NETSCC, HTA

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OPT: The Outpatient Polyp Treatment Trial. PROTOCOL

The OPT Trial is a non-inferiority trial that will determine reliably whether out-patient polyp removal under local anaesthetic is clinically as effective as in-patient surgery for women with uterine polyps, and to determine the relative cost-effectiveness of each strategy.

In order to obtain the large number of patients needed to provide reliable answers, and to maximise the clinical relevance of the findings, the trial is designed to fit in with routine practice as far as possible and to impose minimal additional workload by keeping extra clinic-based tests and evaluations to a minimum. Because the success of the trial depends entirely on the whole-hearted collaboration of many doctors, nurses and others, publication of the main result will be in the name of the collaborative group and not those of the central organisers.

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Version Number

Version 2.2 Dated 20th Oct 2009 Postponing consent following diagnostic hysteroscopy for clinics unable to offer immediate “see & treat” treatment.

Protocol Versions

2.1 Dated 4th Sept 2009 Response to MREC comments

2.0 Dated 16th July 2009

1.5 Following TSC meeting 24.06.08 some elements of the study were refined and sanctioned by the chair.

1.4 Submitted to MREC Changes to stratification variables, primary and secondary outcome measures, removal of repeat hysteroscopy and amendment of sample size calculation and statistical analysis

1.3 Submitted to MREC Changes to wording of sample size

1.2 Submitted to MREC Addition of acceptability questionnaire

1.1 Submitted to MREC Response to MREC comments

1.0 Initial submission to MREC

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The University of Birmingham and Birmingham Women’s NHS Foundation Trust are joint sponsors of the OPT Trial. Mr Justin Clark is the Chief Investigator.

The University of Birmingham is responsible for registration and administration of the study, and ensuring compliance with good clinical practice. Birmingham Women’s NHS Foundation Trust is responsible for provision of the Chief Investigator and responsibility for the study protocol, and ensuring proper pharmacovigilance and reporting of adverse events. The Trial Management Committee is jointly responsible for overseeing good clinical practice and the Investigators are responsible for obtaining informed consent and care of the participants.

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1. BACKGROUND

1.1. Disease: Abnormal uterine bleeding and uterine polyps

Abnormal uterine bleeding is one of the four most common reasons for consulting a general practitioner[1] and accounts for 70% of all referrals to hospital gynaecology clinics[2-3], making this complaint one of the commonest problems in gynaecology. A large proportion of health care resources in both primary care and hospital settings are used up in managing this condition[4]. With the advent of high-resolution pelvic ultrasound and hysteroscopic diagnosis, it has become clear that abnormal bleeding is associated with uterine polyps in between 20-30% of cases[5-6]. This pattern is found to affect both pre- and postmenopausal women across all age groups[7]. The improved diagnostic accuracy, has led to the increased use of surgical intervention for the removal of polyps ('polypectomy'), a procedure that is universally practised to resolve symptoms and to obtain tissue for histological examination[8].

Uterine polyps

Uterine polyps are focal endometrial outgrowths that can occur anywhere within the uterine cavity. They contain a variable amount of glands, stroma and blood vessels, the relative amounts of which influence their visual appearance at hysteroscopy. Polyps may be soft and cystic or firm and fibrous; they may be pedunculated or sessile, single or multiple and vary in size from small with minimal uterine cavity distortion to large, filling the whole cavity. A small proportion of small polyps may regress naturally without treatment but the majority persist. The vast majority are benign with less than 1% frankly malignant.

1.1.1 Population to be studied

All women with abnormal uterine bleeding referred for a diagnostic outpatient hysteroscopy (a test where the uterine cavity is directly visualised to detect pathology using a small rigid or flexible endoscope) will be approached for consent to participate in the OPT trial. Consenting women will be entered into the OPT Trial if the outpatient hysteroscopy detects a benign uterine polyp.

Abnormal uterine bleeding affects women of all ages and the underlying causes and potential significance of AUB patterns vary. With this in mind, the following factors will be considered when a patient's type of AUB is defined: (1) pre or postmenopausal bleeding; (2) type of hormone replacement therapy patient may be taking (3) history of using Tamoxifen; (4) intermenstrual/irregular or heavy menstrual bleeding.

1.2. Current therapy for uterine polyps

Until recently, inpatient blind uterine curettage ('D&C') under general anaesthetic has been the technique routinely employed to perform uterine polypectomy. It involves wide dilatation of the cervix and the use of standard surgical polypectomy forceps to explore the uterine cavity. This technique is still used today, although most gynaecologists perform a hysteroscopy beforehand to locate the polyp to direct blind avulsion of the lesion followed by curettage[8]. Due to the need for inpatient hospital admission and general anaesthesia, this approach is associated with heavy use of health care resources, with 24,000 inpatient procedures being performed during 2005-2006 in the United Kingdom, a figure that was up by 3,000 on the numbers from 1998-1999 confirming a trend towards an increase in the use of inpatient polypectomy[9].

1.3. New therapy for uterine polyps

Recent advances in hysteroscopic technology have enabled polyps to be removed under direct vision. In particular, the development of bipolar intrauterine electrosurgical systems (e.g. Versapoint™ Bipolar Electrosurgical System, Gynecare, Ethicon Inc., Menlo Park, CA, USA) has facilitated rapid, resection of focal uterine lesions such as polyps. Moreover, the miniaturisation of hysteroscopes and ancillary instrumentation coupled with enhanced visualisation, due to improvements in fibre optics and digital imaging, has enabled hysteroscopic surgery to be performed in an outpatient setting without the need for general anaesthesia or inpatient hospital admission, as the need to wide cervical dilatation and blind uterine exploration with forceps is avoided[10]. This development offers potential advantages to women and their doctors in terms of convenience and choice.

The current literature on these techniques demonstrates safety and feasibility, but evidence of effectiveness, patient acceptability and cost- effectiveness is lacking[11-12]. Nevertheless, many gynaecologists are currently using these techniques although opinion regarding their value is not yet solidified[8]. There is thus an urgent need for a robust health technology assessment using a randomised controlled trial.

1.4. Literature review

1.4.1 Systematic Review

Health technology assessment of surgical interventions requires an initial evaluation of the safety and stability followed by randomised trials of effectiveness[13]. We conducted a comprehensive systematic review on the efficacy of uterine polypectomy in the treatment of abnormal uterine bleeding[11]. After searching three electronic databases, 250 citations were identified, of which a total of 10 studies were eligible for inclusion. There were nine case series (534 patients) and a single comparative study (58 patients). There were no randomised controlled trials, nor any studies on patient acceptability or cost-effectiveness. A summary of the evidence is given below:

Technique: Uterine polypectomy was carried out under general anaesthesia utilising hysteroscopic or blind approaches in all studies, although local anaesthetic, outpatient approaches were also employed in three of these series. The hysteroscopic techniques under general anaesthesia involved use of large size endoscopes associated with the need to perform wide cervical dilatation. All studies reported an improvement in symptoms of abnormal uterine bleeding following treatment (range 75%-100%) at follow-up intervals of between 2 and 52 months.

Setting: A single, non-randomised, comparative study of 58 women from our unit[16] showed that outpatient removal under local anaesthesia was no worse than inpatient, general anaesthetic treatment (P=0.7), a result that could partly be explained by the possibility of type II error due to small sample size.

Type of abnormal uterine bleeding: It was only possible to stratify treatment outcome according to type of abnormal bleeding in one small study of 45 women[19], which could not detect a difference between polypectomy for menstrual dysfunction or postmenopausal bleeding (P=0.2), again partly due to small sample size.

In summary, the systematic review evidence suggests that uterine polypectomy is a safe and technically successful procedure for the treatment of abnormal uterine bleeding[11]. However, randomised efficacy data are non-existent and the quality of existing research is poor introducing a substantial potential for bias, making the prospective effectiveness of this approach uncertain at present. The optimal approach to treatment is also unclear due lack of evidence on patient acceptability or cost-effectiveness.

1.4.2 Current clinical practice (Professional consensus)

We conducted a national questionnaire survey of consultant gynaecologists in the United Kingdom to determine current practice regarding removal of uterine polyps[8]. Outpatient hysteroscopy was performed by 324 of 854 respondents (38%) to diagnose uterine polyps. The diagnostic procedure involves use of 1.0-3.0mm endoscope with a 2.5-4.9mm sheath, much smaller than operative hysteroscopy under anaesthesia that uses larger endoscopes and sheaths. In one study[14] diagnostic hysteroscopy was found to be more reassuring for patients, but it was claimed that it did not influence clinical management compared with endometrial biopsy alone in unselected pre-menopausal women with abnormal uterine bleeding. In view of the limitation in patient spectrum and the restriction to a single centre, these findings have had limited generalisability. Therefore it is not surprising that diagnostic hysteroscopy remains well established in practice. In our survey[8], uterine polypectomy was performed by 93% of gynaecologists, although techniques varied. Inpatient uterine polypectomy under general anaesthesia was used by 91% and the favoured method was blind polyp removal using standard surgical forceps following cervical dilatation and hysteroscopic localisation. Outpatient uterine polypectomy was performed by 19% of the 324 gynaecologists with access to outpatient diagnostic hysteroscopy. With a rare exception, follow up of uterine polyps was not suggested as a form of management by any of the respondents. Crucially, this survey indicated that 268 of 854 (31%) of gynaecologists performing uterine polypectomy were supportive of a trial comparing inpatient versus outpatient uterine polypectomy. Of these, 61 had access to outpatient hysteroscopy, performed both inpatient and outpatient uterine polypectomy and were willing to enter patients into the OPT trial. In this situation collective equipoise applies (i.e. the technique has been introduced without definite evidence but opinion regarding its use is not yet solidified) making the need for a trial even more urgent.

1.4.3 Pilot studies

In addition to systematically reviewing the medical literature[5] and performing a national survey of practice[8], we have undertaken two primary clinical studies. The first is an observational cohort study to compare outpatient hysteroscopic polypectomy in the treatment of symptomatic endometrial polyps with inpatient management[10]. This study demonstrated that outpatient treatment was technically feasible and it had the potential to be efficacious and cost effective. From this we launched a pilot randomised controlled trial to assess the acceptability of randomisation to patients[15]. This experience has helped us to optimise the trial design for a robust large scale, multicentre study. Analysis was recently conducted by the applicants when

the first 60 patients completed six months follow-up. A larger study is needed for adequate statistical power to evaluate OPT reliably. However, this pilot study has shown acceptability of randomisation as well as establishing standardised operating procedures for trial management, and piloted questionnaires and consent forms[15].

1.5. The need for a large simple trial of outpatient uterine polypectomy versus inpatient uterine polypectomy in abnormal uterine bleeding

The systematic review evidence[8] suggests that uterine polypectomy is a safe and technically successful procedure for the treatment of abnormal uterine bleeding[11] and results in an improvement in AUB symptoms. However, randomised efficacy data are non-existent and the quality of existing research is poor, introducing a substantial potential for bias, making the prospective effectiveness of this approach uncertain at present. Moreover, with advances in endoscopic technology and miniaturisation of equipment, the optimal approach to treatment in terms of treatment setting and anaesthesia (outpatient, local anaesthetic versus inpatient, general anaesthetic) is also unclear due to the lack of evidence on the relative benefits of OPT compared to traditional inpatient approaches in terms of feasibility, patient acceptability or cost-effectiveness. Thus further research in the form of an adequately powered, randomised controlled trial between treatment settings (outpatient versus inpatient), stratified by type (i.e. pattern) of AUB is required to assess the therapeutic role, patient acceptability, effectiveness and cost-effectiveness of uterine polypectomy in abnormal uterine bleeding both in the short and longer term. The need for such a trial has been corroborated in recent publications[10,16-18] and support by UK consultant gynaecologists, performing both outpatient and inpatient uterine polypectomy, willing to participate in the OPT Trial has been demonstrated[8]. This implies that the newer outpatient approach has been introduced in some centres without definite evidence but opinion regarding its use is not yet solidified (i.e. collective equipoise) making the need for a trial even more urgent.

1.6. Objectives of the OPT Trial

In undertaking the OPT Trial, we aim:

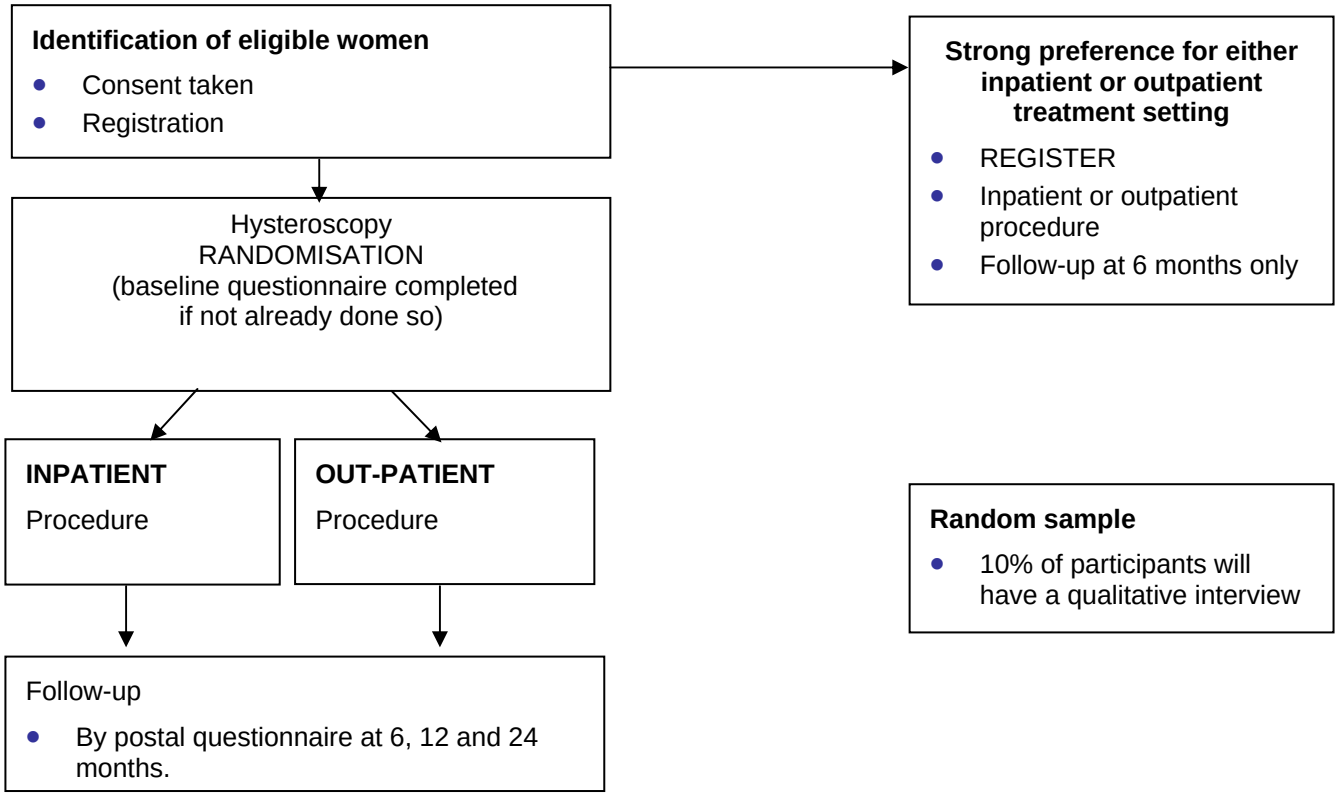
1. To test the hypothesis that in women with abnormal uterine bleeding associated with benign uterine polyp(s), outpatient polyp treatment (OPT) achieves as good, or no more than 25% worse (i.e. 90% successful v 67% successful), alleviation of bleeding symptoms compared to standard inpatient treatment at six months (principal objective).
2. To test the hypothesis that response to uterine polyp treatment differs according to the pattern of abnormal uterine bleeding and menopausal status by three secondary analyses:
    (i) pre- versus postmenopausal women.
    (ii) intermenstrual bleeding versus excessive menstruation
    (iii) postmenopausal women on HRT versus those not on HRT
3. To explore the variation in the effectiveness of OPT versus standard inpatient polyp treatment at different periods of follow-up (12 and 24 months).
4. To assess patient acceptability and impact on health-related quality of life
5. To perform an economic evaluation for cost-effectiveness

2. TRIAL DESIGN

2.1. Design

A pragmatic multicentre randomised controlled non-inferiority trial of outpatient versus in-patient polypectomy, and concurrent non-randomised cohort of women with a strong preference for treatment setting (see Figure 1).

Figure 1: OPT Flow Diagram



2.2. Large, simple trial: minimal extra workload

In order to obtain the large number of patients necessary for the reliable evaluation of non-inferiority of out-patient compared to in-patient treatment policies for polyp removal, the trial will need the participation of many centres. To make this practicable, trial procedures need to be kept simple, with the minimal extra workload placed on participating clinicians, beyond that required to treat their patients. This will be achieved by simple entry procedures (a single phone call or web page), the use of standard local diagnostic and surgical regimens, routine follow-up of patients (with few additional hospital visits or tests to be performed above those done as part of standard care), minimising documentation and largely patient-based evaluation of outcome.

3. ELIGIBILITY, CONSENT AND RANDOMISATION

3.1. Screening and consent prior to outpatient hysteroscopy

All women with abnormal uterine bleeding seen in outpatient clinics and undergoing a diagnostic outpatient hysteroscopy will be considered for the trial. The trial will be introduced to them in the outpatient clinic and a comprehensive, evidence-based patient information sheet will be provided, either at the first clinic visit or with the appointment letter for the hysteroscopy. Participant information sheets (Appendix A) and consent form (Appendix B) will be provided to each centre in English and other languages as appropriate to their local community.

Before the procedure, the women will be given a chance to discuss the risks and benefits of uterine polypectomy in the outpatient setting using local anaesthesia and in the inpatient setting under general anaesthesia, the process of randomisation and the follow-up requirements with the consultant gynaecologist and/or gynaecology nurse. It will be carefully explained that the final decision about eligibility will be taken during the hysteroscopic examination and is dependent on the findings; therefore consent will be required before the procedure, in most instances. For those centres who are unable to offer immediate “see & treat inpatient or outpatient treatment then the informed consent process will be postponed until after the diagnostic hysteroscopy and polyps have been confirmed, written consent will then be obtained prior to randomisation. The patient will then be given a second appointment for her polyp treatment. Women will be informed that the process of randomisation will prolong the diagnostic procedure time by up to two minutes.

She must also appreciate if the allocation is outpatient polypectomy, it will be undertaken immediately in most instances (except those above) and treatment will take an additional 10-15 minutes on average, whereas, if the allocation is inpatient polypectomy, the diagnostic hysteroscope will be removed and she will be given another appointment for the inpatient procedure within 8 weeks. If randomised, the woman's GP will need to be notified, with her consent, and a specimen "Letter to GP" is supplied (Appendix C).

It will also be explained that only about one in four women will have a uterine polyp and therefore be eligible for the OPT trial. If a polyp is not found, appropriate treatment will be offered and the woman will not be recruited into the trial.

3.2. Determining eligibility

All women with abnormal uterine bleeding who provide consent to participation and are eligible in the OPT trial based on the findings of the hysteroscopy will be randomised during the procedure. The gynaecologist will inspect the uterine cavity, according to his/her standard hysteroscopic protocol, to determine the presence of uterine polyp(s), absence of any excluding pathology and technical feasibility for outpatient polypectomy. For the purpose of the OPT Trial a uterine polyp will be defined at diagnostic hysteroscopy as:

A discrete outgrowth of endometrium, attached by a pedicle, which moves with the flow of the distension medium[19]. Polyps may be pedunculated or sessile, single or multiple and vary in size (the variable amount of glands, stroma and blood vessels that constitute the polyp will influence their macroscopic appearance (i.e. glandulocystic polyps or firmer, more fibrous polyps (indistinguishable in some instances from grade 0 submucous fibroids)).

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

***Inclusion criteria*:**

- Aged 16 years or over
- Abnormal uterine bleeding requiring diagnostic hysteroscopy
- Finding of a benign polyp or polyps (glandulocystic or pedunculated / grade 0 fibroid) on diagnostic hysteroscopy
- Feasible to remove polyp as an outpatient
- Need for polypectomy
- Ability to perform polypectomy within 8 weeks of diagnosis
- Baseline questionnaire completed after diagnostic hysteroscopy (if not already done so)
- Written informed consent obtained prior to the hysteroscopy

***Exclusion criteria*:**

- Hysteroscopic features suggesting malignant lesion
- Need for other uterine surgical intervention (i.e. endometrial ablation, resection, myomectomy or hysterectomy)
- Additional pathology necessitating hysterectomy

3.3. Randomisation

If the woman is eligible for the OPT trial, the gynaecologist or member of his/ her team will obtain a randomised allocation during the hysteroscopic examination. Randomisation notepads (Appendix D) will be provided to investigators and may be used to collate the necessary information prior to randomisation. Participants are entered and randomised into the trial via a short telephone call to the Birmingham Clinical Trials Unit on 0800 953 0274 or by logging into a secure web-based randomisation system at https://www.trials.bham.ac.uk/opt. The randomiser will need to provide the name and date of birth of the participant and confirm the eligibility criteria, whereupon a randomised allocation will be provided and a trial number allocated. The trial number should be written upon all trial documents immediately. Telephone randomisations are available Monday-Friday, 09:00-17:00 GMT. Online randomisation is available 24 hours a day, 7 days a week apart from short periods of scheduled maintenance and occasional network problems.

3.4. Patients with strong preference for treatment setting

A minority of women will express a clear preference for immediate outpatient treatment under local anaesthesia or delayed inpatient uterine polypectomy under general anaesthesia and for this reason will not wish to be randomised between surgical treatments. To investigate how outcomes vary by choice, these

women will be followed up in exactly the same way as for those women randomised into the OPT trial. This design will include patients with preferences while drawing on the advantages of randomisation for those who have no clear preference.

3.5. Stratification of randomisation

A 'minimisation' procedure using a computer-based algorithm will be used to avoid chance imbalances in important stratification variables. Stratification variables will be:

- Pre- vs. post-menopausal women
- Post-menopausal women on HRT vs. not on HRT
- Whether the predominant abnormal bleeding complaint is (excessive) heavy menstrual bleeding or intermenstrual/unscheduled bleeding
- History of using Tamoxifen (current or previous user vs. never used)
- Location of uterine polyp (fundal vs. non-fundal)
- Type of uterine polyp (endometrial ('glandulocystic') vs. fibroid (fibrous)).

To avoid any possibility of foreknowledge, the randomised allocation will not be given until all eligibility and stratification data have been given.

4. TREATMENT ALLOCATIONS

4.1. Surgical procedures

A named investigator, who has suitable training and experience in both outpatient and inpatient uterine polypectomy, will perform all surgical procedures.

4.1.1 Outpatient polypectomy

Outpatient polypectomy will be performed immediately following diagnosis at outpatient hysteroscopy in most instances, although some participants may have their outpatient treatment scheduled to a later date, depending upon local circumstances, within the following 8 weeks, as not all clinics are able to offer immediate "see & treat" outpatient treatment. Polyp removal will be carried out under direct hysteroscopic vision using miniature mechanical or electrosurgical instruments, with or without the need for minor degrees of cervical dilatation and local anaesthesia (direct cervical infiltration or paracervical injection). Occasionally blind avulsion with small polypectomy forceps after hysteroscopic localisation may be required.

Data collected will include the type, location, size and number of uterine polyps; the use of local anaesthesia (type, quantity and technique); the need for dilatation of the cervix; the use of a vaginal speculum; the type of hysteroscope; the technique employed to remove the polyp(s) (hysteroscopic (direct vision) vs. non-hysteroscopic (blind) vs. combination); the instruments used to remove the polyp(s) (hysteroscopic (electrosurgery or mechanical or combination) vs. non-hysteroscopic instrumentation); the technique employed to retrieve the polyp(s) (hysteroscopic vs. non-hysteroscopic; the success of OPT (defined as complete removal and retrieval of polyp(s) from the uterine cavity); the time taken to complete OPT (allocation at randomisation to removal of all instrumentation; if OPT is scheduled for a later date then time will be taken from as length of insertion to removal of vaginal instrumentation); time taken to complete the consultation; time in hospital (arrival to discharge), details of any adverse events (note the most common side-effect of outpatient hysteroscopic interventions is a 'vaso-vagal' reaction defined as an episode of hypotension, bradycardia, pallor and fainting associated with feeling cold, sweaty, shivery and vomiting. For the purpose of the OPT trial, a liberal clinical diagnosis to define vaso-vagal episodes will be used i.e. a vaso-vagal reaction should be recorded for any woman who feels 'faint' during or immediately following the hysteroscopic procedure requiring her to lie supine / head down for any length of time) and details of any further treatment prescribed for bleeding.

4.1.2 Inpatient polypectomy

Inpatient polypectomy will be performed within 8 weeks of the initial diagnosis at outpatient hysteroscopy. In-patient polypectomy will be performed by traditional dilatation and endometrial curettage ('D&C'), blind avulsion with or without prior localising hysteroscopy or under direct vision using an operative hysteroscope. In most instances, wide dilation of the cervical canal will be required to accommodate the larger diameter inpatient instruments within the uterus. General or spinal anaesthesia facilitates major degrees of cervical dilatation and manipulation of these larger diameter instruments within the uterine cavity.

Data collected will include the type, location, size and number of uterine polyps; type of anaesthesia (general or regional); the need for dilatation of the cervix; the use of a vaginal speculum; the type of hysteroscope; the technique employed to remove the polyp(s) (hysteroscopic (direct vision) vs. non-hysteroscopic (blind) vs. combination); the instruments used to remove the polyp(s) (hysteroscopic (electrosurgery or mechanical or combination) vs. non-hysteroscopic instrumentation); the technique employed to retrieve the polyp(s) (hysteroscopic vs. non-hysteroscopic; the success of OPT (defined as complete removal and retrieval of polyp(s) from the uterine cavity); the time taken to complete inpatient uterine polypectomy ('checking' the patient in the anaesthetic room to transfer to recovery area); time in hospital as an inpatient (admission to discharge), details of any adverse events and details of any further treatment prescribed for bleeding.

4.1.3 Failure of procedure

Occasionally, outpatient hysteroscopy followed by complete removal of a uterine polyp is not always completed, usually because of pain or anxiety or because of the technical limitations associated with the miniaturisation of equipment. Successful OPT is possible in the majority of women[11], but the probability of success is not readily predictable. In cases where OPT has to be abandoned, a second procedure under general anaesthetic should be scheduled as soon as possible. Women who require a second procedure are not excluded or withdrawn from the OPT trial. It should be sensitively explained to them that follow-up information is still very important, despite the change in treatment, and unless they wish to withdrawn completely from the trial, they will be followed up.

4.2. Concomitant interventions and treatments

It is anticipated that most women presenting with AUB found to be associated with a uterine polyp will require no further intervention other that uterine polypectomy (either as an outpatient or inpatient). However, in some circumstances, particularly those pre-menopausal women with heavy menstrual bleeding, additional medical treatments may be considered necessary by the responsible clinician at the time of polypectomy or subsequently. These may include non-hormonal medical treatments (e.g. non-steroidal anti-inflammatory agents, tranexamic acid) or hormonal medical treatments (e.g. combined oral contraceptive pill, levonorgestrel-releasing intrauterine system (Mirena®), local or systemic hormone replacement therapy). Surgical interventions in the form of endometrial ablations or hysterectomy may subsequently be necessary and the need for such interventions will be recorded. However, if the need for additional surgery *at the time* of polyp diagnosis is indicated, then such patients are excluded for recruitment to the OPT trial (see 3.2. 'exclusion criteria' in the preceding section). The OPT trial is a pragmatic one, and so patients with AUB associated with polyps should be managed, as they would be in routine clinical practice following polyp removal. All therapeutic interventions additional to uterine polypectomy will be recorded and as the trial is randomised we anticipate that these further interventions will be symmetrically applicable.

4.3. Withdrawal from the OPT trial

All women who consent to the randomised OPT trial, or to the non-randomised cohort of treatment preference, should be followed up and asked to complete postal questionnaires, regardless of actual treatment received.

If a woman specifically requests a treatment setting *after* randomisation, then her choices should be respected. This does not necessitate withdrawal from the trial. Similarly, if the outpatient procedure fails, she will require subsequent in-patient treatment. In both circumstances, it should be sensitively explained to them that follow-up information is still very important, and unless they wish to withdrawn completely from the trial, they will be followed up. Any request to withdraw from follow-up should be notified to the OPT Trial Office.

4.4. Serious and unexpected adverse events

There may be mortality and morbidity associated with either polypectomy procedure, therefore all *serious adverse events* (SAE) should be reported by fax to the OPT Trial Office as soon as possible. This report should be followed within 2 days by a completed SAE form (Appendix E). For the purposes of this study, "*serious*" adverse events are those which are fatal, life-threatening, disabling or prolong hospitalisation and have resulted from the hysteroscopy, the polypectomy procedure, the anaesthetic or post-operative recovery e.g. deep vein thrombosis, hospital acquired infections.

4.5. Other management at discretion of local doctors

Apart from the trial treatments allocated at randomisation, all other aspects of patient management are entirely at the discretion of the local investigators.

5. FOLLOW-UP AND OUTCOME MEASURES

5.1. Clinical assessments

5.1.1 Format

Patient orientated outcomes will be collected using a postal questionnaire, which will include a combination of disease specific and generic measurement instruments, tailored according to the initial symptom at presentation.

The postal questionnaires will be sent from the BCTU with postage paid envelopes two weeks before the due date. Reminders will be sent to patient if the questionnaire is not returned within one week of the due date and attempts will be made to contact the patient by phone if the questionnaire is not returned by two weeks after the due date. We have developed a robust system for ensuring high follow up rates through our experience of postal questionnaires in other trials.

5.1.2 Timing of assessments

The primary outcome will be based upon clinical and economic assessments at 6 months post-treatment. In addition, clinical and economic assessments will take place at baseline (i.e. time of recruitment and randomisation to OPT trial), 12 and 24 months post-treatment.

5.2. Primary clinical outcome measure

The patients own assessment of bleeding symptoms, using a dichotomous outcome measure, will be used to establish if the treatment has been successful. The question used for this measure will be dependent on whether the patient is pre or post-menopausal, predominant complaint at randomisation and type of HRT they may be using. Further details can be seen in Figure 2. In all cases a 'yes' response will be defined as a success.

5.3. Secondary clinical outcome measures

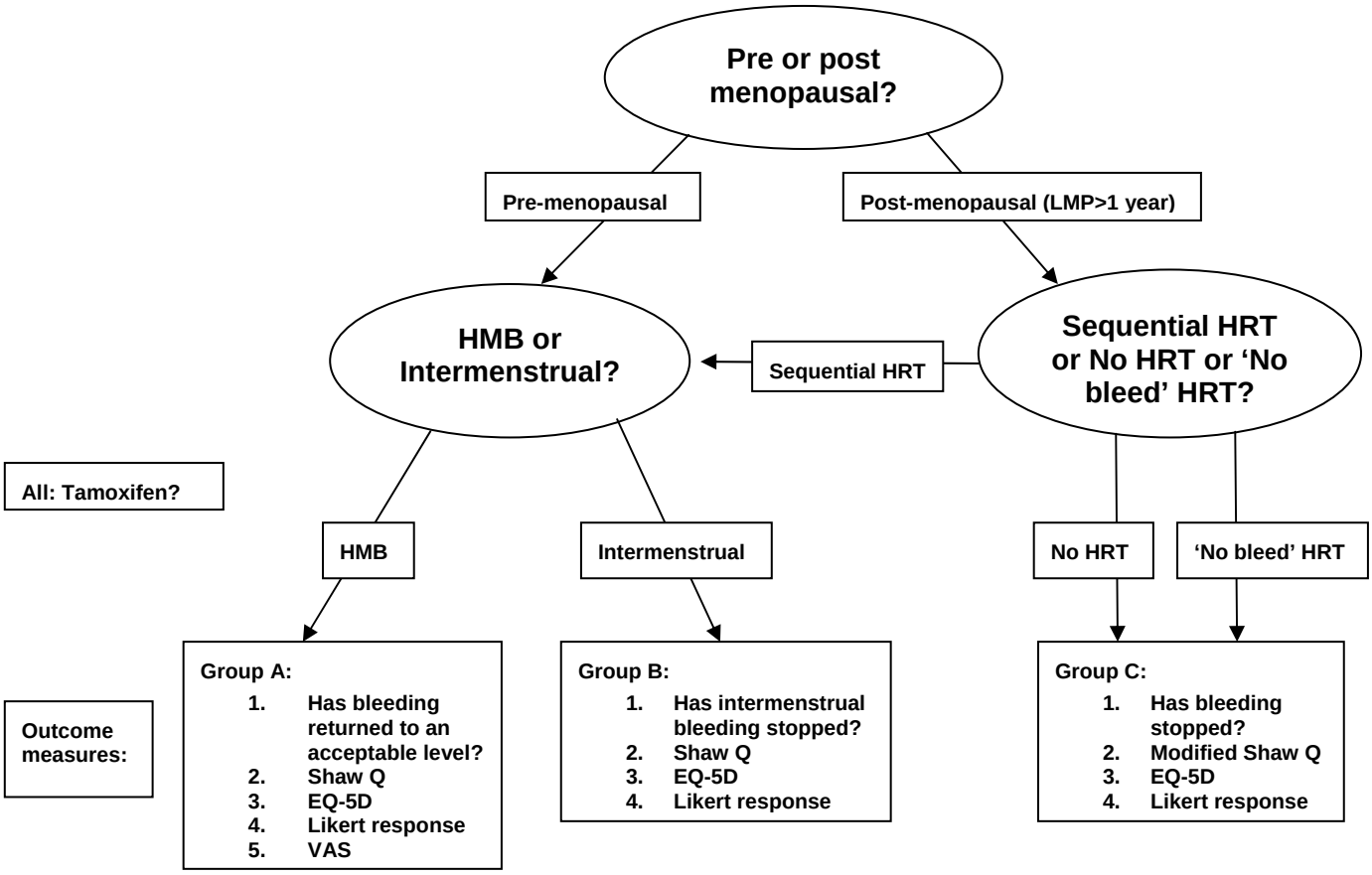
Shaw Menorrhagia assessment scale[25] A multi-attribute utility, designed to measure the impact of heavy menstrual bleeding (menorrhagia) upon HRQL. It has been evaluated for its reliability and face validity (condition-specific instrument). For women where the questions on the form do not specifically relate to their symptoms (group C in figure 2) a modified version of the form will be used. Our objective here it is to use the responses from this group to explore and develop the use of a modified questionnaire for patients where bleeding is not expected. Results will be presented with this limitation in mind for this group.

EuroQol EQ-5D[26] EQ-5D is a standardised instrument for use as a generic measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. Responses will be given valuations derived from published UK population tariffs and the mean number of quality adjusted life-years (QALYs) per patient and incremental QALYs will be calculated.

Likert scale. All patients will be asked how their bleeding has responded to treatment using a Likert scale with four response options.

Visual analogue scale (VAS) It is now well established that objective measures of blood loss are not particularly relevant to women's subjective perception of bleeding symptoms[20] .For those patient with heavy menstrual bleeding (group A in figure 2), our pilot work[10,15,21] has demonstrated that improvements in VAS scores correlate very well with improvements in categorical and condition specific quality of life measures. The reliability of VAS has been established in the assessment of chronic gynaecological conditions like pain[22], and change in individual VAS scores should have sufficient psychometric strengths to be used in the research of abnormal uterine bleeding involving large group comparisons[23]

Figure 2: OPT pathways for outcome measures



5.4. Health economic outcomes

Costs and consequences of the treatment pathways will be collected from health care providers at the time of the procedure and at follow up in order to conduct the cost-effectiveness analyses.

Resource use data will include:

- Surgical treatment of uterine polyp(s)
- Tests and investigations received
- The frequency and duration of out-patient visits and primary care consultations
- Inpatient stays
- Type and volume of medications received
- The number and duration of hospital readmissions and re-treatments.

These data will be collected prospectively from health care providers using a post-operative case report form and patient-completed questionnaires that assess patient health service utilisation at the follow-up time points throughout the trial. Costs incurred by patients will also be collected to conduct an evaluation from a wider societal perspective. Therefore, a patient cost questionnaire will be administered to all trial patients in order to consider the wider cost implications of the interventions which will contain questions to determine out of pocket expenses incurred when attending for treatment and private time costs including time lost from work.

Unit costs obtained from published sources and trial centres will be used to estimate costs associated with resource use. Responses to the EuroQol EQ-5D questionnaire will inform the effectiveness in terms of QALYs and clinical effectiveness will be measured in cured cases at six months.

Data collection will be undertaken prospectively for all trial patients so that a stochastic cost analysis can be undertaken. The process of collecting resource use data will be undertaken separately from data collection on unit costs. The main resource use to be monitored include the following:

1) Consultation time required prior for each procedure for explanation and consent.

2) Costs involved with each procedure including level of health care professional involvement in the procedure, equipment required, overheads, consumables and drugs including anaesthesia.

3) Any additional procedures required where initial treatment is unsuccessful or incomplete.

4) Duration of inpatient stay for the inpatient uterine polypectomy procedure.

Information on any additional related primary or secondary care contacts will also be collected from all patients to ensure any resulting resource use from additional complications is recorded. Unit costs will be obtained and attached to resource items in order that a cost can be calculated for each trial patient. Unit costs will be obtained from published sources and centres participating in the trial. Published sources will include Unit Costs of Health and Social Care[27] and NHS Reference costs. Primary cost data will be collected from a representative sample of participating hospitals. In addition, the set-up costs of OPT will be estimated and additional analyses will be undertaken including these costs. Information will be obtained from a sample of the participating hospitals on the level and extent of training required and any additional resource use required for the initial set-up of the outpatient clinics.

5.5. Data management and validation

5.5.1 Confidentiality of personal data

Personal data and sensitive information required for the OPT Trial will be collected directly from participants, who will informed about the transfer of this information to the OPT trial office at the University of Birmingham Clinical Trials Unit (BCTU) and will be asked to consent to this. The data will be entered onto a secure computer database, either by BCTU staff or directly via a secure internet connection. Any data to be processed outside the BCTU will be anonymised.

All personal information obtained for the study will be held securely and treated as (strictly) confidential. All staff involved in the OPT Trial (clinical, academic, BCTU) share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published.

5.5.2 Long-term storage of data

In line with MRC guidelines, all data will be stored for up to 15 years after the last participant has reached the 2 year follow-up to allow adequate time for review, reappraisal or further research, and to allow any queries or concerns about the data, conduct or conclusions of the study to be resolved. Limited data on the participants and records of any adverse events may be kept for longer if so recommended by an independent advisory board.

5.6. Withdrawal from follow-up

Withdrawal from follow-up is the decision of the participant. However, withdrawn patients can bias clinical trial results and reduce the power of the study to detect important differences, so women should be encouraged to complete all follow-up questionnaires. Methods to reduce the burden of follow-up will be explored e.g. online data entry for participants. If the reason for withdrawal is known, it should be communicated to the OPT Trial Office. To reduce loss to follow-up, we shall record patient's NHS number, which allows us to track patients changing GP practice. With postal and telephone reminders we anticipate that, the completeness of data should surpass 90% although, as set out below incomplete follow-up is incorporated into the power calculations.

6. ACCRUAL AND ANALYSIS

6.1. Sample size

The sample size for this trial has been chosen to give good statistical power to preclude any clinically important inferiority of OPT compared to in-patient treatment and is based on the evidence obtained in the pilot study (section 1.4.3).

Outpatient treatment is more convenient for women in that no inpatient stay is required and is also likely to cost substantially less. We believe, therefore, that outpatient would be the treatment of choice even if 25% less women had alleviated symptoms at 6 months (e.g. inpatient 90% vs. outpatient 67%). Making the assumption that inpatient treatment will be 90% successful (using the criteria set out in section 5.2) and outpatient 80% successful, a sample size of approximately 200 in each arm (400 in total) would be needed to rule out a success rate of less than 67% in the outpatient arm (90% power, p=0.05). This calculation is based on a more conservative two-sided test as opposed to the usual one-sided test associated with non-

inferiority studies, allowing us increased power to detect differences in the planned sub-group analyses. To also allow for a 15% loss to follow-up, the sample size is inflated to 240 patients in each group (i.e. 480 patients in total).

6.2. Projected accrual and attrition rates

It is anticipated that recruitment of patients will take two years. If each of the 22 centres that have provisionally agreed to collaborate and obtain LREC approval, enters one patient per month then the minimum target of 480 patients could be randomised in two years. This recruitment rate should be easily achievable given that all participating centres have at least one outpatient hysteroscopy clinic per week (mean 2.0 per week) seeing a minimum of five women (mean 6.5) with abnormal uterine bleeding and of these between 15% and 25% can be expected to have uterine polyps and 80% may be expected to consent to participation (this is a conservative estimate as pilot OPT data was in excess of 90% approached agreed to consent). The primary assessment of the effectiveness of OPT will be from comparison of outcomes at the 6 month follow-up, although the short-term and longer-term risks and benefits of OPT will also be evaluated. First publication will be possible within four years of trial commencement.

Our sample size calculations have allowed for a 15% loss to follow up rate. In order to minimise rates of attrition we will employ a dedicated research fellow and dedicated research nurse who will provide a flexible and individualised supportive approach to recruiting centres. In addition we will further incentivise collaborating centres by providing per patient payments. The Clinical Trials Unit at the University of Birmingham has expertise and a proven track record in successfully recruiting large multicentre trials and we will use this expertise to optimise recruitment and follow up.

6.3. Statistical Analysis

The proportion of women rating their operation as successful will be compared using a chi-squared test, with corresponding risk ratios and 95% confidence intervals calculated. For this primary analysis, adjustments for other prognostic factors will not be made in the first instance; the effect of the variables listed in section 3.5 will be explored as a secondary analysis. Continuous measures (VAS/Shaw scores) will be analysed using analysis of covariance (adjusting for baseline value). Cochran-Armitage test for trend will be performed on Likert scale output. Multilevel models repeated measures (MMRM) will also be used to compare the mean differences in life quality and VAS scores between groups overall all time points, thereby maximising the power of the data available. Further details are given in the statistical analysis plan.

Analysis will be performed intention to treat in the first instance, although as recommended in the CONSORT[33] statement and by Jones et al[34] a 'per protocol' analysis will also be performed to test the robustness of the results obtained.. As a conservative measure, estimates of effect sizes between the two arms will be presented as point estimates with 2-sided 95% confidence intervals[33] (equivalent to a one-sided p-value of 0.025). The trial can only conclude non-inferiority if the lower band on the confidence limit is not lower than the margin of inferiority (i.e. 25% less successful than inpatient treatment).

Baseline characteristics of the patients enrolled in the two groups will be compared to ensure that randomisation has produced comparable groups of patients, and will be covariates in the modelling procedure. The use of additional treatment (co-intervention) for abnormal uterine bleeding following polypectomy will be assessed for any systematic differences between the two groups.

6.3.1 Subgroup analyses

Subgroup analyses are limited by statistical power and can produce spurious results particularly if many are undertaken. Our literature review[5] and consultation with gynaecologists[1] suggests that the effectiveness of OPT may be greater for intermenstrual bleeding and postmenopausal women. Therefore, subgroup analyses will be limited to the stratification variables (section 3.5), and interpreted suitably cautiously.

6.3.2 Proposed frequency of analyses

1. Twice yearly review of recruitment, compliance and loss to follow-up for OPT Trial Steering Committee.
2. Annual interim analyses of effectiveness for confidential review by Independent Data Monitoring and Ethics Committee to determine whether the principal question has been answered and to monitor adverse events.
4. Main analyses of effectiveness of OPT once all patients have reached 6-month follow up of the total study sample.
5. Additional analysis of longer term effects (completion of one and two years of follow-up).

6.3.3 Handling missing data

The interpretation of missing values in the analysis of clinical trials can be fraught with danger. The methods used to allow for missing data make assumptions about the reasons for data not being present, such as in the "observed case" analysis, where the presence or absence of data is viewed as unrelated to outcome, or in the "Last Observation Carried Forward" analysis where the assumption is that the condition does not improve or worsen following withdrawal from follow-up. To minimise possible biases, participants will continue to be followed up even after protocol treatment violation. Missing data items from the Shaw Menorrhagia Assessment Scale and EQ-5D will be imputed from given values if limited to a single item response. If a form is missing entirely or greater than one item imputation will not be attempted. Sensitivity analyses will be carried out to determine whether or not the results obtained are robust to the methods used to handle missing data. These approaches are in line with the recent recommendations from the European Agency for the Evaluation of Medicinal Products[29].

Questionnaires will only be treated as late if they are returned after the subsequent questionnaire has been sent to the patient. However if this form is the only form available at the later time point it will be included at the subsequent time.

6.4. Health Economic Analysis

6.4.1 Form of the economic evaluation

If OPT is found to be an effective treatment for abnormal uterine bleeding, then it is likely that there will be important cost implications for the health care sector. For example, as the patient will be treated as an outpatient, thus avoiding an inpatient stay, resources may be saved. However, OPT may incur costs due to equipment required and the specialist nature of health care professionals to perform the procedure. Therefore all costs incurred by both procedures need to be assessed in conjunction with measures of effectiveness.

The aim of the economic evaluation is to determine the cost-effectiveness of OPT compared with standard inpatient treatment for abnormal uterine bleeding. Although the trial has been designed as a non-inferiority trial, we feel the most appropriate type of analysis is a cost-effectiveness analysis[30]. Cost-effectiveness will be determined in two ways. A cost-effectiveness analysis will be undertaken to calculate the cost per additional cured case of abnormal uterine bleeding at six months, utilising the clinical outcome data collected within the trial. In addition, a cost-utility analysis will be undertaken to calculate the cost per additional quality-adjusted life year (QALY) gained. The utility values required to calculate QALYs will be obtained by administering the EuroQol EQ-5D questionnaire to all study patients at baseline, six months and twelve months. In the first instance, the evaluation will consider costs incurred by the health service in the delivery of both treatment pathways. However, information on costs incurred by patients will also be collected in order that an evaluation from a wider societal perspective can also be undertaken.

6.4.2 Economic analysis

Given the objective of the trial and limited available evidence in support of the OPT strategy, only a within trial economic analysis will be carried out. The analysis will adopt an incremental approach in that data collection will concentrate on resource use and outcome differences between trial arms. As the majority of cost data are skewed, and the mean cost of each procedure is of importance, a bootstrapping approach will be undertaken in order to calculate confidence intervals around the mean costs. As the time frame of the economic evaluation is not greater than one year, discounting is not required.

Uncertainty in the confidence to be placed on the results of the economic analysis will be explored by estimating cost-effectiveness acceptability curves. These plot the probability that the intervention is cost effective against threshold values for cost-effectiveness. The robustness of the results will be explored using sensitivity analysis. This will explore uncertainties in the trial based data itself, the methods employed to analyse the data and the generalisability of the results to other settings.

6.5. Definition of the end of trial

The end of the OPT trial will be defined as the time when the last patient recruited has completed 2 years of follow up.

7. ASSESSMENT OF PATIENT ACCEPTABILITY

7.1. Measurements for Patient Acceptability

The acceptability of OPT will principally be assessed using a questionnaire designed specifically for the study and administered within 24 hours of treatment to limit recall bias. Pilot testing will be carried out to make certain the questionnaire is usable. In addition to the questionnaire, data will be collected on the women who do not give consent to randomisation (state a preference and agree to be registered for the OPT study), and requested from those who decline to participate.

In order to aid interpretation and understanding of the questionnaire data, and to gain greater depth of experience, the acceptability of OPT will further be assessed using a qualitative methodology. Interviewing after discharge will allow the woman time to reflect on her experience, and will also minimise the chance that gratitude to doctors and other hospital staff results in unduly positive responses. Honesty is also more likely to occur on neutral or the patient's home ground[31]. Interviews will be recorded with patients' permission and transcribed verbatim within two weeks of surgery. The interview schedule will be designed following a literature search on patient acceptability of surgical procedures, and from the focus group discussions. From these, a set of items will be derived which will seem relevant to the participants and cover all the areas thought to be important by participants. The latter will also ensure that the questionnaire is as discriminatory as possible. The interview schedule will be piloted with five women. These procedures will ensure face and content validity, and sending each woman the transcript of her interview with the opportunity to amend any inaccuracy will assess fair and accurate representation.

7.1.1 Sampling of Participants for In-depth Interview

We propose to select a 10% random sample (48 women) from each arm of the research (not restricted by treatment centre) for interview within one week of discharge either face to face, or by telephone. This figure could be reduced if saturation is reached and no new issues emerge[32].

7.2. Evaluation of Patient Acceptability

Analysis of data will be by content analysis with the development of analytical themes. The initial process will be the intensive reading and re-reading of interview transcripts, and a search for regularities, contradictions, patterns and themes by comparing the participants' statements using a coding frame. Inter-rater reliability on the coding of transcripts will be undertaken. A percentage of the transcripts will be coded independently by two members of the qualitative research team and discrepancies discussed and resolved. Emergent themes obtained by this process will be refined until final themes are agreed by all applicants as reflective of the data. 'Researcher triangulation' will offer the first step to verification of the findings. This will be achieved through the independent analysis of 20% of transcripts from the sample by the researchers. Verification occurs through discussion of their analyses, comparison and subsequent consensus. 'Respondent validation' will also be sought by taking the tentative findings back to a sample of participants in order to be verified as reflective of their experience. A final form of verification is the comparison of findings with, and their embededness in, the available literature.

It is anticipated that the questionnaire and the subsequent in depth interviews will measure and provide insight into acceptability and satisfaction in the following areas: the procedure(s) for diagnosis; the information provided when consent is obtained; procedures to protect confidentiality; preference for one arm of the trial over the other; experience of the procedure and the immediate post-operative phase; overall satisfaction with the process; acceptability for the same procedure if polyps are diagnosed in the future; perceptions of being involved in an RCT.

8. DATA ACCESS AND QUALITY ASSURANCE

8.1. In-house Data Quality Assurance

The study will adopt a centralised approach to monitoring data quality and compliance. A computer database will be constructed specifically for the study data and will include range and logic checks to prevent erroneous data entry. Independent checking of data entry of paper questionnaires will be periodically undertaken on small sub-samples. The trial statistician will regularly check the balance of allocations by the stratification variables. Source data verification will only be employed if there is reason to believe data quality has been compromised, and then only in a sub-set of practices.

8.2. Independent Trial Steering Committee

The Trial Steering Committee (TSC) provides independent supervision for the trial, providing advice to the Chief and Co- Investigators and the Sponsor on all aspects of the trial and affording protection for patients by ensuring the trial is conducted according to the MRC Guidelines for Good Clinical Practice in Clinical Trials.

If the Chief and Co-Investigators are unable to resolve any concern satisfactorily, Principal Investigators, and all others associated with the study, may write through the Trial Office to the chairman of the TSC, drawing attention to any concerns they may have about the possibility of particular side-effects, or of particular categories of patient requiring special study, or about any other matters thought relevant.

8.3. Data Monitoring and Ethics Committee: Determining when clear answers have emerged

If outpatient polypectomy is clearly inferior to standard in-patient treatment, with respect to the primary endpoint,then this may become apparent before the target recruitment has been reached. Alternatively, new evidence might emerge from other sources that outpatient polypectomy is definitely more, or less, effective than in-patient. To protect against this, during the period of recruitment to the study, interim analyses of major endpoints will be supplied, in strict confidence, to an independent Data Monitoring and Ethics Committee (DMEC) along with updates on results of other related studies, and any other analyses that the DMEC may request. The DMEC will advise the chair of the Trial Steering Committee if, in their view, any of the randomised comparisons in the trial have provided both (a) “proof beyond reasonable doubt”* that for all, or some, women that out-patient treatment is so inferior from in-patient that non-inferiority can never be demonstrated, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. The TSC can then decide whether to close or modify any part of the trial. Unless this happens, however, the Trial management group (TMG), TSC, the investigators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

* Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least three standard deviations below the margin of non-inferiority (as set out in section 6.1) in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed.

9. ORGANISATION AND RESPONSIBILITIES

To ensure the smooth running of the trial and to minimise the overall procedural workload, it is proposed that each participating centre should designate individuals who would be chiefly responsible for local co-ordination of clinical and administrative aspects of the trial.

All investigators are responsible for ensuring that any research they undertake follows the agreed protocol, for helping care professionals to ensure that participants receive appropriate care while involved in research, for protecting the integrity and confidentiality of clinical and other records and data generated by the research, and for reporting any failures in these respects, surgical complications and other events or suspected misconduct through the appropriate systems.

9.1. Centre eligibility

Centres eligible to participate in the OPT Trial will need to satisfy the following criteria:

(1) Have an established outpatient hysteroscopy service

(2) Routinely perform both outpatient and inpatient uterine polypectomy

(3) Willingness to attend bi-annual collaborators meetings

9.2. Local Co-ordinator at each centre

Each Centre should nominate a Consultant Gynaecologist to act as the *local Principal Investigator* and bear responsibility for the conduct of research at their centre. Close collaboration between all clinical teams is particularly important in OPT in order that patients for whom outpatient polypectomy is an option can be identified sufficiently early for entry. The responsibilities of the local Principal Investigator will be to ensure that all medical and nursing staff involved in the care of OPT are well informed about the study and trained in trial procedures, including obtaining informed consent. The local Principal Investigator should liaise with the Trial Co-ordinator on logistic and administrative matters connected with the trial.

9.3. Nursing Co-ordinator at each centre

Each participating centre should also designate one nurse as *local Nursing Coordinator*. This person would be responsible for ensuring that all eligible patients are considered for the trial, that patients are provided with patient information sheets, and have an opportunity to discuss the study if required. The nurse may be responsible for collecting the baseline patient data and will act as a contact for obtaining missing follow-up evaluations. Again, this person would be sent updates and newsletters, and would be invited to training and progress meetings.

9.4. The OPT Trial Office

The Trial Office at the University of Birmingham Clinical Trials Unit (BCTU) is responsible for providing all trial materials, including the trial folders containing centre specific trial documentation, standard operating procedures and training materials. These will be supplied to each collaborating centre, after relevant ethics committee approval has been obtained. Additional supplies of any printed material can be obtained on request or downloaded from the OPT trial website. The Trial Office also provides the central randomisation service and is responsible for collection and checking of data (including reports of serious surgical complications), for reporting of serious adverse events to the sponsor and/ or regulatory authorities and for analyses. The Trial Office will help resolve any local problems that may be encountered in trial participation.

9.5. Research Governance

The conduct of the trial will be according to the principles of MRC Guidelines for Good Clinical Practice in Clinical Trials (1998) and the appropriate NHS Research Governance Frameworks.

All Principal Investigators will be required to sign an Investigator's Agreement, detailing their commitment to accrual, compliance, Good Clinical Practice, confidentiality and publication. Deviations from the agreement will be monitored and the TSC will decide whether any action needs to be taken, e.g. withdrawal of funding, suspension of centre. The Trusts hosting the research will be required to sign a Clinical Study Site Agreement, detailing the Trust's responsibilities under the relevant Research Governance Framework and accepting the terms and conditions of the per patient payments.

The Trial Office will ensure researchers not employed by an NHS organisation, who will have contact with patients that can have an impact on their quality of care, hold an NHS honorary contract for that organisation, or have an honorary contract research passport.

9.6. Research Governance and Ethical Approval

The Trial has a favourable ethical opinion from South West Research Ethics Committee (MREC) approval, determining that the trial design respects the rights, safety and wellbeing of the participants. The Trust Research and Development Office then need to assess the "locality issues" relating to their population, the investigators, the facilities and resources (as from 1st April 2009 this process has been streamlined so that the issues are not duplicated by both the REC and R&D offices). The Trial Office is able to help the local Principal Investigator in the process of the site-specific assessment approval from their Trust R&D Office by completing much of the 'Site Specific Information Form' of the standard 'NRES form' as possible. The local Principal Investigator will be responsible for liaison with the Trust management with respect to locality issues and obtaining the necessary signatures at their Trust.

As soon as Trust approval has been obtained, the Trial Office will send a folder containing all trial materials to the local Principal Investigator. Entry of patients into the trial can then begin.

As the trial does not involve an investigational medicinal product, clinical trial authorisation from the Medicines and Healthcare products Regulatory Authority is not required.

9.7. Funding and Cost implications

The research costs of the trial are funded by a grant from the NHS Research and Development Health Technology Assessment Programme (HTA), awarded to the University of Birmingham.

The trial has been designed to minimise extra 'service support' costs for participating hospitals. Additional costs associated with the trial, e.g. gaining consent, time taken for nurses to explain the questionnaires to patients, etc., are estimated in 'Site Specific Information Form' of the standard MREC Form. These costs will be met from Trust's translational funding in the initial phase of the trial and via the Comprehensive Research Network later on.

Whilst we recognise that excess service support costs should be met by the hospital Trusts concerned, whilst this funding stream is in transition, we wish to ensure that centres are properly resourced to support the trial. Therefore, all NHS Trusts hosting the research (excluding the Birmingham Women's Hospital – trial centre) will be eligible for a per-patient payment, set at a level to be defined annually by the Trial

Management Group (estimated remuneration for peripheral centres of £100 per participant randomised and baseline data collected). This rate should allow clinicians recruiting four patients per month to receive sufficient for one nurse hysteroscopist session per week. This payment will also help to ensure coverage of extra NHS Treatment costs (i.e. the need for follow up diagnostic hysteroscopy at six months in a subgroup of patients) and provide an incentive for recruitment in collaborating centres by recognising the extra human resource required in recruiting patients to the OPT trial.

9.8. Indemnity

There are no special arrangements for compensation for non-negligent harm suffered by patients as a result of participating in the study. The study is not an industry-sponsored trial and so ABPI/ABHI guidelines on indemnity do not apply. The normal NHS indemnity liability arrangements for research detailed in HSG96(48) will operate in this case.

However, it should be stressed that in terms of negligent liability, NHS Trust hospitals have a duty of care to a patient being treated within their hospital, whether or not that patient is participating in a clinical trial. Apart from defective products, legal liability does not arise where there is non-negligent harm. NHS Trusts may not offer advance indemnities or take out commercial insurance for non-negligent harm.

9.9. Publication

A meeting will be held after the end of the study to allow discussion of the main results among the collaborators prior to publication. The success of the study depends entirely on the wholehearted collaboration of a large number of doctors, nurses and others. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all those who have collaborated in the study. Centres will be permitted to publish data obtained from participants in the OPT Trial that use trial outcome measures but do not relate to the trial randomised evaluation and hypothesis.

9.10. Ancillary studies

It is requested that any proposals for formal additional studies of the effects of the trial treatments on some patients (e.g. special investigations in selected hospitals) be referred to the Trial Management Committee for consideration. In general, it would be preferable for the trial to be kept as simple as possible, and add-on studies will need to be fully justified.

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APPENDIX A PATIENT INFORMATION SHEET

What is the procedure that is being tested?
Outpatient polyp treatment under local anaesthetic will be tested against day case polyp treatment under general anaesthetic.

Outpatient polyp treatment can be performed in a few different ways but generally involves passing a special type of hysteroscope (4 to 6 millimetres in diameter) into the womb through which specifically designed miniature mechanical or electrical operating instruments are passed to remove the polyp(s). In most cases the procedure requires local anaesthetic to be applied to the neck of the womb to help make the procedure easier and more comfortable. Removing polyps in this way takes between 5 and 15 minutes on average. The procedure is generally performed immediately following the initial diagnostic hysteroscopy.

Day case polyp treatment can also be performed in different ways. The simplest and most commonly used method is to dilate the neck of the womb so that slightly larger instruments, measuring around 5 to 8 millimetres in diameter, can be passed into the womb to remove the polyp(s). These instruments either grasp or scrape off the polyp(s). Alternatively, the polyp(s) can be removed using a hysteroscope in the same way as described for outpatient treatment, but more commonly using a slightly larger hysteroscope (5 to 9 millimetres in diameter). The procedure is requires a short general anaesthetic and is usually performed as a 'day case' within 3 months of the initial diagnosis at outpatient microhysteroscopy.

How will I feel during and after outpatient polyp treatment?
During the procedure you may get some crampy period type pains in your lower abdomen which usually settle once treatment is completed. If it does not the nurse will give you some simple pain killers. A minority of women may feel a little faint following the procedure requiring them to lie down for a few minutes until the sensation passes. Light spotting or fresh blood loss is not uncommon but again should settle within a few hours of the procedure, although some women may experience light vaginal blood loss for a few days. After the procedure you will be able to rest and have a cup of tea in comfortable surroundings. It is advisable to have someone with you when you get home. You will need to rest for the remainder of the day. If you do require further pain relief, we suggest simple pain killers such as paracetamol every 6 hours.

How will I feel during and after day case polyp treatment?
You will not experience any discomfort during the procedure because the procedure is performed under general anaesthesia. After the procedure you will be able to rest on a bed in a hospital ward and would normally be allowed home a few hours later. Symptoms you may experience following the procedure are as described for outpatient treatment. Some patients may also experience short-lived side-effects arising from the general anaesthetic and these commonly may include nausea, vomiting, dizziness, a headache and sometimes a sore throat.

What are the alternatives for diagnosis or treatment?

Pelvic ultrasound is the usual first line investigation for women with abnormal uterine bleeding. However this test has limited accuracy for detecting polyps. In contrast outpatient diagnostic hysteroscopy is the gold standard test and is widely used. Therefore the OPT trial will use outpatient hysteroscopy to diagnose polyps and randomisation will take place at the time of diagnosis (i.e. during the hysteroscopic procedure). The vast majority of doctors recommend removing polyps with the aim of improving bleeding symptoms and examining the removed specimen to make sure that they are not precancerous, which would require additional treatment. However, most polyps are not worrying and some may even disappear on their own naturally, but this is uncommon and generally applies to very small polyps only. An alternative to removing polyp(s) is to leave them alone, but bleeding symptoms may continue and examination of the removed tissue to confirm normality cannot be performed.

What are the possible risks and disadvantages of taking part?
Day case and outpatient treatment of polyps in this study are currently being used widely in the NHS and all the doctors involved will have the relevant experience. Both outpatient and day case polyp removal have been shown to be safe.

What happens when the research study stops?

When the results of the OPT study are known they will be published in medical journals and the results circulated to medical staff and participants. The results will influence the way women with polyps are treated in the future.

What are the side effects of treatment received when taking part?
Both outpatient and day case polyp treatments are safe and side-effects are uncommon. Minor side-effects common to both treatment settings include prolonged blood stained vaginal discharge, and infection of the womb lining or bladder (cystitis) requiring a short course of antibiotics. The only serious and rare complication specific to the procedure of polyp removal is making a hole in the wall of the womb ('perforation') which normally heals naturally, but occasionally can cause bleeding or damage to other organs in the abdomen which requires immediate abdominal surgery to repair. A minority of women undergoing outpatient treatment can experience severe, cramping period-like pain and some may feel faint for a few minutes immediately following the procedure. Women undergoing day case treatment may take a few hours to recover from the general anaesthetic because of sickness and drowsiness.

Are there any benefits for me from part in the study?
Participants may not gain any individual benefit but if outpatient polyp treatment is better at improving symptoms, cheaper and acceptable, in future women will benefit in terms of convenience, safety and choice.

What if there is a problem?
Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information is given in Part 2.

Will my taking part in the study be kept confidential?
Yes. The study will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decisions.

To be printed on Local Trust Headed Paper

OPT — **A Randomised Controlled Trial of Outpatient Polyp Treatment (OPT) for Abnormal Uterine Bleeding**

PARTICIPANT INFORMATION SHEET

LOCAL HOSPITAL OPT STUDY RESEARCH STAFF CONTACT DETAILS

GYNAECOLOGIST NAME:

_____

GYNAECOLOGIST TEL:

_____

RESEARCH NURSE NAME:

_____

RESEARCH NURSE TEL:

_____

ISRCTN65868569 OPT Patient information sheet v2.1 04.09.09

OPT

A Randomised Controlled Trial of Outpatient Polyp Treatment (OPT) for Abnormal Uterine

OPT Participant Information Sheet Part 1—this tells you the purpose of the study and what will happen to you if you take part

Invitation to participate in the OPT study

You are invited to take part in a research study to find out which is the best treatment setting to remove polyps causing abnormal uterine bleeding. This study is called OPT and compares outpatient polyp treatment with traditional inpatient (day case) polyp treatment. Day case treatment involves admission to hospital and use of general anaesthetic. The study is entirely voluntary – you do not have to take part, nor give a reason why, if you decide not to. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it would involve if you do choose to take part. Please take your time to read this information carefully. Talk to others such as family, friends or your GP about the study if you wish. If there is anything that is not clear, or you would like more information you should ask your gynaecologist or clinic nurse for further advice.

What is the purpose of the study?

Until recently women with polyps were treated under general anaesthetic in the operating theatre to have them removed. New technology has now allowed for the polyp(s) to be removed in an outpatient hysteroscopy clinic setting using local anaesthetic or no anaesthetic at all. A hysteroscopy is a test that allows your doctor to look inside your womb using a narrow tube-like telescope. This instrument is very slim (about three to five millimetres in diameter). It's carefully passed through the vagina and cervix, and into your womb. The OPT study is being carried out to determine if outpatient treatment is as good as traditional day case treatment.

What is a polyp?

A polyp is an over growth of tissue that may be the cause of your bleeding. Polyps can be found at the cervix (neck of the womb) or inside the uterus (womb). Polyps require removal for examination under the microscope.

How will you find out whether polyps are the cause of my bleeding?

You have been referred by your GP or Consultant to the hysteroscopy clinic so that a procedure called a 'diagnostic hysteroscopy' can be carried out to investigate the cause of your bleeding. The gynaecologist will be able to see if polyps are present during the hysteroscopy.

What happens during the outpatient diagnostic hysteroscopy?

During the examination you will be asked to lie on a couch, with a nurse by your side, and have a vaginal examination similar to having a smear test. A local anaesthetic may then be applied to the neck of the womb as this can sometimes make the procedure easier and more comfortable. However, application of local anaesthetic is not required for most women as the procedure is generally quick (2 to 5 minutes on average) and well tolerated. Most women will experience a short lasting cramping discomfort in their lower abdomen like a 'period pain' You may have also received a separate information leaflet from your local hospital about your hysteroscopy clinic appointment.

Why have I been invited?

All women referred by their GP or Consultant for an outpatient hysteroscopy to investigate abnormal uterine bleeding symptoms will be asked if they would like to take part in the OPT trial because they may have polyps. However, you will only be eligible to join the OPT study if it is determined during the diagnostic hysteroscopy the cause of abnormal uterine bleeding is found to be polyps. Polyps are found to be the cause of abnormal uterine bleeding in approximately 15-30% of cases. We aim to recruit 480 women to take part in the study in over 20 centres in the UK over a period of 2 years.

Do I have to take part?

No. Taking part is entirely voluntary and it is up to you to decide. If you do not wish to take part your decision will not affect the standard of care you will receive. Similarly, if you do decide to take part, you are entitled to withdraw from the study at any time, without having to give a reason, and this will not affect the standard of your medical care in any way.

If I take part will I have treatment in the day case or outpatient setting?

Women who take part in the study are allocated to one of two treatment setting groups, either day case or outpatient, at random by the central study office. There is an equal chance of being allocated to the day case group or the outpatient treatment setting group. Neither you nor your gynaecologist will know which of the groups you will be in until after you have been entered into the study. This means that doctors can't choose which women will receive which treatment and this makes the results much more reliable. This is called a 'randomised clinical trial' and it is the standard medical research method for comparing treatments.

What will happen to me if I take part?

If a polyp is seen when diagnostic hysteroscopy is carried you will be eligible to enter the OPT trial. To have the polyp removed you will be put into one of two groups; either day case or outpatient treatment, at random, by the central study office. The hysteroscopy diagnostic procedure will take between 2 and 5 minutes on average. If you choose to take part in the OPT study the process of randomisation will prolong the diagnostic procedure time by up to two minutes. Depending on which group you are randomly allocated to you will either have the treatment carried out as an outpatient under local anaesthetic in the clinic at the same time (some clinics may offer an appointment for outpatient treatment at a later date within 6 weeks), or we will bring you into hospital within the following few weeks to have treatment as an day case. The polyp will be removed in an operating theatre under a short general anaesthetic, and you will be discharged home on the same day in most instances.

What if I have a preference for either day case or outpatients treatment?

If you decide that you have a definite preference for either the day case or outpatient treatment setting then you could choose to still be part of the OPT study if you wanted to. You would not be eligible to be randomised between the two treatment settings and would instead be registered in the OPT study and have the treatment setting of your choice. If you give your consent and permission we would like collect all of the same data about you and for you to complete questionnaires at 6 months as you would if you were randomised into the trial.

What will I have to do?

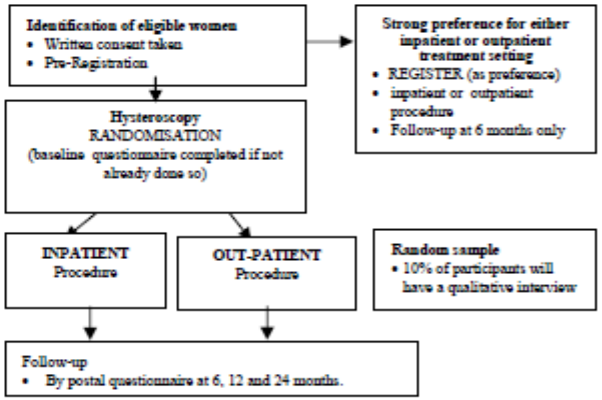
1. Complete pre-paid postal questionnaire (All participants)

We would like you to complete some short, confidential, questionnaires when you attend your clinic appointment to assess how much bleeding you have had and how it affects you. The same questionnaires will be sent to at home 6, 12 and 24 months after treatment. The questions are designed to find out if there are any improvements in your bleeding following treatment. There are several parts to the questionnaire – your assessment of your bleeding, what additional treatment you have taken for your bleeding, and some questions to determine your overall state of health and quality of life. You will not have to make any extra special trips back to hospital. It is important for the reliability of the study to find out how all women are progressing and the study organisers may, therefore, phone, text or email you to remind you to complete the questionnaires.

2. Follow up interview (some participants)

To find out how acceptable the day case or outpatient treatments are to women, 10% of OPT trial participants will be selected at random for an interview about their experience within one week of treatment. This interview will be conducted by one of the research team either face-to-face or by telephone. We would like to record these interviews with your permission.

The flow diagram below summarises what you will need to do:



If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decisions.

What will happen if I don't want to carry on with the study?
If you do decide to take part, you are entitled to withdraw from the study at any time, without having to give a reason (although it would be useful to know why), and this will not affect the standard of your medical care in any way. We would like to use the data collected about your up to your withdrawal. In the unlikely event of you losing the ability to give continued consent during the study we would like to keep data that we have already collected about you for research purposes.

What if there is a problem?
You have the same legal rights whether or not you take part in this study. If you are not satisfied with any aspect of the way you have been approached or treated during the course of this study, you should speak to the researchers who will do their best to answer your questions (Mr Justin Clark, OPT Chief Investigator, Tel: 0121 607 4712). If you remain unhappy and wish to complain formally the normal National Health Service complaints mechanisms are available to you: ask to speak to the complaints manager for the Hospital. Taking part in OPT should not affect any private medical insurance you may have, but you are advised to contact your medical insurance provider to confirm this.
Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, you and your doctor will decide your future care. If you decide to continue in the study you will be asked to sign an updated consent form.

Will information about me be kept confidential?
Yes, all information collected in the study will remain strictly confidential in the same way as your other medical records. If you agree to take part, your doctor will send basic information about you and your condition to the study's central organisers at the University of Birmingham Clinical Trials Unit. This information will be put into a computer and analysed by the OPT study office staff. The questionnaires will not contain your name and will be identified using a code number and will not be seen by your GP or gynaecologist. All information will be held securely and in strict confidence. No named information about you will be published in the study report. Information held by the NHS may be used to keep in touch with participants and follow up their health status. Occasionally, inspections of clinical study data are undertaken to ensure that, for example, all participants have given consent to take part. But, apart from this, only the study organisers will have access to the data.

Involvement of the General Practitioner/Family doctor (GP)
With your consent we will inform your GP of your participation in the OPT Trial.

What will happen to the results of the research study?
The results will be reported in a medical journal. It is expected that the first results will be published about two years after the study closes to recruitment. Everyone who takes part will then be told the results in a newsletter that will be posted directly to them.

Who is funding and organising the research?
The OPT study researchers are receiving a grant from the National Health Service's Health Technology Assessment programme to enable them to carry out this study. The central study organisers are based at the Universities of Birmingham.

The Clinical Trials Unit at the University of Birmingham will collect and analyse the data. The doctors and researchers involved are not being paid for recruiting women into the study. Patients are not paid to take part either, but their help in finding out more about how best to treat polyps is much appreciated. The study is jointly sponsored by the University of Birmingham and the Birmingham Women's NHS Foundation Trust.

Who has reviewed the study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee to protect you safety, rights, wellbeing and dignity. This study has been reviewed and given a favourable opinion by the South West Research Ethics Committee and Local Research Ethics committees for each OPT centre involved. Please keep this copy of the OPT Patient Information Sheet. You will also be given a copy of your signed consent form to keep if you decided to participate in the OPT trial.

Do you have any further questions?
Having read this leaflet, it is hoped that you will choose to take part in the OPT trial. If you have any questions about the study now or later feel free to ask your gynaecologist or clinic nurse. Their names and telephone numbers are given below. Please take the time before your appointment to decide whether you wish to take part in the OPT trial. You may like to discuss your decision with friends or relatives.

The UK Clinical Research Collaboration has produced a guide entitled, 'Understanding Clinical Trials'. This can be down loaded from their website: www.ukcrn.org.uk and maybe useful if you require general information about research. If you require specific information about the research project please either contact any of the OPT Staff listed below or visit our website: www.opt.bham.ac.uk. The OPT Local Organisers can give you advice about whether you should particiapte and if you are unhappy about the study please approach the OPT Study Central Organisers.

Contact details. OPT Study Local Organisers

Doctor: .....

Nurse: .....

Telephone: .....

OPT Study Central Organisers
Mr Justin Clark, OPT Chief Investigator, Consultant Gynaecologist, Birmingham Women's Hospital, Metchley Park Road, Edgbaston, Birmingham B15 2TG Tel: 0121 607 4712.

OPT Study Office, University of Birmingham Clinical Trials Unit, Division of Medical Sciences, Robert Aitken Institute, University of Birmingham, Edgbaston, Birmingham B15 2TT Tel: 0121 415 9109.

Notes: .....

.....

Thank you for taking the time to read this Participant Information Sheet about the OPT trial.

OPT Participant Information Sheet (v2.1 04.09.09)

APPENDIX B: PATIENT CONSENT FORM

TO BE INSERTED ON LOCAL HEADED PAPER

OPT

A Randomised Controlled Trial of Outpatient Polyp Treatment (OPT) for Abnormal Uterine Bleeding

OPT Participant Consent Form

Please initial each box to confirm consent

I confirm that I have read and understand the information sheet dated 4th Sept 2009 Version 2.1 for the above study. I have had the opportunity to consider the information, ask questions and these have been answered satisfactorily. ☐

I understand that my participation is voluntary and that if I take part, I am free to withdraw at any time, without giving a reason, and without my medical care or legal rights being affected. ☐

I accept that the study researchers may telephone or email me, if necessary, to remind me to complete questionnaires, or to ask the questions over the phone. ☐

I understand that medical staff involved in my care will provide a copy of my consent form and personal information about my progress, in confidence, to the central organisers at Birmingham Clinical Trials Unit (BCTU) for use in the OPT trial. I understand that the information held by the NHS may be used to keep in touch with me and follow up my health status. ☐

I understand that the information will be used for medical research only and that I will not be identified in any way in the analysis and reporting of the results. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Birmingham, regulatory authorities or the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

I agree to my GP being informed of my participation in the OPT Trial. I understand my GP may be contacted to obtain information about any complications or further gynaecology consultations. ☐

I understand what is involved in the OPT Trial, agree to participate and be **randomised** between trial treatments. ☐

I understand what is involved in the OPT Trial, agree to participate and express a preference for **inpatient** treatment. ☐

I understand what is involved in the OPT Trial, agree to participate and express a preference for **outpatient** treatment. ☐

Please initial only one of these options

Name of Patient	Date	Signature
Name of Person taking consent	Date	Signature

Copies of OPT Consent Forms: White copy for OPT site file, blue copy for patient, pink copy for patient hospital notes, yellow copy to be returned to BCTU.

OPT Patient Trial Number: ☐ ☐ ☐ ☐ (Please complete when patient is randomised/or expresses a preference for treatment)

ISRCTN65868569 OPT Consent Form (Version: 2.1, 4th Sept 2009)

APPENDIX C: GP LETTER

TO BE INSERTED ON LOCAL HOSPITAL PAPER

ENTER GP Name
ENTER Practice Name
ENTER GP Address 1
ENTER GP Address 2
ENTER GP Address 3
ENTER GP Address 4
ENTER GP Postcode

ENTER Date

Dear Dr. *ENTER GP NAME*

OPT

A Randomised Controlled Trial of Outpatient Polyp Treatment (OPT) for Abnormal Uterine Bleeding

OPT GP Information Sheet

Your Patient: .....

Date of Birth: ☐☐ ☐☐☐ ☐☐☐☐ OPT Trial No.: ☐☐☐☐

Date Randomised: ☐☐ ☐☐☐ ☐☐☐☐ Hospital No.: .....

was referred to the outpatient hysteroscopy clinic. With her written consent, she has agreed to participate in the OPT trial.

On finding a benign intrauterine polyp during diagnostic hysteroscopy, randomisation was carried out to decide whether outpatient treatment should be performed or if the treatment should be carried out as an inpatient. The patient will receive postal questionnaires, including questions on menstrual symptoms, quality of life, and demands on health care resources, at 6, 12 and 24 months post-operatively.

The Chief Investigator for OPT is Dr Justin Clark, Consultant Obstetrician and Gynaecologist, Birmingham Women's Hospital, United Kingdom B15 2TG, Tel: 0121 607 4712. OPT is organised by the University of Birmingham Clinical Trials Unit and funded by the NHS Health Technology Assessment Programme. Please file this letter in the patient's notes. Please contact the OPT Trial Office Tel: 0121 415 9130 if there are any errors in the details above or if she is no longer one of your patients.

Yours sincerely

ENTER LOCAL PRINCIPAL INVESTIGATOR NAME
ENTER LOCAL PRINCIPAL INVESTIGATOR CONTACT NUMBER

APPENDIX D: RANDOMISATION NOTEPAD

OPT

A Randomised Controlled Trial of Outpatient Polyp Treatment for Abnormal Uterine Bleeding

Please pre-register patients; enter **Part A only** and parts B & C before hysteroscopy
Online randomisations: https://www.trials.bham.ac.uk/OPT (24hrs)
Telephone randomisation: 0800 953 0274 (Monday – Friday, 9am – 5pm)

RANDOMISATION NOTEPAD (Version 4.1, 4th Sept 2009)

PART A: PLEASE PRE-REGISTER THE PATIENT

PART A: IDENTIFICATION DETAILS (please complete or attach patient sticker)

Consultant: ..... Hospital: .....

Patient's surname: ..... Patient's Forenames: .....

Patient's title: Mrs Miss Ms Dr Other: ..... Date of birth (dd/mmm/yyyy): / /

Patient NHS No.: ☐☐☐☐☐☐☐☐☐☐ Patient hospital no.: ☐☐☐☐☐☐☐☐☐☐

Patient's address: .....

..... Postcode: .....

Patient's daytime telephone number: ..... Evening telephone number: .....

Mobile telephone number: ..... Patient's email: .....

	Yes	No	
Does the patient have Abnormal uterine bleeding?	☐	■	**Ineligible**

PARTS B & C: PLEASE COMPLETE BEFORE HYSTEROSCOPY

PART B: ELIGIBILTY

	Yes	No	
Baseline questionnaires completed?	☐	■	**If any of the shaded boxes are ticked, the patient is NOT eligible for the OPT Study**
Abnormal uterine bleeding requiring diagnostic microhysteroscopy?	☐	■	
Consent obtained prior to the hysteroscopy?	☐	■	
Ability to perform polypectomy within 8wks of diagnosis?	☐	■	
Does patient have a preference for inpatient or outpatient treatment?	☐	☐	
If Yes, is patient willing to be registered for the OPT study?	☐	■	
If Yes, which treatment has the patient chosen?	Inpatient ☐	Outpatient ☐	
If No, is the patient willing to be randomised into the OPT study?	☐	■	

PART C: CLINICAL INFORMATION

1. Is the patient: A) Pre-menopausal ☐ or B) Post-menopausal (last menstrual period>1 year) ☐
   If B), is the patient taking: No HRT ☐ Sequential HRT ☐ Continuous combined 'no bleed' HRT ☐
2. Is there a history of use of Tamoxifen? No ☐ Yes ☐ If Yes, is this a current ☐ or previous user? ☐
3. If patient is pre-menopausal or post-menopausal on sequential HRT, what is the predominant complaint?
   Heavy menstrual bleeding ☐ Intermenstrual/unscheduled bleeding ☐
4. If allocated outpatient treatment will the procedure be carried out immediately ☐ or at a future date ☐

PART D: CLINICAL INFORMATION (COMPLETE DURING HYSTEROSCOPY)

Site of Uterine Polyp: Fundal ☐ Non-Fundal ☐ (If multiple, report 'Fundal' if any polyp is fundal)

Type of Uterine Polyp: Glandular ☐ Fibrous ☐ ('Fibrous' = no movement with flow or SMF (Gd 0))

Number of Polyps: ☐☐ Other benign pathology: None ☐ SMF (Gd I/II) ☐ Adhesion ☐ Septum ☐

	Yes	No	
Benign polyp(s) (glandulocystic or pedunculated / grade 0 fibroid) found?	☐	■	**If any of the shaded boxes are ticked, the patient is NOT eligible for the OPT Study** (Please inform OPT Office of reason if patient found to be ineligible during diagnostic hysteroscopy)
Does patient requires polypectomy?	☐	■	
Feasible to remove as an outpatient (if allocated)?	☐	■	
Hysteroscopic features suggesting malignant lesion?	■	☐	
Need for other uterine surgical intervention (i.e. endometrial ablation, resection, myomectomy or hysterectomy)?	■	☐	
Additional pathology necessitating hysterectomy?	■	☐	

PART E: RANDOMISED ALLOCATION (COMPLETE AT THE TIME OF RANDOMISATION PHONE CALL ONLY)

Inpatient treatment ☐ Outpatient treatment ☐ OPT study number: ☐☐☐☐

Form completed by: ..... Telephone: .....

Patient found to be ineligible during diagnostic hysteroscopy ☐ Date of randomisation: ...../...../.....

Patient selected for telephone interview Yes ☐ No ☐ Patient selected for repeat hysteroscopy? Yes ☐ No ☐

Please return the Consent Form and Enrolment Questionnaire to: OPT Study Office, BCTU, FREEPOST RRKR-JUZR-HZHG, Division of Medical Sciences, Robert Aitken Institute, University of Birmingham, Edgbaston, Birmingham, B15 2TT or by Fax: 0121 415 9136.

APPENDIX E: SERIOUS ADVERSE EVENT FORM

OPT

SERIOUS ADVERSE EVENT FORM

Please report any serious and unexpected adverse events that are suspected to be due to treatments[1] given as part of the OPT trial by sending or faxing the following details to the OPT Trial Office (Fax: 0121 415 9135) within 2 days of the event.

Patient Identification:

Patient's full name: .....

OPT Trial No: .....

Date of birth: ..... / ..... / .....

OPT Centre Name: .....

Responsible doctor: .....

Associated Treatment:

Inpatient uterine polypectomy ☐ Outpatient uterine polypectomy ☐

Date of treatment: ..... / ..... / .....

SAE description:

Category of event: Death ☐ Life threatening ☐ Hospitalisation (or prolongation of) ☐

Persistent or significant disability/incapacity ☐

Date SAE started: ..... / ..... / ..... Date SAE ceased: ..... / ..... / .....

Outcome: Fatal ☐ Recovered ☐ Continuing ☐

Details of adverse event (please attach copies of relevant reports):

.....

.....

.....

Did the event require or prolong hospitalisation? No ☐ Yes ☐ No. of days ☐

Please give reasons why you consider the event to be treatment related:

.....

.....

.....

Name of person reporting (please print): .....

Signed: .....

Tel No: ..... Date: ..... / ..... / .....

[1]For the purposes of this study, "**serious**" adverse events are those that are fatal, life-threatening, disabling or require hospitalisation. "**Unexpected**" adverse experiences are defined as those that would not be expected among patients given these treatments. It is not required to report in this way side-effects or adverse events that might reasonably be expected.

APPENDIX F: TOXICITY AND KNOWN SIDE EFFECTS

Complications of uterine instrumentation (diagnostic hysteroscopy, 'blind' mechanical polypectomy, mechanical or electrosurgical polypectomy under direct hysteroscopic vision), whether performed as an outpatient or inpatient with or without anaesthesia are as follows:

- Genital tract infection
- Uterine trauma
- Haemorrhage
- Uterine perforation leading to exploratory laparoscopy / laparotomy to exclude or repair damage to internal abdominal structures (e.g. bowel, urinary tract) or stop internal bleeding

Side-effects specific to outpatient polypectomy using local anaesthesia:

- Intravascular injection of local anaesthetic resulting in depression of the central nervous system (dizziness, light-headedness, feeling of inebriation, nausea and vomiting, circumoral anaesthesia and feeling of numbness, auditory disturbance (tinnitus), visual disturbance (difficulty focusing, blurred vision), tingling ('pins and needles'), disorientation and nervousness, drowsiness and loss of consciousness, shivering and twitching, fitting) and cardiac toxicity (arrhythmias, bradycardia, hypotension, asystole (cardiac arrest))
- Vaso-vagal reaction (episode of hypotension, bradycardia, pallor and fainting associated with feeling cold, sweaty, shivery and vomiting. Usually self-limiting but may require medical intervention (e.g. intravenous line, blood pressure support, atropine reversal)

Side-effects specific to inpatient polypectomy using general anaesthesia:

Side-effects related to administration of a general anaesthetic:

- General common side-effects: - (nausea and vomiting, sore throat, dizziness, blurred vision, shivering, headache, itching, aches, pains and backache, pain during injection of drugs, bruising and soreness, confusion or memory loss); General uncommon side-effects: - (chest infection, bladder problems, muscle pains, depressed respiration, damage to teeth, lips, or tongue, an existing medical condition getting worse, awareness, damage to the eyes, serious allergy to drugs, nerve damage, death, equipment failure)
- Side-effects of inhalational anaesthetic agents by system: - Cardiovascular (decreased myocardial contractility, reduced cardiac output, hypotension, arrhythmias, increased myocardial sensitivity to catecholamines); Respiratory (depressed ventilation, laryngospasm and airway obstruction, decreased ventilatory response to hypoxia and hypercapnia, bronchodilatation); Central nervous system (increased cerebral blood flow, reduced cerebral metabolic rate, increased risk of epilepsy, increased intracranial pressure); Others (decreased renal blood flow, stimulate nausea and vomiting, precipitate hepatitis)
- Side-effects of muscle relaxants: -histamine release producing a 'scoline rash', bradycardia, somatic pain resulting from fasciculation, hyperkalaemia, persistent neuromuscular blockade = 'scoline apnoea' (due to pseudocholinesterase deficiency), malignant hyperpyrexia (rapid increase in body temperature with increased PaCO2), increased intra-ocular pressure, increased gastric pressure.

APPENDIX G: TRIAL SCHEMA

OPT

OPT TRIAL SCHEMA

(Version 3.1 4th Sept 2009)

ELIGIBILITY

Inclusion Criteria

- Abnormal uterine bleeding requiring diagnostic hysteroscopy
- Finding of a benign polyp or polyps (glandulocystic or pedunculated / grade 0 fibroid) on diagnostic microhysteroscopy
- Need for polypectomy
- Written informed consent obtained prior to the hysteroscopy
- Feasible to remove polyp as an outpatient
- Ability to perform polypectomy within 8wks of diagnosis
- Patient aged 16yrs or older
- Baseline questionnaire can be completed after the hysteroscopy (if not already done so)

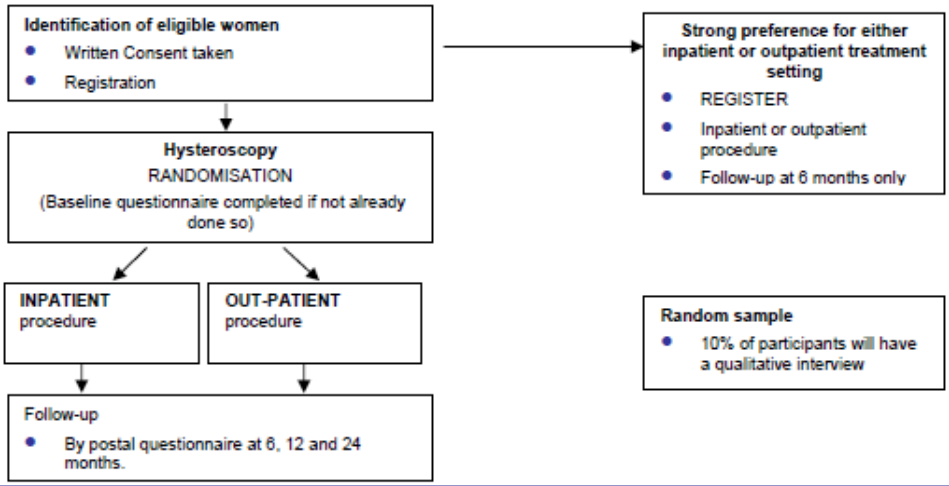
Exclusion Criteria

- Hysteroscopic features suggesting malignant lesion
- Need for other uterine surgical intervention (i.e. endometrial ablation, resection, myomectomy or hysterectomy)
- Additional pathology necessitating hysterectomy

RANDOMISATION

- Enter patients contact details (Part A) onto system prior to attending clinic.
- Obtain patient's written consent, complete baseline questionnaire and prepare for randomisation questions using the Randomisation Notepad.
- Before hysteroscopy pre-register patient online at **https://www.trials.bham.ac.uk/opt** or telephone the randomisation service on **0800 953 0274**. You will have already answered Part A so complete all questions on Parts B and C of the Randomisation Notepad. Pre-registering the patient's details will allow for the fastest possible randomisation when the patient is undergoing hysteroscopy.
- If the patient is found during hysteroscopy to be eligible for OPT please randomise the patient online at **https://www.trials.bham.ac.uk/opt** or telephone the randomisation service on **0800 953 0274**. You will need to answer all the questions in Part D of the Randomisation Notepad.
- When all the relevant questions have been answered, treatment allocation and patient reference number will be given.

OPT FLOW DIAGRAM



CONTACT DETAILS

FOR RANDOMISATION:

ONLINE: https://www.trials.bham.ac.uk/opt OR **TELEPHONE** TOLL FREE IN UK: 0800 953 0274 (OR 0121 415 9109 OR **FAX** 0121 415 9136)

FOR CORESPONDENCE:

FREEPOST ADDRESS: OPT Study Office, FREEPOST RRKR-JUZR-HZHG, BCTU, Division of Medical Sciences, University of Birmingham, Birmingham B15 2TT

POSTAL ADDRESS: OPT Study Office, Division of Medical Sciences, Robert Aitken Institute, University of Birmingham, Birmingham B15 2TT

FAX: 0121 415 9136 **EMAIL**: opt-trial@contacts.bham.ac.uk **WEBSITE**: www.opt.bham.ac.uk