NCCHTA

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THE EFFECTIVENESS OF HYSTERECTOMY, ABLATION AND LEVONORGESTREL RELEASING INTRA-UTERINE DEVICE IN THE MANAGEMENT OF HEAVY MENSTRUAL BLEEDING

Background

Heavy menstrual bleeding (menorrhagia) is a common problem. It affects nearly a third of women (Corrado et al, 1990; Rees, 1991) and prompts 5% of all women of reproductive age to consult their general practitioners with menstrual problems. Menstrual disorders account for 20% of gynaecology outpatient referrals and are responsible for over 23,000 hysterectomies each year in England. One in five women in the United Kingdom is likely to have had a hysterectomy by the age of 55 years (Vessey et al, 1992). Heavy menstrual bleeding affects many aspects of everyday life - including work as well as social activities, and leads to a measurable reduction in quality of life.

A literature search was undertaken using the Cochrane Library**,** Medline (1966-2006), Embase (1980 to July 2006), CINAHL (1982 to July 2006), using the following terms: menorrhagia, hypermenorrhea, (excessive) menstrual blood loss, heavy menstrual bleeding, dysfunctional uterine bleeding, hysterectomy, vaginal hysterectomy, total abdominal hysterectomy, subtotal abdominal hysterectomy, laparoscopic hysterectomy, transcervical resection of the endometrium, TCRE, endometrial ablation, laser ablation, hysteroscopy, electrosurgery, rollerball, (thermal) balloon, hypertherm(ia), thermotherapy, photodynamic therapy, phototherapy, cryoablation, microwave endometrial ablation, radiofrequency, saline irrigation, laser interstitial, Thermachoice, Cavaterm, ELITT, Vesta, Novasure, Microsulis, Cryogen. The metaregister of controlled trials and the ISRCTN register was searched for any trials with menorrhagia and endometrial ablation as keywords.

Current recommendations in the U.K. promote medical methods for the initial management of heavy menstrual bleeding. Mefenamic Acid, Tranexamic Acid and the combined oral pill are considered to be suitable first line drugs (RCOG Guideline, 1998). The levonorgesterol releasing intrauterine system (Mirena) is an effective non-surgical treatment which is reversible and fertility sparing. It reduces estimated menstrual blood loss by up to 96% by 12 months, with up to 44% of users reporting amenorrhoea (Milsom, 1991; Lahteenmaki, 1998), at a cost which is a third that for hysterectomy (Hurskainn et al, 2001). Despite the availability of these options, long term medical treatment is unsuccessful or unacceptable in many and surgery is required (Cooper et al, 2001).

Hysterectomy offers a definitive treatment for menorrhagia and guarantees amenorrhoea, but it is particularly invasive and carries significant morbidity (Lethaby et al, 1999). Overall one in thirty women suffers a major adverse event, and the mortality rate is 0.4 -1.1 per 1000 operations. The need for general anaesthesia, prolonged hospital stay and delayed recovery also makes hysterectomy an expensive treatment (Cameron et al, 1996).

Endometrial ablative techniques aimed at destruction of the functionally active endometrium along with some of the underlying myometrium (Duffy et al, 1991; Duffy et

al, 1992) offer a conservative surgical alternative to hysterectomy. The first generation ablative techniques including Endometrial Laser Ablation (ELA) (Goldrath et al, 1981; Davis, 1989), Transcervical Resection of the Endometrium (TCRE) (Magos et al, 1989) and Rollerball Endometrial Ablation (REA) were all endoscopic procedures. Although they do not guarantee amenorrhoea, their effectiveness (in comparison with hysterectomy - the existing gold standard) has been demonstrated in a number of randomised controlled trials (RCT) (Gannon et al, 1991; Dwyer et al, 1993; Pinion et al, 1994, O'Connor et al, 1997; Crosignanai et al, 1997; Aberdeen Endometrial Ablations group, 1999).

National audits (Overton et al, 1997; Scottish Hysterectoscopy Audit Group, 1995) revealed that although first generation ablative techniques were less morbid than hysterectomy they were associated with a number of complications including uterine perforation, cervical laceration, false passage creation, haemorrhage, sepsis and bowel injury. In addition, fluid overload associated with the use of 1.5% Urological Glycine (non ionic) irrigation fluid in TCRE and RBA, resulting in serious and occasionally fatal consequences due to hyponatraemia (Arrief & Ayus, 1993; Rosenberg, 1995). Mortality from these techniques has been estimated at 0.26 per 1000 (Overton et al, 1997; Scottish Hysteroscopy Audit Group, 1995).

Second generation ablative techniques represent simpler, quicker and potentially more efficient means of treating menorrhagia, which require less skill on the part of the operator. Examples of second generation ablative techniques are fluid filled thermal balloon endometrial ablation (TBEA), radiofrequency (thermoregulated) balloon endometrial ablation, hydrothermal endometrial ablation, 3D bipolar radiofrequency endometrial ablation, microwave endometrial ablation, diode laser hyperthermy, cryoablation and photodynamic therapy. The most common techniques in the U.K. are TBEA (Thermachoice and Cavaterm) (Loffer, 2001; Loffer & Grainger, 2002; Meyer et al, 1998) and Microwave Endometrial Ablation (Cooper et al, 1999; Bain et al, 2002), while the Novasure device (Novacept Inc) Cooper et al, 2002) is gaining in popularity. TBEA destroys the endometrium by means of heated liquid within a balloon inserted into the uterine cavity. It cannot be used in women with large or irregular uterine cavities. MEA uses microwave energy (at a frequency of 9.2 GHz) to destroy the endometrium. Complications associated with second generation techniques include equipment failure, uterine infection, perforation, visceral burn, bleeding and cyclical pain. A limited number of randomised trials indicate that these procedures appear to be as effective as first generation ablative techniques (Lethaby et al, 2005). In addition, some have the added benefit of being performed under local anaesthetic.

The introduction of new endometrial ablation techniques over the last two decades has been accompanied by a series of randomised clinical trials aimed at evaluating their clinical and cost effectiveness. Initially, first generation endometrial ablation techniques such as TCRE and laser ablation were compared with hysterectomy (Lethaby, 1999). Subsequent trials, which compared alternative first generation techniques such as TCRE, laser and rollerball endometrial ablation (REA), established TCRE as the gold standard for this group of treatments. As less invasive and more user friendly second generation techniques such as MEA became available, these were compared with earlier methods of ablation like TCRE and REA. Although not all techniques have been subjected to head to head comparisons in the context of randomised trials, an overview of the literature demonstrates that MEA (second generation) has been shown to be comparable with TCRE (first generation) - which, in turn, has been shown to be an effective alternative to hysterectomy (gold

standard). However, questions about long term clinical and cost implications of alternative forms of surgical treatment remain unanswered. Published data report no more than 5 years of follow up (Aberdeen Endometrial Ablations Trials Group, 1999; Cooper et al, 2005). Inevitably, some women treated by endometrial ablation will eventually require repeat ablation or hysterectomy. Following hysterectomy, a proportion of women will also develop further complications such as post surgical adhesions and pelvic floor dysfunction which may lead to further surgery. The necessity for a head to head comparison between the two most common second generation methods - MEA and TBEA has been identified (NICE, 2004). Our group has recently completed recruitment to such a trial involving over 200 women funded by the Chief Scientist Office Scotland (CZH/4/117), (Sambrook et al, unpublished). Given the widespread use of ablative techniques as first line surgical treatment for menorrhagia at the present time, it is uncertain whether it is either necessary or feasible to compare second generation techniques directly with hysterectomy in a new randomised trial which is unlikely to produce any meaningful results for another 4-5 years. At the same time, the need to obtain comparative information on long term outcomes is clearly accepted, as is the need to identify the best technique for individual women.

From a clinical perspective, we believe that the most relevant research questions at the present time are:

1. How do the currently used ablative techniques and the Mirena IUS system compare with hysterectomy in the medium to long term?
2. Which among the commonly used second generation ablation techniques is the most effective and cost-effective?
3. Are there subgroups of women who are most likely to benefit from either hysterectomy, Mirena or specific types of ablation?

We propose to address these questions by analysis of data from national datasets and randomised trials. We plan to assess long term outcomes by means of record linkage and follow-up of randomised cohorts, and perform individual patient data (IPD) meta-analysis of existing trial data. The output will be used to create a model for the utilisation and costs of the different treatments which can inform an algorithm for clinical decision making.

Overall aims of project

1. To determine, using data from record linkage and follow up of randomised and non-randomised cohorts of British women, long term effects of various second-generation ablative techniques and hysterectomy in terms of failure rates, complications and further surgery.
2. To determine, using individual patient data meta-analysis of existing randomised controlled trials, short to medium term effects of various second-generation ablative techniques, Mirena IUS and hysterectomy, including exploration of outcomes in clinical subgroups.
3. To undertake a model based clinical and cost effectiveness analysis comparing Mirena IUS, various second-generation ablative techniques vs hysterectomy using output from the above analyses and to conduct extensive sensitivity analyses to explore robustness of the results to the assumptions made.
4. To devise a parsimonious algorithm for clinical decision making regarding the choice of surgery for women with heavy menstrual bleeding with failed medical treatment.

Record linkage study protocol

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Aim

To determine, using data from record linkage and follow up of randomised and non-randomised cohorts of British women, long term effects of various second-generation ablative techniques and hysterectomy in terms of failure rates, complications, quality of life and sexual function.

This will be addressed by means of:

Analysis of a large, population based, anonymised, observational dataset generated by the Information Services Division (ISD) Scotland, in order to identify medium and long term effects of hysterectomy and second generation endometrium ablation techniques. This will overcome some of the potential limitations of data from trials which are based on relatively small numbers of women. This is thus an area where observational data will be invaluable in assessing outcomes in all categories of women rather than the highly selected group who have been recruited to trials.

This aim has had to be modified as long term data on quality of life and sexual function as well as variables listed in the previous analysis plan (uterine size, presence of fibroids, coexisting gynaecological pathology) are not available in the ISD dataset.
Predictor variables which are available in the ISD dataset include age, type of procedure, CARSTAIR quintile for social deprivation, year of operation and cancer.

Linkage of data from over 1200 women recruited to Scottish trials over the last 16 years and randomised to hysterectomy vs ablation or alternative endometrial ablative techniques. This will identify treatment failure (repeat surgery) following ablation and further gynaecological surgery in women after hysterectomy.

Analytical approach

Datasets:

Population-based routinely collected data will be used in the analysis to meet this objective. We have confirmation of availability of access to population-based data in Scotland. An

initial search within the ISD dataset has identified over 40,000 hysterectomies (1985-2005) and 14,000 ablative techniques (1989 and 2005) performed in women with dysfunctional uterine bleeding. This includes a sub-set of women randomised to alternative treatments for menorrhagia. The custodians of the ISD registry have given their approval to proceed along these lines and have agreed to generate an anonymised dataset for analysis.

Analysis:
Descriptive statistics will be used to summarise each of the outcomes and potential predictor variables (age, type of procedure, uterine size, presence of fibroids, coexisting gynaecological pathology). Appropriate univariate analyses (two sample t-test, chi square test and non-parametric tests) will be used initially to examine the association between these potential predictors and the outcomes of interest (repeat surgery, hysterectomy, other pelvic surgery).

Multiple logistic regression techniques will be used to examine the mutually adjusted effects of potential predictors identified in the univariate analysis. The predictive ability of the models will not be assessed by determination of the area under the receiver operating characteristics (ROC) curve due to the unavailability of the predictor variables (uterine size, presence of fibroids, coexisting gynaecological pathology). Comparison of the predictive ability of models incorporating only two variables using area under the receiver operating characteristics (ROC) curve was therefore deemed inappropriate. The analysis will generally be carried out stratified by the women's age group.

Appropriate univariate analyses (chi square test, t-test) will examine the association between the ISD-linked Scottish randomised trial women and future re-treatment. The women will be analysed by appropriate sub groups. Multiple logistic regression will be used to quantify the risk of treatment failure among subgroups of women after adjustment for confounders such as age, CARSTAIR quintiles, year of operation and cancer .

Sample size:
From the ISD dataset, we envisage assembling a cohort of at least 13,000 women post-ablation and 40,000 post-hysterectomy. With a dataset of 13,000 ablations, the two-sided 95% confidence interval around an estimated prevalence of re-treatment of 25% would be (24.3%, 25.7%).

THE EFFECTIVENESS OF HYSTERECTOMY, ABLATION AND LEVONORGESTREL RELEASING INTRA-UTERINE DEVICE: INDIVIDUAL PATIENT DATA META-ANALYSIS

Aim: To determine, using individual patient data meta-analysis of existing randomised controlled trials, short to medium term effects of various second-generation ablative techniques, Mirena IUS and hysterectomy, including exploration of outcomes in clinical subgroups.

The International HMB (Heavy Menstrual Bleeding) **IPD-Meta-analysis Collaborative Group**

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OBJECTIVES

To assess the comparative effectiveness of hysterectomy, ablative techniques and LNG-IUS for the treatment of menorrhagia using the following comparisons:

- Hysterectomy v. Ablation
- Ablation v. Ablation (comparison of different techniques)
- Ablation v. LNG-IUS
- Hysterectomy v. LNG-IUS

ELIGIBILITY

TYPES OF STUDIES

Studies will only be included if they are randomised controlled trials with adequate randomisation concealment, excluding quasi-randomisation and non-randomisation.

TYPES OF PARTICIPANTS

Inclusion Criteria:

Participants in the trials will be included in IPD meta-analysis if women have menorrhagia or abnormal/excessive/ prolonged uterine bleeding that is unresponsive to medical treatment without obvious clinically detectable underlying pathology.

As many of the trials have been pragmatic, prior hysteroscopy will not have been performed. Thus they will include women with small fibroids.

Exclusion criteria:

Participants in the trial that have uterine bleeding caused by polyps and other uterine pathologies, will not be included in the main IPD meta-analysis or, if considered necessary, analysed as a subgroup

TYPES OF INTERVENTION

Randomised controlled trials (RCTs) comparing hysterectomy, endometrial resection or ablation, and levonorgestrel-releasing intrauterine system (LNG-IUS) in any of the combinations laid out in the objectives section (2.0). Table 1 shows the range of interventions that will be included.

Table 1 Interventions groups and surgical techniques

Intervention	Type	Trade-name
Hysterectomy	Total (both the body of uterus and cervix removed)	
	Subtotal (the body of the uterus is removed, leaving the cervix in place)	
	± Salpingo-oophorectomy	
	± Bi-lateral salpingo-oophorectomies	
	Wertheim (will be excluded) (body of uterus and cervix, part of the vagina, fallopian tubes, usually the ovaries, parametrium -the broad ligament below the fallopian tubes- and lymph glands and fatty tissue in the pelvis removed. This type of hysterectomy is also called a radical hysterectomy)	
Ablation - Endometrial	1st Generation	
	- TCRE	
	- Rollerball	
	- Laser (Nd:YAG)	
	2nd Generation	
	- Thermal balloon	Thermachoice, Cavaterm
	- Hydrothermal	
	- 3D bipolar radiofrequency	
	- Microwave	NovaSure
	- Diode laser hyperthermy	
	- Cryoablation	
	- Photodynamic therapy	
LNG-IUS	LNG-IUS	Mirena Coil

TYPES OF OUTCOME MEASURES

Primary outcomes:

The primary outcome of interest is subjective reduction in menstrual blood loss. Any studies that do not include a measurement of MBL will be excluded. MBL can be assessed in a number of ways including a Visual Analogue Scale (VAS) or by pictorial blood loss assessment charts (PBAC).

Secondary outcomes:

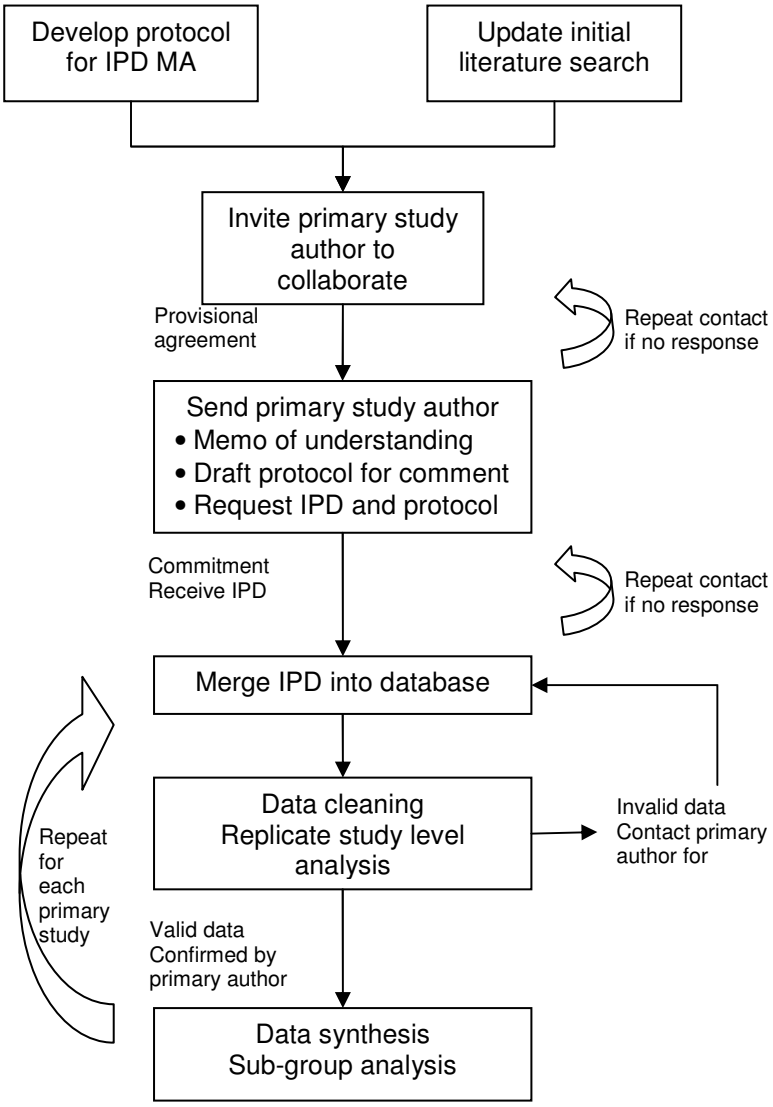
Other outcomes will be collected for meta-analysis to investigate the effect of the interventions on other aspects of HMB on women, adverse effects and resource implications. These will include:

- Patient satisfaction
- Safety of procedure (morbidity, adverse effects, operative complications)
- Length of operating time
- Length of hospital stay
- Fluid deficit
- Pain
- Anxiety, depression, sexual functioning
- Long-term complications
- QoL
- Health-related Quality of Life
- Pre-menstrual symptoms
- Repeated surgery for HMB

METHODS

An overview of the process of collecting and synthesising data is shown in Figure 1.

Figure 1 Summary of steps in undertaking the HMB IPD meta-analysis



LITERATURE SEARCHING

An original literature search was undertaken using the Cochrane Library**,** Medline (1966-2007), Embase (1980 to July 2007) and CINAHL (1982 to July 2007).
To select studies of surgical interventions for menorrhagia the following search terms were used: menorrhagia, hypermenorrhea, (excessive) menstrual blood loss, dysfunctional uterine bleeding, heavy menstrual bleeding, dysfunctional uterine bleeding, hysterectomy, vaginal hysterectomy, total abdominal hysterectomy, subtotal abdominal hysterectomy, laparoscopic hysterectomy, transcervical resection of the endometrium, TCRE, endometrial ablation, laser ablation, hysteroscopy, electrosurgery, rollerball, (thermal) balloon, hypertherm(ia), thermotherapy, photodynamic therapy, phototherapy, cryoablation, microwave endometrial ablation,

radiofrequency, saline irrigation, laser interstitial, Thermachoice, Cavaterm, ELITT, Vesta, Novasure, Microsulis, Cryogen, to focus on the intervention of interest.
To identify any ongoing RCTs the following were searched: the Meta-Register of Controlled Trials and the ISRCTN register with menorrhagia and endometrial ablation as keywords.
All identified trials are shown in Appendix A.
The search will be repeated every three months throughout the project to ensure any newly published studies are identified. Appendix B give the full search strategy.
Once the collaborative group has been established, investigators from the identified studies will be asked to review the included study list to identify any studies that might have been missed.

COLLECTION OF IPD FROM AUTHORS OF PRIMARY RCTs

Initial contact has already been made with the first named author of the included primary studies. Authors that have not as yet responded to the initial invitation will be sent another letter. If attempts from investigators within the collaboration fail, they may be contacted via the British or International Society for Gynaecological Endoscopy. Confirmation of commitment to the Collaboration and ability to supply IPD will then be sought. The responding authors will be sent the overview protocol and a request to send the trial dataset, original study protocol and data collection forms. The data can be supplied in either a Microsoft Access database (preferred choice) or a Microsoft Excel spreadsheet.
Inclusion in the collaborative group and provision of data will be covered by a Memorandum of Understanding – see Section 6.3

Data requested will include the primary and secondary outcomes detailed in Section 3.4. In addition, the baseline demographic and clinical details listed below will need to be collected:

- Age at randomisation
- Parity
- Uterine cavity length
- Presence of fibroids and/or polyps
- Number of previous Caesarean sections

All data received will be incorporated into an overview database, taking care to preserve any referential integrity within relational databases. All the data supplied will be subjected to range and consistency checks. Any missing data, obvious errors, inconsistencies between variables or outlying values will be queried and rectified as necessary by correspondence with the investigators. Study level analysis will be repeated to verified published results.
Once the data has been checked and validated, the original authors will be contacted to confirm their acceptance of individual study results before proceeding to the meta-analysis. If the integrity of the data/ study is questionable they may be excluded from the analysis.

DATA SYNTHESIS

Statistical analysis will be carried out on all the patients ever randomised, and will be based on the intention-to-treat principle. Results from separate trials will be

combined and analysed using suitable methods, including Mantel-Haenszel [53] for dichotomous outcomes at pre-specified time points and multilevel modelling techniques for continuous repeated measurements. The latter method maximises power and allows us to estimate overall treatment effects over time. Trial of origin will be included as a fixed or random effect as deemed appropriate.

Due to different scales of measurement in individual studies, it is anticipated that the Standardised Mean Difference (SMD) will be used for continuous data. It may also be necessary to convert data on different scales using an appropriate transformation, for example the standard correction factor of Π/3 to convert from SMD to log odds ratio [42].

Initially, analyses will be performed using the direct comparisons only (Hysterectomy versus Ablation, Ablation versus ablation and LNG-IUS versus ablation). However, it is anticipated that there may be a limited number of direct comparisons available [51]. In this case, a method of adjusted indirect comparison will be used to estimate comparative efficacy. In simple terms, this approach enables a comparison of interventions **A** and **B** if both have been compared to **C** [43]. This will allow us to explore the ranking of treatment effectiveness.

SUBGROUP ANALYSIS

Subgroup analyses, if not carefully planned, can lead to misleading results e.g. due to the play of chance with multiple testing. Extreme caution will be used in interpretation of subgroup results [44] Any sub-group analysis will be limited to the following parameters:

1. Intervention

2. ± pathology

3. Age <35, 35-45 and >45 years

4. Uterine cavity length <8cm, 8-10cm and >10cm

5. Presence or absence of submucous fibroids >2cm

6. Previous ablation/ treatment

7. Nulliparous

8. Mode of delivery (i.e. Caesarean section)

PROJECT TIMELINE

Months of project	Activity	Responsibility
Sept 07-Jan 08	Delivery and preparation of IPD data	Birmingham researcher, JD, KK
Jan 08-Apr 08	Cleaning and amalgamation of IPD data	Birmingham researcher, SB, JD, KK, IPD MA collaborative group
May 08-Nov 08	Statistical analysis of IPD	Birmingham researcher IPD MA collaborative group
Nov 08-Jan 09	Algorithm development	All

HMB IPD META-ANALYSIS COLLABORATIVE GROUP ORGANISATION

MANAGEMENT OF THE COLLABORATIVE GROUP

The Birmingham Clinical Trials Unit (BCTU) will act as the group secretariat for the IPD meta-analysis and will hold the main database. All data will be held securely and treated with the strictest of confidence. The Overview will be managed by a small group including grant holders and research staff employed on the project grant listed below:

Siladitya Bhattacharya	Lead investigator, overall responsibility for Overview Group
Kevin Cooper	Clinical Lead, BSGE representative, contact with authors
Khalid S. Khan	Clinical Lead, methodology
Richard Gray	Methodology and analysis
Jane Daniels	Project management
Lee Middleton	Overview statistician
Rita Champaneria	Overview systematic reviewer

MEMORANDUM OF UNDERSTANDING FOR THE COLLABORATIVE GROUP

The activities of the IPD meta-analysis will be governed by an initial Memorandum of Understanding, to be agreed by all collaborators within this group including

primary trialists and secondary researchers, at the start of the project. The Memorandum of Understanding will set out the aims, scope, responsibilities and tasks required of all investigators.

RELATIONSHIPS WITH THE OTHER COMPONENTS OF THE GUIDELINES DEVELOPMENT GROUP

The IPD meta-analysis is a component of a larger project aiming to generate evidence based, cost-effective clinical guidelines. The results of the IPD meta-analysis will be incorporated into a decision analytic model, which will then inform the development of guidelines. The International HMB IPD Meta-analysis Collaborative Group will not be directly involved in these processes, other than lead investigators from the Management Group.

OUTPUTS

Outputs from this project will be:

- IPD Meta-analysis of direct comparisons of interventions
- Indirect comparison of rankings of different types of ablations
- Input for the health economics model
- Development of methodological methods for IPD Meta-analyses
- Identification of the need for more primary research (in areas where clinical uncertainties remain)

PUBLICATION POLICY

The results from the IPD meta-analysis will be presented at a collaborators meeting. Any subsequent articles on the results of the meta-analysis will be published under the name of the collaborative group -. The International HMB IPD Meta-analysis Collaborative Group It will also be circulated to the collaborators for comment, amendments and approval before finally being submitted. In the case of any disagreement, the following fundamental principle will be applied; that, the report should provide the meta-analysis results, presenting all of the available evidence, but will not include any interpretations of the data, except those that are unanimously decided upon by all collaborators. Any collaborating group is free to withdraw its data at any stage.

FUTURE COLLABORATION

One outcome of the Overview may be to highlight where clinical uncertainty remains regarding the relative benefits and risks of any intervention. This would provide the rationale for further primary research. If this Collaboration is successful, the members will be in a strong position to develop clinical trials to the address areas of uncertainty and may also provide a platform from which to develop clinical trials in other aspects of gynaecology.

3) Cost effectiveness analysis (not started)

Aim: To undertake a cost effectiveness analysis of 1) hysterectomy versus second generation ablative techniques and 2) alternative forms of second generation ablation using information generated from the above analyses.

This project will involve the development of a decision analytic simulation model as a framework for conducting cost-effectiveness and cost-utility analyses and associated value of information analyses (Felli & Hazen, 1998; Claxton et al, 2001). The economic evaluations will inform current treatment policy in this clinical area, whilst the value of information component will serve to highlight future research needs and agendas, and inform possible future research funding decisions. A modelling framework is ideally suited to demonstrate, and explore the importance of the inherent uncertainty.

The model development process will use, as a starting point, the recently published menorrhagia clinical pathway Markov model (Garside et al, 2004). This model, generated by researchers at the University of Exeter, formed the basis of the national coverage decision by the National Institute for Health & Clinical Excellence (NICE) on microwave and thermal balloon endometrial ablation for menorrhagia. Any requirements for structural model adjustments will be determined through:

- consideration of other recent heavy menstrual bleeding models (such as the model developed as part of the NICE heavy menstrual bleeding guideline prepared by the National Collaborating Centre for Women's and Children's Health – draft out for consultation currently);
- consultation within the research team, drawing on the requisite clinical and modelling expertise; and with appropriate external advisers (such as those involved in the modelling work reported in Garside et al, 2004).

The principal clinical data to be used in populating the model will be drawn from other aspects of our research work, namely the individual patient meta-analyses and data from both national registers and follow up of existing randomised controlled trials (as detailed earlier in this proposal). Assuming that a Markov model is found to be appropriate, it will be constructed using Triage Pro software. This is a widely-used and highly user-friendly software package ideally suited to the construction and analysis of decision tree and Markov models.

The economic evaluation will adopt a broad perspective and seek to include consideration of costs incurred by the health sector, by patients and by the economy more broadly in terms of productivity issues. An incremental approach will be adopted with a focus on additional costs and gain in benefits associated with a move away from current practice to alternative treatment strategies. The cost-effectiveness component of the work will report results in terms of an incremental cost-effectiveness ratio (ICER) of cost per woman successfully treated and cost per hysterectomy avoided. However, quality of life data suitable for use in a cost-utility framework are available from published sources (for example, Sculpher, 1998) and so the economic evaluation will additionally present results in terms of incremental cost per quality-adjusted life year (QALY) gained. Resource use will be estimated from the existing published evidence and additional cost data will be

sought from other sources such as the annual review of unit health and social care costs (by the University of Kent) and national schedule for reference costs.

The results of the cost utility analysis (CUA) will be presented using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value. We shall also include a value of information analysis to quantify the total uncertainty in terms of the value of removing that uncertainty. As appropriate, we shall include partial value of information analysis calculations. In addition to this probabilistic sensitivity analysis on our base-case model, we shall include a range of alternative analyses to explore the robustness of these results to plausible variations in key assumptions and variations in the analytical methods used, and to consider the broader issue of the generalisability of the results.

4) To develop an algorithm for clinical decision-making in women with heavy menstrual bleeding (not started)

<u>Aim:</u> To devise a parsimonious algorithm for clinical decision making, regarding the choice of surgery for women with heavy menstrual bleeding with failed medical treatment.

The call for proposals asks for patient perspectives to be taken into account. For many patients, the choice is likely to be straightforward if there is absolute certainty about comparative outcomes. Where such certainty is lacking, the ultimate decision may be influenced by personal preference. In this proposal we have planned to produce clinical algorithms which will guide practice, without overriding a clear preference a particular patient may have. We accept that for an algorithm to be useful in a pragmatic context, it should be flexible enough to accommodate consumer preference. We therefore plan to develop algorithms for a typical (default) situation in a way which is highly sensitive to the needs and preferences of individual patients.

We will use formal consensus development processes to produce an interim or indicative algorithm because there are many authoritative bodies, such as NICE, whose role this may usurp. The algorithm development is necessary to ensure that the type of statistical information summarised in our HTA report can be transformed into a meaningful care pathway to enable clinicians to provide consistent rational care. We have shown how this project will yield data from:

a. Observational cohort including data-linkage studies on long term follow up.
b. IPD meta-analysis.
c. Cost and cost effectiveness analysis.

Existing guidelines (RCOG 1998, 1999, NICE, 2004) are not always explicitly based on the above types of data. As a consequence, they can be perceived to be unclear about options open to consumers and care providers in specific situations. Formal consensus processes such as the nominal group technique (NGT) or the Delphi survey offer ways of synthesising judgements that are structured, transparent, offer the stimulus of feedback and give an explicit indication of the breadth of support for any conclusions (Delbecq et al 1971; Bayley EW, et al 1994; Jones & Hunter, 1995; Raine et al, 2004). The nominal group technique (NGT) usually involves about 10 members who attend a meeting to discuss and explore areas of disagreement. This reduces the risk of misunderstandings and

exposes the reasons for differences of opinion. The main alternative to it is the Delphi survey which involves two or more rounds of postal questionnaires. While this accommodates geographically dispersed participants and avoids the risk of undue influence from some individuals, the opportunities for clarification and resolution of differences of opinion are more limited. Although modified nominal groups produce closer consensus than Delphi groups, their judgements are less reliable (Raine et al, 2005). A hybrid method (modified Delphi technique) used by the RAND Corporation and other similar organisations (Brook, 1994) combines features of both processes, i.e. a postal questionnaire for the first round of ratings followed by a meeting where the second round of ratings occurs. This is the preferred technique for generating algorithms in the context of this project.

Delphi participants will include a wider panel (of about 50 respondents) selected from the following groups of stakeholders: general practitioners, general gynaecologists, gynaecologists with a special interest in minimal-access surgery (members of the British Gynaecological Endoscopy Society) and representatives selected by sampling from the Royal College of Obstetrics and Gynaecology and Department of Health lists. A questionnaire will be developed for the consensus process, based on the results from clinical and cost effectiveness data. Participants will initially complete the questionnaire by post/email. Potential loss to follow-up will be minimised by postal/email and telephonic repeat reminders. This method has been shown to result in over 90% response rates.

A subset of individuals will subsequently attend a facilitated face-to-face meeting which will be conducted according to a written protocol. At this meeting, each participant will receive a new copy of the questionnaire with a reminder of their own initial ratings and the distribution of ratings for the group as a whole. Each item will be discussed in turn and reasons for any differences explored, after which participants will privately re-rate the questions. Participants at the face-to-face group meeting will also include 2 patient representatives (one with an interest in general practice and the other with an interest in secondary/tertiary care for menorrhagia).

Administration of the project

The project will be administered by a Steering Committee, which will include the grantholders, representatives of the Scottish ISD and the IPD meta-analysis collaborative group. In addition this group will have a member from the British Gynaecological Endoscopy Society and a consumer representative. Face to face meetings of the Steering Committee are planned at months 0, 6, 12 and 18 months. In addition, there will be ad-hoc telephone / video conferences as required. Research activities in each of the participating centres will comply with standard guidelines on research governance. The activities of the IPD meta-analysis will be governed by an initial Memorandum of Understanding, to be agreed by all collaborators within this group including primary trialists and secondary researchers, at the start of the project. This group will meet at 0 and 12 months.

Day to day administration of the project will be co-ordinated by SB with support from a part time secretary and the Aberdeen researcher. The IPD meta-analysis and the cost effectiveness modelling will be performed in Birmingham. Regular updates on progress will be provided to the funding body.

SOURCES OF SUPPORT

The project is support by a grant from UK National Institute of Health Research Health Technology Assessment programme (project number 05/45/02) awarded jointly to the Universities of Aberdeen and Birmingham.

POTENTIAL CONFLICT OF INTEREST

Some primary authors were paid by industry to carry out their trial. Kevin Cooper is a Council member for the British Society of Gynaecological Endoscopy (BSGE).

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APPENDIX A

Table 1a: Characteristics of available trials* (hysterectomy vs ablation)

Abbreviations: ELA Endometrial Laser Ablation; MBL Menstrual Blood Loss; MEA Microwave Endometrial Ablation; REA Rollerball Endometrial Ablation; TBEA, Thermoregulated Balloon Endometrial Ablation; TCRE Transcervical Resection of the Endometrium; TBA Thermal Balloon Ablation

Study reference Number randomised	Country	Eligibility criteria	Randomised comparison	Outcome measures	Measure of Outcome Measure	Response
Crosignanani 1997 N = 92	Italy	Women under 50 years Failed medical treatment Uterine size<12 weeks Submucous fibroid < 3 cm	Vaginal hysterectomy Vs TCRE	Satisfaction MBL QOL Duration of surgery Hospital stay Return to work Retreatment (further surgery)	 Minutes Days Weeks	Not as yet, but trying to contact via Vercellini group
Dickersin 2006 N= 242	USA	Premenopausal women with DUB aged >18 years and over	Hysterectomy vs Ablation	Menstrual status QOL	 EuroQoL (EQ-5D)	Yes, willing to collaborate
Dwyer 1993 N = 200	Weston-Super-Mare, UK	Age under 52 Failed medical treatment Uterus < 12 weeks	Abdominal hysterectomy vs TCRE	Patient satisfaction (4 m and 2.8 yrs) MBL (subjective) QOL at 2.8 years Hospital stay Return to work Retreatment (further surgery) Total resource use at 2.8 years	 Days Weeks £	Not as yet
Gannon 1991 N = 54	Ireland, UK	Women median age 40 years Failed medical treatment Uterine size<12 weeks Submucous fibroid < 3 cm Endometrial prep	Abdominal hysterectomy vs TCRE	MBL Duration of surgery Hospital stay Return to work Retreatment (further surgery) Resource use for surgery	 Minutes Days Days £	Yes, willing to collaborate
O'Connor 1997 N = 202	London, UK	Women age 30- 50 years Failed medical treatment Uterine size<12 weeks Submucous fibroid < 5 cm	Abdominal hysterectomy (28) + vaginal hysterectomy (28) vs TCRE	Patient satisfaction (2 yrs) MBL QOL at 2 years Hospital stay Retreatment (further surgery)	 Days	Yes, NOT willing to collaborate

Study reference Number randomised	Country	Eligibility criteria	Randomised comparison	Outcome measures	Measure of Outcome Measure	Response
Pinion 1994 N = 204	Dundee, UK	Women age < 50 years Failed medical treatment Uterine size<10 weeks	Abdominal hysterectomy vs TCRE + ELA	Patient satisfaction (1 and 4 yrs) MBL QOL Hospital stay Return to work Retreatment (further surgery) Health service and patient costs	VAS Number of nights in hospital Median (weeks/months) £	Yes, willing to collaborate
Zupi 2003 N= 181	Italy	Women age <50 years Failed medical treatment Weight <100kg	TCRE v Hysterectomy	Patient satisfaction Menstrual Blood Loss		

* In addition to the above trials we have identified a further abstract of a study published in the Chinese Medical journal (Lin 2006). We have requested the full paper and need to verify whether this was a randomised trial and therefore suitable for inclusion.

Table 1b: Characteristics of available trials (ablation versus ablation)

Study reference Number randomised	Country	Eligibility criteria	Randomised comparison	Outcome measures	Measure of Outcome Measure	Response
TRIALS COMPARING FIRST GENERATION ABLATIVE TECHNIQUES						
Bhattacharya 1997 N = 372	Aberdeen, UK	Age < 50 years Mean age 41 years Uterine size < 10 weeks Clinical diagnosis of DUB Normal histology	TCRE + roller ball vs laser	Satisfaction at 1 year Amenorrhoea Duration of surgery Complications Retreatment	Minutes	Yes, willing to collaborate
Boujida 2002 N = 120	Denmark	Age > 35 years	TCRE vs rollerball endometrial coagulation	Hysterectomy rate 5 years later Days with bleeding Recommend treatment	Days	Not as yet, but still trying to make contact
McClure 1992 N = 38	Ireland	Mean age 42 Menorrhagia unresponsive to medical treatment MBL > 70 ml	TCRE+ rollerball vs Laser (argon)	MBL reduction Amenorrhoea Duration of surgery Complications	MBL (>70ML) Minutes	Yes, willing to collaborate
TRIALS COMPARING FIRST WITH SECOND GENERATION ABLATIVE TECHNIQUES						
Brun 2006 N = 51	France	Higham blood loss score > 100	TCRE Cavaterm TBA	Amenorrhoea Higham Bleeding score	Higham bleeding score	Yes, willing to collaborate
Cooper 1999 N = 263	Aberdeen, UK	Mean age 41 years Uterine size < 10 weeks Clinical diagnosis of DUB Normal histology	TCRE + rollerball vs MEA	PLAC Satisfaction at 1 year QOL (SF36) Amenorrhoea Duration of surgery Post op stay Return to work Complications Retreatment	PBAC SF36 Minutes Hours Days	Yes, willing to collaborate
Cooper 2002 N = 265	USA	Age 25 – 50 years Menorrhagia (PBLAC > 150) Failed medical treatment	Novasure vs wire loop resection + roller ball	PBAC Duration of surgery Sedation Complications	PBAC Minutes	Deceased, but industry willing to collaborate

Study reference Number randomised	Country	Eligibility criteria	Randomised comparison	Outcome measures	Measure of Outcome Measure	Response
TRIALS COMPARING FIRST GENERATION ABLATIVE TECHNIQUES						
Bhattacharya 1997 N = 372	Aberdeen, UK	Age < 50 years Mean age 41 years Uterine size < 10 weeks Clinical diagnosis of DUB Normal histology	TCRE + roller ball vs laser	Satisfaction at 1 year Amenorrhoea Duration of surgery Complications Retreatment	 Minutes	Yes, willing to collaborate
Boujida 2002 N = 120	Denmark	Age > 35 years	TCRE vs rollerball endometrial coagulation	Hysterectomy rate 5 years later Days with bleeding Recommend treatment	 Days	Not as yet, but still trying to make contact
McClure 1992 N = 38	Ireland	Mean age 42 Menorrhagia unresponsive to medical treatment MBL > 70 ml	TCRE+ rollerball vs Laser (argon)	MBL reduction Amenorrhoea Duration of surgery Complications	MBL (>70ML) Minutes	Yes, willing to collaborate
TRIALS COMPARING FIRST WITH SECOND GENERATION ABLATIVE TECHNIQUES						
Brun 2006 N = 51	France	Higham blood loss score > 100	TCRE Cavaterm TBA	Amenorrhoea Higham Bleeding score	 Higham bleeding score	Yes, willing to collaborate
Cooper 1999 N = 263	Aberdeen, UK	Mean age 41 years Uterine size < 10 weeks Clinical diagnosis of DUB Normal histology	TCRE + rollerball vs MEA	PLAC Satisfaction at 1 year QOL (SF36) Amenorrhoea Duration of surgery Post op stay Return to work Complications Retreatment	PBAC SF36 Minutes Hours Days	Yes, willing to collaborate
Cooper 2002 N = 265	USA	Age 25 – 50 years Menorrhagia (PBLAC > 150) Failed medical treatment	Novasure vs wire loop resection + roller ball	PBAC Duration of surgery Sedation Complications	PBAC Minutes	Deceased, but industry willing to collaborate

Study reference Number randomised	Country	Eligibility criteria	Randomised comparison	Outcome measures	Measure of Outcome Measure	Response
Cooper 2004 N = 322	USA	Mean age 41 Age > 30 Failed/refused medical treatment PBAC > 185 Uterine cavity 6-14 cm	Microwave vs rollerball	PBAC > 75 Satisfaction QOL (SF 36) Amenorrhoea Duration of surgery Sedation Complications	PBAC SF36 Minutes	Deceased, but industry willing to collaborate
Corson 2000 N = 276	USA	PBAC > 150 Distorted uterine cavity Cavity length > 9.75 cm	Vesta balloon vs TCRE + rollerball	PBAC: Proportion > 76 Amenorrhoea Adverse events	PBAC	Not as yet
Corson 2001 N = 276	USA	Age 30-50 Myomas < 4 cm	Rollerball vs HTA (hydroablator)	PBAC Menstrual diary Amenorrhoea Proportion with PBAC < 75 QOL Retreatment	PBAC PBAC PBAC SF36	Not as yet
Duleba 2003 N=279	USA	Age 30-50 years PBAC > 150 Uterine cavity > 10 cm Intramural myomas < 2 cm	Rollerball vs Endometrial cryoablation	PBAC Menstrual diary Bleeding and pain Satisfaction	PBAC PBAC PBAC	Not as yet
Hawe 2003 N= 72	UK	Age 29-51 Uterine length < 12 cm	Cavaterm TBEA vs Nd: Yag laser	Amenorrhoea QOL (SF12) Satisfaction VAS pain Operative details + complications	 SF12 VAS	Yes, willing to collaborate
Meyer 1998 N = 272	USA	Age 29-50 years PBAC score > 150 Ineffective medical therapy Uterine cavity size 4 -10 cm	Roller ball vs TBEA (Thermachoice)	Satisfaction PBAC Complications Duration of surgery Retreatment rate	 PBAC Minutes	Yes, willing to collaborate
Pellicano 2002 N = 82		Mean age 43 years Age < 50 years Weight < 100 kg Uterine size < 12 weeks	TCRE vs Cavaterm TBEA	Satisfaction Complications Duration of surgery Retreatment rate	 Minutes	Not as yet

Study reference Number randomised	Country	Eligibility criteria	Randomised comparison	Outcome measures	Measure of Outcome Measure	Response
Perino 2004 N = 116	Italy	Age 36-48 DUB	TCRE vs ELITT (endometrial laser intrauterine thermal therapy)	Amenorrhoea Complications Duration of surgery Retreatment rate	VAS Minutes	Yes, willing to collaborate
Romer 1998 N = 20	Germany	Age 35 – 52	Rollerball vs Cavaterm TBEA	Satisfaction Amenorrhoea	 VAS	Not as yet
Soysal 2001 N = 96	Turkey	Age 40 – 49 years	Rollerball vs TBEA	Satisfaction Amenorrhoea Complications Duration of surgery	 PBAC	Not as yet
Van Zon-Rabelonk 2003 N = 139	Netherlands	Age unreported	Rollerball vs UBT TBEA	Technical safety Reduction in menstrual bleeding		Yes, willing to collaborate
Vercellini 1999 N = 46	Italy	Age > 35 years Unterine size < 12 weeks Normal cavity	TCRE vs vaporising electrode	Satisfaction Amenorrhoea Complications Duration of surgery PBAC	 PBAC Minutes PBAC	Not as yet
TRIALS COMPARING SECOND GENERATION ABLATIVE TECHNIQUES						
Abbott 2003 N = 57	Australia	Mean ages + 40.5 (Novasure) and 40.5 (Cavaterm) DUB Uterine length < 12 cm	Novasure vs Cavaterm TBEA	Amenorrhoea QOL Satisfaction Acceptability	VAS EuroQoL-5D	Yes, willing to collaborate
Bongers 2004 N = 126 5yr report published 2007 Kleijn J.H. et al	Netherlands	Mean age 43 years PBAC > 150 Uterine length 6 – 12 cm	Novasure vs Thermachoice TBEA	Amenorrhoea Satisfaction Duration of surgery Retreatment	PBAC Minutes	Yes, willing to collaborate
Clark 2007	Birmingham, UK	Unpublished	NovaSure versus Thermachoice			Yes, willing to collaborate
Sambrook 2006 N = 240	Aberdeen, UK		Thermachoice TBEA vs MEA	QOL Satisfaction PBAC	 PBAC	Yes, willing to collaborate

Table 1c: Characteristics of available trials (Mirena versus ablation)

Study reference Number randomised	Country	Eligibility Criteria	Randomised comparison	Outcome measures	Measure of Outcome Measures	Response
Barrington 2003 N=44	Devon, UK	Menorrhagia refractory to medical treatment Uterine length <12cm	LNG IUS Mirena Thermal Balloon ablation	PBAC Score , Improvement in bleeding, need for further treatment	PBAC	Yes, NOT willing to collaborate
Busfield 2006 N=79 Cost-effectiveness study done 2006 Brown et al	New Zealand	Heavy Menstrual Bleeding. Age 25-50 yrs. Regular cycle	LNG-IUS vs. TBA	Menstrual blood loss. Patient satisfaction QoL. Menstrual symptoms. Treatment side-effects	PBAC, SF36	Yes, willing to collaborate
Crosignani 1997 N=70	Italy	Age 38-53 yrs MBL >80mls/ cycle Uterine size <8 weeks	TCRE	PBAC, Patient satisfaction, SF36, Amenorrhoea at 12 months	SF36	Contact again via Vercellini group
Kittelsen 1998 N= 53	Norway	Age 30-49 PBAC >100 Regular uterine cavity	LNG IUS Mirena TCRE	PBAC	PBAC	Not as yet
Malak 2006 N= 56	Egypt	Age 40-50 Cavity <10cm	LNG-IUS TCRE	Amenorrhoea PBAC Score		Not as yet
Shaw 2007 N=66	England	Age 25-49, failed medical treatment, normal biopsy, PBAC<120	TBA v LNG-IUS	PBAC score at 12 months	PBAC	Not as yet
Soysal 2002 N=72	Turkey	Mean age 44	LNG IUS TBA	Reduction in menstrual bleeding QoL		Not as yet
Talis 2003		Age 25-50	LNG IUS TBA	PBAC, satisfaction	PBAC	Not as yet
Tam 2006 N=33	China	Premenopausal women over 40 yrs Uterine cavity <10cm	LNG IUS Thermal balloon endometrial ablation	SF36	SF36	Yes, willing to collaborate

Table 1d: Characteristics of available trials (Mirena versus hysterectomy)

Study reference Number randomised	Country	Eligibility criteria	Randomised comparison	Outcome measures	Measure of Outcome Measure	Response
Hurskainen 2001 N = 236 5yr report published 2007 Halmesmaki K.	Finland	Menorrhagia Age 35-49	LNG IUS Mirena Hysterectomy	EQ5D Rand 36 Menstrual blood loss		Not as yet

Appendix B

Search Strategy for Population:

#1 menorrhagia/ all subheadings
#2 hypermenorrhea/ all subheadings
#3 excessive NEAR ("menstrual bleeding" OR "menstrual blood loss")
#4 dysfunctional NEAR ("uterine bleeding" OR "menstrual bleeding")
#5 heavy NEAR ("menstrual bleeding" OR "menstrual blood loss")
#6 "iron deficient anaemia"
#7 (#3 OR #4 OR #5 OR #6) in TI, AB
#8 #1 OR #2 OR #7

Search Strategy for interventions:
Hysterectomy

#1 EXPLODE "hysterectomy"/all sub-headings
#2 "vaginal hysterectomy"/ all sub-headings
#3 "total abdominal hysterectomy"
#4 "subtotal abdominal hysterectomy"
#5 "laparoscopic hysterectomy"
#6 #1 OR #2 OR #3 OR #4 OR #5

Ablation

#1 EXPLODE "hysteroscopy"/ all sub-headings
#2 ("transcervical resection") NEAR "endometrium"
#3 "TCRE"
#4 "endometrial ablation"
#5 "laser ablation"
#6 "electrosurgery"
#7 "rollerball"
#8 "thermal balloon"
#9 "hypertherm$"
#10 "thermotherapy"
#11 "photodynamic therapy"
#12 "phototherapy"
#13 "cryoablation"
#14 "microwave ablation"
#15 "radiofrequency"
#16 "saline irrigation"
#17 "laser interstitial"
#18 "Thermachoice"
#19 "Cavaterm"
#20 "ELITT"
#21 "Vesta"
#22 "Novasure"
#23 "Microsulis"
#24 "Cryogen"

Mirena

#1 EXPLODE “contraceptive”/all sub-headings
#2 “mirena coil”/ all sub-headings
#3 “levonorgestrel”
#4 “intra uterine device”
#5 #1 OR #2 OR #3 OR #4

Search strategy for Randomised Controlled Trials

#1 Randomized Controlled Trial IN PT.
#2 Controlled Clinical Trial IN PT.
#3 Randomized Controlled Trials IN SH
#4 Random Allocation IN SH.
#5 Double Blind Method IN SH
#6 Single Blind Method IN SH
#7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)
#8 Animal in SH NOT Human in SH.
#9 #7 not # 8
#10 Clinical Trial IN PT.
#11 EXPLODE Clinical Trials/all sub-headings
#12 (clin$ NEAR trial$) IN TI, AB
#13 ((singl$ OR doubl$ OR trebl$ OR tripl$) NEAR (blind$ OR mask$)) IN TI, AB
#14 Placebos IN SH
#15 placebo$ IN TI, AB
#16 random$ IN TI, AB
#17 Research Design IN SH
#18 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19 #18 NOT #8
#20 #19 NOT #9
#21 Comparative Study IN SH
#22 EXPLORE Evaluation Studies/ all-sub-headings
#23 Follow Up Studies IN SH
#24 Prospective Studies IN SH
#25 (control$ OR prospectiv$ OR volunteer$) IN TI, AB
#26 #21 OR #22 OR #23 OR #24 OR #25
#27 #26 NOTt #8
#28 #27 NOT (#9 OR #20)
#29 #9 OR #20 OR #28