treatment such as pelvic floor muscle training (PFMT).[3] A new Interventional Procedures (IP) review has also just been published on the use of mesh in anterior and posterior prolapse surgery.[4]

1.2.1 Conservative management for women with prolapse

Although there are no RCTs to guide the use of mechanical devices (pessaries or rings),[2] these are often used for women who are unfit for surgery or who wish to avoid surgery. They can be very efficacious, but questions remain about the best type of device, the long term adverse effects and the use of supplementary treatment such as oestrogen. Further research is required. Conservative physical treatments such as PFMT are also often recommended as first line management. A recent update of the relevant Cochrane review[3] has found three small and inconclusive trials, suggesting that further research is required. A multicentre RCT is under way in the UK to address this evidence gap (the POPPY trial, Pelvic Organ Prolapse PhysiotherapY).

1.2.2 Surgical management for women with anterior or posterior vaginal wall prolapse

A new update of the Cochrane Review of surgery for prolapse[1] identified 13 RCTs of surgical interventions for women with anterior or posterior pelvic organ prolapse. The IP review[4] for NICE has identified a further nine RCTs which are not yet included in the Cochrane review. The total number of women receiving mesh in the IP systematic review[4] was 4569: mesh was inserted using an introducer device, trochar or kit in 503 of these women. There were no data on the differential effects in women having primary as opposed to secondary surgery: all the trials reported both groups of women together despite their potentially different prognoses.

Differences in inclusion criteria or interventions (e.g. types of women, operations or mesh) precluded much useful meta-analysis or reliable conclusions. There were two small but inconclusive RCTs comparing standard repairs with or without mesh with site specific fascial defect repairs[22;23]. There were another two small and inconclusive RCTs which included a mesh introducer device arm.[24;25]

For anterior vaginal wall prolapse, the limited RCT data from the Cochrane review[1] and the IP review[4] (9 RCTs) suggested that any mesh might reduce subsequent objective anatomical relapse (77/557, 14% relapse) compared with using no mesh (179/591, 30%) (RR 0.48, 95% CI 0.32 to 0.72) in the short term. The IP review[4] also included additional data from non-randomised comparative studies and case series. Using these extra data, non-absorbable synthetic mesh had the lowest failure rate:

- compared with absorbable synthetic mesh (OR adjusted for bias from study design 0.23, 95% CI 0.12 to 0.44);[4] and
- compared with absorbable biological mesh (OR adjusted for bias from study design 0.37, 95% CI 0.23 to 0.59).[4]

On the other hand, the mesh erosion rates increased from 1% (95% CI 0.1% to 4%) with synthetic absorbable mesh to 6% with absorbable biological mesh to 10% with non-absorbable synthetic mesh.[4] The data were too sparse, however, for other

reliable statistical analysis. There were insufficient data on women's subjective prolapse symptoms or complications such as infection, blood loss or dyspareunia, and none on long term outcomes. Particular safety worries are related to the use of introducer devices (trochars) that are needed for the blind insertion of mesh into intra-pelvic spaces.[26]

These and other findings were presented to the Interventional Procedures Advisory Committee (IPAC) in January 2008, and their guidance has now been published: http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11363. The Committee recommended that mesh should only be used under special arrangements for clinical governance, consent and audit or research.

1.2.3 Implications for the study

There is insufficient information about any of the surgical options to guide management of any type of pelvic organ prolapse in any population of women with prolapse. We have identified that the largest group of women are those with anterior and/or posterior prolapse, who comprise around 90% of those having prolapse surgery (including those having a concomitant hysterectomy). The evidence base for treating these women is clearly inadequate, with very little evidence regarding subjective prolapse symptoms, effect on quality of life and safety. In particular, the routine use in the NHS of mesh for prolapse surgery should be informed by well designed RCTs.

The current application will fulfil the research need identified by the Cochrane Review[1] and the IP review[4] for adequately powered RCTs of the use of mesh in prolapse surgery. It will comprise the largest, only adequately powered and independent RCT comparing traditional prolapse operations with new methods incorporating mesh as an inlay or mesh inserted using an introducer system. We will take account of the different clinical characteristics of women having primary as opposed to secondary surgery, and identify confounding factors which may predict outcomes.

1.3 The operations

This trial is concerned with surgical operations for vaginal wall pelvic organ prolapse:

- anterior vaginal wall prolapse (urethrocele, cystocele, paravaginal defect);
- posterior vaginal wall prolapse (enterocele, rectocele, perineal deficiency).

A woman may present with prolapse of one or both of these sites, and she may be having a primary or a secondary procedure. For each of these sites there are several alternative traditional surgical techniques, none of which have been properly evaluated in adequately powered multicentre RCTs. The techniques for performing anterior or posterior repair or implanting mesh or graft can vary widely between gynaecologists. These include:

a) Standard anterior and/or posterior repair

In the standard approach, the vaginal skin is opened in the midline, the fascia is separated from the skin and the fascial defect is plicated (sutured or buttressed), usually in the midline. Any redundant vaginal skin is excised and the skin is closed.

b) Standard repair with mesh inlay

Over the last 10 years, gynaecologists have begun to include small pieces of mesh inlays as an extra support to the fascial defects through which the pelvic organs prolapse, analogous to the use of mesh in hernia surgery.[27] If mesh is used, it can be positioned over or under the fascial defect as a 'mesh inlay' and sutured in place to reinforce the tissues.

The proposed advantage of using mesh is that it will optimise surgical outcome without compromising vaginal capacity or sexual function.[28] The rationale is that it

may help to reduce failure rates from breakdown of weakened tissue or failure to identify all fascial defects.[29] Although the mesh materials used may be stronger than the woman's own fascial tissue, the indications for use and choice of materials remain controversial.[29] The extent to which mesh inlays are currently used is unknown, but recent surveys suggest that many gynaecologists are already incorporating mesh into their practice both in the UK[30] and in America.[31] The decision to use mesh is complicated by the different types available:

- absorbable synthetic (e.g. polyglactin);
- absorbable biological (e.g. fascia lata, porcine dermis);
- combined (e.g. polyglactin and polypropylene); and
- non-absorbable (e.g. polypropylene).

There are theoretical pros and cons to each, but there is not enough evidence available to allow rigorous comparison. Major potential adverse effects include infection, bleeding, erosion and dyspareunia as well as failure of repair and failure to cure symptoms.

c) Mesh insertion using an introducer device or kit

Most recently, some commercial manufacturers of mesh have introduced large mesh systems, analogous to, but much bigger than, the TVT slings used in incontinence surgery.[32] These commercial devices or kits are available for the anterior or posterior compartments, or can be used together for both. The mesh is inserted using introducer devices. They involve blind penetration of pelvic spaces by trocars in order to thread mesh tails into positions from which they support a central mesh layer which corrects the prolapse defect. Currently available devices use non-absorbable synthetic mesh but kits using other types of mesh (combined) are being introduced.

These are being actively promoted and introduced to clinical practice without first being evaluated in rigorous independently-managed RCTs. These meshes are inserted blindly using introducer devices or trocars which may damage surrounding organs or blood vessels.[26] Various systems are available for anterior, posterior or combined defects. Prospective studies have suggested that the mesh devices have been used in at least 500 women worldwide, but it is not clear whether this is driven by gynaecological preference or commercial marketing pressure. However, clearly some women have been willing to undergo this new technology despite lack of evidence for safety or efficacy. Information from one manufacturer suggests that they anticipate a rapidly increasing penetration of the market: while they sold 1,574 systems in 2002, they predict selling 6,367 in 2007 and 10,100 by 2010.

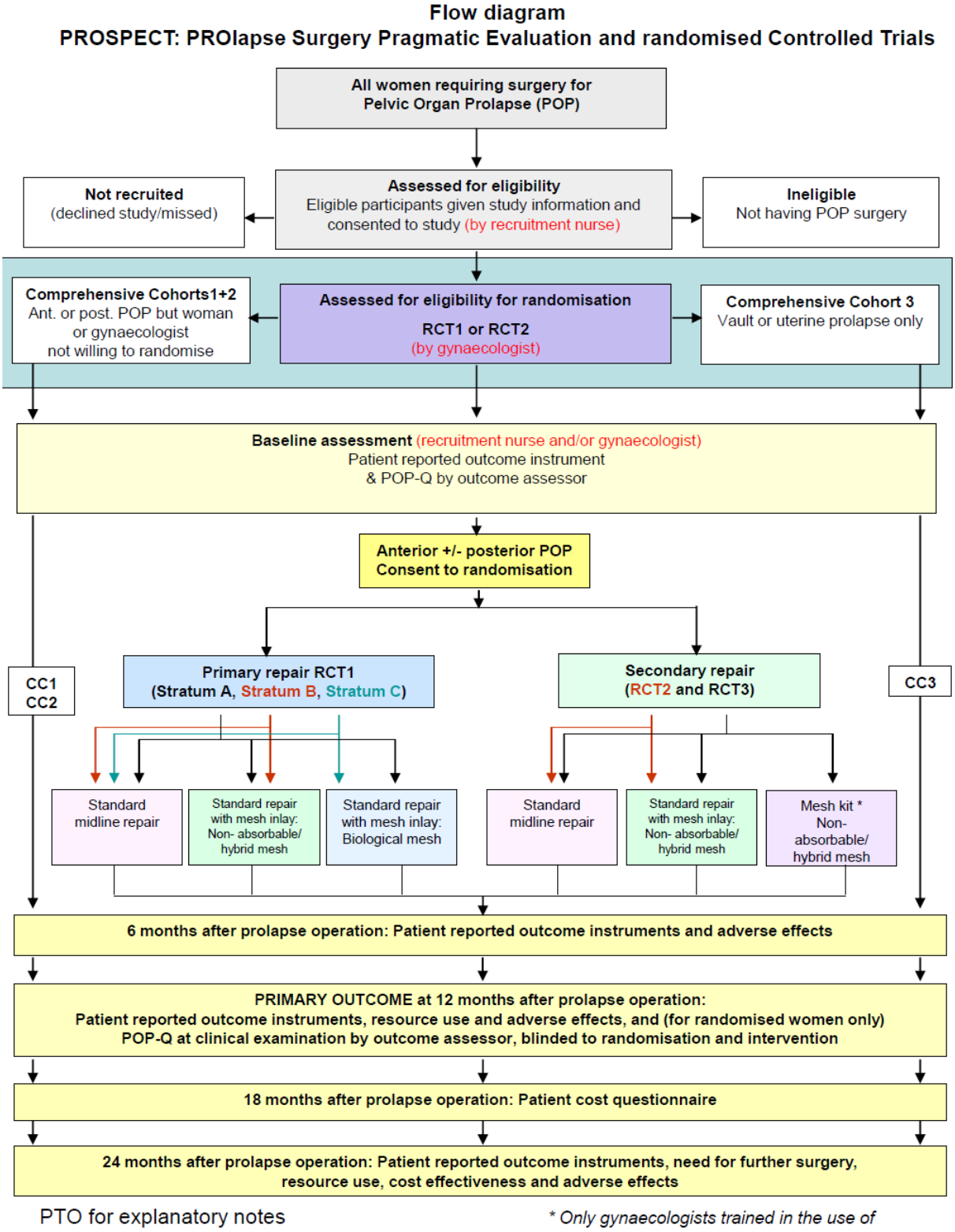
There is no evidence to suggest whether or not the use of mesh (particularly non-absorbable synthetic mesh which has the strongest mechanical strength and remains in situ indefinitely) should be reserved for more complex or recurrent prolapse. Although gynaecologists have stated that this is their belief and practice,[30] evidence suggests that the majority (70%) of the current recipients of mesh are having their first prolapse operation.[4] An Interventional Procedures review with 503 women[4] and a further recent case series of 289[26] women drew attention to the high incidence of serious adverse effects (e.g. 2.8% with damage to surrounding organs) in women having mesh inserted with blind introducer devices. Our opinion is that until their benefits and risks have been properly evaluated, mesh kits using non-absorbable synthetic mesh should be reserved for more complex cases of prolapse. Therefore we will limit this option to women being treated for a recurrence of prolapse in the same site after primary surgery.

The initial purchase cost of mesh inlays (around £200 per woman) and mesh kits (around £400-600) is likely to have a significant impact on the cost of prolapse surgery. The proposed trial will provide evidence to indicate whether the extra costs of mesh are justified in terms of better outcomes for women and for the NHS.

1.4 The gynaecologists

For a gynaecologist to join the PROSPECT study, he or she must be uncertain regarding the best operative technique for repairing prolapse, and hence be willing to randomise the majority of patients. All the gynaecologists must be able to perform standard and mesh inlay repairs. Gynaecologists who are not trained (beyond the learning curve) in the use of the mesh introducer kits will only be able to randomise women to the other options.

APPENDIX II FLOW DIAGRAM



PTO for explanatory notes

** Only gynaecologists trained in the use of*

Explanatory Notes for Flow Chart

1. Definitions of primary and secondary repairs:

Randomisation for women who had a previous repair will be based on the site of the previous surgery.

- A primary procedure is defined as the first prolapse repair in that compartment.
- A secondary procedure is defined as a repeat repair of a prolapse previously repaired in that compartment.
- If the woman has had a previous prolapse repair but she only needs a repair of a prolapse in a different compartment (de novo prolapse) she will be randomised as having primary surgery for that compartment.
- If a woman had a new (de novo) prolapse and a previously repaired prolapse which also needs a second repair, she will be randomised as having secondary surgery for that compartment. The de novo prolapse will be treated as a concomitant procedure (i.e. not subject to randomisation, the gynaecologist can choose the most appropriate prolapse procedure).

2. Concomitant procedures

All the following concomitant procedures will be allowed but must be recorded and described:

- Continence procedure
- Hysterectomy (vaginal or abdominal) including method of vault support
- Vault repair
- Sacrospinous suspension

3. Definition of trials and cohorts

Women having Primary Surgery RCT1

Stratum A: RCT in women having Primary surgery for Anterior and/or Posterior vaginal wall prolapse and surgeon able to randomise between all three arms

Stratum B: RCT in women having Primary surgery for Anterior and/or Posterior vaginal wall prolapse and surgeon able to randomise between the first two arms

Stratum C: RCT in women having Primary surgery for Anterior and/or Posterior vaginal wall prolapse and surgeon able to randomise between the first and third arm

CC1: Non-randomised Comprehensive Cohort 1 women who were eligible (having Primary surgery for Anterior or Posterior vaginal wall prolapse) but not randomised.

Women having Secondary Surgery

RCT2: RCT in women having Secondary surgery for Anterior and/or Posterior vaginal wall prolapse and surgeon able to randomise between the first two arms only and

RCT3: RCT in women having Secondary surgery for Anterior and/or Posterior vaginal wall prolapse and surgeon able to randomise between all three arms and

CC2: Non-randomised Comprehensive Cohort 2 women who were eligible (having Secondary surgery for Anterior or Posterior vaginal wall prolapse) but not randomised.

Women having other prolapse surgery

CC3: Comprehensive Cohort 3, women having other prolapse surgery only (not Anterior or Posterior vaginal wall prolapse).

APPENDIX III POP-Q GRID

POP-Q RECORDING (Example of normal values)

Cervix present?	Yes ☑
	No ☐

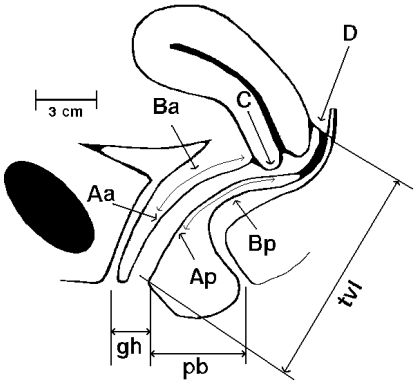
genital hiatus	perineal body	total vaginal length
3 cm	**3** cm	**10** cm

	External									Hymen			Internal								
cm	+10	+9	+8	+7	+6	+5	+4	+3	+2	+1	0	-1	-2	-3	-4	-5	-6	-7	-8	-9	-10
Aa														X							
Ba														X							
C																			X		
D																					X
Bp														X							
Ap														X							
	Stage 3 or 4 (depending on TVL)									Stage 2			S1	Stage 0 or 1 (depending on TVL)							

POP-Q MEASUREMENTS:

The 9 measurements described below make up the POP-Q. All measurements are in centimetres. Record all measurements to the nearest 1cm using the disposable rulers provided.

The first 3 measurements are recorded in the boxes. All values are positive.



gh (genital hiatus)	is measured from the middle of the external urethral meatus to the posterior midline hymen.
pb (perineal body)	is measured from the posterior margin of the genital hiatus to the midanal opening.
tvl (total vaginal length)	is the greatest depth when point C or D is reduced to its normal position.

The remaining 6 measurements are vaginal points which can be negative (internal) or positive (external). Record each point on the grid by marking a cross in the centre of the corresponding box.

Points on the anterior vaginal wall:

Aa is located in the midline of the anterior vaginal wall 3cm proximal to the external urethral meatus (range -3 to +3cm).

Ba is a point that represents the most distal (most dependent) position of any part of the upper anterior vaginal wall from the vaginal cuff/anterior fornix to point Aa.

Points on the upper vagina:

C is a point that represents either the most distal (most dependent) edge of the cervix or the leading edge of the vaginal cuff (hysterectomy scar/vault).

D is a point that represents the location of the posterior fornix (or pouch of Douglas) in a woman who still has a cervix. Point D is omitted in the absence of the cervix.

Points on the posterior vaginal wall:

Ap is located in the midline of the posterior vaginal wall 3cm proximal to the hymen (range -3 to +3cm).

Bp is a point that represents the most distal (most dependent) position of any part of the upper posterior vaginal wall from the posterior vaginal fornix (D) or vaginal cuff (C) to point Ap.

All 9 values must be filled in, except D if the woman has had a total hysterectomy: then record vault = C.

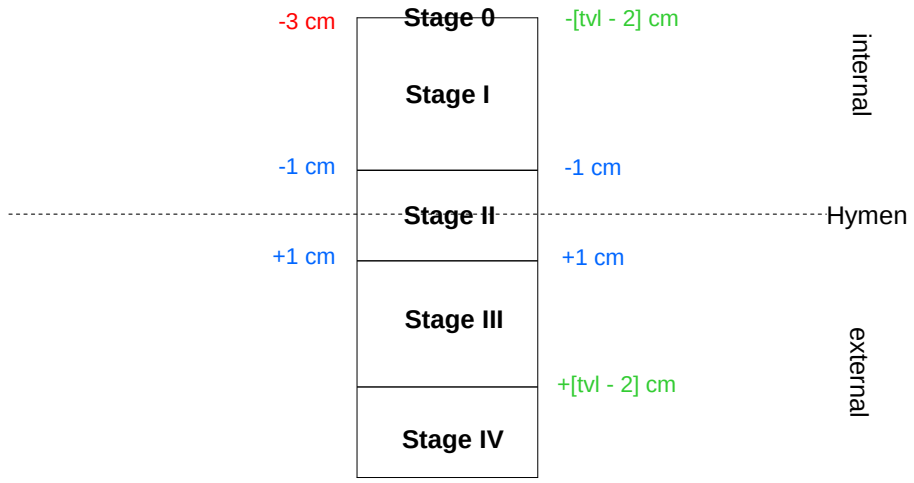
EXAMINATION CONDITIONS:

1. Ideally bladder should be emptied by spontaneous void prior to examination.
2. Woman positioned supine on examination couch with head rest raised to 45^0.
3. Record content of rectum and bladder.
4. Ensure maximum protrusion of prolapse is seen (all measurements except total vaginal length are taken while patient is bearing down).
5. Use vaginal speculum to examine vaginal walls separately.

STAGING THE PROLAPSE:

Stages are assigned according to the most severe portion of the prolapse when the full extent of the protrusion has been demonstrated.

Stage 0	No prolapse is demonstrated. Points Aa, Ap, Ba and Bp are all at -3cm and point C or D is between –tvl and –(tvl-2) cms.
Stage I	The criteria for stage 0 are not met, but the most distal portion of the prolapse is >1cm above the level of the hymen.
Stage II	The most distal portion of the prolapse is ≤1cm proximal (above) to or distal (below) to the plane of the hymen (≥ -1cm but ≤+1cm)
Stage III	The most distal portion of the prolapse is >1cm below the plane of the hymen but protrudes no further than 2cm less than the tvl in cm.
Stage IV	Essentially, complete eversion of the total length of the lower genital tract is demonstrated. The distal portion of the prolapse protrudes to at least tvl-2cm. In most instances, the leading edge of stage IV prolapse will be the cervix or vaginal cuff scar.



BLUE reference measurements apply for all points
RED for points Aa, Ba, Ap, Bp only
GREEN for points C and D only

APPENDIX IV LONG TERM FOLLOW-UP

Background

PROSPECT (PROlapse Surgery, Pragmatic Evaluation by randomised Controlled Trial) is the largest randomised controlled trial conducted to date of the use of mesh in women having prolapse surgery. It addresses the use of no mesh, a biological mesh inlay, and a nonabsorbable mesh inserted as an inlay or used in a kit; and separately in women having their first prolapse operation or repeat surgery.

PROSPECT recruited 3091 women from 35 centres across the UK between January 2010 and August 2013. There were two trials, one amongst women having their first prolapse operation (Primary trial, where 1353 women were randomised to no mesh, non-absorbable mesh inlay or biological mesh inlay); and those having repeat surgery (Secondary trial, where 155 women were randomised to no mesh, non-absorbable mesh inlay or mesh kit). Women who were not eligible for randomisation were enrolled into the Comprehensive Cohort (1583 women). The following information was collected:

- Demographic and surgical information at recruitment and at operation;
- Patient reported outcome data (prolapse symptoms, urinary, bowel and sexual function and EQ-5D) through questionnaires at 6, 12 and 24 months;
- Randomised women were examined 12 months after surgery to identify treatment success and adverse effects;
- Information about complications, readmissions, reoperations and costs.

Within the main PROSPECT trial short term failure (within two years of the prolapse operation) was captured. However, as prolapse is a progressive and relapsing condition, with surgery having a high failure rate[1] (repeat surgery occurs on average 12 years later) it is essential to capture the long term failure in order to truly evaluate the potential benefits of mesh versus its adverse effects, which may also occur many years later.[2] In addition, there is very little information about the long term effects of this condition on urinary, bowel and sexual function,

Current evidence

The Surgery for Prolapse Cochrane Review was updated in 2013.[3] The review authors found 22 trials of mesh in prolapse surgery (3 used absorbable synthetic mesh; 7 used biological mesh; 12 used non-absorbable mesh). The data on biological mesh were at best conflicting, while women had both fewer symptoms and less objective prolapse after non-absorbable mesh at one year after surgery. However, few of the trials reported outcomes at two years or more, reporting of complications was sparse and none differentiated between primary and secondary repairs. Therefore, the overall benefits and costs of mesh in prolapse surgery remain undetermined. The Cochrane Review further identified the lack of long term follow-up data as a serious limitation.

The importance of long term follow-up has also been highlighted in the literature by the gynaecology community[4] and NICE.[5] Furthermore, lack of long term follow-up has been highlighted by NICE as a discussion point when counselling the patient for POP surgery. Long term follow-up of all of the PROSPECT participants is therefore necessary to inform health-care commissioners, health-care professionals and consumers alike. Such long term follow up will establish the (anticipated) benefits of mesh versus the likelihood of adverse effects such as mesh exposure, which may occur many years later.[2]

Methods
The PROSPECT participants will be contacted at 2-yearly intervals starting at 4 years after surgery and continuing to 14 years after surgery (6 questionnaires in total). For those women who were recruited into PROSPECT but who never received a prolapse operation as part of the trial, questionnaires will be issued at 2-yearly intervals starting at 4 years post-randomisation and continuing to 14 years post-randomisation. Woman who did not consent to be contacted in the future for long term follow-up or who had previously withdrawn from PROSPECT will be excluded from the long term follow-up study.

The questionnaire at each time-point will be identical and collect the same patient-reported outcome measures used in PROSPECT: prolapse symptoms; urinary, bowel and sexual function; EQ-5D; treatment failure including the need for additional surgery, pessaries, drugs or physiotherapy; postoperative complications including the need for additional surgical or conservative treatment; costs; and cost-effectiveness. In addition to postal questionnaire, HES (England) and ISD (Scotland) data will be requested to verify all preceding hospital re-admissions. Furthermore, case report verification will be carried out in the three lead centres (Aberdeen, Manchester and Plymouth) after the 6 year data collection is complete to verify and validate the other two data collection methods.

During the extended follow-up phase the same efficient retention system used in PROSPECT will be employed to ensure questionnaire return rates are maximised. This involves sending a reminder letter and further questionnaire three weeks after the original questionnaire is issued and not returned, followed by a postal or phone call reminder for continuing non-responders. The death notification service provided by the Health and Social Care Information Centre (HSCIC) will be utilised to minimise the risk of issuing a questionnaire to a participant who has subsequently died.

Loyalty and interest in the long term follow-up study will be maintained by continuing to send annual newsletters and Christmas cards to trial participants.

Primary outcome and power calculation
The primary clinical outcome measure for the main PROSPECT trial is the prolapse symptom score (POP-SS) at 12 months. In the long term follow-up study, the primary clinical outcome measure will be the POP-SS at 14 years. We estimate that if 400 patients in each arm of the primary trial respond to a questionnaire at 14 years (i.e. the current response rate is maintained over time), this will provide 96% power to detect a mean difference of 2 points (assuming SD=7 and alpha=0.025). If the response rate were to fall to 50% by 14 years, we would have 78% power to detect a difference of 2 POP-SS points.

Because of the importance of mesh in (theoretically) reducing the repeat surgery rate, we further propose that an additional primary clinical outcome will be the rate of repeat surgery for prolapse (any compartment). For repeat prolapse surgery within 14 years, if the event rate for the standard midline repair is assumed to be 25%, the power to detect a 10% absolute difference in reoperation rates compared with either biological or synthetic mesh would be 90% if the current response rate was maintained and 66% if the response rate falls to 50%.

The primary economic outcome measure of cost effectiveness will remain the same: the incremental cost per QALY (QALYs based on the EQ-5D[6]). In addition, because of all the potential problems associated with the use of mesh in prolapse surgery, serious adverse events will be included as a secondary outcome.

Following completion of the 14 year dataset, the full trial data will be reported for the randomised and the corresponding comprehensive cohort according to the trial

Statistical Analysis Plan. Analyses related to the two randomised trials (primary and secondary surgery) will be undertaken on an intention-to-treat basis allowing for repeated (two-yearly) symptom and quality of life measurements. Data from Cohort women will be analysed according to treatment received (mesh or no mesh surgery), separately according to primary or secondary procedure, or upper vaginal prolapse surgery only.

Management

Trial management, data collection and analysis will be undertaken in the PROSPECT Trial Office, HSRU, University of Aberdeen, under the supervised of the PROSPECT Project Management Group. This group consists of the grant holders and representatives from the Study Office.

References

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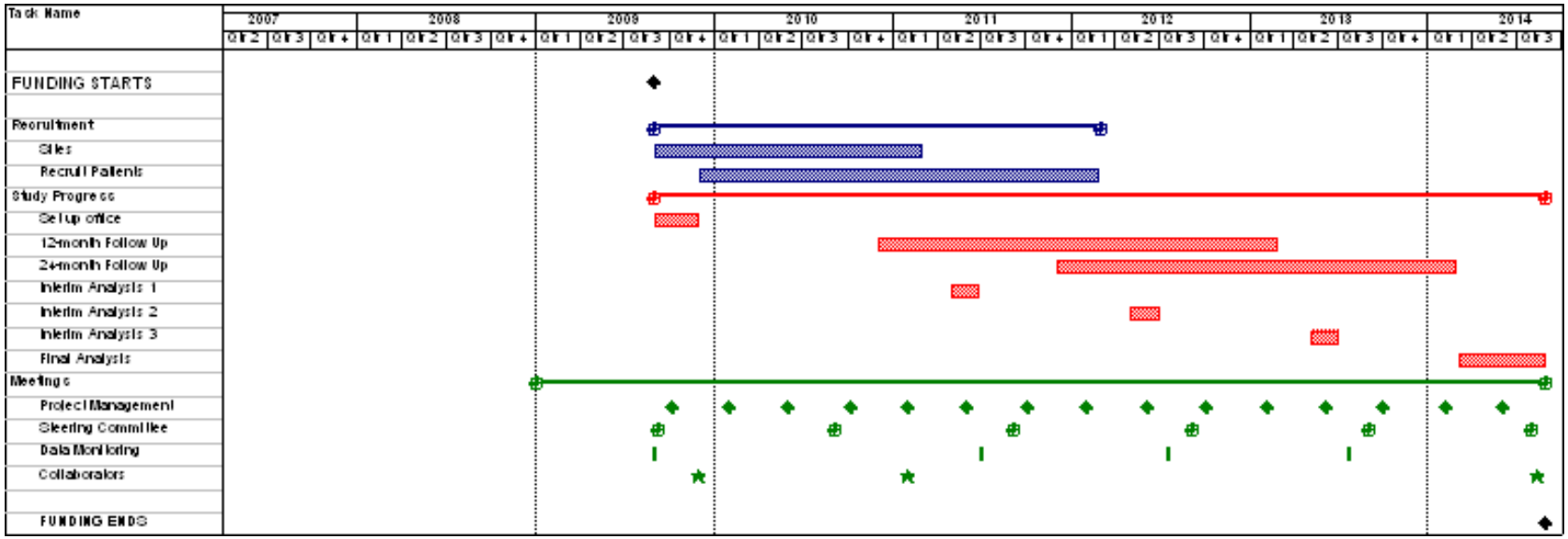
APPENDIX V GANTT CHART



APPENDIX VI PUBLICATION POLICY

AUTHORSHIP POLICY

1. PRINCIPLES OF AUTHORSHIP

The following principles of authorship have been derived from editorial publications from leading journals (see references) and are in accordance with the rules of the International Committee of Medical Journal Editors.

a. Group authorship

Group authorship will be appropriate for some publications, such as main reports. This will apply when the intellectual work underpinning a publication 'has been carried out by a group, and no one person can be identified as having substantially greater responsibility for its contents than others'.[1] In such cases the authorship will be presented by the collective title - The PROSPECT Trial Group - and the article should carry a footnote of the names of the people (and their institutions) represented by the corporate title. In some situations one or more authors may take responsibility for drafting the paper but all group members qualify as members; in this case, this should be recognised using the byline 'Jane Doe *and* the Trial Group'.[2] Group authorship may also be appropriate for publications where one or more authors take responsibility for a group, in which case the other group members are not authors but may be listed in the acknowledgement (the byline would read 'Jane Doe *for* the Trial Group'). [2]

b. Individual authorship

Other papers, such as describing satellite studies, will have individual authorship. In order to qualify for authorship an individual must fulfil the following criteria[1]:

i. Each author should have participated sufficiently in the work represented by the article to take public responsibility for the content.

ii. Participation must include three steps:

- conception or design of the work represented by the article OR analysis and interpretation of the data OR both; AND
- drafting the article or revising it for critically important content; AND
- final approval of the version to be published.

Participation solely in the collection of data is insufficient by itself and those persons who have contributed intellectually to the article but those contributors do not justify authorship may be acknowledged and their contribution described.[1]

c. Determining authorship

Tentative decisions on authorship should be made as soon as possible.[1] These should be justified to, and agreed by, the Project Management Group. Any difficulties or disagreements will be resolved by the Steering Committee.

2. AUTHORSHIP FOR PUBLICATION ARISING FROM PROSPECT

a. Operationalising authorship rules

We envisage two types of report (including conference presentations) arising from the PROSPECT trial and its associated projects:

i. *Reports of work arising from the main PROSPECT trial* - If all grant-holders and research staff fulfil authorship rules, group authorship should be used under the collective title of 'The PROSPECT Trial Group'; if one or more individuals have made a significant contribution above and beyond other group members but where all group members fulfil authorship rules, authorship will be attributed to 'Jane Doe and the PROSPECT Trial Group'.

ii. *Reports of satellite studies and subsidiary projects* - Authorship should be guided by the authorship rules outlined in Section 1 above. Grant-holders and research staff not directly associated with the specific project should only be included as authors if they fulfil the authorship rules. Grant-holders and research staff who have made a contribution to the project but do not fulfil authorship rules should be recognised in the Acknowledgement section. The role of the PROSPECT Trial Group in the development and support of the project should be recognised in the Acknowledgement section. The lead researcher should be responsible for ratifying authorship with the Project Management Group.

For reports which specifically arise from the PROSPECT trial but where all members do not fulfil authorship rules (for example, specialist sub-study publications), authorship should be attributed to 'Jane Doe for the PROSPECT Trial Group'. If individual members of the group are dissatisfied by a decision, they can appeal to the Management Group for reconciliation. If this cannot be achieved, the matter should be referred to the Steering Group.

b. Quality assurance

Ensuring quality assurance is essential to the good name of the trial group. For reports of individual projects, internal peer review among members of the Project Management Group is a requirement prior to submission of papers. All reports of work arising from the PROSPECT trial including conference abstracts should be peer reviewed by the Project Management Group.

The internal peer review for reports of work arising from the PROSPECT project is mandatory and submission may be delayed or vetoed if there are serious concerns about the scientific quality of the report. The Project Management Group will be responsible for decisions about submission following internal peer review. If individual members of the group are dissatisfied by decisions, the matter may be referred to the Steering Group.

The Project Management Group undertake to respond to submission of articles for peer review at the Project Management Group Meeting following submission (assuming the report is submitted to the trial secretariat in Aberdeen at least two weeks prior to the meeting).

REFERENCES

1. Huth EJ (1986). Guidelines on authorship of medical papers. *Annals of Internal Medicine*, **104**, 269-274.
2. Glass RM (1992). New information for authors and readers. Group authorship, acknowledgements and rejected manuscripts. *Journal of the American Medical Association*, **268**, 99.