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

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

MANAGEMENT GROUP

Aberdeen, UK	Siladitya Bhattacharya[1]	s.bhattacharya@abdn.ac.uk
	Kevin Cooper[2]	Kevin.Cooper@arh.grampian.scot.nhs.uk
Birmingham, UK	Khalid S. Khan[3]	k.s.khan@bham.ac.uk
	Jane Daniels[3]	j.p.daniels@bham.ac.uk
	Lee Middleton[4]	l.j.middleton@bham.ac.uk
	Rita Champaneria[3]	r.champaneria@bham.ac.uk
	Richard Gray[4]	r.gray@bham.ac.uk

1 University of Aberdeen, Aberdeen Maternity Hospital, Foresterhill, Aberdeen, AB25 2ZD
2 University of Aberdeen, Dept of Obstetrics & Gynaecology, Grampian Hospitals NHS Trust, Foresterhill, Aberdeen, AB25 2ZD
[3] Birmingham Women's Hospital, Metchley Park Road, Edgbaston, Birmingham, B15 2TG, UK
[4] Birmingham Clinical Trials Unit, Robert Aitken Institute, University of Birmingham, Birmingham, B15 2TT, UK

THE SECRETARIAT

The International HMB IPD Meta-analysis Collaborative Group Secretariat
Birmingham Clinical Trials Unit
Division of Medical Sciences
Robert Aitken Institute
University of Birmingham
Edgbaston
Birmingham
B15 2TT

Tel: +44 (0)121 415 9100

Fax: +44 (0)121 415 9135

Email: bctu@bham.ac.uk

Website: http://www.bctu.bham.ac.uk/systematicreview/hmb

Corresponding Author: Jane Daniels
Corresponding Address: University of Birmingham
Dept. of Obstetrics & Gynaecology
Birmingham Women's Hospital
Metchley Park Road
Birmingham
B15 2TG

Email: j.p.daniels@bham.ac.uk
Telephone: +44 121 623 6837
Fax: +44 121 623 6875

Authors who have agreed to collaborate:

Dr J Abbott
Gynaecology Dept.
Royal Women's Hospital
University of New South Wales
Randwick
NSW 2031
Australia abbott@sesahs.nsw.gov.au

Prof Siladitya Bhattacharya
Dept. of Obstetrics & Gynaecology,
University of Aberdeen
Aberdeen Maternity Hospital
Foresterhill
Aberdeen
AB25 2ZD s.bhattacharya@abdn.ac.uk

Dr M.Y. Bongers
Dept of Obstetrics and Gynaecology
Máxima Medisch Centrum
De Run 4600
PO Box 7777,
5500 MB Veldhoven
The Netherlands my.bongers@iae.nl / M.Bongers@mmc.nl

Dr J.L. Brun
Dept of Obstetrics & Gynecology
Pellegrin University Hospital
Bordeaux
France

Dr M.C. Sowter (on behalf on Busfield)
23 Mount St. John Avenue
Epsom
Auckland 1051
New Zealand martinsowter@xtra.co.nz

Mr T.J. Clark
Dept of Obstetrics & Gynaecology
Birmingham Women's Hospital
Metchley Park Road
Edgbaston
Birmingham
B15 2TG JUSTIN.CLARK@bwhct.nhs.uk

Dr K Cooper
Dept of Obstetrics & Gynaecology
Grampian Hospitals NHS Trust
University of Aberdeen
Foresterhill
Aberdeen
AB25 2ZD kevin.cooper@nhs.net / Kevin.Cooper@arh.grampian.scot.nhs.uk

Dr J Cooper (deceased, but correspondence to below for 2002 trial)
Charlotte Malone
Regional Business Manager
Cytyc surgical products
Northern Europe Charlotte.Malone@cytyc.com

Dr J Cooper (deceased, but correspondence to below for 2004 trial)
Maria Plentl / Stuart McIntyre
Microsulis Medical Limited
Pompano Beach
Florida
USA mplentl@earthlink.net / mcintyre.stuart@btinternet.com

Professor K Dickersin
Dept. of Epidemiology
Director, Center for Clinical Trials
John Hopkins University
Bloomberg School of Public Health
615 North Wolfe Street, Mail Room W5010
Baltimore MD 21205
USA. kdickers@jhsph.edu

Dr M Gannon
Midland Regional Hospital
Mullingar Co.
Westmeath Michael.gannon@mailg.hse.ie

Dr J Hawe
Countess of Chester Hospital
Liverpool Road
Chester
CH2 1UL Ged.hawe@coch.nhs.uk / jedhawe@hotmail.com

Professor N McClure
Dept of Maternal & Child Health
Queens University
University Road
Belfast
BT7 1NN n.mcclure@qub.ac.uk

Dr W.R. Meyer
University of North Carolina Hospitals
Dept of Obstetrics& Gynecology
CB# 7570
Old Clinic Building
Chapel Hill
NC 27599
USA

Dr A Perino
Dept of Obstetrics & Gynecology
Istituto Materno Infantile
University of Palermo
Via Liberta 112
90100 Palermo
Italy perino@unipa.it

Dr S Pinion
Dept of Obstetrics & Gynaecology
Forthpark Hospital
Kirkcaldy
KY2 5AH sheena.pinion@faht.scot.nhs.uk

Dr A. Sambrook
Dept of Obstetrics & Gynaecology
Aberdeen Royal Infirmary
Foresterhill Road
Aberdeen
AB25 2ZN
UK amsambrook@doctors.org.uk

Professor Robert W. Shaw
Academic Department of Obstetrics & Gynaecology
University of Nottingham
The Medical School
Derby City General Hospital
Uttoxeter Road
Derby
DE22 3DT robert.shaw@nottingham.ac.uk

Dr W.H. Tam
Dept of Obstetrics & Gynecology
The Chinese University of Hong Kong
Hong Kong
SAR
China

Dr I.A.A. van Zon-Rabelink
Dept of Obstetrics & Gynecology
Medical Spectrum Twente
PO Box 50 000
7500 KA
Enschede
The Netherlands robinzon@wxs.nl

Dr E. Zupi
Universita degli Studi di Roma
Tor Vergata
Via Orazia Raimondo, 18
00173 Roma
Italy ezupi@libero.it

ABSTRACT

Background
At present, there are no comprehensive literature reviews summarising relative effectiveness of hysterectomy, ablation and levonorgestrel releasing intra-uterine systems (LNG-IUS) for alleviating heavy menstrual bleeding (menorrhagia). Meta-analysis using individual patient data (IPD) is considered the gold standard analytic method in reviews of randomised controlled trials and will be used in this review to compare the effectiveness of the aforementioned approaches.

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

Methods
Our IPD meta-analysis will follow existing guidelines and our output will comply with the QUOROM statement. Individual patient data will be collected from all relevant completed and ongoing randomised controlled trials identified through a comprehensive literature search. Raw data will be merged into a single database, cleaned and study level analysis repeated to confirm published results. Any discrepancies will be clarified with the primary author. Results of all studies will be combined using the appropriate methods. For the primary outcome measure of reduction of menstrual bleeding, multilevel modelling will be used to maximise power and estimate overall treatment effects over time. Primary study will be used as a fixed or random effect in the model. Sub-group analysis will be performed on pre-specified groups.

Outputs
The IPD meta-analysis will allow direct comparison of the main interventions, indirect comparisons where direct comparisons are not available and identify where future primary studies are required and can be initiated with the international collaboration formed by this overview.

Keywords

Menorrhagia, individual patient data, meta-analysis, hysterectomy, ablation

1.0 - INTRODUCTION

Menorrhagia (heavy menstrual bleeding) is a common problem, amongst women of a reproductive age, accounting for more than one third of the hysterectomies performed annually in Europe and North America (1). The majority of women are refractory to conservative treatment, resulting in up to 100,000 hysterectomies being performed annually in the United Kingdom (2). Heavy menstrual bleeding is often incapacitating, expensive to treat and often makes the sufferer socially uncomfortable. Menorrhagia is defined as menstrual bleeding in the ovulatory woman that lasts longer than 7 days, or menstrual blood loss (MBL) exceeding 80ml (3-5)

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 (6). 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 (7;8), at a cost which is a third that for hysterectomy (9). Despite the availability of these options, long term medical treatment is unsuccessful or unacceptable in many and surgery is required (10).

Hysterectomy is the leading treatment for menorrhagia, once conservative treatment has failed (11-14). However, hysteroscopic endometrial ablation and other second generation ablative techniques have been shown to be both effective and cost-effective alternatives.

Endometrial ablative techniques aimed at destruction of the functionally active endometrium along with some of the underlying myometrium (15;16) offer a conservative surgical alternative to hysterectomy. The first generation ablative techniques including Endometrial Laser Ablation (ELA) (17;18), Transcervical Resection of the Endometrium (TCRE) (19)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) (20-25).

National audits (26-28) 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 (29;30). Mortality from these techniques has been estimated at 0.26 per 1000 (26;28).

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) (31-33)and Microwave Endometrial Ablation (34;35), while the Novasure device (Novacept Inc) (36) 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 (37). 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 (38). 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 (25;39). 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 (40). Our group has recently completed recruitment to such a trial involving over 200 women funded by the Chief Scientist Office Scotland (CZH/4/117) (41). 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, relevant research questions at the present time are:

1.How do the currently used ablative techniques 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 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. This will be the first IPD meta-analysis to compare hysterectomy and ablation, but also ablation to other kinds of ablation.
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.
The Birmingham Team will only be involved in one part of this three part project, namely the IPD meta-analysis of existing trial data.

2.0 - 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

3.0- ELIGIBILITY

3.1- TYPES OF STUDIES

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

3.2 - 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

3.3 - 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

3.4 - 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:

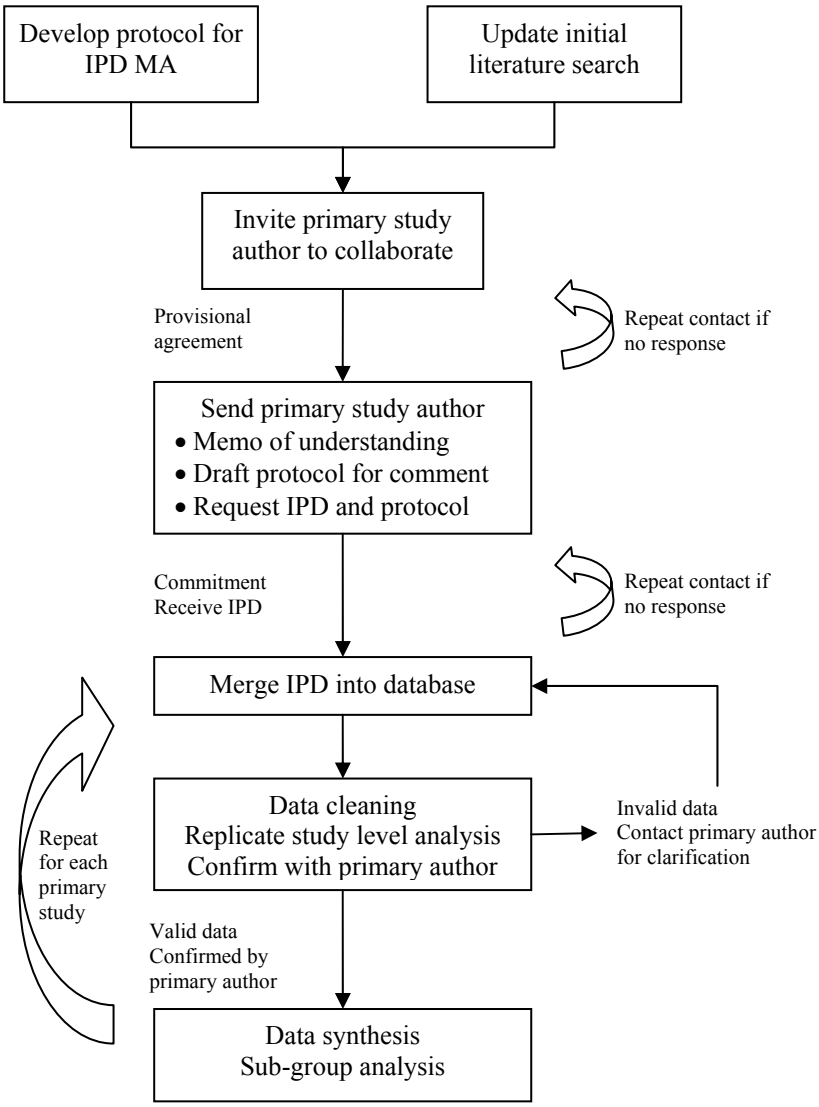
Other outcomes will be collected for meta-analysis to investigate the effect of the interventions on other aspects of HMB on women, adverse effects and resource implications. These will include:

- 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

4.0 – 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



4.1 – 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.

4.2 – 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 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.

4.3 – 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.

4.4 – 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)

5.0 - 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

6.0 - HMB IPD META-ANALYSIS COLLABORATIVE GROUP ORGANISATION

6.1 – 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

6.2- 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.

6.3 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.

7.0 – 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 uncertainities remain)

8.0 - 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.

9.0 - 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.

10.0 - 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.

11.0 - 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).

12.0 REFERENCE LIST

(1) Clarke A., Black N., Rowe P., Mott S., Howle K. Indications for and outcome of total abdominal hysterectomy for benign disease: a prospective cohort study. British Journal of Obstetrics and Gynaecology 1995; 102:611-620.

(2) Maresh M.J.A., Metcalfe M.A., McPherson K., Overton C., Hall V., Hargreaves J. The VALUE national hysterectomy study: description of the patients and their surgery. British Journal of Obstetrics and Gynaecology 2002; 109:302-312.

(3) Long C.A., Gast M.J. Menorrhagia. Obstetrics and Gynecology clinics of North America 1990; 17:343-359.

(4) Shah A.A., Grainger D.A. Contemporary Concepts in Managing Menorrhagia. Medscape Womens Health 1996; 1(12):8.

(5) Carlson K.J., Nichols D.H., Schiff I. Indications for hysterectomy. New England Journal of Medicine 1993; 328(12):856-860.

(6) Royal College of Obstetricians and Gynaecologists. The Initial Management of Menorrhagia (Evidence Based Guidelines No. 1). Royal College of Obstetricians and Gynaecologists 1998.

(7) Milsom I., Andersson K., Andersch B., Rybo G. A comparison of flurbiprofen, tranexamic acid and a levonorgesrel releasing intrauterine contraceptive device in the treatment of idiopathic menorrhagia. American Journal of Obstetrics and Gynecology 1991; 164:879-883.

(8) Lahteenmaki P., Haukkamaa M., Puolakka J. Open randomised study of use of levonorgestrel releasing intrauterine system as alternative to hysterectomy. BMJ 1998; 316:1122-1126.

(9) Hurskainen R., Teperi J., Rissanen P., Aalto A.M., Grenman S., Kivela A. Quality of life and cost-effectiveness of levonorgestrel-releasing intrauterine system versus hysterectomy for treatment of menorrhagia: a randomised trial. Lancet 2001; 357(9252):273-277.

(10) Cooper K.G., Jack S.A., Parkin D.E., Grant A.M. Five-year follow up of women randomised to medical management or transcervical resection of the endometrium as treatment for heavy menses. British Journal of Obstetrics and Gynaecology 2001; 108:1222-1228.

(11) Carlson K.J., Miller B.A., Fowler F.J.Jr. The Maine women's health study. I. Outcomes of hysterectomy. Obstetrics and Gynecology 1994; 83(4):556-572.

(12) Wilcos L.S., Koonin L.M., Pokras R. Hysterectomy in the United States, 1988-1990. Obstetrics and Gynecology 1994; 83:549-555.

(13) Coulter A., Bradlow J., Agass M. Outcomes of referrals to gynaecology outpatient clinics for menstrual problems: An audit of general practice records. British Journal of Obstetrics and Gynaecology 1991; 98:789-796.

(14) Vessey M.P., Villard-Mackintosh L., McPherson K. The epidemiology of hysterectomy: Findings in a large cohort study. British Journal of Obstetrics and Gynaecology 1992; 99:402-407.

(15) Duffy S., Reid P.C., Smith J.H., Sharp F. In vitro studies of uterine electrosurgery. Obstetrics and Gynecology 1991; 78(2):213-220.

(16) Duffy S., Reid P.C., Sharp F. In-vivo studies of uterine electrosurgery. British Journal of Obstetrics and Gynaecology 1992; 99(7):579-582.

(17) Goldrath M.H., Fuller TASS. Laser photovaporisation of endometrium for the treatment of menorrhagia. American Journal of Obstetrics and Gynecology 1981; 140:14-19.

(18) Davis J.A. Hysteroscopic endometrial ablation with the neodymium-YAG laser. British Journal of Obstetrics and Gynaecology 1989; 96(8):928-932.

(19) Magos A., Baumann R., Turnbull A.C. Transcervical resection of the endometrium in women with menorrhagia. BMJ 1989; 298:1209-1212.

(20) Gannon M., Holt E.M., Fairbank J. A randomised control trial comparing endometrial resection and abdominal hysterectomy for the treatment of menorrhagia. BMJ 1991; 303:1362-1364.

(21) Dwyer N., Hutton J., Stirrat G.M. Randomised controlled trial comparing endometrial resection with abdominal hysterectomy for the surgical treatment of menorrhagia. British Journal of Obstetrics and Gynaecology 1993; 100:237-243.

(22) Pinion S.B., Parkin D.E., Abramovich D.R., Naji A., Alexander D.A., Russell I.T. Randomised trial of hysterectomy, endometrial laser ablation, and transcervical endometrial resection for dysfunctional uterine bleeding. BMJ 1994; 309(6960):979-983.

(23) O'Connor H., Broadbent J.A., Magos A.L., McPherson K. Medical Research Council randomised trial of endometrial resection versus hysterectomy in the management of menorrhagia. Lancet 1997; 349(9056):891-901.

(24) Crosignani P.G., Vercellini P., Apolone G., De Giorgi O., Cortesi I., Meschia M. Endometrial resection versus vaginal hysterectomy for menorrhagia: long-term clinical and quality-of-life outcomes. American Journal of Obstetrics and Gynecology 1997; 177(1):95-101.

(25) Aberdeen Endometrial Ablation Trials Group. A randomised trial of endometrial ablation versus hysterectomy for the treatment of dysfunctional uterine bleeding: outcom at four years. British Journal of Obstetrics and Gynaecology 1999; 106(4):360-366.

(26) Overton C., Hargreaves J., Maresh M. A national survey of the complications of endometrial destruction for menstrual disorders: the MISTLETOE study. Minimally Invasive Surgical Techniques- Laser, EndoThermal or Endoresection. British Journal of Obstetrics and Gynaecology 1997; 104(12):1351-1359.

(27) Overton C., Maresh M.J.A. Audit of currently available endometrial ablative techniques. Baillieres Clinical Obstetrics and Gynaecology 1995; 9(2):357-372.

(28) Scottish Hysteroscopy Audit Group. A Scottish audit of hysteroscopic surgery for menorrhagia: complications and follow up. British Journal of Obstetrics and Gynaecology 1995; 102(3):249-254.

(29) Arieff A.I., Ayus J.C. Endometrial ablation complicated by fatal hyponatremic encephalopathy. JAMA 1993; 270(10):1230-1232.

(30) Rosenberg M.K. Hyponatremic encephalopathy after rollerball endometrial ablation. Anesthesia and analgesia 1995; 80(5):1046-1048.

(31) Loffer F.D. Three-year comparison of thermal balloon and rollerball ablation in tretament of menorrhagia. Journal of the American Association of Gynecologic Laparoscopists 2001; 8(1):48-54.

(32) Loffer F.D., Grainger D. Five-year follow-up of patients participating in a randomised trial of uterine balloon therapy versus rollerball ablation for treatment of menorrhagia. Journal of the American Association of Gynecologic Laparoscopists 2002; 9(4):429-435.

(33) Meyer W.R., Walsh B.W., Grainger D.A., Peacock L.M., Loffer F.D., Steege J.F. Thermal Balloon and rollerball ablation to treat menorrhagia: a multicenter comparison. Obstetrics and Gynecology 1998; 92:98-103.

(34) Cooper K.G., Bain C., Parkin D.E. Comparison of microwave endometrial ablation and transcervical resection of the endometrium for treatment of heavy menstrual loss: a randomised trial. Lancet 1999; 354(9193):1859-1863.

(35) Bain C., Cooper K.G., Parkin D.E. Microwave endometrial ablation versus endometrial resection: a randomized controlled trial. Obstetrics and Gynecology 2002; 99(6):983-987.

(36) Cooper J., Gimpelson R., Laberge P., Galen D., Garza-Leal J.G., Scott J. A randomised, multicenter trial of safety and efficacy of the NovaSure system in the treatment of menorrhagia. Journal of the American Association of Gynecologic Laparoscopists 2002; 9(4):418-428.

(37) Lethaby A., Hickey M. Endometrial destruction techniques for heavy menstrual bleeding. Cochrane Database of Systematic Reviews 2005.

(38) Lethaby A., Sheppard S., Cooke I., Farquhar C. Endometrial resection and ablation versus hysterectomy for heavy menstrual bleeding. Cochrane Database of Systematic Reviews 1999.

(39) Cooper K.G., Bain C., Lawrie L., Parkin D.E. A randomised comparison of microwave endometrial ablation with transcervical resection of the endometrium; follow up at a minimum of five years. British Journal of Obstetrics and Gynaecology 2005; 112(4):470-475.

(40) National Institute for Clinical Excellence. Fluid-filled thermal balloon and microwave endometrial ablation for heavy menstrual bleeding. Technology Appraisal Guidance No 78 2004; 78.

(41) Sambrook A. A randomised trial of microwave endometrial ablation versus thermal balloon ablation. Unpublished 2007.

(42) Chinn S. A simple method for converting an odds ratio to effect size for use in meta-analysis. Statistics in Medicine 2000; 19:3127-3131.

(43) Coomarasamy A., Knox E.M., Gee H., Song F., Khan K.S. Effectiveness of nifedipine versus atosiban for tocolysis in preterm labour: a meta-analysis with an indirect comparison of randomised trials. British Journal of Obstetrics and Gynaecology 2003; 110:1045-1049.

(44) Oxman A.D., Guyatt G.H. A consumer's guide to subgroup analysis. Annals of Internal Medicine 1992; 116(1):78-84.

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		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
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)	Novasure vs wire loop resection + roller ball	PBAC Duration of surgery Sedation	PBAC Minutes	Deceased, but industry willing to collaborate

		Failed medical treatment		Complications		
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
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	Germany	Age 35 – 52	Rollerball vs	Satisfaction		Not as yet

N = 20			Cavaterm TBEA	Amenorrhoea	VAS	
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
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