PENINSULA MEDICAL SCHOOL
UNIVERSITIES OF EXETER & PLYMOUTH

MICROWAVE AND THERMAL BALLOON ENDOMETRIAL ABLATION FOR HEAVY MENSTRUAL BLEEDING.

STRIPPED OF CIC DATA*

Report commissioned by: NHS R&D HTA Programme

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LIST OF ABBREVIATIONS

AE	Adverse effect
DUB	Dysfunctional uterine bleeding
EA	Endometrial ablation
ELA	Endometrial laser ablation
GA	General Anaesthetic
GnRH	Gonadotrophin releasing hormone
GP	General Practitioner
HES	Hospital Episode Statistics
HMB	Heavy menstrual bleeding
HTA	Hydrotherm ablator
ICER	Incremental cost effectiveness ratio
ITT	Intent to Treat
IUS	Intrauterine system
IUD	Intrauterine device
LA	Local anaesthetic
LNG	Levonorgestrel
LTFU	Lost to follow up
MEA	Microwave endometrial ablation
MRI	Magnetic resonance imaging
PBAC	Pictorial blood loss assessment chart
PID	Pelvic inflammatory disease
QALY	Quality adjusted life year
QoL	Quality of life
RCOG	Royal College of Obstetrics and Gynaecology
RCT	Randomised controlled trial
TBEA	Thermal balloon endometrial ablation
S/C	Subcutaneous
TCRE	Transcervical resection of the endometrium
TVS	Transvaginal ultrasound (/sonography)
UTI	Urinary tract infection

GLOSSARY

Adenomyosis	The presence of endometrium in the myometrium. Can cause heavy menstrual bleeding and pain.
Amenorrhoea	Absence of periods
Cervix	The lower, narrower end of the uterus
Cornua	The horn shaped top of the uterus leading to the Fallopian tubes.
Cystometry	A method for measuring the pressure/volume relationship of the bladder.
Diathermy	Use of a high frequency electrical current to produce heat which destroys tissues through cutting or electrocoagulation. The patient's body forms part of the circuit.
Dysmenorrhoea	Painful periods.
Electrocautery	Cauterization of tissue using an electric current to generate the heat. Cauterization destroys the tissue and causes scarring.
Endometriosis	A condition where tissue resembling the endometrium occurs outside the uterus. The tissue responds to the menstrual cycle causing internal bleeding and pain.
Endometrium	The inner lining of the uterus that thickens and sloughs off during the menstrual cycle.
Eumenorrhoea	Normal periods
Fibroids	Benign, smooth muscle tumours of the uterus.
Fundus	The higher, wider end of the uterus.
Haematometra	A collection of blood and other menstrual fluids in the uterus which causes it to distend.
Haematosalpinx	A collection of blood in the fallopian tubes– post endometrial ablation, this may be caused by bleeding from untreated islands of endometrium at the cornea.
Hyperplasia	The abnormal increase in the number of normal cells in a tissue.
Hypomenorrhoea	Regular periods with blood loss less than normal.
Hysterectomy	The surgical removal of the uterus, may include removal of the cervix.
Hegar	A German gynaecologist who gave his name to a series of graduated, cylindrical instruments used to dilate the cervix.
Hysteroscope	An instrument using fibreoptic technology which allows direct visualization of the uterine cavity. Channels in the instrument allow instruments to be inserted to perform ablations.
Iatrogenic	An adverse effect inadvertently induced through treatment.
Laparoscope	A device used in surgery which allows visualisation through the use of fibre optics.
Leiomyomas	Fibroids
Menopause	Cessation of menstruation, usually around the age 50.
Meno-metrorrhagia	Frequent, excessive menstrual bleeding.
Menorrhagia	Heavy menstrual bleeding, clinically defined as more than 80ml of blood per cycle, but more usually defined subjectively by the woman.
Menstruation	The cyclic, physiologic discharge of blood and mucosal tissues through the vagina from the non-pregnant uterus. It is under hormonal control and recurs at approximately four week intervals.
Metrorrhagia	Irregular, sometimes prolonged, menstrual bleeding.
Myometrium	The outer muscular layer of the uterus.
Necrosis	Cell death
Oligomenorrhoea	Few or scanty periods
Pelvic inflammatory disease	An inflammatory process that may be caused by sexually transmitted infection, ovarian cystic disease or infections after childbirth.
Peri-menopausal	Around the time of the menopause.
Polyp	A mass of tissue on the mucosal lining. In this case, in the uterus.
Post ablation sterilization syndrome	In previously sterilised women accumulation of the blood in the Fallopian tubes which may cause severe pelvic pain.
Pre-menstrual syndrome	A combination of emotional and physical features which occur cyclically in women. May include mood changes, bloating, breast tenderness, fatigue and other symptoms.
Pyrexia	Fever
Salpingo-oophorectomy	Surgical removal of the Fallopian tubes and the ovaries
Uterus	The womb. A hollow, muscular, pear shaped organ in which the embryo is nourished

1 EXECUTIVE SUMMARY

1.1 Description of proposed service

The technologies examined in this review are microwave endometrial ablation and thermal balloon endometrial ablation (MEA and TBEA) for the treatment of heavy menstrual bleeding. Both of these, also referred to as second generation ablation techniques, aim to destroy the endometrial lining of the uterus thereby reducing or eliminating menstrual bleeding. To achieve endometrial destruction, thermal balloon ablation uses a balloon catheter in which hot water is circulated for a prescribed amount of time. Microwave ablation uses microwaves of a wavelength that will be absorbed to a defined depth of tissue. Both treatments may be performed under local or general anaesthetic and are performed without direct visualisation of the uterus.

1.2 Epidemiology and background

Heavy menstrual bleeding (HMB or menorrhagia) is defined as the cyclical loss of more than 80ml of blood over several consecutive cycles. HMB is a common complaint for which one in twenty women aged 30-49 consult their GP each year (approximately one and a half million women in England and Wales). Quality of life may be impaired by such bleeding.

Current treatments for HMB include various drug regimens, such as tranexamic acid, mefenamic acid, the combined pill and the progestogen releasing intrauterine system (IUS). Danazol, gestrinone and gonadotrophin releasing hormone analogues may be used as second line medical treatment. Current surgical interventions include hysterectomy or minimally invasive procedures such as transcervical resection (TCRE) and rollerball ablation (first generation endometrial ablation techniques).

Over 51,000 hysterectomies were performed in the public sector in England in 1999-2000. In about half of these cases, heavy menstrual bleeding would have been the presenting complaint, and in half of these, the uterus would have been normal. In 1998-1999 more than 16,000 admissions for endometrial ablation were recorded.

This report assesses the effectiveness and cost effectiveness MEA and TBEA compared to specific existing surgical techniques for HMB i.e. first generation endometrial ablation techniques (by resection (TCRE) and/or rollerball) and hysterectomy.

1.3 Number and quality of studies, and direction of evidence

A detailed search strategy was carried out to identify systematic reviews and controlled trials of MEA and TBEA versus first generation techniques for endometrial ablation. In addition to electronic database searching, reference lists were hand-searched and information sought from manufacturers of EA devices and by experts in the field.

Two good quality systematic reviews, of the effectiveness of hysterectomy versus first generation ablation methods and endometrial destruction techniques for heavy menstrual bleeding (2002), were included.

Two randomised controlled trials (RCTs) of microwave endometrial ablation (MEA) and seven trials of thermal balloon ablation (TBEA) versus first generation techniques were

identified. These trials include a total of 1409 women, with sample sizes ranging from 20 to 322 (median 139). One of the TBEA trials is a non-randomised controlled trial and the rest are RCTs. Details of one TBEA study were provided as commercial in confidence material and have been excluded from this report.

The quality of the trials was variable. One TBEA study was not randomised; controls were women who underwent first generation EA at the same institution. Of the RCTs, seven used appropriate allocation to groups; one MEA study reported blind assessment of outcomes; one MEA and four TBEA studies showed that the groups were comparable at baseline and six studies (one MEA and five TBEA) gave the same intervention and control treatment to all women. Both MEA studies used subcutaneous GnRH analogues as and endometrial pre-thinning agent in both intervention and control groups. Of the TBEA trials, one gave a D&C immediately prior to the operation in both arms if the trial, two gave GnRH analogues to women in both arms of the trial and one gave no pre-treatment to those undergoingTBEA and GnRH to those in the control group.

Only one MEA and one TBEA study reported undertaking a sample size calculation. Loss to follow up was between zero and 46% (median 2%) - the highest figure at 5 years of follow up. Of the five studies which reported some loss to follow up, two reported using intent to treat analysis although one appears to have used different denominators for some variables. Based on the adequacy of the description of participant characteristics and inclusion criteria, the generalisability of the studies was judged by reviewers as high in one MEA and three TBEA cases, medium in one TBEA study and low in one MEA and two TBEA studies. Main outcome measures were measured independently in six cases and were uncertain in two TBEA studies.

1.4 Summary of benefits

The systematic review of first generation endometrial ablation techniques versus hysterectomy found that EA offered an alternative to hysterectomy for heavy menstrual bleeding with fewer complications and a shorter recovery period. Satisfaction and effectiveness was high for both techniques. Costs were lower with EA although the difference narrows over time.

Due to clinical heterogeneity between trials of first and second generation EA techniques, meta-analysis was not undertaken.

Only one study showed a first generation technique (rollerball) to be significantly superior for the outcome of amenorrhoea measured at one year, and this difference was not found to be superior in intent to treat analysis. All other trials found no significant difference in amenorrhoea rates. The median proportion of women with the outcome of amenorrhoea is higher among those treated with MEA (46%) than those with TBEA (14%), although the ranges overlap (MEA 36-55%; TBEA 10-40%). No other measure of bleeding was found to indicate significant differences between first and second generation techniques of EA.

No significant differences between the results of first and second generation EA were found dysmenorrhoea or pre-menstrual symptoms.

Differences in patient satisfaction reported between first and second generation EA techniques were not significant. One study used the SF-36 to measure quality of life and found that six of the measures improved significantly after MEA as did seven of the items for women in the TCRE/RB treatment group.

Compared to first generation EA techniques, second generation techniques resulted in significantly shorter operating and theatre times, but not in post-operative length of stay or recovery time.

Peri-operative and post-operative adverse effects were few with both first and second generation techniques, but there were fewer peri-operative adverse effects with MEA and none with TBEA compared to first generation techniques. Post operative adverse effects rates were similar.

Second generation EA techniques are an alternative treatment to first generation techniques for HMB. First generation techniques are known to offer an alternative to hysterectomy. Although no trials of second generation techniques and hysterectomy have been undertaken, it seems reasonable to assume that second generation techniques also offer an alternative surgical treatment. No head to head trials of second generation techniques have been undertaken and there is not enough evidence to identify differences between the clinical effectiveness of TBEA and MEA.

1.5 Costs

Costs of technologies were estimated for 2002. The costs of TBEA and MEA were similar at £1,273 and £1,295 per procedure respectively. Methods used to calculate costs may not have been sufficiently sensitive to measure such small apparentt differences with precision. The cost of second generation ablation is slightly less than combined TCRE and rollerball ablation at £1614 but slightly more than rollerball at £1,191. Abdominal hysterectomy costs £2,275.

1.6 Cost effectiveness

A deterministic Markov model was developed to assess cost-effectiveness. Data for the model were taken from a range of sources. For MEA compared to TBEA, costs were slightly higher for MEA (£1,448 vs £1,324 per woman), and differences in QALYs were negligible (8360.70 vs 8360.77 for the whole cohort).

For MEA compared to TCRE and rollerball ablation, costs were slightly lower with MEA (£1,448 vs £1,732 TCRE, £1,752 RB and £1,785 TCRE/RB combined) and MEA accrued very slightly more QALYs (8.361 vs 8.357 TCRE, 8.360 RB and 8.358 TCRE/RB). Compared to hysterectomy, MEA costs less (£1,448 vs £2,320) and accrues slightly fewer QALYs (8.361 vs 8.774).

For TBEA compared to TCRE and rollerball ablation, costs were lower with TBEA (£1,324 vs £1,732 TCRE, £1,752 RB and £1,785 TCRE/RB combined) and TBEA accrued slightly more QALYs (8.361 vs vs 8.357 TCRE, 8.360 RB and 8.358 TCRE/RB). Compared to hysterectomy, TBEA costs moderately less (£1,324 vs £2,320) and accrues moderately less QALYs (8.361 vs 8.774).

1.7 Sensitivity analyses

The economic model was found to be particularly sensitive to changes in the utility value for women who had recovered from having an endometrial ablation, in other words, women who were “well”. To a lesser extent, recurrence of heavy menstrual bleeding and the cost of the procedures were important.

1.8 Limitations of the calculations

Given the paucity of data about utility values for the health states relating to heavy menstrual bleeding, endometrial ablation and post-convalescence, accurate estimates of costs per QALY are difficult to ascertain.

1.9 Other important issues regarding implications

Longer term follow up is required to collect further data on failure rates and subsequent re-treatment.

TBEA is not suitable for women with larger uterine cavities (>12cm) and those with uterine pathology or abnormalities. This may account for as many as 60% of women with heavy menstrual bleeding although estimates are uncertain.

1.10 Notes on the generalisability of the findings

Of the nine included trials, five TBEA studies excluded women with fibroids and one TBEA study included only women with fibroids. This may not represent those women considered suitable for EA in routine practice and may influence effectiveness. In addition, only one MEA study uses self-reported menorrhagia as an inclusion criteria, as would be usual in clinical practice. For the five studies (one of MEA and four of TBEA) using stringent measurements of heavy menstrual bleeding based on high Pictorial Blood Loss Assessment Chart scores, higher rates of satisfaction may result as all have objectively measured menorrhagia initially. Such women have been shown to rate treatment as more satisfactory than women with less bleeding. Finally, one TBEA study includes some women who are post-menopausal but who did not wish to stop taking hormone treatment. The authors believe this group is unlikely, currently, to be treated by EA in the UK.

1.11 Need for further research

- Head to head comparisons of the cost-effectiveness of second generation EA techniques should be undertaken.

- Longer term follow up for all methods of EA in RCTs will provide better information about failure rates and repeat procedure rates and longer term complications.

- Further research in larger groups of women with heavy menstrual bleeding and the general public to establish health state utility values for heavy menstrual bleeding, its surgical treatment, convalescence and complications of treatment are required. This will allow better estimates of cost-utility to be calculated.

- Future studies of heavy menstrual bleeding should use validated quality of life measures and established methods of measuring patient satisfaction both with the procedure and with the outcomes based on expectancy.

- Further research into the effect of the constellation of symptoms associated with menstruation and the part that these symptoms play in women's perceptions of bleeding and the effects of treatment could help to establish which women will find treatment of bleeding alone acceptable.

2 AIM OF THE REVIEW

The aim of the project was to estimate the clinical effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding, compared to the existing (first generation) endometrial ablation techniques of transcervical resection and rollerball ablation, and hysterectomy.

3 BACKGROUND

3.1 DESCRIPTION OF UNDERLYING HEALTH PROBLEM

Heavy menstrual bleeding (HMB, menorrhagia) affects many women. One in 20 women aged 30-49 consults her GP with this complaint each year, approximately one and a half million women in England and Wales.[1] Referrals for menstrual disorders account for about 20% of all those to specialist gynaecology services.[2] By its nature, HMB is a chronic, cyclical problem which may have physical, emotional and social impacts as well as affecting a woman's ability to carry out her normal activities. A study of 348 women in general practice found that over half said HMB was the cause of anxiety or depression and moodiness or irritability. In addition, over a third said HMB interfered with relationships, spoilt their sex life, and interfered with hobbies or holidays. For 14% of women, HMB had an impact on their ability to carry out their job.[3] Regular blood loss of 50-60ml per cycle will lead to a negative iron balance for most women.[4]

3.1.1 Defining menorrhagia

Menorrhagia is objectively defined as the loss of more than 80ml of blood per cycle over several consecutive cycles.[5] However, objective measurement is difficult and several studies have shown that between 35-60% of women who present with the complaint of heavy menstrual bleeding have objectively measured blood loss in the normal range.[6;7] Conversely, there is also a proportion of women who do not seek help although they can be shown to have "abnormally heavy" blood loss.[8]

Issues in the measurement of heavy menstrual bleeding, associated problems and their impact are discussed further in section 3.1.3 (page 17).

3.1.2 Causes of heavy menstrual bleeding

Possible causes of heavy menstrual bleeding are shown in Figure 1. Non pathological causes are poorly understood and are usually referred to under the name dysfunctional uterine bleeding, which is the commonest cause.[9]

Figure 1: Possible causes of heavy menstrual bleeding and associated factors[10]

Anatomic	Biochemical	Endocrine	Haematologic	Iatrogenic	Associated factors
Fibroids Polyps Adenomyosis Infection Malignancies	Prostaglandins	Hypothalamic-pituitary-gonadal-adrenal axis dysfunction Oestrogen producing tumours Thyroid dysfunction	Von Willebrand's disease Leukaemia Increased endometrial fibrinolytic activity	IUDs Anticoagulants Exogenous Hormones	Obesity Heavy smoking Excessive alcohol Depression Endometriosis

Studies examining the efficacy of drug treatments in women with heavy menstrual bleeding have suggested that women who fail to respond to effective drug treatment may have an underlying cause that may only be detected at later hysterectomy.[11;12] It is recommended by Royal College of Obstetricians and Gynaecologists guidelines that women should be examined by transvaginal ultrasound (TVS) or hysteroscopy for polyps or fibroids.[13] A large prospective study in Italy of 793 women referred for HMB who had a uterus <12cm found pathology in 57%, leaving 43% of women with no identifiable cause for their heavy bleeding.[14] However, a UK RCT of 370 women randomised to receive hysteroscopy examination or endometrial biopsy alone, found pathology in only 20% of women.[15]

3.1.3 Measurement of blood loss

Direct and indirect measurement methods

The definition of menorrhagia is specific and quantitative. Accurate measurement of blood loss may be difficult and perception of blood loss may be as, or more important, than actual loss in defining the presence of a health problem for which treatment may be considered appropriate.

The current "gold standard" method of measuring blood loss is the alkaline hematin technique.[16] Although this method has been modified by several researchers (e.g. Gannon and colleagues, 1996[17]) to simplify and quicken the procedure, all versions require women to collect their used sanitary wear. This is subsequently treated to extract haemoglobin, which is then measured and related back to actual blood loss. This method is rarely used outside of a research setting.

Another method of assessing menstrual blood loss is the pictorial blood loss assessment chart (PBAC).[18] This is a simple scoring system, which takes into account the number of items of sanitary wear used, and the degree of staining of each item (see Appendix 1, page 115). This technique is now more widely used than the alkaline hematin method although a recent study showed that, in a group of 103 women with menorrhagia, there was poor correlation between actual measured blood loss and PBAC score.[19] Furthermore, methods which rely on directly or indirectly estimating blood loss from the effect on sanitary wear do not take account of extraneous blood loss (blood lost during changing sanitary wear).

Another indirect method for estimating blood loss is the 'Menstrual Pictogram'.[20] This is similar to the PBAC but also asks women to distinguish between the absorbency of the towel or tampon and to estimate extraneous blood loss.

Objectivity and subjectivity in heavy menstrual bleeding

Subjective and objective estimates of menstrual blood loss do not correlate well. Some women with bleeding within the normal range describe their bleeding as heavy, whilst some with objectively measured HMB regard their bleeding as normal.[19;21] A recent study validating a new technique of assessing blood loss investigated women presenting at clinic with heavy menstrual bleeding and controls who considered their blood loss to be 'normal'. Only 36% of women presenting with the complaint of heavy menstrual bleeding had their condition objectively verified while 14% of the controls had blood loss in excess of 80ml despite considering their loss to be normal.[20]

Clearly, women's expectations of normal menstrual loss are important in determining the definition of bleeding as a "problem". Such expectations may also have an influence on the demand for and perceived success of interventions. For example, over 50% of women who have surgery for heavy menstrual bleeding do not have objectively measured blood loss of 80ml or more.[7] Interpretation of blood loss has an impact on the effectiveness of treatment: one study found that women with objectively confirmed menorrhagia were more likely to rate the outcome following surgery as "successful" than those presenting for surgery without a confirmed, objective measurement of menorrhagia.[17]

Associated menstrual symptoms

The presence of other menstrual symptoms may have an impact on perceptions of bleeding and account for some of the difference between objective and subjective estimates of menorrhagia. A recent study found that women perceived their bleeding to be heavier if they were also experiencing associated pain.[22] The 39th Scientific Study Group of the Royal College of Obstetricians and Gynaecologists (RCOG) on Disorders of the Menstrual Cycle, recommended that 'decisions related to the treatment of menstrual cycle disorders must be based on all the relevant symptoms'.[23] A study of 348 women presenting with heavy menstrual bleeding in general practice found that over half described themselves as having painful periods in addition to heavy menstrual bleeding.[3]

Definition of heavy menstrual bleeding, and corresponding demand for specialist treatment, may also be affected by the perceptions of GPs in response to the clinical history of a woman presenting with menstrual symptoms. In a study of 952 women in Scotland, Warner and colleagues found that, among women referred to specialist gynaecology services, 78% were reported by their GP to have heavy menstrual bleeding while only 38% of women reported that menstrual loss was a severe problem to the GP.[24] Again, this may affect perceived treatment outcome if women are treated for HMB while another menstrual symptom was their prime concern.

3.1.4 Measuring the impact of heavy menstrual bleeding

The impact of any condition can be measured using one of three types of quality of life scale:

- **Condition specific scales** These have the advantage of incorporating attributes of quality of life which are specifically affected by the condition of interest. They may therefore be more sensitive to small but important changes and may be considered to have greater face validity (that is, they include items that are of are importance to sufferers and reflect their experience and concerns).

- **Generic scales**. These have the advantage of allowing comparison between conditions of impact on quality of life. However, they may be relatively insensitive to aspects of a particular condition. They may provide a single index or a profile of scores across dimensions of quality of life.

- **Preference based scales**. A particular type of generic measure, these elicit the respondent's preference for a given health state and, if appropriately scaled, provide weights which can be used in cost utility analyses.

A recent systematic review of quality of life measures used in studies of heavy menstrual bleeding found 15 generic and two condition specific scales reported in 19 scale development, epidemiological and intervention studies.[25] Quality of the scales was judged using a checklist derived from generic quality of life measure appraisal tools, broadly assessing face validity and measurement properties. The authors, Clark and colleagues, conclude that measurement scales in heavy menstrual bleeding perform better in relation to measurement properties than face validity and that improved condition specific measures are required to assess the impact of heavy menstrual bleeding on quality of life.[25]

Condition specific scales

Two condition specific outcome measures have been developed for women with heavy menstrual bleeding: the Menorrhagia Outcomes Questionnaire[26] and the Multi-attribute Questionnaire.[27] The Menorrhagia Outcomes Questionnaire includes items on symptoms and satisfaction with care, physical function, psychological and social well-being, global judgement of health and quality of life, and personal constructs. The Multi-attribute Questionnaire includes items on practical difficulties, social function, psychological function, physical health, interruption to work and family life.

Generic measures

A range of generic measures of quality of life have been used in heavy menstrual bleeding: SF36, Nottingham Health Profile, health status structured history and single global item. The SF36 was the most frequently cited in the systematic review by Clark and colleagues, and is generally a well validated measure used to assess health related quality of life.[25] This includes items on global health perception, physical function, social function, role-physical and mental, pain, mental health and energy/vitality. The validity of the SF-36 in assessing the quality of life in women with heavy menstrual bleeding has been determined in a population of women presenting with heavy menstrual bleeding in a study by Jenkinson and colleagues (1994).[28] Although the authors commented that it was a 'feasible' means of looking at quality of life, responding to changes over time, they have subsequently suggested that the SF-36 may have some problems when applied to this group of women.[29] In interviews with 49 women with heavy menstrual bleeding who had completed the SF-36, Jenkinson and colleagues (1996) found that women commented on some questions being difficult to answer or inappropriate for women with HMB, which may affect the measure's validity.[29] In addition, comparing the results given by 425 women with heavy menstrual bleeding to those from the Oxford healthy lifestyle survey in a general population sample

(n=9219), the authors found that internal reliability, as assessed with Cronbach's α-statistic, was lower in the heavy menstrual bleeding group, especially for general health perception and mental health scales.

Clark and colleagues[25] also report the use of generic measures which address particular aspects of quality of life such as physical (Modified Townsend Score), mental (General Health Questionnaire) and sexual health (Revised Saabatsberg Sexual Rating Scale) and social function (Lifestyle Index) in studies of women with heavy menstrual bleeding.

Preference based measures

Clark and colleagues report the use of the EQ5D in two intervention studies as a measure of quality of life in heavy menstrual bleeding. The EQ5D includes a multi-attribute scale, with dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and a global rating scale for quality of life (visual analogue scale). Both studies in heavy menstrual bleeding used the visual analogue scale for global quality of life rating.

The table below shows the baseline ratings for quality of life in women with heavy menstrual bleeding, compared to those in a range of other conditions, measured using a range of approaches to obtain a utility estimate (Table 1). These values are taken from the website http://www.healthpriorities.uci.edu.

Table 1: Examples of utility values for heavy menstrual bleeding and other health states

Health state	Utility	Source	How value obtained
Menorrhagia	0.55	Sculpher et al[30]	Women with menorrhagia, time trade off
Menopause, symptoms of	0.99	Weinstein[31]	Author judgement
Breast Cancer, reversible complication	0.99	Carter et al[32]	Standard gamble, clinical experts
Breast cancer chemotherapy after surgery, major toxicity	0.8	Hillner & Smith[33]	Clinician judgement
Breast cancer chemotherapy after surgery, minor toxicity	0.9	Hillner & Smith[33]	Clinician judgement
Breast cancer after surgery - first recurrence	0.7	Hillner & Smith[33]	Clinician judgement
Breast cancer after surgery after first recurrence	0.85	Hillner & Smith[33]	Clinician judgement
Breast cancer after surgery - second recurrence	0.5	Hillner & Smith[33]	Clinician judgement
Breast cancer after surgery after second recurrence	0.7	Hillner & Smith[33]	Clinician judgement
Endometrial cancer	0.9 0.95	Hillner et al [34] Carter et al[32]	Clinical judgement Standard gamble – clinical experts
Myocardial infarction, chest pain	0.67	Tsevat et al[35]	Patient rating scale
Lower third molar extraction, mild post-operative pain	0.7011	Brickley et al[36]	Patient rating scale
Lower third molar extraction, moderate post-operative pain	0.4262	Brickley et al[36]	Patient rating scale
Lower third molar extraction, severe post-operative pain	0.1583	Brickley et al[36]	Patient rating scale
Lower third molar, no extraction occasional low grade pain	0.6571	Brickley et al[36]	Patient rating scale
Gallstones, symptoms or chronic pain	0.95	Weinstein et al[37]	Author judgement
Gallstones, acute surgical complication	0.92	Bass et al[38]	Clinical expert rating scale
Gallstones, endoscopic sphincterotomy	0.9	Bass et al[38]	Clinical expert rating scale
Gallstones, surgical scar	0.993	Bass et al[38]	Clinical expert rating scale

The value of 0.55 for menorrhagia shown above may be considered low – endometrial cancer, chest pain due to myocardial infarction and recurrence of breast cancer after initial surgery, for example, are all estimated to carry higher values for utility. In the same study, women were asked to rate their own current health state which had a mean of 0.65 (SE 0.04) and a median of 0.75 (range 0-1.0), higher than that given for the state of menorrhagia, which the author ascribes to most women not menstruating at the time of the interview. The author acknowledges that there are problems eliciting values for chronic health states that may affect quality of life on a daily basis but for which the worst effects are episodic. Even in the extreme cases most HMB remains cyclical and is not usually a permanent condition. The discrepancies may also be due to different techniques for eliciting utility values, and their use in different groups (clinicians or sufferers). Research by Dolan and Kind[39] has also suggested that inconsistency rates in respondents' own ratings are higher for interview than postal survey studies and are also affected by age and educational attainment.

Although utility provides a metric which can be used to compare the value of technologies across different conditions, the variation in values demonstrated here should be borne in mind by those interpreting such analyses.

Patient satisfaction measurement

Patient satisfaction is widely used as a primary outcome measure in studies of treatments for heavy menstrual bleeding. It is not a measure of the impact of heavy menstrual bleeding, but is discussed here alongside other outcome measures in heavy menstrual bleeding.

"Satisfactory" means "adequate … leaving no room for complaint … meeting expectations or needs".[40] Satisfaction is necessarily a subjective and relative concept. In this context, it is the extent to which a service meets users' expectations. It is not clear whether satisfaction can be measured on a continuum, from dissatisfied through to satisfied, or whether factors resulting in satisfaction are different from those leading to dissatisfaction.

Satisfaction with services is related to patient characteristics,[40] notably age and health status. Older people are more likely to report higher satisfaction with healthcare, for reasons that are poorly understood. The relationship between health status and satisfaction is not straightforward. Among hospitalised patients, worse health is generally associated with lower reported satisfaction with health care. One study reviewed by Crow and colleagues[40] showed improvements in health resulted in higher satisfaction, though another study showed that satisfaction was related more to health status on discharge than on improvement in health status during the hospital stay.

The relationship between health status and satisfaction is important in the current context as satisfaction is a key outcome in trials of endometrial ablation. The debate on this point is balanced. On the one hand, satisfaction can be determined by the experience of the care setting, which may have a minimal relationship with change in health status - such as whether staff were polite or the ward surroundings aesthetically pleasing. Therefore, satisfaction may be regarded as a poor outcome measure by which to judge the effectiveness of a health technology. On the other hand, satisfaction is a global measure which incorporates process and outcome aspects of the health technology and therefore may be considered as a legitimate measure. The authors of this assessment regard patient satisfaction as an important measure of outcome, but as a complement to appropriate measures of quality of life.

Patient satisfaction measures come in a wide range of formats.[40] In common with other types of measure, they are prone to several important biases arising from design and delivery. Single item satisfaction measures, such as have been used in trials of endometrial ablation, may be less valid than well-constructed multi-item scales.[40]

The range of methods for eliciting satisfaction ratings is large, and details are frequently not reported. It is therefore difficult to consider whether satisfaction in one study is similar to that measured in another, rendering comparison between technologies difficult on this measure.

Satisfaction can be interpreted according to general or personal referents. In other words, people may report on their satisfaction with their personal care, or whether they felt the care was, in general, satisfactory. Adopting these different perspectives produces systematically different ratings of satisfaction, with the general referent more likely to produce a higher rating.

Finally, several important response biases occur in satisfaction measurement:

- Social desirability bias - where the respondent gives what they believe to be the questioner's preferred response, this may be a particular issue in face to face interview where the interviewer is a member of the team providing care.
- Cognitive consistency pressure - where responses are given congruent with their continued use of the service.
- Acquiescent response sets - the tendency to respond positively to all questions.

The extent to which these potential biases are addressed in the patient satisfaction measures used in studies of endometrial ablation cannot be judged as detailed accounts of the development and validation of the measures used are not available. While the use of similar methods to measure subjective satisfaction for women in both arms of an RCT may provide a comparative measure between these groups, it may remain unclear exactly what is being measured for the reasons outlined above. In addition, the range of techniques and scales used to elicit a measure of satisfaction across studies precludes pooling of results through meta-analysis. Finally, some women who are recorded as being satisfied with ablation treatment, will have had a subsequent hysterectomy, which is known to confer high satisfaction rates in clinical trials.

3.2 CURRENT SERVICE PROVISION

Treatment for heavy menstrual bleeding aims to improve quality of life through reducing menstrual loss. Two evidence-based guidelines for the management of menorrhagia, one for medical management[5] (1998) and one for management in secondary care[13] (1999) have been produced by the Royal College of Obstetricians and Gynaecologists (RCOG). It is recommended by the RCOG that women with heavy menstrual bleeding should receive hysteroscopy and/or transvaginal ultrasound (TVS) to examine for uterine pathology (p.15). In addition, endometrial biopsy may be required to diagnose carcinoma or hyperplasia (p.18). Dilation and Curettage (D&C) is no longer considered the best way to assess abnormal bleeding (p.19).[13]

3.2.1 Drug Therapy

For women presenting with heavy menstrual bleeding, a number of drug treatment options are available. These are addressed by the RCOG guidelines. Some women, whose bleeding is relatively manageable, and for whom investigation has shown no underlying pathology, may benefit from counselling and reassurance that the experience is normal. For these women watchful waiting is appropriate.

According to RCOG guidance, if treatment is required, heavy menstrual bleeding should initially be treated medically for at least three cycles.[5] However, one 1991 study of 205

women in an English Health Authority found that only about half of patients referred to a gynaecologist had previously been prescribed drug therapy by their GP.[2] The RCOG guidelines for medical management state that tranexamic acid (an anti-fibrinolytic drug) and mefenamic acid (a non-steroidal anti-inflammatory drug) are considered effective treatments in the initial management of heavy menstrual bleeding.[5] A meta-analysis of seven studies found tranexamic acid reduced menstrual blood loss by 47%.{Coulter, Kelland, et al. 1995 550 /id} A meta-analysis of ten trials found that mefenamic acid reduced blood loss by 29%.[41] Treatments have side effects such as headache, diarrhoea, nausea, vomiting, dizziness, fatigue and skin irritation. Although these are usually mild, they may affect up to 50-80% of women taking these medications.[5]

Women requiring contraception as well as treatments for heavy menstrual bleeding may benefit from combined oral contraceptives (COCs) or the progesterone (levonorgestrel) releasing intra-uterine device (LNG IUS, marketed as Mirena®). This was originally designed as a contraceptive device but has been licensed for use in heavy menstrual bleeding since 2001. Both are considered effective although hormone treatments have well known side effects.[5]

Although evidence suggests that tranexamic acid is the most effective drug treatment for heavy menstrual bleeding, a recent UK survey of primary care prescribing showed that 35% of treatment prescriptions for heavy menstrual bleeding were for this.[42] Women for whom one type of medical treatment has been unsuccessful may be reluctant to try alternative medication, even though this may be more effective. Prescribing practice in primary care may therefore affect referral and surgery rates in secondary care. Wide variations have been described in all aspects of management for heavy menstrual bleeding: general practice management, referral patterns and rates of hysterectomy.[13]

3.2.2 Surgical Treatment

If drug therapy is not effective, surgical interventions, including endometrial ablation techniques and hysterectomy, may be considered. For women referred to a gynaecologist following the failure of medical management in primary care, surgical intervention is likely. In an RCT of medical management versus TCRE in secondary care, of 94 women randomised to receive medical treatment, only 10% remained in this arm after five years. A total of 77% of women had undergone subsequent surgery, 18% having had a hysterectomy (in two cases in addition to TCRE treatment.)[43] Furthermore, this study found that women who received endometrial ablation initially were significantly more likely to be totally satisfied with their treatment than those women initially given medical treatment in secondary care (39% versus 61%; p=0.01).

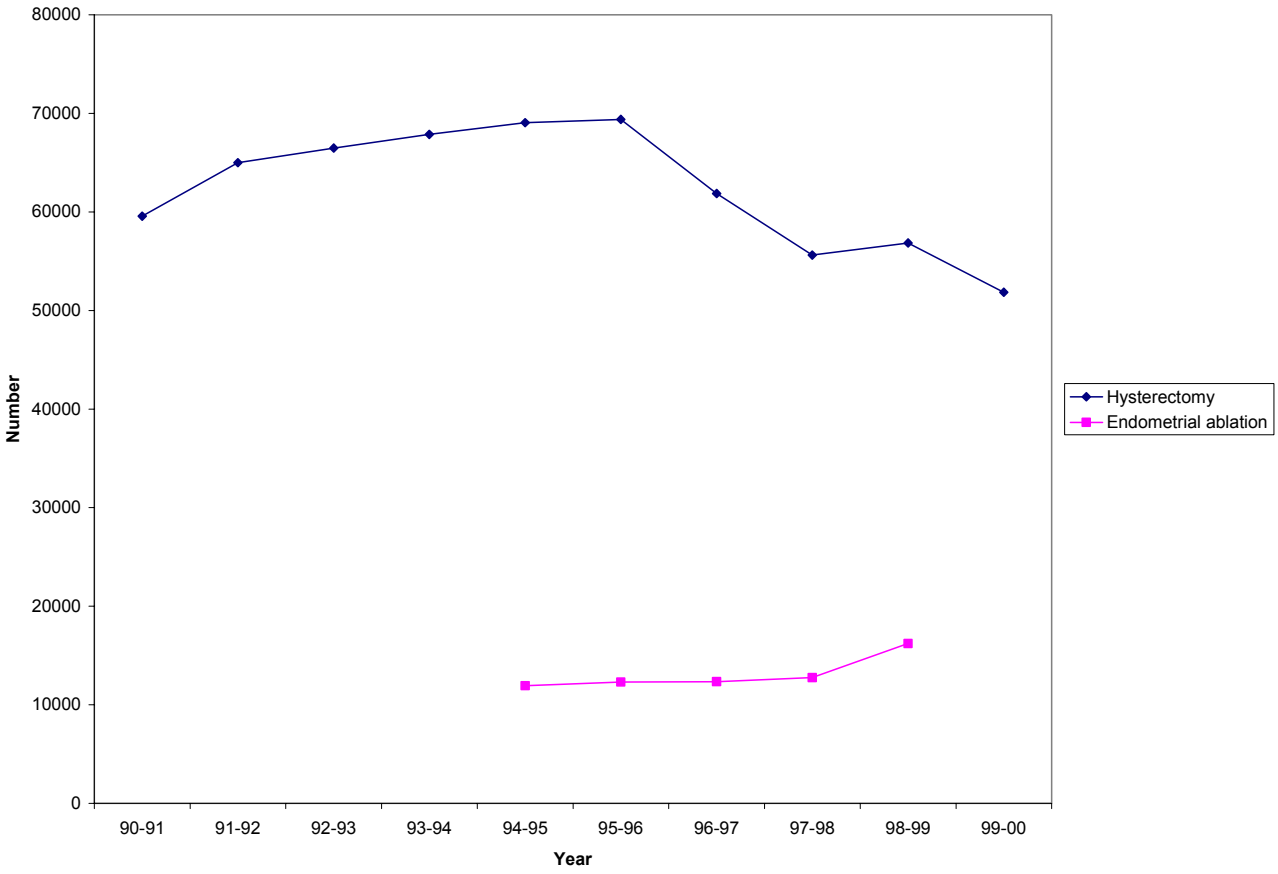
Incidence of surgical operations for heavy menstrual bleeding

There were 51,858 hysterectomies in the public sector in England in 1999-2000, including operations coded as secondary procedures in the OPCS Hospital Episode Statistics (HES). About 80% of these are likely to have been abdominal hysterectomies.[44] About half of all hysterectomies are likely to be for heavy menstrual bleeding. In 1998/99, there were 16,219 admissions for endometrial ablation. Hysterectomy and ablation have a large place in private practice, although no numbers for operations performed are available. In addition, it is possible that changes in practice in the private sector may influence patient behaviour in the NHS. For example, a quicker uptake of new minimal intervention ablation techniques into private practice could remove some patients wishing to avoid hysterectomy from the NHS, while some women wishing immediate hysterectomy may prefer to pay privately rather than wait for an NHS operation.

Early enthusiasts felt that EA might replace hysterectomy for heavy menstrual bleeding. In reality, diffusion has not been straight forward. A study of English hospital admission data between 1989/90 and 1995/96 concluded that EA was not replacing hysterectomy.[45] However, since then numbers of endometrial ablations have increased whilst hysterectomies have fallen. The rise in the numbers of EA procedures for 1997 coincides with the introduction of second generation devices into clinical practice. (Amso, personal communication)

Figure 2 plots HES codes Q08 and Q09 combined for hysterectomy and Q16 and Q17 combined for endometrial ablation.

Figure 2: Number of hysterectomies and endometrial ablation operations in England



Although there appears to be a trend toward increased ablation and decreasing hysterectomy, these figures may mask more complex local variations. A recent study[46] in the USA examined the diffusion of endometrial ablation using State Inpatient and Ambulatory Surgery Databases of the Healthcare Cost and Utilization Project in six states for 1990-97. While the rate of EA increased in all states, the rate of hysterectomy decreased in three, remained static in two and increased in one. The ratio of hysterectomy rate to EA rate decreased in all states. The combined rate of EA and hysterectomy increased in all but one state. The authors suggest that EA is being used as an adjunct rather than a replacement therapy for HMB. It is possible that availability of EA may decrease the threshold for surgical treatment.

Hysterectomy

Hysterectomy is the only treatment for heavy menstrual bleeding which can guarantee complete removal of symptoms (amenorrhoea) in all women. In the UK, 20% of women will have a hysterectomy by the age of 55.[47] In about half of all hysterectomies, heavy menstrual bleeding is the presenting complaint and in half of hysterectomies performed for heavy menstrual bleeding, a normal uterus is removed.[48]

Different approaches to hysterectomy are possible. In abdominal hysterectomy the uterus is approached through the anterior abdominal wall, via a vertical or horizontal incision. In vaginal hysterectomy, the uterus is removed through the vagina and may be carried out with the assistance of a laparoscope. Different degrees of hysterectomy are also possible; removing the complete uterus (total hysterectomy), leaving the cervix (sub-total hysterectomy) and removing the ovaries and fallopian tubes in addition to the uterus (total hysterectomy with bilateral salpingo-oophorectomy). The VALUE study of over 37,000 hysterectomies performed in the UK in 1994-5, found that two-thirds were abdominal (of which 4% were sub-total) and that ovaries were removed in 57% of hysterectomies.[48]

Hysterectomy is an inpatient procedure and full recovery may take four to six weeks. One in 30 women suffer peri-operative adverse events. Post-operative complications affect at least one in 10 women and include incontinence and other urinary problems, fatigue, infection, pelvic pain, hot flushes, dry vagina and sexual problems. In addition, women undergoing bilateral salpingo-oophorectomy at the time of hysterectomy will experience the menopause.[48] (See Table 2)

Table 2: Adverse events following hysterectomy

Very common (>1/10)	Common (>1/100 <1/10)	Uncommon (>1/1000 <1/100)
Sepsis	Haemorrhage	Death
Pyrexia	Blood transfusion	Fluid overload
Wound haematoma	Anaemia	Visceral damage
Hypergranulation	Vault haematoma	Resp./heart complications
UTI	Anaesthetic	Deep vein thrombosis
	GI obstruction/ileus	
	Diarrhoea	

Calculated from – The VALUE study[48] and Cochrane review of hysterectomy and first generation EA[9] DVT and UTI added by correspondence with Expert Advisory Group.

A systematic review of studies examining the effect of hysterectomy on sexuality found little evidence that hysterectomy had a detrimental affect. In most women, sexuality was unchanged or enhanced following the operation. However, the quality of the trials included in the review was considered generally poor.[49] There is evidence that long term, women who have undergone hysterectomy may suffer increased risk of some symptoms such as urinary incontinence,[50] vasomotor symptoms and some psychological symptoms than their peers.[51] However, in clinical studies, satisfaction with hysterectomy is reportedly very high.[52]

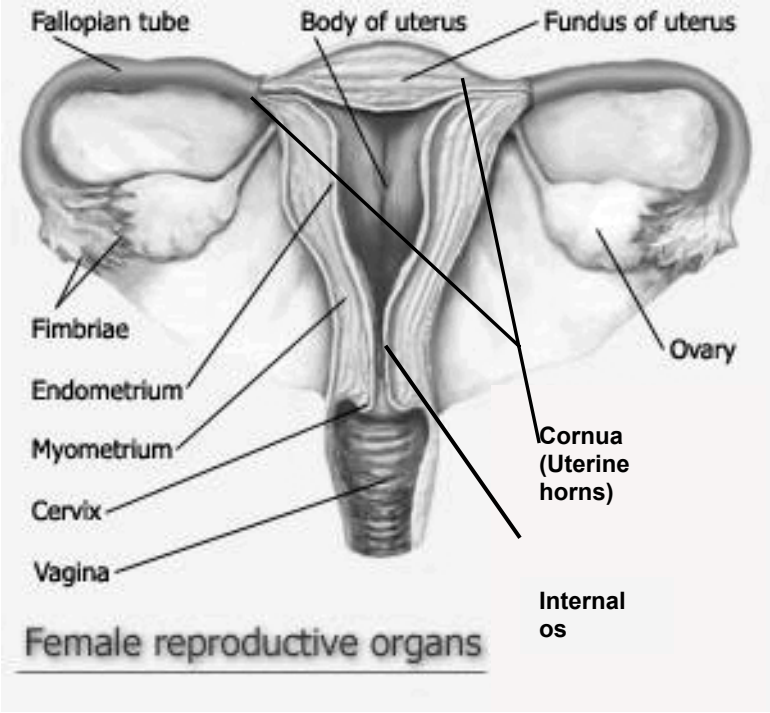
First Generation Endometrial Ablation Techniques

Since the 1980s, more conservative surgical interventions have been developed as alternatives to hysterectomy. The three most commonly used methods are transcervical resection (TCRE), roller-ball and laser ablation, collectively known as “first generation” endometrial ablation techniques. All first generation techniques require direct visualization of the endometrium using a hysteroscope. They rely heavily on the skill and experience of the operator [53] In particular, greater experience has been shown to be significantly associated with a reduction in the risk of uterine perforation.[54]

In this project, TCRE and rollerball methods are the first generation comparators for the technologies of interest as these are the most commonly used methods in the UK.

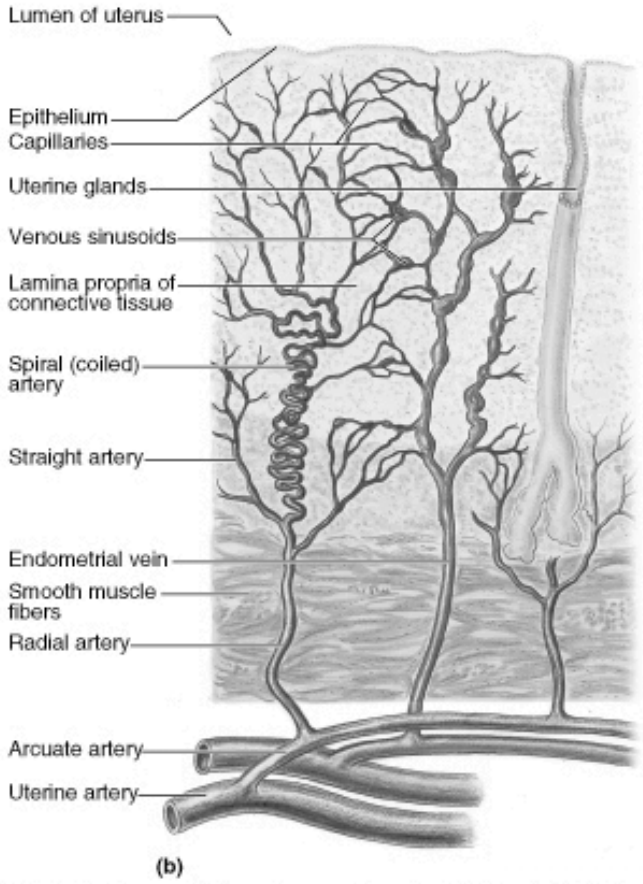
All methods of endometrial destruction aim to destroy the inner lining of the uterus (endometrium) (See Figure 3 and Figure 4, page 26 and 27). The endometrium is capable of regeneration and techniques must therefore cause necrosis of the endometrial cells in order to suppress menstruation. This involves removing the full thickness of the uterine lining together with the superficial myometrium, and the basal glands thought to be the focus of endometrial growth. Endometrial ablation is not a contraceptive and pre-menopausal women need to continue to use contraception as pregnancies after EA have been reported.

Figure 3: The female reproductive system



Copyright 2002, www.mydr.com.au (Medimedia Australia) (Adapted)

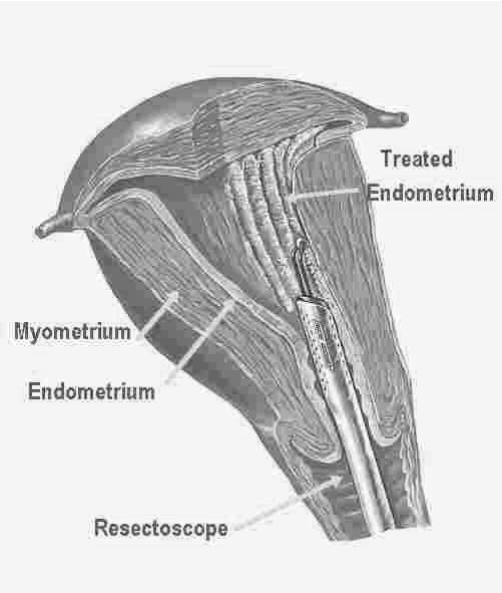
Figure 4: Section through the endometrium



In order to minimise the depth of endometrial lining, thinning agents, such as danazol or gonadotrophin-releasing hormone analogues (GnRH) may be used prior to ablation. A good quality systematic review of thinning agents found that endometrial thinning prior to ablation improved the operating conditions for the surgeon and, at short term follow up, increased amenorrhoea.[55] GnRHs were found to produce slightly more consistent endometrial thinning than danazol, though both agents produce satisfactory results.[55] Although it is possible to undertake first generation endometrial ablation under local anaesthetic, this is rare. A national survey, the MISTLETOE study, carried out between 1993 and 1994, showed that general anaesthetic was used on 99% of cases.

TCRE requires a rigid or flexible hysteroscope with a fibreoptic cable to transmit light from an external power source. The cervix must be dilated to allow the hysteroscope to be admitted. The resectoscope itself provides an 0-30^{o} angle of view. A continuous flow outer sheath circulates liquid (usually glycerine) to rinse the uterus of debris and provide a clear view. A cutting loop is used to remove the endometrial lining. TCRE provides good samples of endometrium for biopsy. TCRE may also be used for the removal of fibroids, usually those not larger than 2cm. The operation takes 13-45 minutes[52] and may be done as a day case procedure.

Figure 5: Transcervical resection



(From: http://www.gynalternatives.com/ablation.htm)

The rollerball technique also requires visualization and irrigation using a resectoscope. A rollerball electrode is used rather than a cutting loop. A current is passed through the ball and this is moved across the surface of the endometrium, thereby destroying the tissue.[56] Because the rollerball fits better in the thin-walled uterine horns and lessens the chance of perforation, some surgeons use a combination of cutting loop and rollerball equipment in the same ablation procedure. As no "chips" of removed endometrium are generated with rollerball coagulation, there may be better visibility through the hysteroscope than with TCRE. Rollerball also results in fewer operative adverse effects.[54] In the UK, it is usual for TCRE to be supplemented by rollerball at the fundus and in the thin parts of the uterus around the openings of the Fallopian tubes.[10]

Possible perioperative adverse effects with TCRE and rollerball include electrosurgical burns, uterine perforation, haemorrhage, gas embolism, infection and fluid overload (which may cause congestive cardiac failure, hypertension, haemolysis, coma and death). Strategies for avoiding fluid absorption include maintaining the minimum intrauterine pressure for safe surgery, having a efficient system to retrieve circulated fluid, and maintaining an account of fluid volumes.[57] Fluid overload may be of particular concern when fibroids are being removed, as open blood vessels are capable of rapid fluid absorption.

The MISTLETOE study examined complications with first generation EA techniques. Possible adverse effects, both operative and post-operative, are shown below in Table 3.

Table 3: Adverse effects with first generation endometrial ablation techniques

Very common (>1/10)	Common (>1/100 <1/10)	Uncommon (>1/1000 <1/100)
	Haemorrhage Uterine perforation Sepsis Pyrexia Fluid overload	Death Pregnancy Cardio-vascular/ respiratory Visceral burn Blood transfusion HAEMATOMA GI obstruction / ileus Laparotomy

Calculated from - Overton et al 1997[54], Lethaby 2002[9]

The Endometrial Ablation Group (a special interest group) consensus paper (2002)[58] concluded that EA is contraindicated when there is:

1. Uterine malignancy or its precursors.
2. Acute pelvic infection.
3. Desire for future pregnancy
4. Excessive cavity length (>12cm).

In addition, the group recommends that women undergoing EA are counselled that:

1. Amenorrhoea cannot be guaranteed, and its occurrence depends on technique, operator experience and the nature of any associated pathology.
2. The vast majority of patients will ultimately be satisfied with the procedure.
3. Further ablation or hysterectomy will be required by some women.

3.2.3 Choosing treatment for heavy menstrual bleeding

Given the range of treatments for heavy menstrual bleeding, women, in consultation with their doctors, will choose the intervention that is best for them based on their own priorities for treatment including aspects such as future pregnancy, attitude to major surgery, conservation of the uterus, tolerance of pain, speed of return to normal activities and so on. Research has found that about a third of women have a strong treatment preference.[59] These women are likely to be older, in social classes I or II, have higher levels of education and to have previously consulted a GP or consultant about menstrual problems. Within this group, women with more severe symptoms and those without higher education are more likely to prefer surgery.[59] A prospective MRC study of 2,547 women showed that the chance of having hysterectomy was highest in those with minimal qualifications (28% of these women had a hysterectomy by the age of 52) and lowest in those with the most educated women (12% by age 52), although this gap appears to be lessening over time.[60]

Patient preferences for treatment for heavy menstrual bleeding may be affected by knowledge of treatment options. In a study of 425 women attending their GP for heavy menstrual bleeding, similar proportions strongly preferred surgical (15%) and drug treatment (17%).[59] This same study found that doctors were unaware of their patients' preference in nearly two-thirds of cases where a strong preference existed. The fact that some women have strong preferences for a particular type of treatment has led to some clinical trials in this area adopting a partially randomised patient preference design in order to encourage participation.[61] The study found that women who chose medical treatment were significantly

more likely to find this acceptable and to wish to continue with it than those who were randomised to receive it. However, there was no similar significant difference between those who chose or were randomised to TCRE.[61]

While amenorrhoea may be the clinical aim of treatment for heavy menstrual bleeding, some women will find a treatment acceptable if it reduced bleeding symptoms, without amenorrhoea. A study of over 100 women who had undergone endometrial ablation regarded the three most important advantages of EA over hysterectomy as: the avoidance of major surgery, the ability to return to normal activities quickly, and short hospitalisation.[62] More than half indicated they would find EA acceptable even if there was no chance of amenorrhoea. By contrast, a survey of 225 UK women with heavy menstrual bleeding who had not yet received treatment in secondary care found the characteristics of treatment that women rated most frequently as "very important" were getting back to normal activities as quickly as possible, experiencing least pain and discomfort and permanent stopping of periods.[63] These aims are incompatible given the results of current treatment options and women may need good information and careful counselling to help them prioritise their needs. This study found that 28% of women regarded amenorrhoea as the most important aspect of surgical treatment, while 18% thought that conservation of the uterus was most important, showing that individuals have different priorities for treatment.

3.3 DESCRIPTION OF NEW INTERVENTION

3.3.1 Second generation endometrial ablation techniques

Since the 1990s, several new methods of endometrial ablation have been developed. These are often referred to as "second generation" techniques. They do not require direct visualization of the uterine cavity and employ a variety of means to destroy the endometrium – circulation of heated saline within the uterine cavity, use of a diode laser (ELITT), punctual vaporizing methods, photodynamic methods, radiofrequency, microwaves, a balloon catheter filled with heated fluid and cryotherapy. Apart from the direct circulation of hot liquid within the uterus, none of the second generation methods require direct visualisation of the uterus. The treatments are much less dependent on the skill of the surgeon than first generation techniques, and much more dependent on the reliability of the machines used to ensure safety and efficacy. For this review we have been asked to consider thermal balloon and microwave endometrial techniques, both of which are performed without direct visualization of the uterine cavity and require no distension fluid.

3.3.2 Microwave endometrial ablation

The microwave endometrial ablation (MEA) technique was developed in Bath, England, in 1993. The microwave frequency (9.2GHz) was chosen to ensure that tissue penetration no more than 6mm. An 8mm applicator inserted through the cervix delivers the microwaves using a dielectrically loaded waveguide.[64] Power is controlled by the surgeon using a footswitch and the temperature inside the uterus is monitored by thermocouples on the surface of the waveguide. Prior to microwave ablation treatment oral and vaginal thinning agents may be given. Immediately prior to MEA, hysteroscopy is performed to exclude false passages, wall damage and perforation.

The uterus is measured and the measurement checked with a metal rule. Under general or local anaesthetic, the cervix is dilated to Hegar 8 or 9 and the length of the uterine cavity measured. The microwave probe is inserted until the tip reaches the fundus. Graduated centimeter markings on the applicator shaft confirm the length and if these three

measurements of uterine length are the same, the device is activated.[65] When, after a few seconds, the temperature reaches 80°C the probe is moved laterally so that the tip is placed in one of the uterine cornu. The temperature briefly falls and rises again and when 80°C is reached again the probe is moved to the other cornual region and the procedure repeated. Maintaining a temperature of 70-90°C the probe is withdrawn with side to side movements. The temperature measured by the thermocouple is actually the heat transmitted back from the tissue through the plastic sheath to the applicator shaft. Tissue temperature is higher than these measured levels during active treatment. As a marker on the probe appears at the external os, the applicator is switched off to avoid treating the endocervix. The procedure takes two to three minutes.[64] Following the procedure, analgesia is provided as required. A watery discharge for about three weeks is usual.[65]

MEA is contraindicated where there has been previous uterine surgery and where previous Caesarean section has left a uterine scar thinner than 8mm thickness.

3.3.3 Thermal Balloon endometrial ablation

The thermal balloon method of endometrial ablation relies on transfer of heat from heated liquid within a balloon which is inserted into the uterine cavity (see Figure 6, page 32). Several devices are available including Thermachoice™ and Cavaterm™. All systems involve an electronic controller, a single use latex or silicone balloon catheter (5mm) which houses a heating element and two thermocouples, and an umbilical cable. The thermal balloon cannot be used on women with large or irregular uterine cavities as the balloon must be in direct contact with the uterine wall to cause ablation. Cavaterm™ is contraindicated where the uterine cavity is greater than 10cm from the internal os to the fundus, and Thermachoice™ when the cavity is greater than 12cm in length.

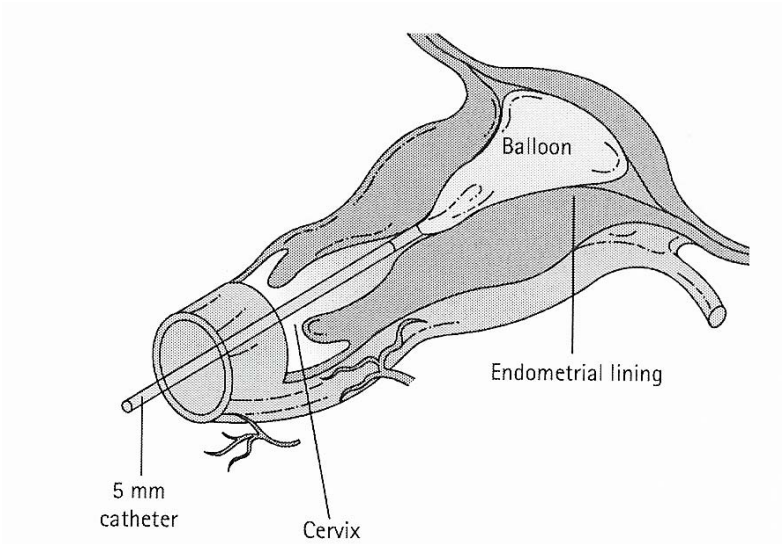
With the Thermachoice™ device, the cervix is dilated to about 5 mm. After insertion into the uterine cavity, the balloon is filled with sterile fluid (5% dextrose in water) and expands to fit the cavity. Intrauterine pressure is stabilised to 160-180 mmHg. The fluid is then heated to 87°C for 8 minutes. Newer versions of the balloon use a convection circulation approach to distribute heat more evenly and a silicone balloon. Pressure, temperature and time are continuously monitored and controlled by computer. Automatic shut-off is evoked if parameters are exceeded. Passive heat transfer causes cauterization of the endometrium. Non-steroidal anti-inflammatory drugs are given post-operatively. The treated lining sloughs off over the following week to ten days.

The process is similar for the Cavaterm device™, with some differences in detail. The cervix is dilated to about 6mm. After insertion, a silicone balloon is filled with sterile 5% glucose solution to a pressure of 230-240mmHg. The liquid is heated to a target temperature of 78°C for 10 minutes, during which time the fluid is circulated vigorously.

Endometrial thinning agents are not recommended. The endometrium may be pre-thinned by curettage immediately prior to the procedure. Non-steroidal anti-inflammatories given to reduce perioperative cramping.

Prognostic factors for the failure of thermal balloon ablation, based on a study of 130 women who underwent TBEA with Thermachoice™ in the Netherlands, are; younger age, retroverted uterus, pre-treatment endometrial thickness of at least 4mm and duration of menstruation.[66]

Figure 6: Thermal Balloon ablation



Modified from Gynecare™ (http://www..elsevier-international.com/e-books/pdf/431.pdf)

3.3.4 Adverse Effects with second generation EA devices

Include:

- Uterine Infection
- Perforation
- Visceral burn
- Bleeding
- Haematometra
- Laceration
- Intra-abdominal injury
- Cyclical pain

The differences between the second generation techniques considered in this assessment report are summarised below in Table 4 which shows the manufacturers' descriptions of contraindications for the Microsulis microwave device and the two types of thermal balloon, Cavaterm™ and Thermachoice™.

Table 4: Contraindications for the three second generation methods of endometrial ablation

Contraindication	Microwave	Cavaterm	Thermachoice
Uterine cavity size	> 14cm	> 10 cm	> 12cm
Pervious surgery or trauma leading to uterine wall thickness of at least 8 mm	✓	-	-
Previous Caesarean section as scar would be positioned in the operative field.	✓	-	-
Previous ablation/resection as this thins the uterine wall.	✓	-	-
Fibroids distorting the uterine cavity	✓	-	-
Repeat ablations should never be performed in conjunction with mechanical preparation.	✓	-	-
D&C should not be performed as preparation.	✓	-	-
Women who are pregnant or who wish to become so should not undergo MEA	✓	✓	✓
Active pelvic inflammatory infection	✓	✓	-
Undiagnosed vaginal bleeding	✓	✓	-
Known or suspected endometrial carcinoma	✓	✓	✓
Gross abnormalities such as myomas that prevent balloon lying uniformly on the endometrium.	-	✓	✓
Separate uterus (septum dividing the uterus in two) or other abnormalities /lesions that would result in inadequate balloon contact	-	✓	✓
Uterine wall weakness	-	✓	-
Cervical canal <6cm in length	-	✓	-

3.3.5 Use of local anaesthetic

Use of local anaesthetic (LA) is a stated advantage of second generation EA techniques, although this will not be suitable for all women. Ninety-eight women in the UK undergoing microwave ablation took part in a partially randomised trial of general and local anaesthetic.[67] Sixty-two women (63%) expressed a preference and were about equally divided between preferring general and preferring local anaesthetic. The remainder were randomised. The procedure was considered acceptable under general anaesthetic in both preferred (100%) and randomised (97%) groups. However, under LA, 97% of those who chose this method and 85% of those allocated to LA found the procedure acceptable. The trial authors suggest that LA should therefore be an option, rather than standard procedure. In addition, five (16%) of the 32 women choosing LA actually required general anaesthetic due to dilation difficulties (n=3), equipment failure (n=1) and in one case due to identifying a submucosal fibroid which required general anaesthetic for removal. The trial found that the operation time was not reduced in the randomised arms, but was in the preference groups (19 vs 25 minutes).[67].

If local anaesthetic is chosen, it has been suggested that danazol may be a preferable pre-operative endometrial thinning agent, as goserelin may increase cervical resistance.[67]

Summary

Chapter 3: Background

- *Heavy Menstrual Bleeding is a common complaint among women aged 30-49.*

- *Blood loss measurement may be direct or indirect, objective or subjective. Objective and subjective measures do not correlate well yet the clinical definition of HMB (>80ml blood loss) is not often used outside a research setting. Perceptions of HMB may be further influenced by other associated menstrual symptoms.*

- *The impact of menorrhagia is largely on quality of life, although anaemia may also occur. Measuring the impact of HMB has been attempted using a range of generic and disease specific measures. In addition, satisfaction with treatment has been regarded as an important outcome, although there are difficulties in interpreting its meaning.*

- *A number of medical and surgical treatment options are currently available. Surgical treatments include hysterectomy, which offers a permanent solution, but is major surgery and has associated morbidity and mortality, and more minimally invasive hysteroscopic surgical techniques such as resection and rollerball ablation which rely on considerable surgeon skill and also have associated morbidity and reported mortalities. This report assesses two newer ablation techniques which destroy the endometrial lining through microwave or thermal energy.*

4 METHODS

Methods for reviewing the effectiveness of microwave and thermal balloon endometrial ablation were specified *a priori* and are outlined in the research protocol (Appendix 3, page 117).

4.1 Research Questions

- What is the efficacy of microwave and thermal balloon ablation in the treatment of heavy menstrual bleeding?
- What is the cost effectiveness of microwave and thermal balloon ablation in the treatment of heavy menstrual bleeding?

4.2 Review Team and Advisory Group

The review was carried out by a review team comprising Dr Ken Stein, Ruth Garside, Dr Katrina Wyatt, Dr Ali Round and Alison Price

In addition, an external advisory group of clinical experts provided advice during the assessment and comments on an early draft. Details of this group appear in Appendix 2: Expert Advisory Panel (page 116).

4.3 General Methods

The methods of the review generally adhered to guidance laid out in the York CRD guidelines.

Interventions considered were thermal balloon and microwave methods of endometrial ablation for heavy menstrual bleeding.

First generation methods of endometrial ablation, TCRE, rollerball and combined methods are considered as comparators.

In order to provide a more complete picture of surgical management of heavy menstrual bleeding, information about hysterectomy compared to first generation methods has been examined using an existing systematic review of these treatments, updated with further literature search.

4.4 Assessment of Microwave and Thermal Balloon Ablation

4.4.1 Search Strategy

Electronic databases were searched for published studies, recently completed and ongoing research. Appendix 4 (page 123) shows the databases searched and the strategy in full. Bibliographies of articles were also searched for further relevant papers. Experts in the field and relevant industry bodies were also asked to provide information.

4.4.2 Inclusion and exclusion criteria

Systematic reviews, RCTs and controlled trials of microwave and thermal balloon endometrial ablation versus TCRE, rollerball or TCRE and rollerball combined were included.

Systematic reviews and RCTs of first generation EA techniques versus hysterectomy published after 1999 were included.

Studies were excluded if they were:

- Animal models
- Preclinical and biological studies
- Narrative reviews, editorials, opinions
- Non controlled studies
- Non English language papers
- Reports published as meeting abstracts only

Identification of studies was made in two stages, abstracts were examined independently for inclusion by two researchers (RG and KS). Disagreements were resolved by discussion. Then inclusion and exclusion of full text articles was made independently by two researchers (RG, KW) and disagreements were resolved in discussion with a third (KS).

4.4.3 Data extraction strategy

Data were extracted by one researcher (RG) and checked by another (KW). Actual numbers were extracted where possible and where necessary, analyses were repeated on an intention to treat basis from original data.

4.4.4 Quality assessment strategy

Relevant systematic reviews were assessed using the QUOROM checklist[68], which uses the following criteria:

1. The clinical question is made explicit.
2. The database and other information sources in detail and any restrictions.
3. Inclusion and exclusion criteria are specified.
4. The selection criteria, methods for validity assessment, data abstraction, study characteristics and quantitative data synthesis in sufficient detail to permit replication.
5. Characteristics of the included and excluded RCTs, details of study design, interventions and outcomes are reported. How clinical heterogeneity was assessed is reported.
6. Principal measures of effects, method of combining results, handling of missing data, how statistical heterogeneity is assessed. Rationale for (and *a priori*) sub-group analysis, and any assessment of publication bias are provided.
7. A profile summarizing trial flow through the systematic review is shown.
8. Descriptive data for each included trial are given.
9. Agreement on the selection and validity assessment is reported.
10. Simple summary statistics and data needed to calculate effect sizes and confidence intervals in intent to treat analyses are given.

Assessments of quality of RCTs were performed using quality indicators as shown below. Due to the nature of the intervention, the presence of blinding to treatment received was not considered an appropriate measure of quality, although concealment of allocation and blind assessment of outcomes remain valid as quality markers.

Internal validity

Trial characteristics:

1. Appropriate method of randomisation
2. Blind assessment of outcomes
3. Number of women randomised, excluded and lost to follow up.
4. Whether an intent to treat analysis is performed.
5. Whether a power calculation is done
6. Timing, duration and location of study.

External validity

Study participants:
1. Age and any other recorded characteristics of women in studies
2. Inclusion criteria
3. Exclusion criteria
4. Length of follow up

Generalisability was categorised as high, (detailed description of the exclusion criteria and patient group) medium (description of exclusion criteria and patient group) or low (no description of exclusion criteria or patient group.)

Interventions used:
1. Type of endometrial ablation technique and route of hysterectomy surgery
2. Endometrial thinning agents used.

4.4.5 Methods of analysis

There was considerable clinical and methodological heterogeneity among studies included in the review. Quantitative synthesis through meta-analysis was therefore not undertaken. Study results are tabulated and for outcomes where there are a multiple data points at the same follow up point and with similar methods of outcome measurement, these are illustrated using forest plots.

4.5 Economic evaluation

4.5.1 Cost Effectiveness Model

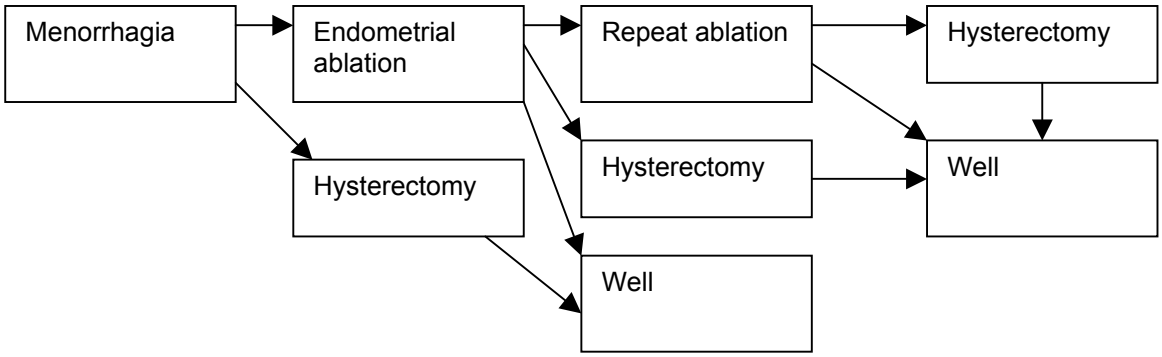
A state transition (Markov) model was developed by the authors using Microsoft Excel. The structure was informed by clinical input. The model examines the progress of five hypothetical cohorts of women with heavy menstrual bleeding who are treated separately by either thermal balloon, microwave, TCRE or rollerball endometrial ablation, or hysterectomy. The model takes the perspective of the NHS and calculates incremental cost utility between options.

Main assumptions

Structure of the Economic Model

The clinical pathway modelled is shown in the decision tree below (Figure 7)

Figure 7: Clinical Pathway Modelled

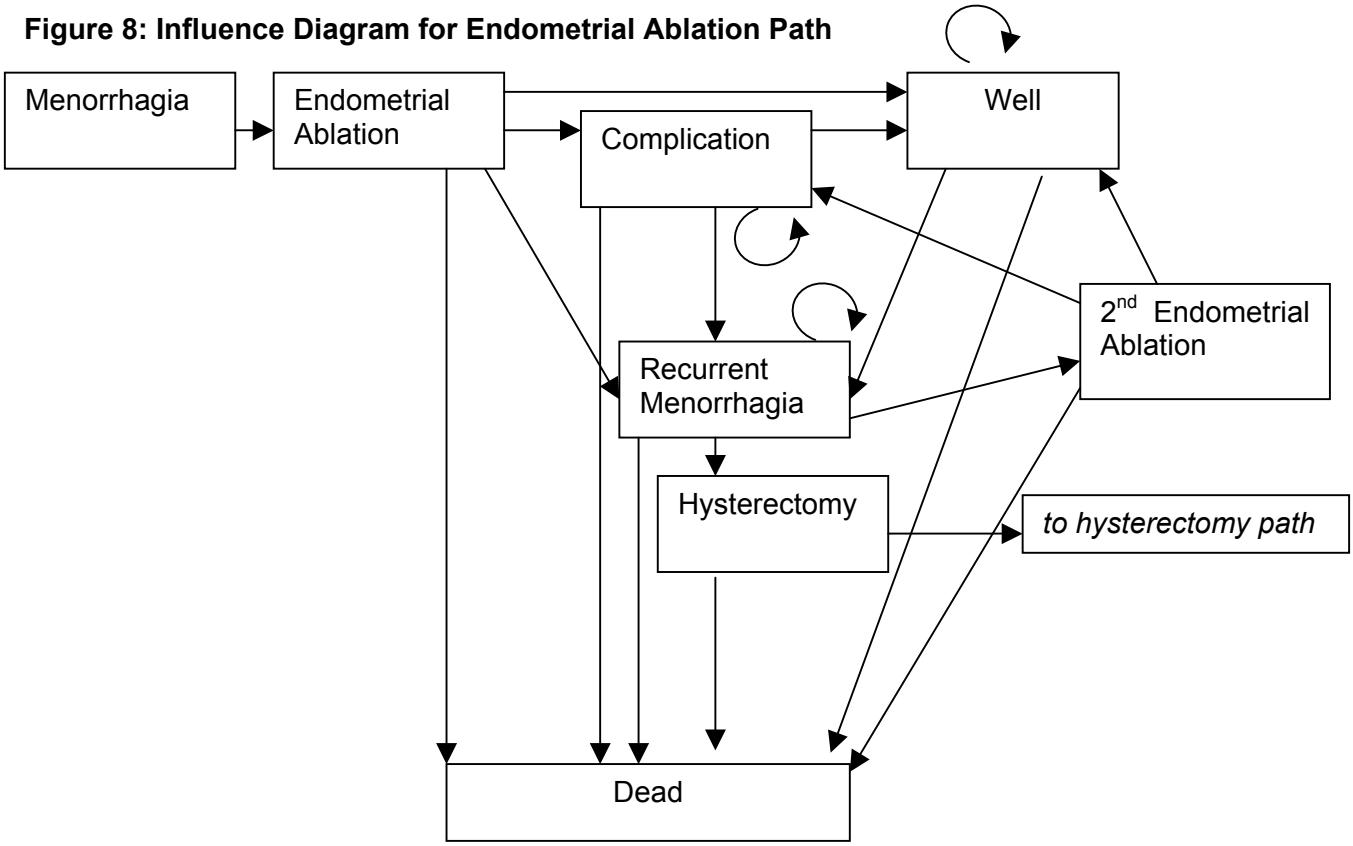


The structure of the model is shown in more detail in Figure 8 (pathway for patients undergoing any type of endometrial ablation) and Figure 9 (pathway for patients undergoing hysterectomy). Health states are shown in boxes and arrows show the transitions that can occur. For example, from hysterectomy, patients can either move to a state of convalescence (recovery from the operation in the absence of complications), have complications or die through direct or other causes.

The health states and pathways are the same for all types of endometrial ablation. The health states in the endometrial ablation model are:

- Menorrhagia – all patients in the cohort have pre-operative heavy menstrual bleeding.
- Endometrial ablation – the women undergo endometrial ablation by MEA, TBEA or resection.
- Complication – following EA, some women will experience complications in the perioperative or immediately post –operative period.
- Well – following EA or complication women are well.
- Recurrent menorrhagia – following EA, heavy menstrual bleeding may reoccur (treatment failure) at any time, including immediately post operatively. Women may stay in this state, or be re-treated, or have a hysterectomy.
- Repeat EA – if heavy menstrual bleeding recurs post-operatively, women may choose to have a second ablation. Only one repeat EA is permitted. Repeat ablations are by the same technique as the initial ablation.
- Hysterectomy – if heavy menstrual bleeding recurs after first ablation, women may choose to have hysterectomy. All those failing a second ablation will be treated by hysterectomy. These women then follow the pathway outlined in the hysterectomy diagram (Figure 9, page 40).
- Death – It is possible to die from causes other than EA during any health state. At hysterectomy and endometrial ablation, women may also die as a direct result of the surgical procedure.

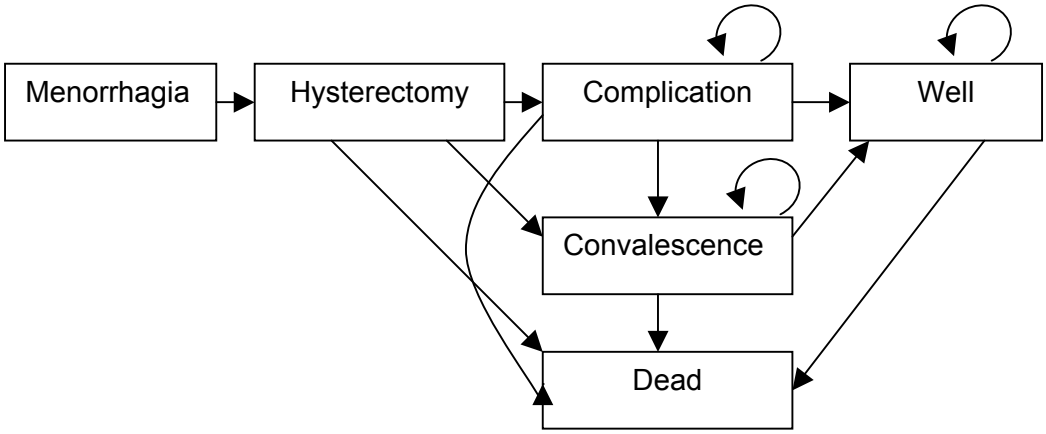
Figure 8: Influence Diagram for Endometrial Ablation Path



The health states in the hysterectomy model (shown in Figure 9) are:

- Menorrhagia – all women in the cohort have pre-operative heavy menstrual bleeding.
- Hysterectomy – all women undergo hysterectomy.
- Complication – following hysterectomy, some women will experience complications in the perioperative or immediately post-operative period. The effects of these may last for a median of one or two months.
- Convalescence – following hysterectomy both with and without complications, a period of convalescence is experienced.
- Well – following convalescence, women are well.
- Death – it is possible to die from causes other than hysterectomy from any health state. At hysterectomy, women may also die as a direct result of the surgical procedure.

Figure 9: Influence diagram for Hysterectomy path



A cohort of 1000 women eligible for each procedure are modelled for each operation. The starting age of women in the model is 42, based on the median age of women in the trials of endometrial ablation included in this review Table 5, page 51). The model runs for a total of 10 years. The model assumes that all women become menopausal after 10 years, at age 52 which is the average age of menopause in the UK.

Each cycle is one month long. In reality, complications following a second generation ablation may be experienced for less than one month.

The death rate from causes other than procedure is based on values for women in the Life Tables of England and Wales for the years 1998 to 2000 starting at age 42 and correspondingly increasing each year.[69]

Clinical Processes

Hysterectomy is assumed to be abdominal hysterectomy in the economic model as two-thirds of UK hysterectomies are by this route.[48]

Only peri-operative and complications immediately following procedure are modelled, subjects cannot enter the health state “complications” from any state except that of the operation.

After an unsuccessful endometrial ablation treatment, heavy menstrual bleeding can return at any time (treatment failure) including immediately after the procedure. Recurrent menorrhagia has been assumed to be mostly evident in the first three years. This was based on evidence in this assessment (Table 8 page 66 and Table 19 page 85). It was assumed that the total number of women with recurrent menorrhagia counted at each point of follow up would include both those reporting heavy menstrual bleeding and those who had undergone a previous repeat procedure.

If EA of any type fails, repeat ablation or hysterectomy is offered. The model assumes that ninety per cent of those with recurrent menorrhagia will have a repeat procedure, with 60% having repeat EA and 30% having a hysterectomy. This further procedure takes place within 6 months of menorrhagia returning. Only one repeat ablation is offered, if the treatment fails a second time, only hysterectomy is available. 90% of women with recurrence following repeat EA have a hysterectomy within 6 months.

There is no convalescence state after ablation as all women are assumed to have fully recovered within one month and this is the cycle length. Convalescence following ablation is therefore captured in the utility value for the EA health state.

Parameters included

The following parameters were included in the model:

- The proportion of women who have recurrent menorrhagia following EA.
- Death rates directly associated with each type of operation
- Complication rates associated with each procedure, and with repeat procedures
- The proportion of women with recurrent menorrhagia who receive repeat ablation or hysterectomy.
- Utility values associated with each health state shown in Figure 8 (page 39) and Figure 9 (page 40).
- Costs of each procedure (including cost of equipment, pre-operative endometrial thinning, time in theatre, proportion of women undergoing ablation who have general and local anaesthetic, time spent in hospital post-procedure).

Sources of Estimates

The initial search for this assessment was broad in scope. In populating the model, a hierarchy of evidence was used. Firstly, data from good quality systematic reviews of RCTs were sought (including data obtained as part this report's effectiveness assessment). If these were not available then data from good quality individual RCTs were sought. Where these were not available large prospective, observational studies conducted in the UK were used. Finally, if no published evidence could be found, the opinion of clinical experts was sought.

The exception to this hierarchy were data for peri-operative complications and death. The infrequency of these events means that the small RCTs provide imprecise estimates. Large national audits of hysterectomy and first generation endometrial ablation exist – the VALUE and the MISTLETOE studies (see Section 5.4.3, page 87). These were therefore used as they are likely to provide more accurate information about rare events. For complications following repeated ablation, data were taken from a prospective cohort study of 800 primary and 75 repeat ablations.[70] For second generation techniques large cohort studies investigating complication rates were used.[71;72]

Utility values for different health states fall between one (perfect health) and zero (dead). In this model, the state of being well is less than one as it encompasses general health values for women of this age. Health state utility values were taken from the literature and are shown in Table 24 (page 90). One published cost utility analysis of surgery for menorrhagia[30] describes utility values which were obtained from 60 women with menorrhagia using a set of scenarios describing health states relating to menorrhagia and its treatment, using the time trade off (TTO) technique. Menorrhagia and recurrent menorrhagia following a failed treatment have been assumed to have the same utility value.

The utility value of convalescence after hysterectomy is assumed to be one third less than the state of "well" following recovery following hysterectomy.

Resource Use and Costs

Aspects of care in the model

In order to calculate the costs of each of the procedures a range of health service costs have been obtained. A cost per procedure for each type of endometrial ablation technique and for hysterectomy has been calculated based on the details described below. Data for costs

were taken from the literature and from Southampton University Hospital costings unit. The cost of procedures include costs of endometrial thinning agents, anaesthetic, dedicated equipment, operating time and inpatient stay.

Pre-operative treatment

It is assumed that once referred to secondary care, all women with heavy menstrual bleeding will have the cause investigated. The RCOG recommends that women receive a transvaginal ultrasound (TVS) initially, in order to identify those who have an abnormal uterine cavity.[13] This should be followed up by hysteroscopy as required. Hysteroscopic examination may be carried out under either local or general anaesthetic. The majority of women have the latter. A biopsy is also undertaken to exclude endometrial carcinoma or hyperplasia and should be undertaken even where hysteroscopy or ultra sound suggests a normal uterus.[13] This may also be done as an outpatient, blind procedure, for example using the Pipelle sampler.

The economic model assumes that all women with HMB receive these investigations as routine care prior to being offered any treatment. These costs have not, therefore, been included in the model as they are not relevant to the marginal analysis.

All patients undergoing first generation ablations and MEA are assumed to receive four to five weeks pre-treatment with thinning agents: oral danazol (200mg daily) if undergoing local anaesthetic treatment or the LHRH analogue Zoladex if undergoing general anaesthetic.

Surgical Procedures

Details for average length of stay in hospital and waiting time for hysterectomy are taken from hospital episode statistics 2000-01 (Code Q07 – abdominal hysterectomy) for the UK. These data were used because they give average national figures and the surgery coding for hysterectomy contains only abdominal hysterectomies. Duration of surgery for hysterectomy is the mean time of surgery in minutes taken from a systematic review carried out in 1999.[52]

Details of resource use for 1st generation endometrial ablation were taken from a systematic review rather than routine NHS statistics which give costs at Healthcare Resource Group level.[9] The hospital episode statistics code for first generation endometrial ablation may also include a number of other procedures (at Southampton Hospital these include a variety of procedures such as polypectomy, diagnostic examination of the uterus, occlusion of Fallopian tubes) which may distort the actual costs of EA. Instead, the means from the systematic review were used.[52] Hospital episode statistics for 2000-2001 were used to obtain waiting times for surgery.[73]

It is assumed that all hysterectomies are undertaken with general anaesthetic. Data on the proportion of first generation EA procedures using local anaesthetic were taken from a systematic review[9] while those figures for second generation techniques are taken from a patient preference RCT of general (GA) and local anaesthetic (LA) for MEA. In this study of 98 women in Scotland, 63% had a preference about which type of anaesthetic they preferred of which 52% chose LA.[67] This has been assumed to be the proportion of women who would chose LA in the clinical setting.

Equipment Cost

There are two main types of thermal balloon ablation equipment used in the UK, Cavaterm™ and Thermachoice™ and one type of microwave equipment, made by Microsulis Medical Ltd. Equipment costs were based on details provided by the manufacturers of these devices. The costs of thermal balloon is the mean cost of the two devices.

Staff Costs

It is assumed that all hysterectomy and all first endometrial ablation techniques are undertaken by a consultant. Staff needed in the operating theatre for a general anaesthetic procedure are assumed to include a junior anaesthetist, a trolley nurse, instrument nurse and circulating nurse. Given the relative simplicity of second generation ablation techniques, the costs were also calculated assuming that a more junior surgeon (registrar) undertook the operation.

Discounting

Costs were discounted at 6% and benefits at 1.5%.

Analyses

An incremental analysis of costs and benefits was performed for each of the following comparisons:

- MEA vs TBEA
- MEA vs TCRE
- MEA vs TCRE and rollerball
- MEA vs rollerball
- MEA vs hysterectomy
- TBEA vs TCRE
- TBEA vs TCRE and rollerball
- TBEA vs rollerball
- TBEA vs hysterectomy

Dealing with uncertainty

To examine uncertainty within the model, one way sensitivity analyses were undertaken to establish which estimates have the greatest effect on the marginal cost utility for thermal balloon and microwave ablation. The sensitivity analysis focussed on:

- Complication rates
- Death rates due to the procedure
- Percentage of women with recurrent menorrhagia
- Percentage of women with recurrent menorrhagia who have repeat procedure and have hysterectomy.
- Percentage of women failing the ablation after repeat procedure
- Utility values for EA state, well and menorrhagia.
- Aspects of procedure costs including proportion of procedures done under anaesthetic, length of hospital stay etc.
- Duration of the model

4.4.2 Industry submissions

Three submissions from industry were provided to the National Institute for Clinical Excellence by manufacturers of thermal balloon and microwave ablation equipment. The submissions were used in a number of ways. Firstly, they were examined for additional information which met the inclusion criteria for the systematic review of effectiveness or the economic model. Secondly, the economic evaluations they provided were appraised using the frameworks proposed by Sculpher and colleagues[74] for decision analytic models and Drummond and colleagues.[75] for general cost-effectiveness analyses.

Finally, a brief comparison of the model constructed by the review team, and those supplied by industry was undertaken.

5 RESULTS

5.1 Systematic Review – Effectiveness

This section describes the studies identified through the search strategy, and those included in this assessment. The quality and main findings of systematic reviews and controlled trials are then described.

5.1.1 Studies identified

The search for controlled studies including microwave or thermal balloon endometrial ablation identified 215 abstracts. A total of 67 full text articles were acquired. (See Appendix 5: Excluded studies, page 126 for further details of excluded papers). Fourteen of these were possible controlled studies. A total of twelve trial reports relating to nine studies were identified as suitable for inclusion. Data from one study of TBEA vs TCRE has been removed from this version of the report as the trial was provided as confidential material.

The search to update the Cochrane review of first generation techniques and hysterectomy identified 80 additional abstracts, of which 13 full text articles were obtained none of which were ultimately included. See Appendix 5: Excluded studies (page on page 126) for details of inclusion and exclusion.

5.2 Included Systematic Reviews

Eight Cochrane reviews have examined treatments for heavy menstrual bleeding. Five review the evidence for various medical methods of controlling heavy menstrual bleeding: oral contraceptives,[76] cyclical progestogens,[77] danazol,[78] non-steroidal anti-inflammatory drugs[79] and antifibrinolytics.[80] One reviews the evidence for the progesterone releasing intra-uterine device.[81] One examines the use of pre-operative thinning agents before hysteroscopic surgery.[55]

Two reviews were included in the current evaluation, on endometrial destruction techniques for HMB[9] and TCRE and rollerball versus hysterectomy for HMB.[52]

5.2.1 Quality of included systematic reviews

See Appendix 6 (page126) for a summary of the QUOROM checklist used to assess quality.[68] Both reviews used a structured format. The clinical problems, and rationale for the interventions examined were outlined in the background sections and review objectives were described. Sources of data and additional sources of data were described, and details of study selection criteria (population, intervention, and study design) given. No restrictions on publication status, language or year of publication were listed.

In both reviews, methodological quality of included RCTs was assessed in relation to adequate concealment prior to randomisation, the presence of power calculation for sample size, intention to treat analysis and attrition rates.

In both reviews, data were extracted independently by two reviewers. Heterogeneity was examined by inspecting the scatter in data points on graphs and the overlap of the confidence intervals (CI), and by checking the results of statistical tests for heterogeneity.

Dichotomous data were pooled as Peto (fixed effect) odds ratios with 95% CI, apart from one outcome (use of local anaesthetic) in the review of endometrial destruction techniques[9] which used a random effects model. Continuous data were pooled using weighted mean difference with 95% CI. For a number of outcomes comparing pooled first generation and all second generation EA techniques in one review[9] the data presented in the graphs and those reported in the text were different. For one outcome (post operative amenorrhoea) the text data suggested that the difference between the techniques was significant while the data presented graphically did not.

Sensitivity analyses were planned *a priori* and performed in the review of EA versus hysterectomy[52]. It is stated that this did not change the direction of results although point estimates are not given. Sensitivity analyses were not planned *a priori* in the other review.[9]

Diagrammatic descriptions of the flow of trials through the inclusion and exclusion processes were not included in either review. Details of the study characteristics were tabulated in both reviews although no references to individual studies were given in the tables in one.[9] The level of agreement on selection and validity assessment were not reported in either review. Neither review discussed potential biases in the review.

5.3 Existing Systematic Reviews – Findings

Details of the data extracted from the existing systematic reviews are shown in Appendix 7: Included Systematic Reviews (page 131).

5.3.1 Systematic review of hysterectomy versus first generation EA techniques

Five RCTs were included in the review, including a total of 752 participants. Follow up was between one and four years (median two years).

The Cochrane review of hysterectomy versus first generation endometrial ablation techniques[52] found that there was a significant advantage in improved HMB and satisfaction rates up to 2 years, but not beyond (OR=0.31, 95% CI =0.16, 0.59) for women undergoing hysterectomy. However, duration of surgery, hospital stay and time to return to work were all shorter following EA (WMD = 23.1 minutes, 95% CI 23.8, 22.3; WMD 4.0 days 95% CI 4.9, 4.8); WMD 4.6 weeks, 95%CI 4.8, 4.4 respectively). Most adverse effects, both major and minor, were more likely with hysterectomy – sepsis, blood transfusion, urinary retention, anaemia, pyrexia, haematoma, and hypergranulation tissue. Only fluid overload was more likely with first generation endometrial ablation. Other adverse effects showed no difference between the groups.

The reviewers concluded that first generation EA techniques offer an alternative to hysterectomy for HMB and that effectiveness and satisfaction rates for both procedures were high. The higher rate of complications and longer recovery period for hysterectomy were off-set by permanent relief from symptoms. Costs were lower for EA but due to re-treatment in the EA group, the difference narrows over time with EA costing between 5% and 11% less than hysterectomy at four years.

5.3.2 Systematic review of endometrial destruction techniques

The Cochrane review of endometrial destruction techniques[9] identified two RCTs[82;83] of thermal balloon ablation (TBEA) versus rollerball. Three papers were published on one of these studies at 12,[82] 24,[84] and 36 months[85] follow up. One paper, relating to a study comparing MEA with combined TCRE and rollerball was also included.[86] In addition, six further RCTs were included. Three trials compared first generation methods, and two compared other second generation techniques (vesta system, heated saline HTA) with first generation techniques.

The studies contained a total of 1,595 participants and follow up was between 6 and 15 months (median 12 months).

For TBEA some anomalies were found; amenorrhoea was more likely in the rollerball group at 12 and 36 months (OR = 0.55, 95% CI 0.31, 0.99 and OR=0.5, 95% CI 0.25, 0.97, respectively) but not at 24 months. Likewise, while additional surgery was significantly more likely in the rollerball group at 24 months (OR 0.35, 95% CI 0.12, 0.99) this was not seen at 12 or 36 months. Other outcomes were not found to be significantly different.

For MEA, most outcomes were not significantly different from the TCRE group. Odds of haemorrhage were lower in the MEA group (OR=0.14, 95% CI 0.02, 0.8), whilst equipment failure was more likely (OR=4.07, 95% CI 1.1, 15).

The review concluded that, overall, second generation techniques had similar success rates and were significantly quicker to perform (WMD 11 minutes, 95% CI –18.6 to –2.6) than first generation techniques and were significantly more likely to be performed under local anaesthetic (OR 7.6, 95% CI 1.1, 52.7) However equipment failure was more likely in second generation techniques (OR 4.1, 95% CI 1.1, 15.0)

However, as noted above, there are differences in the text and graph figures for some of the findings. Attempts to contact the author to clarify these data were unsuccessful.

The study concluded that second generation techniques compare favourably with first generation techniques but that equipment problems needed to be resolved.

As the systematic review included only RCTs, did not include an economic assessment and had undertaken the primary search in 2001, we performed a new search for this assessment as outlined in Appendix 4 (page 123). The results are described in Section 5.4 below.

5.4 Controlled trials of second generation EA techniques

A total of twelve publications were found using the search strategy shown in Appendix 4 (page 123). Three were of microwave endometrial ablation (MEA)[86-88] and nine were of thermal balloon endometrial ablation (TBEA)[82-85;89-93]. However, two of the MEA papers report on the same trial at 12 (Cooper and colleagues) [86] and 24 (Bain and colleagues)[87] months of follow up. In this report, these papers will be referred to by the first and main trial publication, Cooper and colleagues (1999).[86] Four of the TBEA papers report the same trial at 12 months (Meyer and colleagues), [82] 24 months (Graigner and colleagues)[84] and 36 months (Loffer, 2001)[85] and 60 months (Loffer and colleagues, 2002)[93] of follow up. In addition, an erratum page appeared for the paper by Loffer which corrected the labelling of figures in the original and added a chart which had been omitted from the original publication.[94] These will be referred to in this report by the first, main publication, Meyer and colleagues (1998).[82]

Of the included trials, three were provided by industry. Wallsten Medical, the makers of Cavaterm™ provided a translation of a small RCT of TBEA versus rollerball ablation which had been published in German[83] and confidential, unpublished trial details of an RCT of TBEA versus TCRE. Details of this second study have been removed from the public version of this assessment. Microsulis Medical Ltd., the manufacturers of MEA equipment, provided details of an RCT they conducted as part of their submission to the USA's Food and Drug Administration (FDA) approval process.[88]

In summary, two MEA and seven TBEA trials have been included in the review although data has been taken from all published accounts of these trials. Details of these studies are described below and summarised in Table 5, p. 51, with summary details in Appendix 8: Included Controlled Study Details (page 137.)

Most of the included studies are RCTs. One is a non-randomised, controlled trial. This study, by Gervaise and colleagues[89] (TBEA vs TCRE) obtained patient, surgical and outcome details from the hospital notes of those undergoing TCRE at their institution during the same time period as women were undergoing TBEA.

Publication date / country and sample size

The studies were published between 1996 and 2002 with recruitment between 1994 and 2001. The TBEA vs rollerball (RB) studies by Romer and Zon-Rabelink did not state the dates of recruitment.[83;92] The number of women randomised in each trial ranged from 20 to 322 (median 121). A total of 1,409 women were randomised across all trials of second generation EA techniques.

The MEA vs TCRE/RB study by Cooper and colleagues was based at a single centre in the UK while the Microsulis study (MEA vs RB) recruited women from eight sites in the UK and the USA. The TBEA vs TCRE study by Gervaise and colleagues was recruited from a single centre in France[89]. Pellicano and colleagues (TBEA vs TCRE/RB)[91] used a single centre in Italy. Soysal and colleagues (TBEA vs RB) recruited women from a single centre in Turkey.[90] The study by Meyer and colleagues[82] (TBEA vs RB) recruited women from multiple centres in the USA and Canada. The Zon-Rabelink study (TBEA vs RB) is from the Netherlands but the number of centres involved is not stated.

Indications for surgery

The indication for surgery was variously described as dysfunctional menstrual bleeding,[86] menorrhagia,[82;85;92] excessive menstrual bleeding,[84] recurrent therapy refractory menorrhagia[83], menorrhagia unresponsive to medical treatment,[91] abnormal uterine bleeding[88] and abnormal menstrual bleeding.[89] Methods of measuring bleeding also varied. The MEA vs TCRE/RB study by Cooper and colleagues [86] included women who self-defined their menstrual loss as heavy. Meyer and colleagues[82] (TBEA vs RB) and Soysal and colleagues[90] (TBEA vs RB) used a PBAC score of at least 150. The Microsulis study (MEA vs RB) and the Zon-Rabelink study (TBEA vs RB) defined heavy menstrual bleeding as more than a score of 185 or more.[88;92] Gervaise and colleagues (TBEA vs TCRE)[89] quantified heavy menstrual bleeding through the number of pads used per cycle. No description of how heavy menstrual bleeding was measured is given by Romer[83] (TBEA vs RB) or Pellicano and colleagues[91] (TBEA vs TCRE/RB).

Participant characteristics

The median average age of the women included in the studies was 42.6 years (range 40.2 to 46.3) for the intervention arms and 43.2 (range 40 to 47.4) in the control arms. The

Microsulis study[88] (MEA vs RB) and that by Zon-Rabelink[92] (TBEA vs RB) did not report the ages of participants.

Fibroids greater than 2cm were reported in 12% of the women in the MEA trial by Cooper and colleagues[86] (MEA vs TCRE/RB). Fibroids less than 3cm diameter were reported in 22% of women in the Microsulis study of MEA.[88] (MEA vs RB).

All women in the study by Soysal and colleagues[90] (TBEA vs RB) had fibroids of less than 5cm diameter. Meyer and colleagues[82] (TBEA vs RB), Gervaise and colleagues[89] (TBEA vs TCRE), Romer[83] (TBEA vs RB) and Pellicano and colleagues[91] (TBEA vs TCRE/RB) excluded women with submucous fibroids from their study. Zon-Rabelink[92] (TBEA vs RB) did not state whether or not women with fibroids were included.

Only Gervaise and colleagues[89] (TBEA vs TCRE) included women who were post-menopausal, 7% of those receiving TBEA and 27% of those receiving TCRE were post-menopausal and unwilling to discontinue HRT. The study by Cooper[86] (MEA vs TCRE/RB) and the study by Meyer and colleagues[82] (TBEA vs RB) explicitly excluded menopausal women. Soysal and colleagues[90] (TBEA vs RB), Romer[83] (TBEA vs RB), Pellicano and colleagues[91] (TBEA vs TCRE/RB), Zon-Rabelink[92] (TBEA vs RB) and the Microsulis study[88] (MEA vs RB) did not specifically exclude menopausal women.

Details of surgery

The Microsulis study[88] (MEA), Meyer and colleagues[82] (TBEA), Romer[83] (TBEA) and Zon-Rabelink[92] (TBEA) used rollerball ablation (RB) as the comparator while the studies by Gervaise and colleagues (TBEA), and Soysal and colleagues (TBEA) used TCRE as the control technique.[89;90] The control surgery for the trial by Cooper and colleagues[86] (MEA) and Pellicano and colleagues[91] (TBEA) was combined TCRE and rollerball (TCRE/RB).

Cooper and colleagues (MEA vs TCRE/RB) pre-treated the endometrium with 3.6mg of subcutaneous goserelin five weeks before surgery.[86] In the Microsulis trial (MEA vs RB), a GnRH injection (leuprolide acetate) was given 3-5 weeks before surgery.[88]

Soysal and colleagues (TBEA vs RB) and Romer (TBEA vs RB) used 2 monthly injections of a GnRH prior to surgery.[83;90] Zon-Rabelink[92] (TBEA vs RB) used Zoladex six and two weeks prior to surgery as pre-thinning in both groups. Meyer and colleagues (TBEA vs RB) used a timed three minute curettage as pre-treatment.[82] Gervaise and colleagues (TBEA vs TCRE) did not use pre-treatment.[89] Pellicano and colleagues[91] (TBEA vs TCRE/RB) did not use pre-treatment in the TBEA group but pre-treated those in the control group with GnRH six and two weeks prior to surgery.

In three trials (Cooper and colleagues – MEA vs TCRE/RB, Gervaise and colleagues –TBEA vs TCRE and Romer – TBEA vs RB), general anaesthetic was used for all women in both treatment and control groups.[83;86;89] Meyer and colleagues (TBEA vs RB) used local anaesthetic in 16% of women undergoing rollerball ablation and 47% of women undergoing TBEA.[82] In the other TBEA trials, local anaesthetic was used in 38%[89], 47%[82] and 100%[90] of women undergoing TBEA. In the Microsulis trial (MEA vs RB), 37% of those undergoing MEA and 76% of those undergoing rollerball ablation had a general anaesthetic with the remainder having local or regional anaesthetic.[88] All women undergoing both TBEA and TCRE in the trial by Pellicano and others had a spinal anaesthetic. Zon-Rabelink[92] (TBEA vs RB) did not report the type of anaesthetic used.

Most reports state that the surgeons performing the first generation techniques were experienced, and that all were trained in second generation methods. In the trial by Cooper and colleagues[86] (MEA vs TCRE/RB) trained senior registrars performed the majority of the

operations in both treatment and control arms. Details of surgeon experience are not given in the Microsulis (MEA vs RB), Romer (TBEA vs RB), Gervaise (TBEA vs TCRE) or Zon-Rabelink (TBEA vs RB) studies.[83;88;89;92]

Table 5: Characteristics of trials reported in all included papers and treatment

Author/ Date/ Design	No. pts	Average age (years)	Women with Fibroids excluded?	Intervention	Control treat-ment	Pre-treatment	Surgeon experience	Anaesthetic	Length of Follow up (months)
Cooper et al 1999 RCT	263	MEA 41.1 (SD 6.7) TCRE/RB 42.0 (SD 8.4)	No	Microwave	TCRE / RB	3.6mg goserelin 5 weeks prior	At least 50 prior TCREs, at least 5 prior MEAs	100% GA	12
Bain et al 2002 RCT	263	MEA 41.4 (SD 5.4) TCRE/RB 42.2 (SD5.8)	No	Microwave	TCRE / RB	3.6mg goserelin 5 weeks prior	At least 50 prior TCREs, at least 5 prior MEAs	GA	24
Microsulis 2002 RCT	322	Not stated	No	Microwave	RB	Leuprolide acetate depot 3-5 weeks prior	Not stated	GA: MEA 37% RB 76%	12
Meyer et al 1998 RCT	275	TBEA 40.2 (SD 4.9) 30-51 RB 40.9 (SD 5.2) 29-50	Yes	Thermachoice™ thermal balloon	RB	None stated	All had extensive experience of rollerball .	GA: TBEA 53% RB 84%	12
Grainger et al 2000 RCT	255	Not stated	Yes	Thermachoice™ thermal balloon	RB	3 minute curettage using 5mm curette prior to ablation	All experienced in rollerball and trained in TBEA	Not stated	24
Loffer 2001 RCT	255	Not stated	Yes	Thermachoice™ thermal balloon	RB	Timed 3 minute suction curettage given to all prior to ablation	All experienced in rollerball and trained in TBEA	Local, local with sedation and general. More GA with RB	36
Loffer et al 2002 RCT	255	TBEA 40.4 RB 40.9	Yes	Thermachoice™ thermal balloon	RB	3 minute suction curettage	All experienced in rollerball and trained in TBEA	Not stated	60
Gervaise 1999 Non-random CT	147	TBEA 46.3 (+/- 1.4 34-66 TCRE 47.4 (+/- 0.2) 34-65	Yes	Thermachoice™ balloon	TCRE	None	Not stated	General TCRE General and local (38%) for TBEA	18

Author/ Date/ Design	No. pts	Average age (years)	Women with Fibroids excluded?	Intervention	Control treatment	Surgery pre-treatment	Surgeon experience	Anaesthetic	Length of Follow up (months)
Pellicano 2002 RCT	96	TBEA 42.6 (+-4.4) TCRE/RB: 43.2 (+-3.5)	Submucous	Cavaterm™ balloon	TCRE/ RB	Treatment group none Control group GnRH 6 and 2 weeks prior to surgery.	Surgeons "proficient" in TCRE.	Spinal anaesthesia	24
Romer 1998 RCT	20	TBEA 42 (37-52) RB 40 (37-50)	Yes	Cavaterm™ balloon	RB	2x monthly injections of GnRH (leuprolide 3.75mg) operation 2 weeks after injection.	Not stated	All GA	9-15 months
Soysal et al 2001 RCT	96	TBEA 43.6 (+/-2.5,40-49) RB 44.3 (+/-2.6,40-49)	No – all pts had fibroids	Thermachoice™ balloon	RB	2x monthly injections of GnRH analogue (3.6mg goserelin acetate)	One experienced surgeon performed all rollerball, TBEA by staff surgeons supervised by residents	All RB GA, all TBEA local.	12
Zon-Rabelink 2001 RCT	139	Not stated	Not stated	Thermachoice™ balloon	RB	Pre-treatment with Zoladex 6 and 2 weeks prior to surgery.	Not stated	Not stated	24

Key

RB = Rollerball
TCRE = Trans cervical Resection
TBEA = Thermal Balloon Endometrial Ablation
MEA = Microwave Endometrial Ablation
GA = General Anaesthetic

5.4.1 Quality Assessment of RCTs

The quality of the reports of RCTs is summarised in Table 6 (page 57).

Internal validity

Sample size

The eight studies included 20,[83] 96,[90] 96,[91] 139,[92] 147,[89] 263,[86], 275[82] and 322[88] women. Sample size calculations were performed in three of the randomised trials.[82;86] Sample size calculations were not reported by Microsulis[88] (MEA vs RB), Pellicano and colleagues[91] (TBEA vs TCRE/RB) Soysal and colleagues[90] (TBEA vs RB), Gervaise and colleagues[89] (TBEA vs TCRE), Romer[83] (TBEA vs RB) or Zon-Rabelink[92] (TBEA vs RB).

The trial by Cooper and colleagues[86] (MEA vs TCRE/RB) is based on an 80% power to detect a 15% difference in satisfaction (p=0.05) based on 78% women satisfied with TCRE. Actual levels of total or general satisfaction were 77% in the MEA group and 75% in the TCRE and rollerball group at 12 months (significant difference not found). A patient questionnaire was used to measure this outcome.

In the trial by Meyer and colleagues[82] (TBEA vs RB), sample size was calculated based on 90% power to detect 20% less effectiveness in the treatment group (p=0.05) based on 85% response rate for rollerball. "Effectiveness" is not defined. However, 86% of women undergoing TBEA and 87% of women undergoing rollerball ablation were reported as "very satisfied" with treatment and there was no significant difference in the two groups in the percentage of women who had a 90% reduction in PBAC scores (62% with TBEA vs. 68% with rollerball).

Selection bias

Allocation to intervention or control arm in the MEA trial by Cooper and colleagues[86] (MEA vs TCRE/RB) was random and treatment allocation was concealed. Women were randomised through a telephone call to a secretary who opened a series of sealed opaque sequentially numbered envelops showing a treatment code. The sequence was predetermined by computer generated random number blocks of 20. Allocation to study arm in the Meyer and colleagues trial[82] (TBEA vs RB) was random, but there was no account of steps taken to conceal allocation. Soysal and colleagues[90] (TBEA vs RB) used computer generated randomisation and opaque, sealed envelopes for allocation concealment. Pellicano and colleagues[91] (TBEA vs TCRE/RB) also used a computer generated random number sequence but do not report on allocation concealment. Patient characteristics in the two arms of each of these studies appear similar. Zon-Rabelink[92] (TBEA vs RB) states that women were first stratified by age (over or under 45) and parity (nulliparous or parous women) and then randomised with allocation via blind envelopes.

The Gervaise study[89] (TBEA vs TCRE) was not randomised. Women in the intervention arm were consecutive patients receiving TBEA during the study period. Controls, who received TCRE, were matched retrospectively from the records of women receiving TCRE during the same time period. Inclusion and exclusion criteria were applied. There were significant differences at baseline between the two groups, with the TCRE groups having lower parity (1.9 vs 2.4) and containing more women who were post menopausal (27% vs 7%) than the TBEA group, although the number of pads used per cycle was similar. Higher parity is associated with increased HMB (see Section 3.1.2, page 17.)

The Microsulis trial[88] (MEA vs RB) and the study by Romer[83] (TBEA vs RB) do not report on randomisation, allocation or blinding methods. The patient groups reported by Romer[83] seem to have similar characteristics.

Performance bias

TCRE and rollerball ablation are skilled operations which, like most surgical procedures, are difficult to standardise. The RCTs vary in the extent to which standardization of procedures are reported.

All TCRE/rollerball ablations were undertaken by two experienced, senior specialist registrars in the MEA trial by Cooper and colleagues[86] (MEA vs TCRE/RB) who used a combined TCRE and electrocoagulation technique, ablating the fundus and cornual regions with a rollerball. Glycine (1.5%) was used as the distension medium. A 90^{o} loop 7mm in diameter and 3mm deep was used for TCRE.

No details of surgeon experience are given in the Microsulis trial[88] (MEA vs RB) and as this is an eight centre trial, differences in technique and experience are possible. Indeed, one study centre performed all operations under general anaesthetic. Analysis by centre showed that at one centre only, patients treated with MEA were significantly more likely to have amenorrhoea at 12 months than those treated by rollerball (p=0.007). It is possible that this is related to inexperience with the rollerball technique. No significant differences in amenorrhoea were shown at the other seven centres.

In the trial by Meyer and colleagues[82] (TBEA vs RB) it is stated that all surgeons had extensive experience of rollerball ablation. However, this was a 14 centre trial so variation in technique and experience is possible, although all are described as “skilled”. Either 1.5% glycine or 3% sorbitol was used as distension fluid and the specifics of surgery and equipment depended on surgeons’ preference.

Neither the number of surgeons performing TCRE nor surgeon experience is mentioned in the non-randomised study by Gervaise and colleagues[89] (TBEA vs TCRE).

Pellicano and colleagues[91] (TBEA vs TCRE/RB) reports that all surgeons were “proficient” at combined TCRE and rollerball ablation. 2.7% sorbitol and 0.54% mannitol was used as distension solution.

Romer[83] (TBEA vs RB) and Zon-Rabelink[92] (TBEA vs RB) do not report on the extent of surgeon experience or the operating procedure.

One experienced surgeon performed all the rollerball ablations in Soysal and colleagues[90] (TBEA vs RB). Glycine was the distension medium and a 3mm rollerball electrode was used for coagulation. Staff surgeons performed the TBEAs under the supervision of residents.

Detection bias

It is not possible to blind patients or surgeons to which procedure was being undertaken. While it would be possible to blind those who are assessing outcomes or carrying out analyses, none of the studies report this.

Attrition bias

At 24 months follow up, the trial by Cooper and colleagues[87] (MEA vs TCRE/RB) reported that 14 patients (5%) were lost to follow up, nine (7%) in the MEA arm and five (4%) in the TCRE and rollerball arm. This is fewer than were reported as lost to follow up at 12 months;

23 (9%) overall, 13 (10%) in the MEA arm and 10 (7%) in the TCRE and rollerball arm. Follow up was by postal questionnaire, but at 24 months those who had not returned their questionnaire were contacted by telephone to request its return or to be interviewed by phone where necessary. It is stated that ITT analysis is undertaken but some analyses are carried out only on treatment completers followed up.

Microsulis (MEA vs RB) reports that 7% of women were lost to follow up at 12 months, 13 women (6%) in the MEA arm and 9 (8%) in the rollerball arm. All analyses are reported on an ITT basis.

In the trial by Meyer and colleagues[82] (TBEA vs RB), 275 patients were randomised but 15 electively withdrew before the procedure was performed. A further four were discovered to be ineligible whilst one had a uterine perforation and was not treated under protocol. These numbers are not reported consistently and are given as 11 withdrew, eight ineligible and one perforation in the paper of three year results.[85] 255 women were therefore treated under protocol and these are referred to most often in all the papers as the original sample. However, only the details of 245 women that were available at six months are reported on in the 12 month paper[82] although it is stated that there were no significant differences between these and the original sample. Intent to treat analysis is not performed. Numbers of the original 275 women allocated to treatment and control arms is only reported in the three-year follow up paper. 46% of the recruited participants were lost to follow up by 60 months. This includes women from two centres that did not provide 5-year follow up data. Furthermore, in the 5-year paper[93] patient who have undergone repeat surgery are excluded from calculations of bleeding and pain outcomes.

Gervaise and colleagues[89] (TBEA vs TCRE) reported no loss to follow up at 18 months. However, details of the women in the TCRE group were obtained from records retrospectively which introduces the potential for bias (direction unknown), as they have been selected on the basis that follow up information was available.

Pellicano and colleagues[91] (TBEA vs RB) had 29% loss to follow up at 2 years.

Romer[83] (TBEA vs RB) had no loss to follow up of the original 20 women at 12 months.

The study by Soysal and colleagues[90] (TBEA vs RB) lost three patients from the TBEA groups prior to the procedure being performed, but reported no other loss to follow up at 12 months. These three patients were excluded from analysis.

Two patients were excluded after randomisation by Zon-Rabelink[92] (TBEA vs RB). Both had been allocated to the rollerball group. One was discovered to have polyps at the time of operative hysteroscopy, while one was discovered to have a PBAC score of less than 185. Both of these women were excluded from analysis. One further women, also in the rollerball group, was lost to follow up by 24 months. It is unclear whether or not she was included in the analysis as all data are reported as percentages, not numbers.

External Validity

The generalisability of most of the included studies was rated as high (see Section 4.4.4, page 38 for the classification of generalisability). All studies except the Microsulis study[88] (MEA s RB), and Zon-Rabelink[92] (TBEA vs RB) gave details about the patient characteristics and inclusion and exclusion criteria. In the case of studies with multiple papers (Meyer and colleagues[82] and Cooper and colleagues[86]), good descriptions of patient characteristics and inclusion criteria were provided in at least one of the study reports. The study by Gervaise and colleagues[89] (TBEA vs TCRE) included women who were post-menopausal but unwilling to discontinue HRT. The results of surgery for these women were not reported

separately. Microsulis[88] (MEA vs RB) provides information about the subgroup of women with fibroids separately for some outcomes.

The failure rate for ablation techniques, as measured through repeat ablation or hysterectomy, is time dependent. Longer follow up is likely to lead to increased failure rate due to endometrial regeneration. However, with increasing time, more women will become peri-menopausal or menopausal. Peri-menopause may increase symptoms of heavy menstrual bleeding, whilst post-menopausal women will no longer menstruate. Shorter study follow up among younger women may under-estimate the costs and disbenefits of endometrial ablation. One trial had five year follow up,[82] three had two year follow up,[86;91;92] one had 18 months follow up,[89] three had 12 months follow up[83;88;90] and one had 3 months follow up. Romer[83] (TBEA vs RB) followed patients up for 9 to 15 months.

Table 6: Methodological characteristics of included controlled trials

Author/ Date	No. of pts	Adequate allocation to groups	Blinding	Comparability of groups	Same interven-tion to all pts?	% loss to follow up	Sample size calc.	ITT	General-isability	Main outcome measured indepen-dently	Inter-centre variability	Conflicts of interest
Cooper et al 1999	263	Yes	Yes	Yes	Yes	12 months 9% 24 months 5%	Yes	Stated that it is, but some data points appear to use different denominators – missing data?	High	Yes	Not applicable	Yes
Microsulis 2002	322	Uncertain	Uncertain	Uncertain	Uncertain	7%	Un-certain	Yes	Low	Yes	Yes	Yes
Meyer et al 1998	275	Yes	Uncertain	Yes	Yes	12 months 11% 24 months 17% 36 months 22% 60 months 46%	Yes	No. pts lost between randomisation and treatment are excluded, in addition some data points appear to use different denominators – missing data?	High	Yes for bleeding – uncertain for satisfaction	None found	Yes
Gervaise 1999	147	No	No	No – 27% of women given TCRE and 7% given TBEA were post-menopausal.	Yes	None	No	N/A	Medium	Uncertain	N/A	None

Author/ Date	No. of pts	Adequate allocation to groups	Blinding	Comparability of groups	Same interven-tion to all pts?	% loss to follow up	Sample size calc.	ITT	General-isability	Main outcome measured indepen-dently	Inter-centre variability	Conflicts of interest
Pellicano 2002	96	Yes	Uncertain	Yes	Yes	29% at 2 yrs	No	No	High	Yes		
Romer 1998	20	Uncertain	Uncertain	Yes	Yes	None	Un-certain	N/A	Low	Uncertain	N/A	None
Soysal et al 2001	96	Yes	Uncertain	Yes	Yes	None	No	3 pts allocated to TBEA did not receive treatment and were excluded – no other LTFU	High	Yes	No	None
Zon-Rabelink 2001	139	Yes	Yes	Uncertain	Yes	2% at 2 yrs	No	No	Low	Yes	Not stated	None

5.4.2 Assessment of effectiveness

Reporting of outcomes

Outcome percentages recorded in the following tables are given as reported in the trials and also have been re-calculated on an intent to treat (ITT) basis where necessary. ITT figures are given in parenthesis.

A wide range of outcomes of surgery were reported across the studies and these are shown in Table 7 to Table 19 below. Broadly, the outcomes can be grouped into the following categories:

- Bleeding outcomes
- Pre-menstrual symptoms (PMS) related outcomes
- Dysmenorrhoea
- Anaemia/haemoglobin outcomes
- Satisfaction
- Quality of life
- Operation details
- Further surgery
- Adverse effects (Perioperative and post-operative).

The way in which outcomes were reported differs between studies. For example, some bleeding outcomes use mean Pictorial Blood Loss Assessment Chart (PBAC) scores, or changes in these, whilst others report the numbers of women with various bleeding patterns. This means that it is not always possible to compare results across studies, or to combine them for meta-analysis.

Bleeding patterns

Amenorrhoea, the absence of menses, is reported by six of the included studies, and has a consistent definition. Table 7 shows the rates of post operative amenorrhoea. Amenorrhoea at 12 months was reported for a median of 45% of women undergoing MEA (range 36-40%) and a median of 14% (range 10-40%) for TBEA. At 12 months, a median of 30% of women undergoing TCRE or rollerball had amenorrhoea (range 17-46%). The lowest percentage (10%) is found in the TBEA arm of the trial containing women who all had fibroids.[90]

Amenorrhoea at 24 months was experienced by 44% of women undergoing MEA, a median of 17% (13-22%) of those undergoing TBEA and by a median of 24% (range 21-40%) of women undergoing TCRE or rollerball. Only Meyer and colleagues report on longer term follow up. At 36 months, 13% of women undergoing TBEA and 21% of women undergoing rollerball had amenorrhoea and at 60 months 10% of women undergoing TBEA and 14% of those undergoing rollerball were amenorrhagic.

Pellicano and colleagues[91] (TBEA vs TCRE/RB) and Zon-Rabelink[92] (TBEA vs RB) do not report amenorrhoea.

At 12 months, Meyer et al[82] (TBEA vs RB) reported a statistically significant difference between TBEA (14%) and rollerball (22%) groups ($p<0.05$).

Figure 10 illustrates the findings for amenorrhoea at 12 months for first generation versus second generation endometrial ablation techniques and Figure 11 shows those at 24 months. The size of the data points indicates the relative size of each study. In most cases

the confidence intervals cross the central line indicating that differences were not statistically significant. The significant difference detected by Meyer and colleagues at 12 months (TBEA vs RB) is not seen in the forest plot because the data have been re-calculated here on an intent to treat basis whilst the original study analysis excluded women lost to follow up.

At 24 months, only the Gervaise study[89] (TBEA vs TCRE) indicates a more favourable outcome for TBEA. The study results have not been statistically combined due to clinical heterogeneity between the trials.

Table 7: Post operative amenorrhoea - % (ITT%)

	Immediate post/op		12 months		24 months		36 months		60 months	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
MEA Cooper et al 1999	-	-	40 (36)	40 (36)	-	-	47 (44)	41 (40)	-	-
MEA Microsulis 2002	-	-	55 (55)	46 (46)	-	-	-	-	-	-
TBEA Meyer et al 1998	-	-	15 (14)	27 (22)	15 (13)	26 (21)	15 (13)	26 (21)	23 (10)	33(14)
TBEA Gervaise et al 1999	25 (25)	38 (38)	-	-	-	-	36 (22)	38 (24)	-	-
TBEA Pellicano 2002	-	-	-	-	-	-	-	-	-	-
TBEA Romer 1998	-	-	40 (40)	31 (30)	-	-	-	-	-	-
TBEA Soysal et al 2001	-	-	11 (10)	17 (17)	-	-	-	-	-	-
TBEA Zon-Rabelink 2001	-	-	-	-	-	-	-	-	-	-

Figure 10: Forest plot of amenorrhoea at 12 months – 1st generation vs 2nd generation EA methods (random effects model, results not pooled)

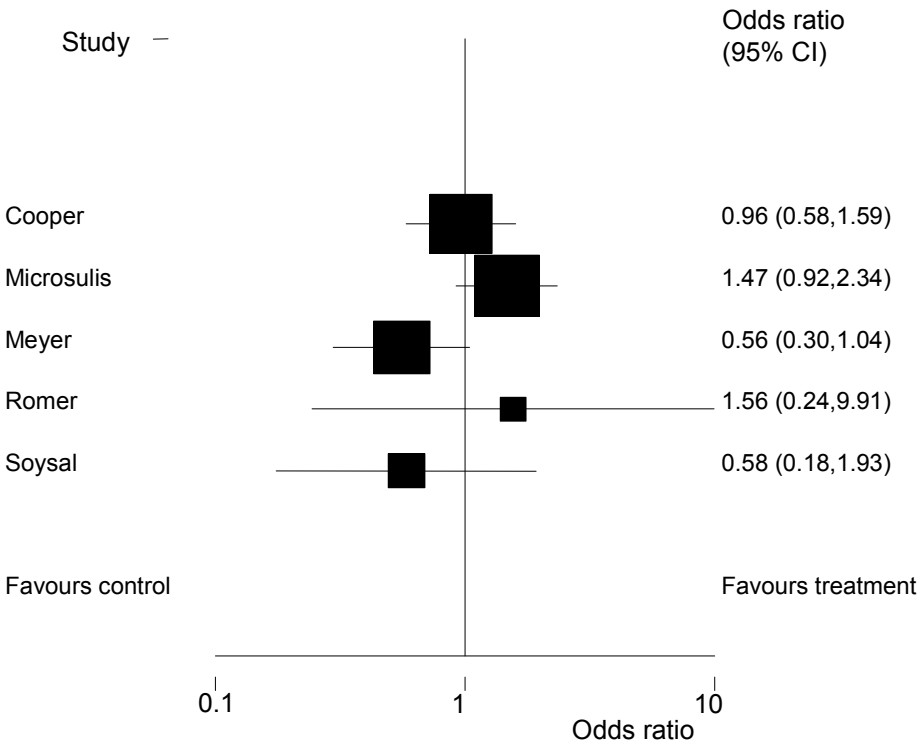
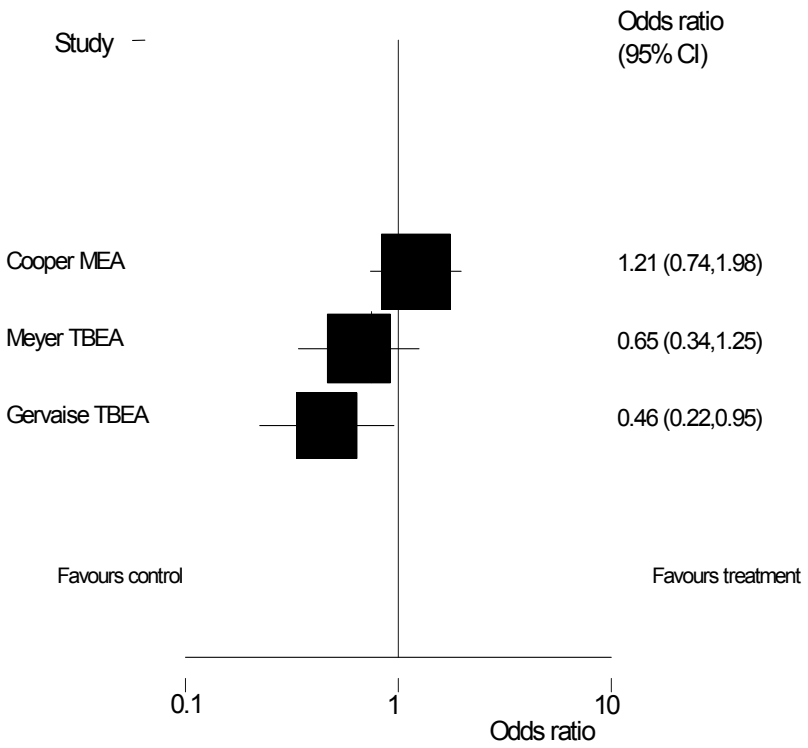


Figure 11: Forest plot of amenorrhoea at 24 months – 1st generation vs 2nd generation EA methods (random effects model, results not pooled)



Other recorded outcomes for bleeding are shown in Table 8 to Table 9. Note that data for 24 months (Meyer[82], TBEA vs RB) were estimated from data presented in graph form in the original study report. Three trials reported post-operative bleeding in terms of spotting, hypomenorrhoea, eumenorrhoea, menorrhagia, or metrorrhagia; Romer and colleagues[83] (TBEA vs RB) at 12 months, Meyer and colleagues[82] (TBEA vs RB) at 24 and 36 months follow up, and Gervaise and colleagues[89] (TBEA vs TCRE) immediately and at 24 months. At 24 months, 5-8% of patients who had undergone TBEA and 9-15% of those who had undergone TCRE or rollerball were still experiencing menorrhagia. At 60 months, this figure was 2% and 1% respectively. For further details, see Table 8. No trial reported statistically significant differences between the groups for recurrent menorrhagia.

Five trials reported changes in PBAC score. At 12 months Meyer and colleagues[82] (TBEA vs RB) report that 73% of the TBEA and 70% of the rollerball group had a score of less than 100 (normal bleeding). More stringently, the Microsulis[88] (MEA vs RB) uses a PBAC score of less than 76 to indicate normal bleeding levels and this is reported by 87% of women in the MEA group and 83% of women in the rollerball group. Soysal and colleagues[90] (TBEA vs RB) reported a mean PBAC score of 41.1 in the TBEA group (a mean reduction of 343), and a mean PBAC score of 40 in the rollerball group (a mean reduction of 345). Zon-Rabelink[92] (TBEA vs RB) do not report actual PBAC scores, but state that these were significantly better for the TBEA group at two years (p=0.01), though not at six or 12 months. Zon-Rabelink[92] (TBEA vs RB) also reports that there was a significantly greater reduction in bleeding scores (p=0.03) at two years for the TBEA group than the RB group, but again

does not provide the data. Zon-Rabelink[92] (TBEA vs RB) measures success by a post-operative PBAC score of less than 185, and 79% of women in the both groups achieve this after one year. After two years, 78% of women in the TBEA groups and 76% of women in the TCRE group have a score of less than 185.

Cooper and colleagues[86] (MEA vs TCRE/RB) report a median 12 month bleeding score of three in both groups at 12 months, falling to one at 24 months for the MEA group and zero for the TCRE group. (Table 9 page 67) This bleeding score was obtained through women being asked to grade the heaviness of their period on a scale of five points for each day of their period, and these scores were added together to give a total score.[96] Differences in bleeding patterns between the groups were not reported as statistically significant for any of these measures.

Only the trial by Cooper and colleagues[86] (MEA vs TCRE/RB) reports bleeding patterns in terms of the length of bleeding (more than three days heavy bleeding at 12 months: 6% MEA, 5% TCRE/RB and 24 months 2% MEA, 5% TCRE/RB) and heaviness as measured by the percentage of women requiring double or more than their usual sanitary protection (at 12 months TBEA 11%, TCRE/RB 12%; at 24 months 7% TBEA, 13% TCRE/RB). See Table 10 (page 68) for further details. Differences between the groups were not statistically significant.

Pellicano and colleagues[91] (TBEA vs TCRE/RB) report that "bleeding recurred" at one year for 5% of women undergoing TBEA and 14% of those undergoing TCRE/RB, and that at two years this was the case for 8% and 19% respectively. This difference is significant ($p<0.05$) although it is unclear to what "bleeding recurs" refers.

Dysmenorrhoea

Four trials[82;86;88;91] report on post-operative dysmenorrhoea. However, none report using a validated pain score. In the trial by Cooper and colleagues[86] (MEA vs TCRE/RB) 19% of those undergoing MEA and 16% of those undergoing TCRE/RB reported that dysmenorrhoea was unchanged or worse at 12 months post-operatively. This was also the case for 17% of MEA and 22% of TCRE/RB groups at 24 months follow up (see Table 11 page 69). In addition, the MEA study by Cooper and colleagues reports a post-operative pain score after 12 months of one for both treatment and control, and at 24 months of 0 for MEA and 1 for TCRE (see Table 11 page 69).

Thirty one percent of women in both trial arms reported post-operative dysmenorrhoea in the Microsulis trial[88] (MEA vs RB) compared to 82% and 80% having pre-operative dysmenorrhoea in the MEA and rollerball arms respectively. In the trial by Meyer and colleagues,[82] 27% of those treated with TBEA and 20% of those treated with rollerball ablation reported that dysmenorrhoea was unchanged or worse at 12 months post-operatively. At 60 months, Meyer and colleagues report that 13% of women who had undergone TBEA and 9% of those who had undergone rollerball had moderate to severe dysmenorrhoea. The data for 60 months have been estimated from a graph in the original paper and so may be subject to inaccuracy. Pellicano and colleagues[91] report that at 12 months, 2% of women had recurrence of pain in the TBEA group compared to 14% in the TCRE and rollerball arm, at 24 months these figures were 4% and 18% respectively. This difference was found to be statistically significant – the only trial to find such a difference.

In addition to reporting dysmenorrhoea at 60 months, Meyer and colleagues[82] (TBEA vs RB) also report on pelvic pain that is not related to menses – they are the only trial to do so. Most (69% (31% ITT) TBEA, 80% (35% ITT) RB) do not report any such pain, but 10% (4% ITT) of women in the TBEA group and 8% (4% ITT) in rollerball group, reported moderate to severe pain.

Figure 12 (page 70) shows the dysmenorrhoea rates at 12 months for first generation versus second generation endometrial ablation techniques. The data points have been produced from the numbers describing dysmenorrhoea as the same or worse as pre-operatively. In all cases the confidence intervals cross the central line indicating no statistically significant differences between the groups. Study results have not been combined due to clinical heterogeneity between the trials.

Pre Menstrual Syndrome symptoms

Two studies[82;86] report post-operative pre-menstrual syndrome (PMS) symptoms although in different ways. The study by Cooper and colleagues[86] (MEA vs TCRE/RB) reports prevalence of individual symptoms of PMS at 12 months post operatively; bloating, breast discomfort, irritability, headaches and depression (see Table 12, page 71). There was no statistically significant difference between the groups for any PMS measures. Meyer and colleagues[82] (TBEA vs RB) report the number of women who do not have PMS symptoms at 12, 24 and 36 months post-operation, and the number of women who have moderate or severe PMS at 12 (TBEA 30%, Rollerball 24%) and 24 months (TBEA 25%, rollerball 22%). There were no statistically significant differences in pre menstrual symptoms between the study arms (Table 12, page 71).

Table 8: Results: Type of post operative bleeding - % (% ITT)

	Length FU	Intervention	Spotting	Hypomenorrhoea	Eumenorrhoea	Menorrhagia	Metrorrhagia
Cooper et al 1999	**12**	MEA	-	-	-	-	-
		TCRE /RB	-	-	-	-	-
	24	MEA	-	-	-	-	
		TCRE /RB	-	-	-	-	-
Microsulis 2002	**12**	MEA	-	-	-	-	-
		RB	-	-	-	-	-
Meyer et al 1998	**12**	TBEA	-	-	-	-	-
		RB	-	-	-	-	-
	24	TBEA	11(9)	45 (40)	21 (19)	9 (8)	-
		RB	13 (10)	30 (22)	21 (16)	12 (9)	-
	36	TBEA	10 (8)	39 (33)	29 (24)	7 (6)	-
		RB	16 (12)	26 (19)	25 (18)	6 (4)	
	60	TBEA	10 (4)	38 (17)	25 (11)	5 (2)	-
		TCRE	11 (5)	25 (11)	28 (12)	3 (1)	-
Gervaise et al 1999	**1**	TBEA	25 (25)	22 (22)	38 (38)	11 (11)	4 (4)
		TCRE	38 (38)	31 (31)	13 (13)	12 (12)	5 (5)
	24	TBEA	36 (22)	16 (10)	34 (20)	9 (5)	4 (3)
		TCRE	38 (38)	28 (28)	17 (17)	15 (15)	2 (2)
Romer 1998	**12**	TBEA	-	50 (50)	10 (10)	-	-
		RB	-	60 (60)	10 (10)	-	-
Pellicano et al 2002	**12**	TBEA	-	-	-	-	-
		TCRE/RB	-	-	-	-	-
	24	TBEA	-	-	-	-	-
		TCRE/ RB	-	-	-	-	-
Soysal et al 2001	**12**	TBEA	-	-	-	-	-
		RB	-	-	-	-	-
Zon-Rabelink 2001	**12**	TBEA	-	-	-	-	-
		RB	-	-	-	-	-
	24	TBEA	-	-	-	-	-
		RB	-	-	-	-	-

Table 9: Post operative PBAC scores - % (%ITT)

	Length FU	Intervention	Mean PBAC Score	PBAC <185	PBAC <100	PBAC <76	PBAC decreased by 90%	PBAC decreased by 50%+	Mean decrease in PBAC	Bleeding score Mean (range)
Cooper et al 1999	**12**	MEA	-	-	-	-	-	-	-	3 (0-8)
		TCRE/RB	-	-	-	-	-	-	-	3 (0-10)
	24	MEA	-	-	-	-	-	-	-	1 (0,7)*
		TCRE/RB	-	-	-	-	-	-	-	0 (0,7)*
Microsulis 2002	**12**	MEA	-	-	-	87 (87)	-	-	-	-
		RB	-	-	-	83 (83)	-	-	-	-
Meyer et al 1998	**12**	TBEA	-	-	80 (73)	-	62 (56)	At least 90 (81)	85%	-
		RB	-	-	84 (70)	-	68 (56)	At least 90 (75)	92%	-
	24	TBEA	-	-	-	-	-	-	-	-
		RB	-	-	-	-	-	-	-	-
	36	TBEA	-	-	-	-	-	-	-	-
		RB	-	-	-	-	-	-	-	-
	60	TBEA	-	-	-	-	-	-	-	-
		RB	-	-	-	-	-	-	-	-
Gervaise et al 1999	**1**	TBEA	-	-	-	-	-	-	-	-
		TCRE	-	-	-	-	-	-	-	-
	24	TBEA	-	-	-	-	-	-	-	-
		TCRE	-	-	-	-	-	-	-	-
Pellicano et al 2002	**12**	TBEA	-	-	-	-	-	-	-	-
		TCRE/RB	-	-	-	-	-	-	-	-
	24	TBEA	-	-	-	-	-	-	-	-
		TCRE/RB	-	-	-	-	-	-	-	-
Romer 1998	**12**	TBEA	-	-	-	-	-	-	-	-
		RB	-	-	-	-	-	-	-	-
Soysal et al 2001	**12**	TBEA	41.1 +/-29	-	-	75 (71)	-	-	343.2 +/-87	-
		RB	40.2 +/-45	-	-	79 (79)	-	-	345.5 +/-113	-
Zon-Rabelink 2001	**12**	TBEA	-	79 (79)	-	-	-	-	-	-
		RB	-	78 (76)	-	-	-	-	-	-
	24	TBEA	-	78 (78)	-	-	-	-	-	-
		RB	-	76 (74)	-	-	-	-	-	-

* Median (25^{th}, 75^{th}) percentiles

Table 10: Post operative bleeding patterns - % (% ITT)

	Length FU	Intervention	3-7 days bleeding	>7 days bleeding	> 3 days heavy bleeding	2x sanitary protection needed	Menstruation unchanged or worse	Reduction in number of women with anaemia
Cooper et al 1999	**12**	MEA	42 (38)	5 (5)	7 (6)	12 (11)	8 (7)	-
		TCRE /RB	41 (38)	7 (7)	6 (5)	13 (12)	9 (8)	-
	24	MEA	-	-	2 (2)	14 (7)	7 (6)	-
		TCRE/RB	-	-	5 (5)	22 (13)	11 (10)	-
Microsulis 2002	**12**	MEA	-	-	-	-	-	-
		RB	-	-	-	-	-	-
Meyer et al 1998	**12**	TBEA	-	-	-	-	-	60 approx. (55)
		RB	-	-	-	-	-	60 approx. (49)
	24	TBEA	-	-	-	-	-	-
		RB	-	-	-	-	-	-
	36	TBEA	-	-	-	-	-	-
		RB	-	-	-	-	-	-
Gervaise et al 1999	**1**	TBEA	-	-	-	-	-	-
		TCRE	-	-	-	-	-	-
	24	TBEA	-	-	-	-	-	-
		TCRE	-	-	-	-	-	-
Pellicano et al 2002	**12**	TBEA	-	-	-	-	2 (5)*	-
		TCRE/RB	-	-	-	-	6 (14)*	-
	24	TBEA	-	-	-	-	3 (8)*	-
		TCRE/RB	-	-	-	-	8 (19)*	-
Romer 1998	**12**	TBEA	-	-	-	-	-	-
		RB	-	-	-	-	-	-
Soysal et al 2001	**12**	TBEA	-	-	-	-	-	-
		RB	-	-	-	-	-	-
Zon-Rabelink 2001	**24**	TBEA	-	-	-	-	-	-
		RB	-	-	-	-	-	-

* Values for “Bleeding recurs”

Table 11: Post operative menstrual pain - % (% ITT)

	Length FU	Intervention	Dysmen. Decreased	Dysmen. Same or worse	Dysmen.	Pain recurs	Mean pain score (mean, range)	Mild dysmen.	Moderate dysmen.	Severe dysmen.
Cooper et al 1999	**12**	MEA	-	21 (19)	-	-	1 (0-9)	-	-	-
		TCRE/RB	-	18 (16)	-	-	1 (0-7)	-	-	-
	24	MEA	-	18 (17)	-	-	0 (0, 6) +	-	-	-
		TCRE/RB	-	22 (22)	-	-	1 (0, 8)+	-	-	-
Microsulis 2002	**12**	MEA	-	-	31 (31)	-	-	-	-	-
		RB	-	-	31 (31)	-	-	-	-	-
Meyer et al 1998	**12**	TBEA	70 (64)	30 (27)*	-	-	-	-	-	-
		RB	75 (62)	25 (20)*	-	-	-	-	-	-
	24	TBEA	-	-	-	-	-	-	-	-
		RB	-	-	-	-	-	-	-	-
	36	TBEA	-	-	-	-	-	-	-	-
		RB	-	-	-	-	-	-	-	-
	60	TBEA	-	-	-	-	-	21 (9)	21 (9)	5 (4)
		RB	-	-	-	-	-	26 (12)	13 (5)	8 (4)
Gervaise et al 1999	**1**	TBEA	-	-	-	-	-	-	-	-
		TCRE	-	-	-	-	-	-	-	-
	24	TBEA	-	-	-	-	-	-	-	-
		TCRE	-	-	-	-	-	-	-	-
Pellicano et al 2002	**12**	TBEA	-	-	-	1 (2)	-	-	-	-
		TCRE/RB	-	-	-	7 (14)	-	-	-	-
	24	TBEA	-	-	-	2 (4)	-	-	-	-
		TCRE/RB	-	-	-	9 (18)	-	-	-	-
Romer 1998	**12**	TBEA	-	-	-	-	-	-	-	-
		RB	-	-	-	-	-	-	-	-
Soysal et al 2001	**12**	TBEA	-	-	-	-	-	-	-	-
		RB	-	-	-	-	-	-	-	-
Zon-Rabelink 2001	**24**	TBEA	-	-	-	-	-	-	-	-
		RB	-	-	-	-	-	-	-	-

* Calculated from given categories “Dysmenorrhoea unchanged” and “dysmenorrhoea increased.”
\+ Median, (25th, 75th percentile)

Figure 12: Forest plot of dysmenorrhoea 12 months post-operatively 2nd generation vs first generation endometrial ablation (random effects model, results not pooled)

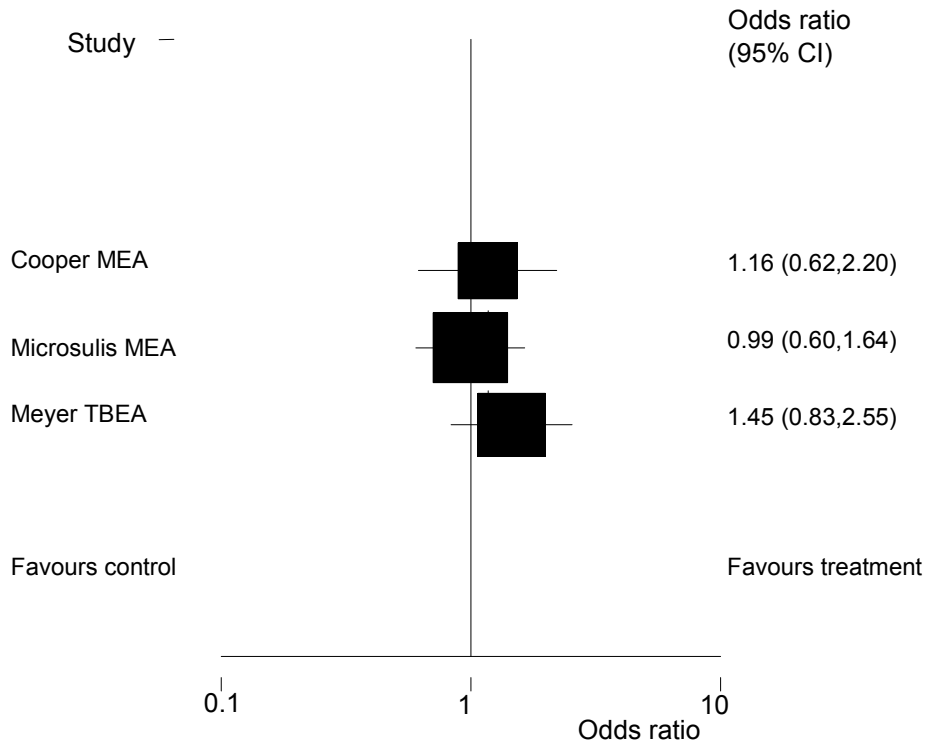


Table 12: Post operative pre-menstrual syndrome symptoms - % (% ITT)

	Length FU	Intervention	Bloating	Breast discomfort	Irritability	Head-aches	Depression	No PMS	PMS mod/ severe
Cooper et al 1999	**12**	MEA	65 (58)	55 (50)	58 (52)	48 (43)	36 (33)	-	-
		TCRE/RB	51 (47)	49 (45)	52 (48)	44 (40)	40 (37)	-	-
	24	MEA	-	-	-	-	-	-	-
		TCRE/RB	-	-	-	-	-	-	-
Microsulis 2002	**12**	MEA	-	-	-	-	-	-	-
		RB	-	-	-	-	-	-	-
Meyer et al 1998	**12**	TBEA	-	-	-	-	-	27 (25)	33 (30)
		RB	-	-	-	-	-	28 (23)	29 (24)
	24	TBEA	-	-	-	-	-	29 (26)	29 (25)
		RB	-	-	-	-	-	35 (27)	29 (22)
	36	TBEA	-	-	-	-	-	32 (26)	-
		RB	-	-	-	-	-	37 (27)	-
	60	TBEA	-	-	-	-	-	-	-
		RB	-	-	-	-	-	-	-
Gervaise et al 1999	**1**	TBEA	-	-	-	-	-	-	-
		TCRE	-	-	-	-	-	-	-
	24	TBEA	-	-	-	-	-	-	-
		TCRE	-	-	-	-	-	-	-
Pellicano et al 2002	**12**	TBEA	-	-	-	-	-	-	-
		TCRE/RB	-	-	-	-	-	-	-
	24	TBEA	-	-	-	-	-	-	-
		TCRE/RB	-	-	-	-	-	-	-
Romer 1998	**12**	TBEA	-	-	-	-	-	-	-
		RB	-	-	-	-	-	-	-
Soysal et al 2001	**12**	TBEA	-	-	-	-	-	-	-
		RB	-	-	-	-	-	-	-
Zon-Rabelink 2001	**24**	TBEA	-	-	-	-	-	-	-
		RB	-	-	-	-	-	-	-

Satisfaction with treatment

Soysal and colleagues[90] (TBEA vs RB) did not report patient satisfaction. The others use slightly different measures of satisfaction.

The study by Cooper and colleagues[86] (MEA vs TCRE/RB) reports whether women were "totally or generally satisfied" with treatment at 12 and 24 months after their operations. At 12 months, 69% of both groups were totally or generally satisfied and at 24 months 74% of those undergoing MEA and 64% of those undergoing TCRE and rollerball were totally or generally satisfied. Differences between groups were not statistically significant (Table 13 page 74). However, this study was designed to be able to detect 20% less satisfaction in the MEA arm assuming that 85% of the TCRE patients were satisfied (90% power, 95% precision) and so is underpowered to detect if the observed difference is significant.

Cooper and colleagues[86] (MEA vs TCRE/RB) also report that 70% of women in both groups regarded their treatment as affecting a cure or acceptable improvement in symptoms, and that 84% of both groups found their treatment acceptable. Over 80% of participants in both arms would recommend their treatment to a friend (Table 13 page 74).

Microsulis[88] (MEA vs RB) report that 98% of women undergoing MEA and 99% of those undergoing rollerball ablation were very satisfied or satisfied and that 99% of those undergoing MEA and all those undergoing rollerball reported "acceptance of the operation was positive".

Women in the trial by Meyer and colleagues[82] (TBEA vs RB) were rated as "very satisfied", "satisfied" or "not satisfied" with their treatment at all four follow up points. Eighty seven percent of women who had undergone TBEA were reported as "very satisfied" or "satisfied" at 12 months as were 82% of those who had undergone RB. At 24 months, results were 86% and 75% respectively. These differences were not statistically significant. It should be noted that these figures were estimated from a graph and therefore may be subject to slight inaccuracies (Table 13 page 74). At 60 months, the majority of women followed up in both groups were reported to be satisfied with treatment. In addition, 22/25 women who had received a repeat procedure or hysterectomy by 60 months were also reported to be satisfied with their treatment.

Pellicano and colleagues[91] (TBEA vs TCRE/RB) found that satisfaction was "excellent" at 12 months for 43% of women undergoing TBEA and 24% of women undergoing TCRE and rollerball. These figures were 35% and 4% respectively at 24 months. Differences between the groups were statistically significant.

Romer[83] (TBEA vs RB) states that all patients in their trial were satisfied.

Soysal and colleagues[90] (TBEA vs RB)report that 31% of those undergoing TBEA and 39% of those undergoing rollerball ablation were not very satisfied. As the study reports that women were asked if they were "very satisfied", "satisfied" or "dissatisfied", it is assumed that this figure includes those in the "satisfied" and "dissatisfied" categories although this is not made clear. Differences between the two techniques were not statistically significant (Table 13 page 74).

Zon-Rabelink[92] (TBEA vs RB) reports that 80% of women who had undergone TBEA and 75% of those who had undergone rollerball ablation were satisfied after two years. It is not stated how this was measured. This difference was not significant.

Figure 13 (page 75) and Figure 14 (page 76) illustrate satisfaction rates at 12 and 24 months for first generation versus second generation endometrial ablation techniques. The data

points have been produced by combining the categories for “satisfied” and “very satisfied” in the study by Meyer and colleagues,[82] and the “Totally and generally satisfied” category in the study by Cooper and colleagues.[86] The size of the data points indicates the relative size of each study. At 24 months, the Meyer study[82], on this dichotomous measure, shows a statistically significant effect on satisfaction in favour of first generation techniques which is not seen at 12 months. The study results have not been statistically combined due to clinical heterogeneity between the trials.

Quality of Life

Table 14 (page 76) shows various aspects of quality of life reported in the included studies, of which only two used measures relating to quality of life.[82;86] The trial by Cooper and colleagues[86] (MEA vs TCRE/RB) reports that work absence of two or more days was significantly reduced in both groups of women with 3% of those who had undergone MEA and 6% of those undergoing TCRE and rollerball still experiencing such work absences at 12 months post operation.

Meyer and colleagues[82] (TBEA vs RB) report a significant post-operative decrease in the proportion of women unable to work outside the home at all times of follow up, with 4% of women in both arms unable to work outside home at 36 months (see Table 14 page 77). In addition, while two thirds of women reported that heavy menstrual bleeding had a severe impact on life prior to the operation, this was reduced to 1% in both arms at 36 months. Differences between the groups were not significant. See Table 14 (page 77) for more details.

Only the MEA study by Cooper used a quality of life instrument validated in heavy menstrual bleeding, the SF-36 (See page 78). Prior to treatment, mean scores were lower across six of the eight items than a general population of the same age prior to treatment, and the SF-36 pain score was significantly lower in the MEA group than the TCRE group. Following treatment, six of the eight items improved significantly in the MEA group as did seven items in the TCRE group. Analysis of co-variance showed that the only difference between the groups was on physical role, in which there was greater improvement with MEA than TCRE.

Table 13: Satisfaction with treatment and its acceptability % (%ITT)

	Length FU	Intervention	Very satisfied	Satisfied	Not very satisfied	Not satisfied	Excellent	Good	Moderate	Totally or generally satisfied	Cure or acceptable improve-ment	Treatment acceptable	Menstrual loss acceptable	Re-commend treatment ?
Cooper et al 1999	**12**	MEA	-	-	-	-	-	-	-	77 (69)	78 (70)	94 (84)	-	91 (81)
		TCRE/RB	-	-	-	-	-	-	-	75 (69)	76 (70)	90 (84)	-	89 (82)
	24	MEA	-	-	-	-	-	-	-	79 (74)	-	-	96 (89)	90 (84)
		TCRE/RB	-	-	-	-	-	-	-	67 (64)	-	-	88 (84)	90 (87)
Microsulis 2002	**12**	MEA	-	98 (98)*	-	2 (2)	-	-	-	-	-	99 (99)+	-	-
		RB	-	99 (99)*	-	1 (1)	-	-	-	-	-	100 (100)+	-	-
Meyer et al 1998	**12**	TBEA	86 (78)	10 (9)	-	4 (4)	-	-	-	-	-	-	-	-
		RB	87 (72)	12 (10)	-	1 (1)	-	-	-	-	-	-	-	-
	24	TBEA	86 (77)	10 (9)	-	4 (3)	-	-	-	-	-	-	-	-
		RB	87 (66)	11 (9)	-	2 (1)	-	-	-	-	-	-	-	-
	36	TBEA	88 (72)	9 (6)	-	3 (2)	-	-	-	-	-	-	-	-
		RB	92 (67)	6 (4)	-	2 (1)	-	-	-	-	-	-	-	-
	60	TBEA	-	93 (42)	-	-	-	-	-	-	-	-	-	-
		RB	-	100 (44)	-	-	-	-	-	-	-	-	-	-
Gervaise et al 1999	**1**	TBEA	-	-	-	-	-	--	-	-	-	-	-	-
		TCRE	-	-	-	-	-	--	-	-	-	-	-	-
	24	TBEA	-	-	-	-	-	-	-	-	-	-	-	-
		TCRE	-	-	-	-	-	-	-	-	-	-	-	-
	3	TBEA	-	-	-	-	27 (59)	13 (28)	0	-	-	-	-	-
		TCRE/RB	-	-	-	-	21 (42)	12 (24)	9 (18)	-	-	-	-	-
Pellicano et al 2002	**12**	TBEA	-	-	-	-	20 (43)	10 (22)	5 (11)	-	-	-	-	-
		TCRE/RB	-	-	-	-	12 (24)	12 (24)	10 (20)	-	-	-	-	-
	24	TBEA	-	-	-	-	16 (35)	12 (26)	5 (11)	-	-	-	-	-
		TCRE+RB	-	-	-	-	2(4)	18 (36)	3 (6)	-	-	-	-	-
Romer 1998	**12**	TBEA	-	100 (100)	-	-	-	-	-	-	-	-	-	-
		RB	-	100 (100)	-	-	-	-	-	-	-	-	-	-
Soysal et al 2001	**12**	TBEA	-	-	33 (31)	-	-	-	-	-	-	-	-	-
		RB	-	-	39 (39)	-	-	-	-	-	-	-	-	-
Zon Rabelink 2001	**24**	TBEA	-	80 (80)	-	-	-	-	-	-	-	-	-	-
		RB	-	75 (73)	-	-	-	-	-	-	-	-	-	-

*"Very satisfied" and "satisfied" combined.
+ "Acceptance of operation positive"

Figure 13: Forest plot of satisfaction at 12 months follow up or first generation versus second generation EA techniques (random effects, results not pooled)

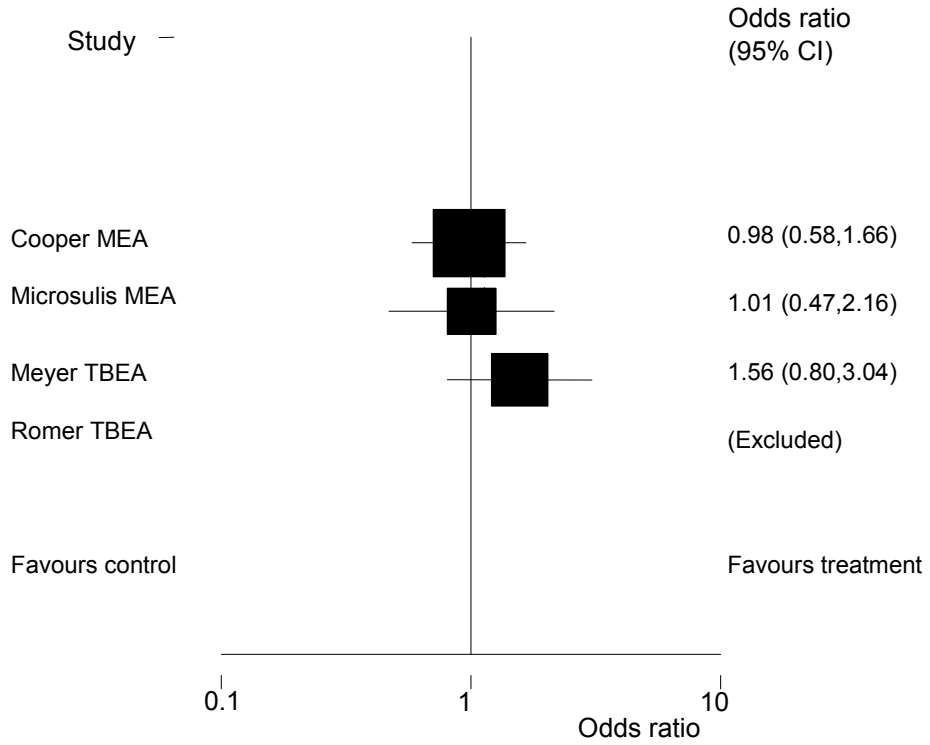


Figure 14: Forest plot of satisfaction at 24 months follow up or first generation versus second generation EA techniques (random effects, results not pooled)

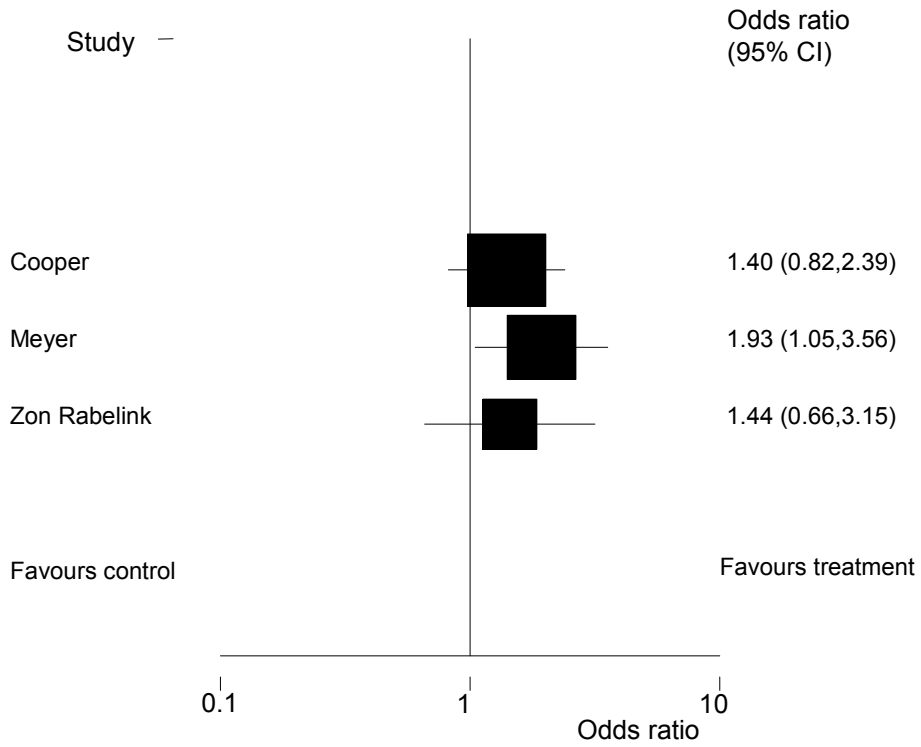


Table 14: Pre and post operative impact of symptoms on life % (% ITT)

	Length FU	Intervention	Unable to work outside the home		2 or more days work absence		Severe impact on life		Moderate impact on life		Minor impact on life	
			Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
Cooper et al 1999	**12**	MEA	-	-	36 (36)	3 (3)	-	-	-	-	-	-
		TCRE/RB	-	-	37 (37)	7 (6)	-	-	-	-	-	-
	24	MEA	-	-	-	-	-	-	-	-	-	-
		TCRE/RB	-	-	-	-	-	-	-	-	-	-
Microsulis 2002	**12**	MEA	-	-	-	-	-	-	-	-	-	-
		RB	-	-	-	-	-	-	-	-	-	-
Meyer et al 1998	**12**	TBEA	40 (37)	4 (4)	-	-	70 (66)	3 (3)	-	-	-	-
		RB	38 (33)	3 (2)	-	-	79 (67)	2 (2)	-	-	-	-
	24	TBEA	40 (37)	1 (1)	-	-	-	-	-	-	-	-
		RB	38 (36)	3 (2)	-	-	-	-	-	-	-	-
	36	TBEA	40 (33)	4 (4)	-	-	70 (66)	2 (1)	28 (28)	8 (7)	2 (1)	90 (75)
		RB	38 (36)	5 (4)	-	-	79 (67)	2 (1)	20 (20)	8 (6)	1 (1)	90 (64)
	60	TBEA	-	-	-	-	-	-	-	-	-	-
		RB	-	-	-	-	-	-	-	-	-	-
Gervaise et al 1999	**1**	TBEA	-	-	-	-	-	-	-	-	-	-
		TCRE	-	-	-	-	-	-	-	-	-	-
	24	TBEA	-	-	-	-	-	-	-	-	-	-
		TCRE	-	-	-	-	-	-	-	-	-	-
Pellicano 2002	**3**	TBEA	-	-	-	-	-	-	-	-	-	-
		TCRE/RB	-	-	-	-	-	-	-	-	-	-
	12	TBEA	-	-	-	-	-	-	-	-	-	-
		TCRE/RB	-	-	-	-	-	-	-	-	-	-
	24	TBEA	-	-	-	-	-	-	-	-	-	-
		RB	-	-	-	-	-	-	-	-	-	-
Romer 1998	**12**	TBEA	-	-	-	-	-	-	-	-	-	-
		RB	-	-	-	-	-	-	-	-	-	-
Soysal et al 2001	**12**	TBEA	-	-	-	-	-	-	-	-	-	-
		RB	-	-	-	-	-	-	-	-	-	-
Zon Rabelink 2001	**24**	TBEA	-	-	-	-	-	-	-	-	-	-
		RB	-	-	-	-	-	-	-	-	-	-

Figure 15: Mean SF36 scores pre- and post operation from Cooper et al 1999

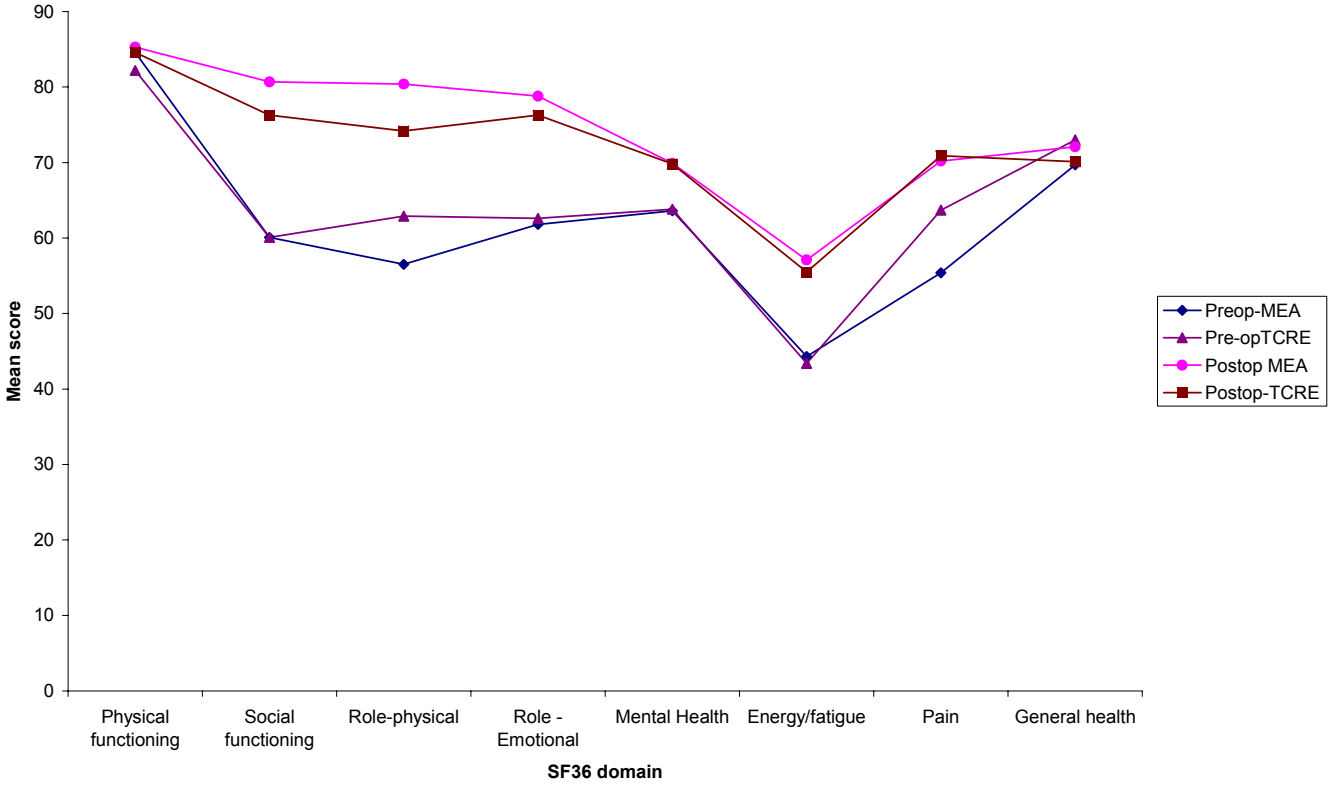


Table 15: Data used in Figure 15: SF-36 scores

	Preop-MEA	Change Postop-MEA	Post op MEA	Pre-op TCRE	Change Postop-TCRE	Postop TCRE
Physical functioning	84.6	0.7	85.3	82.2	2.4	84.6
Social functioning	60.1	20.6	80.7	60.1	16.2	76.3
Role-physical	56.5	23.9	80.4	62.9	11.3	74.2
Role – Emotional	61.8	17	78.8	62.6	13.7	76.3
Mental Health	63.6	6.3	69.9	63.8	6	69.8
Energy/fatigue	44.3	12.8	57.1	43.4	12.1	55.5
Pain	55.4	14.8	70.2	63.7	7.2	70.9
General health	69.7	2.4	72.1	73	-2.9	70.1

Operation Details

Table 16 (page 80) reports the results for duration of operations. Two studies[82;89] report on the percentage of operations that took less than 30 minutes to perform. For TBEA this was 65-100% and for TCRE and rollerball 24-53%. This difference was significant in both studies ($p<0.05$). In addition, Meyer and colleagues[82] report that 2% of TBEA and 14% of rollerball procedures took over 50 minutes. (Difference significant $p<0.05$).

Mean operating time is reported in four studies, although approaches to measurement varied.[86;89-91] A mean theatre time is also given by Cooper and colleagues[86] (MEA vs TCRE/RB) In this study the mean operating time for MEA was 11.4 minutes and for TCRE/RB it was 11.5-24 minutes. However, it may be that the time reported by Gervaise (TBEA vs TCRE) as operating time, is what Cooper and colleagues refer to as theatre time (see Table 16, page 80). For TCRE and rollerball, mean operating time ranges from 15.0 to 44.8 minutes (median 37.3) The Microsulis study[88] (MEA vs RB) reports an "anaesthetic time" of 41.7 minutes for MEA and 50 minutes for rollerball and a "treatment time" of 3.45 minutes for MEA and 20.26 minutes for rollerball.

Differences between procedure times were significant in all studies at the $P=0.0001$ level for Cooper and colleagues[86] (MEA vs TCRE/RB) and Soysal[90] (TBEA vs RB), at 0.009 for Microsulis (MEA vs RB) and at the 0.05 level for the study by Gervaise and colleagues[89] (TBEA vs TCRE). Zon-Rabelink[92] (TBEA vs RB) reports that the mean operating time for TBEA was significantly shorter than that for rollerball ($p<0.001$) but does not provide the data.

Cooper and colleagues[86] (MEA vs TCRE/RB) also report on the mean post-operative stay, and the percentage of women who were fully recovered in four weeks. Differences between the groups were not statistically significant.

Romer[83] did not give operating times.

Table 16: Operation Details

	Intervention	<30mins - % (%ITT)	>50mins - % (%ITT)	Mean (SD) Operating time –mins	Mean (SD) Theatre time-mins	Mean (SD) Post operative stay –hrs	Fully recovered in 4 wks – % (%ITT)	Return to normal domestic activities-days	Return to work-days	Resumption of sexual activity - days
Cooper et al 1999	MEA	-	-	11.4 (10.5)	20.9 (11.3)	13.4 (17.6)hrs	72 (67)	-	-	-
	TCRE/RB	-	-	15.0 (7.2)	26.2 (8.7)	16.7 (21.2)hrs	66 (61)	-	-	-
Microsulis 2002	MEA	-	-	3.45 (1.02)+	41.7(25.4)*	-	-	-	-	-
	RB	-	-	20.26 (15.6)+	50.0 (23.0)*	-	-	-	-	-
Meyer et al 1998	TBEA	71 (65)	2 (2)	-	-	-	-	-	-	-
	RB	27 (24)	18 (14)	-	-	-	-	-	-	-
Gervaise 1999	TBEA	100 (100)	-	20.3	-	-	-	-	-	-
	TCRE	53 (53)	-	44.8	-	-	-	-	-	-
Pellicano 200298	TBEA	-	-	24 (4.0)	-	1.0 (0.4)days	-	4.1 (+-1.8)	0.7 (+-0.1)	9.6 (+-0.6)
	TCRE/RB	-	-	37 (6.0)	-	1.3 (0.6)days	-	6.2 (+-3.3)	0.9 (+-0.3)	9.8 (+-0.7)
Romer 1998	TBEA	-	-	-	-	-	-	-	-	-
	RB	-	-	-	-	-	-	-	-	-
Soysal et al 2001	TBEA	-	-	11.5 (+-0.8)	-	-	-	-	-	-
	RB	-	-	37.3 (+-7.5)	-	-	-	-	-	-
Zon-Rabelink 2001	TBEA	-	-	-	-	-	-	-	-	-
	RB	-	-	-	-	-	-	-	-	-

* Given as “anaesthetic time” and excluding one centre whose patients all had GA.
+ Given as “treatment time”

Adverse Effects

Microsulis[88] and Romer[83] did not report adverse effects of treatment. Table 17 (page 83) and Table 18 (page 83) show intra-operative and post-operative adverse effects reported in the other trials.

Only the trial by Cooper and colleagues[86] (MEA vs TCRE/RB) reported equipment failure, which occurred in 9% of MEA operations and 2% of TCRE operations. This difference between the groups was significant (p=0.02). The procedure was abandoned in 4% of both MEA and TCRE procedures. It is reported that the equipment failures for MEA all occurred early in the study with a prototype microwave generator.

Among all trials, only the MEA trial by Cooper and colleagues[86] reported any intra-operative adverse effects with second generation techniques, where one women was affected. In this trial, adverse effects were reported in 1% of MEAs (one blunt uterine perforation). TCRE and rollerball operations resulted in between 0 and 19% (median 5%) intraoperative adverse effects; these included fluid overload, cervical laceration, uterine perforation and haemorrhage (Table 17, page 83).

Zon-Rabelink[92] (TBEA vs TCRE) does not give the numbers of adverse effects occurring, but lists those experienced by women in the rollerball group. He also states that significantly more post-operative pain relief was required by women who had undergone TBEA than those who had undergone rollerball (p=0.01) but does not give data.

The recording of post operative adverse effects may be affected both by length of follow up and loss to follow up. In both trials resulting in multiple papers[82;86] at different follow up times, an additional recorded adverse effect beyond 12 months is pregnancy. Two TBEA studies[82;89] and the MEA study[86] reported on one pregnancy each, in all cases at 12-24 months of follow up. No pregnancies were reported in the control groups of the included trials.

In the trial by Pellicano and colleagues[97], one women each in the TBEA and TCRE/RB group (3%) was reported to have CIN grade one at two years post ablation procedure. This is the only trial reporting the outcomes of post-operative cervical smears.

Zon-Rabelink[92] (TBEA vs RB) reports that there were no complaints in 95% of women who had undergone TBEA and 97% of women who had undergone rollerball ablation at six weeks of follow up.

Haemorrhage and pain are not reported in all trials. Haemorrhage was reported after 0-12% of TCRE/rollerball procedures.

Three studies of TBEA report post-operative endometritis, occurring in 0-4% (median 2%) after TBEA, and 1-4% (median 2%) for TCRE and rollerball. Two studies[82;90] report post operative haematometra; after 0-2% of TBA procedures and 1-4% of rollerball procedures. In addition, one study[82] reports a single case of urinary tract infection in the TBEA group and post tubal sterilization syndrome in the rollerball group (Table 17, page 83).

Post ablation-tubal sterilization syndrome, is characterised by intense, piercing unilateral or bilateral pelvic pain at cyclical intervals. This is caused by the accumulation of blood in the Fallopian tubes (haematosalpinx) from ectopic endometrial tissue responding to cyclical hormonal changes. It has been suggested that this may also be due to underlying inflammatory changes secondary to electrosurgery, which results in residual functioning endometrium and tubal obstruction.[98] Treatment is usually by hysterectomy. A US study of 50 consecutive EA patients followed for 10 years[99] found an incidence of symptomatic

cornual hematometra of 10% (n=5) on examination with ultrasound and MRI (magnetic resonance scan). Of these, two (4%) had cornual hematometra and three (6%) had post-ablation tubal sterilization syndrome.

Table 17: Intra-operative adverse effects – Number (%)

	Intervention	ITT (No. reported on)	Procedure abandoned	Equipment failure	Total intra-operative	Fluid overload	Cervical laceration / burn	Uterine perforation/ laceration	Haemo rrhage	Electrolyte imbalance
Cooper et al 1999	MEA	129 (129)	5 (4)	11 (9)	1 (1)	0	0	1 (1)	0	-
	TCRE/RB	134 (134)	5 (4)	3 (2)	6 (5)	0	0	1 (1)	5 (4)	-
Microsulis 2002	MEA	215 (215)	-	-	-	-	-	-	-	-
	RB	107 (107)	-	-	-	-	-	-	-	-
Meyer et al 1998	TBEA	134 (125)	-	-	0	0	0	0	0	-
	RB	126 (114)	-	-	4 (3)	2 (1)	1 (1)	1 (1)	0	-
Gervaise 1999	TBEA	73 (73)	-	-	0	0	0	0	0	-
	TCRE	74 (74)	-	-	0	0	0	0	0	-
Pellicano 2002	TBEA	40(46)	-	-	0	0	0	0	0	-
	TCRE/RB	42 (50)	-	-	8 (19)	5 (12)	1 (2)	2(5)+	0	-
Romer 1998	TBEA	10 (10)	-	-	-	-	-	-	-	-
	RB	10 (10)	-	-	-	-	-	-	-	-
Soysal 2001	TBEA	48 (45)	-	-	0	0	0	0	0	-
	RB	48 (48)	-	-	5 (10)	2 (4)	1 (2)	0	0	-
Zon-Rabelink 2001	TBEA	77 (77)	-	-	0	0	0	0	0	0
	RB	62 (60)	-	-	-	No	Yes	Yes	No	yes

+ Both these patients had an emergency conversion to hysterct0my at the time of the procedure due to uterine perforation.

Table 18: Post operative adverse effects – Number (%)

	FU	Intervention	Total post-operative (Cum)	Endo-metritis	UTI	Hemato metra	Urinary in-continence	Fever	Haem-orrhage	Pain	Symptomatic hydrosalpinx	Preg-nancy	CIN grade 1
Cooper et al 1999	**12**	MEA n=129	4 (3)	-	-	-	-	-	3 (2)	0	-	-	-
		TCRE/RB n=124	4 (3)	-	-	-	-	-	0	3 (pelvic)(2) 1 (chest) (1)	-	-	-
	24	MEA n=120	5 (4)	-	-	-	-	-	-	-	-	1 (1)	-
		TCRE/RB n=129	4 (3)	-	-	-	-	-	-	-	-	-	-
Microsulis 2002	**12**	MEA n=215	-	-	-	-	-	-	-	-	-	-	-
		RB n=107	-	-	-	-	-	-	-	-	-	-	-
Meyer 1998	**12**	TBEA n=126	4 (3)	3 (2)	1 (1)	0	-	-	-	-	0		-
		RB n=114	3 (3)	1 (1)	0	1 (1)	-	-	-	-	1 (1)		-
	24	TBEA n=122	5 (4)	-	-	-	-	-	-	-	-	1 (1)	-
		RB n=105	3 (3)	-	-	-	-	-	-	-	-	0	-
	36	TBEA n=114	5 (4)	-	-	-	-	-	-	-	-	-	-
		RB n=99	3 (3)	-	-	-	-	-	-	-	-	-	-
	60	TBEA n=61	-	-	-	-	-		-	-	-	-	-
		RB n=61	-	-	-	-	-		-	-	-	-	-
Gervaise 1999	**24**	TBEA n=44	1 (2)	0	-	-	-	-	-	-	-	1 (2)	
		TCRE n=47	2 (4)	2 (4)	-	-	-	-	-	-	-	0	-
Pellicano 2002	**3**	TBEA n= 40	-	-	0	-	-	1 (2)	5 (12)	-	-	-	-
		TCRE/RB n=42	-	-	1 (2)	-	-	2 (5)	4 (10)	-	-	-	-
	12	TBEA n= 40	-	-	-	-	-	-	-	-	-	-	-
		TCRE/RB n=42	-	-	-	-	-	-	-	-	-	-	-
	24	TBEA n= 40	-	-	-	-	-	-	-	-	-	-	1 (3)
		TCRE/RB n=42	-	-	-	-	-	-	-	-	-	-	1 (3)
Romer 1998	**12**	TBEA n=10	-	-	-	-	-		-	-	-	-	-
		RB n=10	-	-	-	-	-		-	-	-	-	-
Soysal 2001	**12**	TBEA n=45	3 (7)	2 (4)	-	1 (2)	-		-	-	-	-	-
		RB n=48	3 (6)	1 (2)	-	2 (4)	-		-	-	-	-	-
Zon Rabelink 2001	**12**	TBEA n=77	-	-	-	-	-	-	-	-	-	-	-
		RB n=60	-	-	-	-	-	-	-	-	-	-	-

In addition:
Pellicano et al 2002 report post-op. vaginal bleeding for a mean of 7.8 days (+-1) in the TCRE groups and 5.2 days (+-1.8) in the TVBEA group.
VAS pain score - at discharge: TCRE 1.5 (+-0.6) TBEA 1.9 (+-0.3), at 3 days: TCRE 0.5 (+-0.2) TBEA 0.4 (+-0.1), at 7days TCRE 0, TBEA 0.

Table 19 shows the percentage of women who subsequently underwent a repeat procedure of endometrial ablation or hysterectomy at different follow up times. In order to report the most conservative success rate, percentages based on the number of women available for follow up are reported in the text, and shown in the Table in parenthesis. Data have been calculated on an intent to treat basis where necessary and are shown in square brackets in the table. For those studies with multiple follow up periods, the figures are cumulative for repeat procedures. Only one woman was recorded as having a repeated second generation procedure.[86]

Repeat EA

In all studies there were fewer repeat ablations than hysterectomy following treatment failure. At 12 months, Cooper and colleagues[86] (MEA vs TCRE/RB) reported one (1%) TCRE procedure in the intervention arm. Meyer et al[82] (TBEA vs RB) reported one rollerball procedure in the intervention arm at 36 months. Neither of these studies had repeat TCRE/RB in the control arm. However, at 60 months follow up, Meyer and colleagues[82] reported that two women in each of the intervention (TBEA 3%) and control arm (rollerball 3%) had undergone repeat ablation.

At 24 months Gervaise and colleagues (TBEA vs TCRE) reported five (7%) patients in the control arm had a repeat TCRE.

Hysterectomy

By 12 months, <1-9% (median 4.5%) of women had had hysterectomy following initial second generation ablation. At 24 months, this was the case for 3-10% (median 6%) of women. At 36 months, Meyer and colleagues[82] (TBEA vs RB) report that 7% of women who had TBEA had also undergone a hysterectomy, and at 60 months this figure was 25%.

For women undergoing first generation procedures, <1-9% (median 5.5%) had also undergone hysterectomy at 12 months. At 24 months, the figure was 1-10% (median 5.5%), and at 36 months follow up 14% had also had a hysterectomy. Meyer and colleagues (TBEA vs RB) report that 14% of women initially undergoing rollerball ablation had also had a hysterectomy, as had 11% of women at 60 months.

Pellicano and colleagues[91] (TBEA vs TCRE/RB) only report a total repeat surgery figure, i.e. not divided by type of procedure. By 12 months, 5% of women undergoing TBEA and 10% of women undergoing TCRE and rollerball had had an additional procedure and this rose to 6% and 15% respectively at 24 months. This difference in repeat surgery rate was significant ($p<0.01$)

Zon-Rabelink reports the percentage of women who have had “intervention therapy” at two years of follow up; 17% of those undergoing TBEA and 15% of those undergoing TCRE are reported as having intervention therapy although it is not clear whether this refers only to further ablations and hysterectomies, or whether other gynaecological treatments or drug treatments for HMB have been included in this figure.

Table 19: Repeat surgery – Number (%) [ITT%]

	Length FU	Intervention	Total repeat surgery	Hysterectomy	TCRE	Other ablation
Cooper et al 1999	**12**	MEA n=116	9 (9) [8]	8 (7) [6]^	1 (1) [1]*	1 (1) [1]
		TCRE/RB n=124	11 (9) [8]	11 (9) [8]^	-	0#
	24	MEA n= 120	-	-	-	-
		TCRE/RB n= 129	-	-	-	-
Microsulis 2002	**12**	MEA n= 215	1 (<1) [<1]	1 (<1) [<1]	0	0
		RB n= 107	1 (1) [1]	1 (1) [1]	0	0
Meyer 1998	**12**	TBEA n= 125	2 (2) [1]	2 (2) [1]	-	-
		RB n= 114	3 (3) [2]	3 (3) [2]	-	-
	24	TBEA n=122	4 (3) [3]	4 (3) [3]	-	-
		RB n= 105	11 (10) [8]	11 (10) [8]	-	-
	36	TBEA n=114	9 (8) [7]	8 (7) [6]	1 (1) [1]	-
		RB n=99	14 (14) [10]	14 (14) [10]	0	-
	60	TBEA n= 61	15 (25)[11]	13 (21) [9]	2 (3) [1]	-
		RB n= 61	10"(16)[7]	7 (11) [5]	2 (3) [1]	-
Gervaise 1999	**24**	TBEA n=73	7 (10) [10]	7 (10) [10]	0	-
		TCRE n=74	6 (8) [8]	1 (1) [1]	5 (7) [7]	
Pellicano et al 2002	**12**	TBEA n= 37	2 (5) [4]	-	-	-
		TCRE/RB n= 38	4 (10) [8]	-	-	-
	24	TBEA n=35	2 (6) [4]	-	-	-
		TCRE/RB n= 33	5 (15) [10]	-	-	-
Romer 1998	**12**	TBEA n= 10	0	-	-	-
		RB n= 10	0	-	-	-
Soysal 2001	**12**	TBEA n= 45	4 (9) [8]	4 (9) [8]	-	-
		RB n= 48	4 (8) [8]	4 (8) [8]	-	-
Zon-Rabelink 2001	**24**	TBEA n= 77	-	-	-	-
		RB n= 60	-	-	-	-

*In addition, 4 women had a TCRE as a primary procedure instead of MEA, due to equipment failure.
1 women had MEA as her primary procedure having been allocated to TCRE group.
^ In addition, 1 women allocated to each group had hysterectomy as primary procedure.
' In addition, 2 women the TBEA group underwent hysterectomy at the time of the primary procedure (see Table 17)
" Includes 1 D&C

5.4.3 Adverse effect data from other sources

Large observational studies provide the most comprehensive information about adverse events, especially where events are rare. The MISTLETOE study[54;100] (Minimally Invasive Surgical Techniques – Laser, Endothermal or Endoscopic) collected data on 10,686 cases of endometrial ablation from 300 UK NHS hospitals from April 1993 to October 1994. These included 4,291 cases of combined techniques (TCRE with loop and rollerball), 3776 of loop (TCRE) and 650 of rollerball ablation which will be reported here. MISTLETOE also reports on 1,792 laser treatments, 140 radiofrequency and 36 cryoablation which are not reported here. Overall rates have been re-calculated to included TCRE and rollerball only.

Immediate complications are shown in Table 20. The data refer to the number of complications. Some women experienced more than one complication.

Table 20: Immediate complications reported in the MISTLETOE study – n(%)

	Loop + ball N=4291	Loop alone N=3776	Ball alone N=650	Total N=8717
Haemorrhage	99 (2.57)	129 (3.53)	6 (0.97)	234 (2.68)
Perforation	52 (1.29)	88 (2.47)	4 (0.64)	144 (1.65)
Cardiovascular/ respiratory	22 (0.54)	20 (0.5)	3 (0.48)	45 (0.52)
Visceral burn	3 (0.07)	3 (0.08)	0	6 (0.07)
Total	171 (3.98)	229 (6.06)	13 (2.00)	413 (4.74)

Women having ablation by rollerball alone had consistently fewer immediate operative complications and fewer occasions where emergency surgery was needed. Combined loop and rollerball approach had significantly fewer total immediate operative complications than loop alone ($p<0.00005$)

The overall intra-operative complication rate of 4.74% in the MISTLETOE study compares well with the median reported adverse effects of 5% for TCRE and rollerball in the trials included in this assessment.

The MISTLETOE paper reports ten deaths, of which two were considered to be directly related to the ablation procedure: one case of brain stem coning in association with malignant glioma during a combined procedure, and one case of streptococcal septicaemia three weeks after loop resection. Direct mortality rates were therefore 2/10,000 (0.0002%) for combined procedure and 3/10,000 (0.0003%) for loop alone. As these rates are so small, it is perhaps not surprising that the relatively small trials included in this assessment did not record any deaths.

A prospective cohort study of Canadian women reported the rate of peri-operative complications in women undergoing repeat ablation.[70] Data for complication rates following repeat ablations were not available from the trials included in this assessment. Eight hundred women undergoing primary ablation, and 75 women undergoing repeat ablation by the same surgeon between 1990 and 2000 were assessed. Serious complications (uterine perforation, haemorrhage and fluid absorption) occurred in 9.3% of repeat ablations compared to 2.05% of primary ablation ($p=0.006$). Actual figures are shown in Table 21 page 88.

Table 21: Adverse effects in primary and repeat ablations[70]

	Primary EA N=800	Second EA N=75	OR (95% CI)
Perforation	7	5	8.09 (2.49, 25.88)
Fluid absorption >800dl	8	2	2.71 (0.565, 13.00)
Haemorrhage	5	0	Not calculated
Total	20 (2.05%)	7 (9.30%)	4.01 (1.63, 9.87)

No national audit of second generation techniques has been undertaken. However, a prospective series of 1,433 MEA procedures (460 from one UK centre) in 13 centres in the UK and Canada has been reported.[72] The series included all patients from 1994, when the first experimental procedure was undertaken, to 1999. Only one major complication (a visceral burn) was reported, giving a serious complication rate of 0.7/1000. Results are shown in Table 22.

Table 22: Adverse effects of MEA in 1433 cases[72]

		Number	Rate /1000
Major complications	**Visceral burn**	1	0.7
Minor complications	**Blunt perforation**	4	2.6
	Perforation with dilator	2	1.3
	Endometritis	14	9.8
	Total	21	14.6

A prospective study of 296 women undergoing TBEA between 1994 and 1996 in 15 centres in Canada and Europe assessed complications of thermal balloon ablations after one year.[101] 12 months data were available for 163 women. No intra-operative complications were reported. Minor post-operative ablations were reported as one case of cystitis, six cases of febrile morbidity (diagnosed as low grade endometritis), two haematometra, one hospitalisation for pain. The minor complication rate was therefore 3% (30/1000).

An unpublished European survey of clinicians by Rogerson and Duffy reported on complications with TBEA in 5800 women[71]. The study used the outcomes described in the MISTLETOE study. The survey achieved a 33% response rate from gynaecologists thought to be actively using Thermachoice™. Reported adverse effects are shown below in Table 23.

Table 23: Complications with TBEA reported by Rogerson and Duffy

Intraoperative complication	Incidence (%) n=5859	Rate/1000
Haemorrhage	0.03	0.003
Uterine perforation	0.17	0.017
CVS/ respiratory complication	0.02	0.002
Visceral burn	0.02	0.002
Equipment failure	0.23	0.023
Total (excluding equipment failure)	0.42	0.042

Caution should be taken in comparing across uncontrolled observational studies as it is not possible to assess the existence and effect of possible biases. In addition, when considering adverse effects, the definition, and method of data collection may be different for the different studies.

Summary

Chapter 5: Effectiveness

- *Two systematic reviews and eight controlled trials were included in the review. The systematic reviews were of good quality and the controlled trials were of variable quality. Two trials were of MEA and six of TBEA and the comparators were either TCRE or rollerball or combined technique.*

- *Overall, there were few significant differences between the outcomes of first generation techniques including bleeding, satisfaction and quality of life measures as well as repeat surgery rates. Significant differences were reported most often by Pellicano, which was a relatively poor quality study.*

- *Second generation techniques had significantly shorter operating and theatre times.*

- *There appear to be fewer peri-operative adverse effects with second generation techniques and post operative effects are similar.*

- *There are no studies directly comparing second generation techniques and hysterectomy and so this comparison can only be indirectly inferred from studies of first generation techniques and hysterectomy. Compared to hysterectomy, TCRE and rollerball are quicker to perform and result in shorter hospitalisation and faster return to work. Hysterectomy results in more adverse effects and is more expensive, although the need for re-treatment leads this difference to decrease over time. Satisfaction with hysterectomy is initially higher, but there is no significant difference after 2 years.*

5.5 Economic evaluation of microwave and thermal balloon ablation

5.5.1 Assumptions used in the model

Table 24 shows the assumptions for transition probabilities between states, costs of procedures, discounting and utilities used in the model and their source.

Table 24: Assumptions used in the model

Assumptions	Value	Source	Justification for source
Transitions			
Background death rate (Death)	0.001234	Life Tables	UK figures – starting age 42 as given in the studies included in this assessment, and increasing year on year.
Complications after hysterectomy	0.035	VALUE study[48]	Large UK observational study
Death after hysterectomy (direct cause)	0.00025	VALUE study[48]	Large UK observational study
Median length of complications after hysterectomy	2 months	Clinician estimate	
Length of convalescence period post hysterectomy	2 months	Lethaby et al 2002[52]	Mean time of return to work/ normal activities in systematic review of hysterectomy
Waiting time – mean (median)	94 (54) days	HES 2000/01[73] Table 5 Q07	UK data set
Complications after TCRE + rollerball	0.0398	MISTLETOE study [54]	Large UK observational study
Death after TCRE + rollerball (direct cause)	0.0002	MISTLETOE study [54]	Large UK observational study
Complications after rollerball	0.0200	MISTLETOE study [54]	Large UK observational study
Death after rollerball (direct cause)	0	MISTLETOE study [54]	Large UK observational study
Complications due to TCRE alone	0.0606	MISTLETOE study [54]	Large UK observational study
Death after TCRE alone	0.0003	MISTLETOE study [54]	Large UK observational study
Median length of complications following 1st generation techniques	1 month	Professional estimate	
Complications due to MEA	0.0007	Case series 1433 women[72]	Large UK observational study
Death after MEA (direct cause)	0	Case series 1433 women[72]	Large UK observational study
Complications due to TBEA	0.0023	See Table 23 page 88	European survey of complications in 5800 women
Death after TBEA (direct cause)	0	Adverse effect evidence in this report (Table 17 and 83)	Systematic review of controlled trial evidence
Median length of complications after 2nd generation techniques	1 month	Professional estimate	
TBEA treatment failure (recurrent menorrhagia)	0.11	Gervaise data (immediate post-op)[89]	Controlled trial. Only data available for immediate post-operative failure rates
TBEA treatment failure years 2 and 3	0.1	See Table 19	RCTs in this assessment
Proportion of women with recurrent menorrhagia who undergo hysterectomy	0.6	5 year follow up women undergoing TCRE (vs medical management)[43]	Long term RCT data for TCRE
Proportion of women with recurrent menorrhagia who repeat ablation.	0.4	5 year follow up women undergoing TCRE (vs medical management)[43]	Long term RCT data for TCRE

Proportion of women with second EA failure who undergo hysterectomy within 6 months	0.9	Professional estimate	
Complications after repeat TCRE or rollerball ablation	Twice the rate after 1st ablation	Maclean-Fraser et al 2002 [70] and professional estimate	Comparative case series study of primary and repeat ablations. Only data on complications after repeat ablation.
Death after repeat TCRE/ rollerball ablation to	0.0003	MISTLETOE study [54]	Large UK audit
First year return of menorrhagia post TCRE/rollerball	0.11	Effectiveness data median at 12 months (Table 8 page 66)	RCT data, best available evidence
Second and third year return of menorrhagia following TCRE/RB	0.1	Effectiveness data median at 24 months (Table 8 page 66) plus repeat surgery rate (Table 19, page 86)	RCT data, best available evidence
First year return of menorrhagia post TBEA/MEA	0.11	Effectiveness data median at 12 months (Table 8 page 66)	RCT data, best available evidence
Second and third year return of menorrhagia following TBEA/MEA	0.1	Effectiveness data median at 24 months (Table 8 page 66) plus repeat surgery rate (Table 19, page 86)	RCT data, best available evidence
Discount rates			
Costs	6%	NICE	As recommended by the National Institute for Clinical Excellence (NICE).
Benefits	1.5%	NICE	As recommended by the National Institute for Clinical Excellence (NICE)
Health state utilities:	**Value**	**Source**	**Justification for source**
Chronic states			
Menorrhagia	0.55	Sculpher 1998[30]	Median value based on interviews with 60 women with menorrhagia
Premenopausal following recovery from successful TCRE	0.9	Sculpher 1998[30]	Median value based on interviews with 60 women with menorrhagia
Premenopausal following recovery from hysterectomy	0.95	Sculpher1998 [30]	Median value based on interviews with 60 women with menorrhagia
Dead	0		Usual value
Temporary States			
Complications after Hysterectomy	0.55	Assumption	Same as menorrhagia
Hysterectomy	0.63	Assumption	One third less than recovery after hysterectomy
Convalescence after Hysterectomy	0.95	Sculpher1998[30]	Median value based on interviews with 60 women with menorrhagia
MEA/ Convalescence after MEA	0.85	Sculpher1998[30]	Convalescent states post ablation assumed to be the same for all types of ablation. Based on the Sculpher1998[30] score for TCRE
TBEA/.Convalescence after TBEA	0.85	Sculpher1998[30]	Convalescent states post ablation assumed to be the same for all types of ablation. Based on the Sculpher1998[30] score for TCRE
TCRE and rollerball/ Convalescence after TCRE and rollerball	0.85	Sculpher1998[30]	Median value based on interviews with 60 women with menorrhagia

Costs

Details of resource use which informed the calculation of costs in the model are shown in Table 25 (page 92).

Table 25 Surgical Management: assumptions used in the cost effectiveness for model

Procedure	Data	Source	Justification
Abdominal Hysterectomy			
Length of stay (median)	4 days	Local median waiting time (Mid Devon PCT residents) and expert opinion	UK data based on all women, uncomplicated menorrhagia will be shorter
Day cases	0%	HES 2000/01 table5 Q07	UK data set
Duration of surgery	59 mins	Lethaby 2000[52]	Good quality systematic review
% under general anaesthetic	100%	Assumed	
1st generation EA			
Waiting time – mean (median)	79 (45)	HES 2000/01 table5 Q17	UK data set
Length of stay – weighted mean	2.0	Lethaby 2000[52]	Good quality systematic review
Day cases	60%	HES 2000/01 table5 Q17	UK data set
Duration of surgery - TCRE	40.9 mins	Median from Effectiveness data in this report (Table 16 page 80)	RCT data – best available evidence
Duration of surgery – RB	50 mins	Effectiveness data in this report (Table 16 page 80)	RCT data – best available evidence
Duration of surgery – TCRE/RB	31.6 mins	Median from Effectiveness data in this report (Table 16 page 80)	RCT data – best available evidence
% under General anaesthetic	78%	Lethaby 2002[9]	Systematic review
2nd generation EA			
Waiting time – mean (median)	80 (50)	HES 2000/01 table5 Q16	UK data set
Length of stay – mean (median)	1.6 (1)	HES 2000/01 table5 Q16	UK data set
Day cases	65%	HES 2000/01 table5 Q16	UK data set
Duration of surgery MEA	31.3 mins	Effectiveness data for theatre in this report (Table 16 page 80)	Median from RCT data – best available evidence
Duration of surgery TBEA	18.6 mins	Effectiveness data for theatre in this report (Table 16 page 80)	Median from RCT data – best available evidence
% under general anaesthetic	52%	Bain et al 2001[67]	Partially randomised study of LA vs. GA among 98 women in the UK

Costs of the equipment for microwave and thermal balloon ablation are shown in Table 26. The two sets of costs for the microwave system are based on different systems of supply. One involves purchase of the system and the other, under which the majority of UK centres using MEA operate, is a placement arrangement. Under this arrangement, centres pay a list price of £375 per treatment. Fifty-one UK centres operate this arrangement in all, of which six are in Scotland (information supplied by Microsulis Medical Ltd.).

Table 26: Microwave and Thermal Balloon equipment costs

Equipment	Cost (£)	Life-time	Source	Notes
Thermal Balloon				
Cavaterm™ control unit	3990	10 years	Manufacturer	
Cavaterm™ disposable balloon catheter	280	Single use	Manufacturer	
Thermachoice™ generator	6000	10 years	Manufacturer	Cost from manufacturer, life time assumed.
Thermachoice™ disposable balloon catheter	335-350	Single use	Manufacturer	The list price is £350, manufacturers informs that due to various discounts, £335 is the UK average price
Thermachoice™ cost of surgical devices	290	Per patient	Manufacturer	Calculated from cost given in Euros
Microwave				
Microwave EA system	39,950		Manufacturer	
Maintenance contract for MEA system	5000	Annual	Manufacturer	
Placement arrangement	375	Price per treatment	Manufacturer	According to the manufacturer, this arrangement is used by 51 UK centres.

Staff costs are shown in Table 27 and costs of general and local anaesthetic in Table 28.

Table 27: Staff costs

Staff	Cost/minute (£)	Source
Surgeon (consultant)	0.77	Southampton University Hospital
Anaesthetist (consultant)	0.77	Southampton University Hospital
Anaesthetist nurse (Grade H)	0.28	Southampton University Hospital
Instrument nurse (Grade G)	0.25	Southampton University Hospital
Trolley nurse (Grade G)	0.25	Southampton University Hospital
Circulating nurse (Grade G)	0.25	Southampton University Hospital
Recovery nurse	0.25	Southampton University Hospital
Senior house officer	0.29	Southampton University Hospital
Registrar	0.26	Southampton University Hospital
Nurse practitioner	0.28	Southampton University Hospital

Table 28: Costs of anaesthesia, ward costs

Resource	Cost £	Source
General anaesthetic	1.08 per minute	Microsulis submission
Local anaesthetic	7.7 per minute	Microsulis submission
Inpatient bed	231 per day	Southampton University Hospital – estimated from own cost +50%

Table 29: Total procedure costs

Procedure	Baseline price (£)
Hysterectomy	2096
TCRE	1110
TCRE/RB	1027
RB	1190
MEA	942
TBEA	826

5.5.2 Baseline results

The total costs for the modelled cohort of 1000 women over 10 years are shown below. Table 30 shows the cost effectiveness of MEA compared to each of the other procedures and Table 31 shows the cost effectiveness of TBEA compared to each of the other procedures.

Table 30: Summary of cost-utility analysis for MEA at 10 years

Procedure	Total costs (£)	Total QALYS	Incremental costs	Incremental QALYS vs MEA	ICER (£/QALY)
MEA - baseline	1,448,470	8,360.70	-	-	-
TBEA	1,323,925	8,360.77	124,545	-0.06	TBEA dominates
TCRE	1,731,734	8,357.03	-283,264	3.67	MEA dominates
TCRE+rollerball	1,785,045	8,357.99	-336,574	-2.71	MEA dominates
Rollerball	1,752,359	8,359.92	-303,889	0.78	MEA dominates
Hysterectomy	2,320,512	8,774.34	-872,042	-413.63	2,108

With MEA, very slightly fewer QALYs are accrued for a slightly higher cost compared to TBEA. Compared to TCRE, TCRE combined with rollerball, and rollerball alone, MEA accrues more QALYS and costs less. Compared to hysterectomy, MEA is cheaper, but accrues fewer QALYS.

Table 31: Summary of cost-utility analysis for TBEA at 10 years

Procedure	Total costs (£)	Total QALYS	Incremental costs	Incremental QALYS	ICER
TBEA - baseline	1,323,925	8,360.77	-	-	-
MEA	1,448,470	8,360.70	-124,545	0.06	TBEA dominates
TCRE	1,731,734	8,357.03	-407,809	3.73	TBEA dominates
TCRE+rollerball	1,785,045	8,357.99	-461,119	2.78	TBEA dominates
Rollerball	1,752,359	8,359.92	-428,434	0.85	TBEA dominates
Hysterectomy	2,320,512	8,774.34	-996,587	-413.57	2,410

Compared to MEA, TBEA costs slightly less and accrues very slightly more QALYs. Compared to TCRE, TCRE combined with rollerball and rollerball, TBEA costs less and accrues more QALYS. Compared to hysterectomy, TBEA costs less and accrues fewer QALYs.

Sensitivity analyses

The sensitivity of the results to changes in various model parameters was examined by varying these parameters from the base case assumption across a range of values. Parameters tested through such sensitivity analyses together with the values used are shown in Table 32. Each variable was varied independently.

Table 32: Inputs varied in sensitivity analyses

Assumptions	Values used in sensitivity analyses	Source	Justification for source
Transitions			
Complications following MEA	0.0001-0.0023	Upper value based on numbers for TBEA. Lower on rate in RCTs.	Upper from large UK audit of TBEA, lower on RCTs
Death following MEA - direct cause	0-0.0002	Values for EA reported in this review Table 24 (page 90)	Minimum and maximum death rates reported for EA procedures included in this review
Complications following TBEA	0.001-0.005	Effectiveness evidence in this report (Table 17 and Table 18 page 83	Based on RCTs -best available evidence
Death following TBEA - direct cause	0-0.0003	Values for EA reported in this review Table 24 (page 90)	Minimum and maximum death rates reported for all procedures included in this review
Proportion of complications lasting more than one month for TBEA/MEA	0.1-0.9	Authors' assumption	Values give wide range to test to sensitivity.
Complication rate with repeat ablation	Same rate as first ablation to 4 times that in first ablation	Maclean-Fraser et al 2002 [70] and assumption	Minimum assumed the same as first ablation, upper limit based on case series study of first and second ablation complication rates.
First year return of menorrhagia post TBEA/MEA	0.05-0.02	Effectiveness data median at 12 months (Table 8 page 66)	RCT data.
Second and third year return of menorrhagia after TBEA/MEA	0.05-0.2	Total return of menorrhagia at 3 years 21-51% (Table 8 page 66) and Table 19 page 66)	Menorrhagia assumed to include al those reporting menorrhagia at a given follow up plus those who have had a repeat EA or hysterectomy in that time period.
Percentage of women with recurrent menorrhagia receiving hysterectomy over repeat ablation	0.2-0.8	Expert opinion and assumption	Upper limit based on expert opinion, lower limit assumed.
Utilities			
Menorrhagia	0.5 - 0.8	Sculpher 1998 [30] and assumption	Lowest value from mean reported in interviews with women with menorrhagia. Upper value estimated in comparison to other health state utilities.
TBEA and MEA	0.5-0.9	Authors' assumption	Lower limit same as menorrhagia mean – varies amount of discomfort and adverse effects.
Well following EA	0.75-0.99	Authors' assumption	Lower limit half way between menorrhagia and well, allowing for some long term adverse effects, upper limit close to full health.
Costs (£)			
Local Anaesthetic	0-100%	Author's assumption	Full range of none to all procedures under anaesthetic
Proportion of second generation procedures done in an office setting	0-100%	Authors' assumption	Full range of none to all procedures done in an office /non-theatre setting.

Length of hospital stay	0.5-1.0	Lower level clinician opinion, upper level form HES UK average	Input form clinical experience and national data.
Procedure time	20-42mins	This review Table 16.	Lowest and highest recorded theatre times
Equipment costs MEA	187-562	Author's assumption	Cost plus and minuses 50%
Equipment costs TBEA	158-474	Authors' assumption	Cost plus and minus 50%
Model			
Duration of model	3-10 years	Authors' assumption	

In order to investigate the sensitivity of the model to these various parameters, graphs showing the incremental cost effectiveness ration (ICER) for TBEA and MEA vs each other, first generation EA and hysterectomy are shown in the figures in Appendix 9 (page 164).

In comparing TBEA and MEA head to head, relatively small changes have greater effect, in some cases changing the direction of effect. Cost associated with each procedure and the procedure time of each procedure were important. In addition, the model is sensitive to aspects which affect the total QALYS accrued such as relative percentage of women having complications, length of complications and death rate.

Compared to first generation ablation and hysterectomy, the model was found not to be sensitive to the following variables:

- Complication rate of treatment (in either first or repeat ablations).
- Length of complication state
- Percentage of those being treated for recurrent menorrhagia who are treated by hysterectomy versus repeat EA.
- Utility for menorrhagia
- Utility for TBEA and MEA state

The model is slightly sensitive to:
- Percentage recurrence of menorrhagia post ablation
- Cost of equipment per treatment
- Procedure time
- Percentage of operations performed under local anaesthetic.
- Length for which the model is run.
- Death rate as direct result of treatment

The model is highly sensitive to:
- Utility value for "well" post ablation.

For MEA vs TBEA the cost of the procedure is very important in assessing incremental cost-effectiveness. The length of the procedure, which is related to theatre cost, is also important. The model is sensitive to the length of time for which the model is run. As absolute costs and QALYs for MEA and TBEA are very similar, changes in these numbers lead to large effects in the model outputs.

There must be considerable uncertainty around these results given the model is sensitive to the utility state "Well" and there are few data for this parameter. In addition, the difference in cost and utility between TBEA and MEA is small, so small changes in these change the marginal cost effectiveness.

Summary

Chapter 5: Cost-effectiveness

- *The economic model suggests that second generation techniques are more cost-effective than first generation techniques of EA for HMB.*
- *The model is sensitive to utility values after recovery around which there is considerable uncertainty.*
- *Indirect comparisons should be viewed with caution. However there appears to be little difference in costs or utilities between TBEA and MEA and small changes in these affect relative cost-effectiveness.*
- *Both TBEA and MEA appear to be less costly than hysterectomy although the latter results in more QALYS.*

5.6 Economic analyses supplied by industry

Three economic analyses were submitted to NICE by industry sponsors of MEA and TBEA:

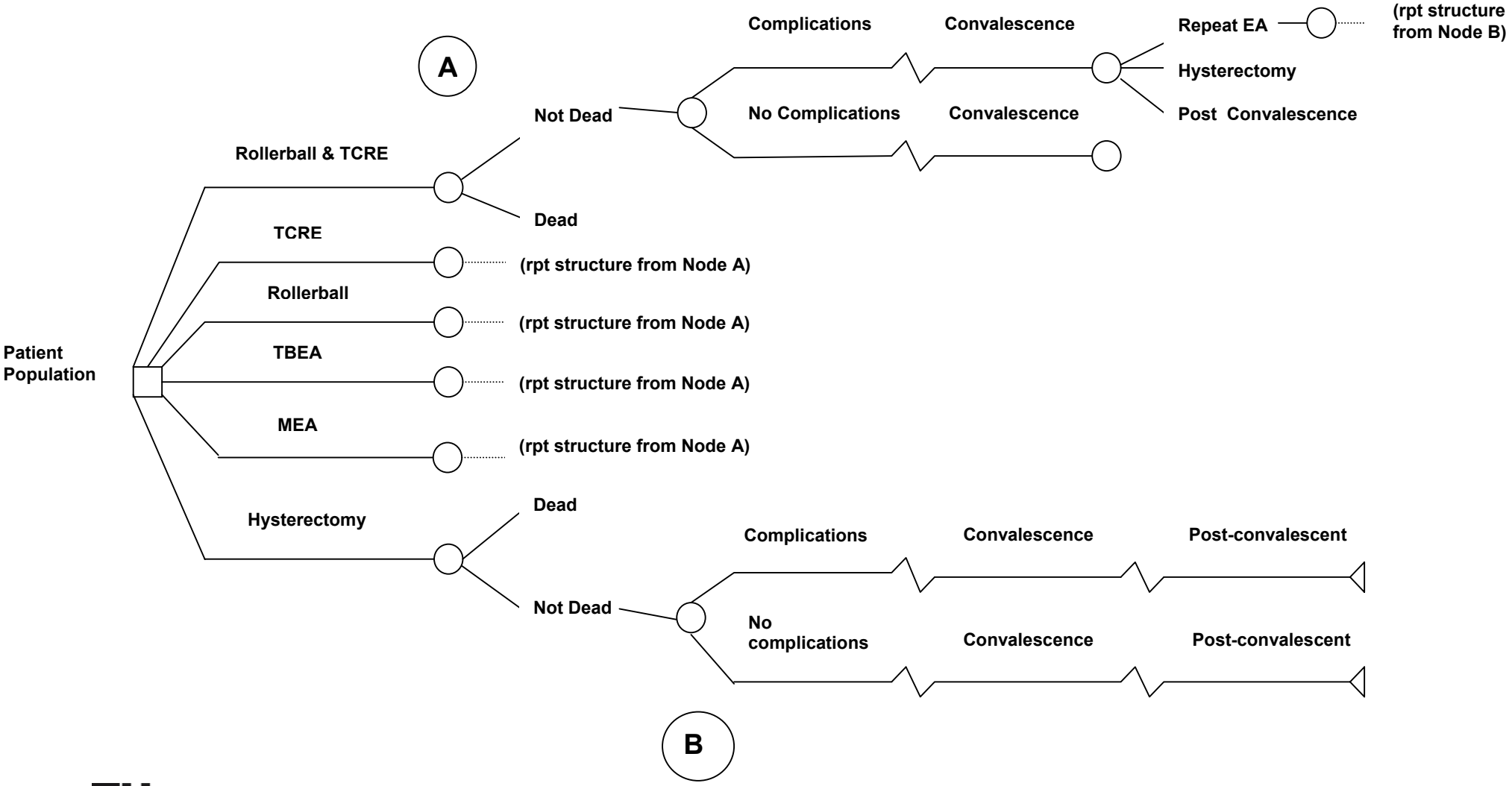
- A cost utility analysis of MEA submitted by Microsulis Medical Ltd.
- Cost minimization and cost effectiveness analyses of the Thermachoice™ TBEA device submitted by Gynecare
- A cost effectiveness analysis of the Cavaterm™ TBEA device submitted by Wallesten Medical.

The analyses are of variable quality. Details of the appraisals of each analysis, carried out within the frameworks proposed by Drummond and colleagues[75] and Sculpher and colleagues[74], are given at Appendix 9 (page 164).

5.6.1 Microsulis model

The Microsulis model was carried out as an "independent analysis" by the York Health Economics Consortium. The model structure is of high quality, and includes comparisons between all the options addressed in this assessment. The model is a decision tree design (see Figure 16), but handles the time to events by weighting the QALY calculation associated with each possible path through the tree. The design allows precise account to be taken of time spent with complications of the procedures. A five year time horizon is taken, justified on the grounds that almost all repeat procedures would be carried out within this period in the event of initial treatment failure. The increasing risk of second operation is modelled using a logarithmic function. A single repeat procedure is permitted. For MEA this is assumed to be TCRE+rollerball while for other ablation techniques the original option is repeated (i.e. TCRE, TCRE+rollerball, rollerball or TBEA). The sources for estimates used in the model are predominantly taken from the literature. A range of one and two-way sensitivity analyses, and a Monte Carlo simulation, in which all parameter estimates are varied (sampling from triangular distributions), were carried out.

Figure 16: Microsulis Model Structure



The Microsulis submission concludes that MEA is a cost-saving treatment. Total discounted costs at five years are estimated at £1,238. Cost savings of 14% to 55% over other treatments are estimated. Total discounted costs and quality adjusted life years (QALYs) according to the Microsulis model are shown below in Table 33.

Table 33: Total discounted costs and QALYS by procedure and cost-effectiveness at five years: Microsulis model

Procedure	Total Costs (£)	Total QALYs	Incremental Costs (vs MEA) (£)	Incremental QALYs (vs MEA)	ICER (MEA)
MEA	1,238	3.76	-	-	-
TBEA	1,611	2.97	373	-0.79	Dominated
Rollerball	1,550	3.54	312	-0.21	Dominated
RB+TCRE	1,441	3.48	203	-0.28	Dominated
TCRE	2,032	3.56	793	-0.20	Dominated
Hysterectomy	2,728	4.08	1,489	0.32	£4,594

Costs of complications, which differ according to technology, are listed but methods for their estimation are not detailed. However, as complication rates are low for all procedures, this is unlikely to have a major effect on the overall findings.

A key parameter determining difference in cost utility is the utility weight attached to the health state of post convalescence. This is estimated as being 0.86 following hysterectomy, 0.73 for TCRE and TCRE+rollerball, 0.74 following rollerball, 0.79 following MEA and 0.57 following TBEA. Methods of calculating these values are described in Appendix 10 (page 173) Counter-intuitively, the utility weights for post convalescent states after all technologies except hysterectomy and MEA appear to be lower than the convalescent states. The utility weight associated with heavy menstrual bleeding is 0.50.

Sources for the estimates of repeat operation are not detailed. Comparison with the repeat surgery rates reported in the available comparative trials of endometrial ablation techniques suggests these are taken from studies not included in the systematic review reported in this assessment. The repeat surgery rate is important as a determinant of the overall cost of ablation procedures. The repeat hysterectomy rate is important as the post convalescent state following hysterectomy carries a higher utility weight than the health state following other operations. A higher repeat rate for one ablation technique will therefore lead to more time spent in a health state valued more highly than that experienced by women opting for alternative ablation techniques.

The sensitivity analysis included a scenario in which post convalescent utilities were assumed to be equal. MEA no longer dominated TCRE, which could yield additional QALYs at additional cost of £35,000. Hysterectomy provides additional QALYs at additional cost at all levels of post convalescent utility weight, with a maximum ICER of £35,213 per QALY when this parameter is at its lowest level assumed (0.73).

The incremental cost effectiveness of hysterectomy is estimated at a level that has been considered by many decision makers as representing acceptable value for money under most assumptions. This may be related to the time horizon of the model. This option results in women entering the health state with highest value and spending most time in it. Even under the assumption that all post convalescent states have the same utility, hysterectomy has implicit advantage as there is no probability of heavy menstrual bleeding or the disutility

associated with further procedures. However, this assumes that women prefer amenorrhoea to eumenorrhoea or lighter menstrual loss.

Following sensitivity analysis and Monte Carlo simulation, it is concluded that MEA would continue to dominate RB and TCRE in over 95% of cases and that hysterectomy would continue to yield additional benefits for extra cost. The cost effectiveness of hysterectomy over MEA is subject to considerable uncertainty with a range of £2,000 to over £130,000 per QALY. MEA is shown to dominate TBEA under almost all scenarios considered, although Monte Carlo simulation showed that this may not be the case in as many as 95% of circumstances.

5.6.2 Thermachoice™ Model

The industry submission from Gynecare provides two pieces of evidence regarding the economics of Thermachoice™ :

1. A cost analysis of Thermachoice™ versus TCRE and vaginal hysterectomy
2. A crude cost effectiveness analysis based on costs required to achieve several outcomes of interest: amenorrhoea, eumenorrhoea, satisfaction, avoidance of surgical re-intervention

Cost analysis

The cost analysis is not a complete economic analysis, as is acknowledged by the industry submission to NICE. The study, which has not yet been published elsewhere, was carried out in 1995-7 in Paris, based on 147 people undergoing thermal ablation (n=47), hysteroscopic electro-resection (n=50) and vaginal hysterectomy (n=50). Limited methodological details are reported and it is therefore difficult to judge the usefulness of the study in judging the costs, and relatedly, cost effectiveness of Thermachoice™.

The analysis is restricted to in-hospital costs accruing to each technology, with differences in time in operating theatre accounting for almost all the difference in technology costs. The results suggest that vaginal hysterectomy has a higher cost than thermal ablation or TCRE (€ 2,799 vs €1,424 and €1,508 respectively).

Although the study is reported as a micro-costing study, methods are not clearly reported and it is therefore impossible to judge, comprehensively, the validity of the results. Particularly important issues that cannot be addressed include:

- the methods of calculating resource consumption are not reported
- the completeness of resource use ascertainment is not reported and how missing data were handled
- potential uncertainty in the estimates has not been addressed
- the base year for cost estimates is not reported
- the methods for allocating overheads is not reported and overheads are not applied to the costs of follow up or of ward-based care.

These methodological limitations, which may be addressed by more comprehensive reporting in the final published version of this study, make it difficult to comment on the results. However, the following observations can be made on the reported data:

- The summary measures are not defined (assumed to be means) and no measures of spread in the data are reported.
- Resource use and costs in France are likely to be different from those in the UK, limiting the applicability of the findings to the UK. For example, the cost of a hospital bed day is

considerably lower than the UK. In addition, vaginal hysterectomy makes up a minority of UK hysterectomies and the length of operation, length of hospital stay and complication rates are different to those for abdominal hysterectomy.

- The assumption that there are no overnight stays as a result of complications arising from endometrial ablation may reflect the experience of the small population studied. However, such overnight stays may occur and therefore the reported cost difference may be biased in favour of Thermachoice™, though by an uncertain amount
- The analysis is predominantly driven by difference in time spent in operating theatre, calculated per minute for a range of professionals. This unit of measurement does not reflect the opportunity cost of the resources.
- The analysis does not include prior hysteroscopy in patients as part of the work-up for Thermachoice™.
- Five follow up visits are recorded for women after hysterectomy, compared to one in each of the ablation techniques. The number of follow up visits seems high, particularly for vaginal hysterectomy. If the number of follow up visits in the UK is less than that reported, then the difference in costs between hysterectomy and ablation will have been overestimated. However, since the costs of follow up are based only on surgeon's time (and methods for calculating this are not given) the amount remains very small.

Cost effectiveness analysis

The analysis is acknowledged in the industry submission to NICE to be simplistic. Thermachoice™ TBEA is compared to TCRE and hysterectomy at three years. It has been appraised using the framework by Drummond and colleagues and this is shown in Appendix 9 (page 164). The analysis reports the following outcomes:

- **Cost per additional case of amenorrhoea**. The ICERs for TCRE and hysterectomy, compared to Thermachoice TBEA are €1,736 and €1,378 respectively.
- **Cost per additional case of eumenorrhoea or less**. The ICERs for TCRE and hysterectomy, compared to Thermachoice TBEA are €19,789 and €16,751 respectively.
- **Cost per reintervention case avoided**. Thermachoice TBEA dominates TCRE. The ICER for hysterectomy, compared to Thermachoice is estimated as €16,994.
- **Cost per additional satisfied patient**. The ICERs for TCRE and hysterectomy, compared to Thermachoice TBEA are €14,135 and €26,650 respectively.

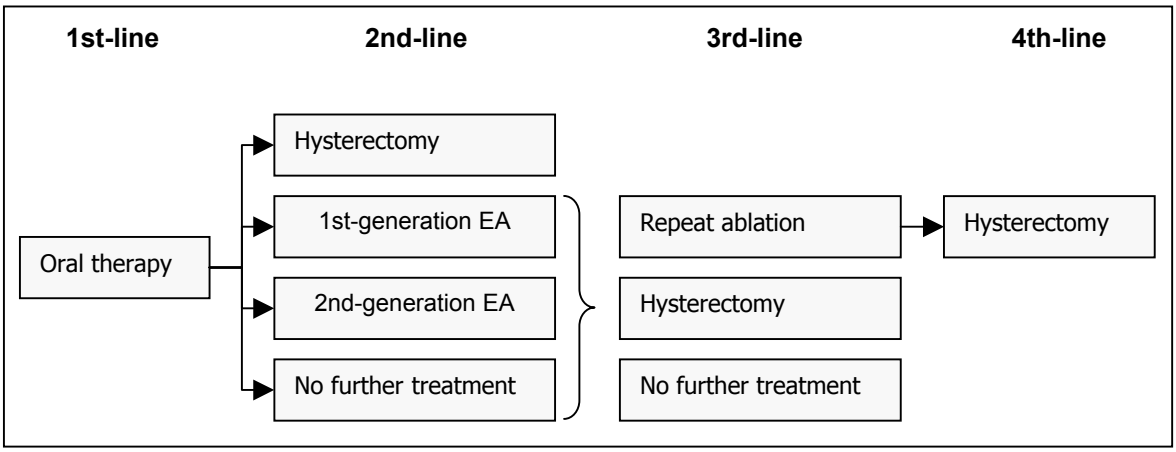
The analysis has a number of weaknesses in addition to those reported for the cost analysis on which the cost effectiveness estimates are based. The model does not allow the timing of events to be taken into account within the overall timeframe of the analysis. The outcome measures used do not allow the disbenefits of treatments to be taken into account e.g. adverse events and the different times to convalesce following hysterectomy and ablation procedures. Importantly, no account is taken of the uncertainty in the probabilities of outcome or costs in the analysis and so no estimate of the likelihood of the estimates of cost effectiveness being achieved in practice is possible.

5.6.3 Cavaterm™ model

The Cavaterm™ model is a decision tree model with a three year time horizon. The comparisons are between hysterectomy, first generation and second generation endometrial ablation. Use of the two types of TBEA equipment are considered separately in the analysis. Since the economic evaluation uses a decision analytic approach, its quality is considered in detail using the framework proposed by Sculpher and colleagues.[74] This appraisal is reported in detail in Appendix 10.

The estimates for effectiveness in the Cavaterm™ model are based on a meta-analysis of all reported studies of Cavaterm™. The authors suggest that the inclusion of a large number of patients (over 2,000) from over 30 trials will "override anomalies and experimental differences" and that this approach is preferable to restricting effectiveness data to that reported from randomised controlled trials. This position is open to debate: the quality of a meta-analysis depends on the quality of the studies it includes and will be valid only if there is not significant clinical and statistical heterogeneity between the included studies. The Cavaterm™ analysis includes a sensitivity analysis in which only data from RCTs are included, noting that no RCTs have shown a significant difference in the effectiveness of first and second generation techniques, though the probability of a type II error remains.

Figure 17: Flow chart of treatment pathway considered in the Cavaterm™ model



The effectiveness analysis is flawed in that it does not take account of the different timing of the underlying trials with respect to treatment failure. Cavaterm™ is assumed to be successful in 90% of cases (100 minus the repeat procedure rate), based on data up to one year, while Thermachoice is successful in only 83.3% of cases, based on a weighted mean of data up to three years. Since treatment failure appears to be time dependent, the analysis appears to be biased in favour of Cavaterm™.

The model estimates that Cavaterm™ is the most cost effective option based on cost per treatment success (based on RCT data) of £767 vs £828 for Thermachoice™, £865 for first generation EA and £2,050 for hysterectomy. Sensitivity analysis identified initial procedure cost and failure rate as important sources of uncertainty. The results of one way sensitivity analyses incorporating a wide range of values for these parameters suggest that Cavaterm™ would produce a lower cost per treatment success at failure rates of up to 74% or an initial procedure cost of less than £1,910. The corresponding thresholds for Cavaterm™ versus TCRE were estimated as 18% and £800.

The analysis also reports potential savings from Cavaterm™ on resource use (operating theatre time, anaesthetics, length of hospital stay), mortality and labour market productivity (based on reduced convalescence time). In these analyses, the impact of Cavaterm™ is considered as a replacement for all hysterectomies currently performed for heavy menstrual bleeding. This is not a realistic scenario given the evidence for patient preferences in a proportion of women seeking treatment for heavy menstrual bleeding.

5.6.4 Comparison between cost effectiveness analyses

The four models included in the NICE appraisal process for endometrial ablation differ in design, inputs and, consequently, outputs.

The models of TBEA alone, produced by the manufacturers, do not estimate cost utility. The Thermachoice™ analysis shows that TBEA is likely to have lower surgical costs than hysterectomy or TCRE. The cost effectiveness analysis is relatively simplistic and suggests that additional benefits may be realised with comparator treatments, but at additional cost. The model has significant methodological shortcomings.

The Cavaterm™ analysis is derived from a decision tree model run over three years. Results suggest that treatment success using Cavaterm™ would cost less than with all alternatives, and considerably less than with hysterectomy. Considerable resource savings are postulated as are the avoidance of some deaths from hysterectomy and a reduced burden of morbidity through reduced complications. Uncertainty is addressed through the use of limited sensitivity analysis and Monte Carlo simulation. The distributions chosen for the Monte Carlo simulations in this, and the Microsulis model, are simple and may not adequately model the uncertainty in the parameters concerned.

The Microsulis analysis is the most sophisticated of those submitted by industry sponsors to NICE. Although a decision tree design, the model takes account of the timing of events and allows for increasing risk of repeat procedures over time. Structurally, this is the most robust of the models supplied by industry sponsors. Importantly, only this model, and that constructed by the authors of this assessment, provide estimates for cost utility.

The Microsulis model concludes that MEA is likely to be more effective and less costly than all alternatives except hysterectomy under most of the assumptions modelled. The model incorporates uncertainty in the parameter values through sensitivity analysis and Monte Carlo simulation. In this respect, the method provides some reassurance of the robustness of the results. However, the model has a number of weaknesses, arising mainly from the quality of the data used to inform all cost effectiveness analyses in this area. In particular the available utility estimates and the way in which they are used in the model may give rise to some concern about the validity of estimates of cost effectiveness.

The table below highlights some of the key differences between the modelling studies of EA. Appendix 11 (page 180) provides a more detailed comparison of the differences between parameters included in the models. Only the study carried out for Microsulis provided a very detailed breakdown of individual cost elements that informed their procedure costs and these have been omitted from the table for the sake of brevity. All Thermachoice™ figures were provided in Euros and have been converted to pounds sterling based on one Euro = £0.635.

Table 34: Comparison between four economic analyses of endometrial ablation techniques

	PenTAG	Microsulis	Cavaterm™	Thermachoice™
Type of model	State transition (Markov)	Decision tree	Decision tree	(a) Cost analysis (b) Simple cost effectiveness analysis
Output	Cost per QALY	Cost per QALY	Cost per treatment success	Cost per: - additional case of amenorrhoea - additional case of eumenorrhoea or less - per reintervention rate avoided - additional satisfied patient
Time horizon	10 years	5 years	3 years	3 years
Procedure costs - Hysterectomy - TCRE - Cavaterm - Thermachoice - MEA	 £2,096 £1110 £826 £826 £942	 £2,644 £1,129 £712 £712 £674	 £2,050 £593 £584 £905 £793	 £1777 £958 - £904 -
Probability of Hysterectomy: - after TBEA - after MEA - after rollerball	 0.248 (year 5) 0.248 (year 5) 0.248 (year 5)	 0.321 (year 5) 0.208 (year 5) 0.368 (year 5)	 - - -	 0.077 (year 3 Thermachoice) 0.0595 (year 3 Cavaterm) 0.0252 0.065 - 0.195
Utility values – Convalescence after TBEA – Convalescence after MEA – Convalescence after TCRE or RB or TCRE+RB – Convalescence after hysterectomy – Post convalescence after TBEA – Post convalescence after MEA – Post Convalescence after TCRE or RB or TCRE+RB – Post Convalescence after hysterectomy – Utility in menorrhagia	 0.8 0.8 0.8 0.63 0.9 0.9 0.9 0.95 0.55	 0.76 0.76 0.76 0.74 0.57 0.79 0.73 / 0.74 0.86 0.5	 N/A	 N/A

The results of the cost effectiveness analyses vary. This is to be expected given the differences in modelling approaches and the complexity of the analyses. All models show that endometrial ablation is less resource intensive than hysterectomy. There is therefore a potential for resource savings arising from more widespread use of endometrial ablation as

first line surgical management in cases where there is not a strong preference for amenorrhoea. However, the size of any savings remains uncertain due to difficulty in estimating costs accurately.

Based on the available evidence, second generation EA techniques appear to offer advantages in terms of value for money to the NHS over first generation techniques. Analyses suggest that cost advantages may be accompanied by effectiveness and safety gains, leading to the dominance of second generation techniques in both our analysis and that submitted by Microsulis. However, the differences in both costs and effects are not large and are subject to considerable uncertainty. A major source of uncertainty in estimating cost utility is the value that should be placed on the relevant health states.

Although some of the analyses submitted to NICE suggest a difference between second generation techniques, decision makers should bear in mind that the evidence base for clinical effectiveness in this area is small, and in some respects very weak, depending on indirect comparisons. Any consideration of the cost effectiveness between second generation alternatives is further complicated by limited detailed data on costs during the entire clinical course of a patient and should therefore be viewed with great caution.

Summary

Chapter 5: Cost effectiveness information supplied by industry

- *The quality of economic analyses submitted by industry is variable and results uncertain.*
- *Only one provides a cost-utility analysis.*
- *All find second generation EA techniques offer value for money compared to first generation EA techniques. The size of the savings is uncertain due to the difficulties of estimating costs accurately.*
- *Each industry submission found their own product to be the cheapest or the most cost-effectiveness treatment.*
- *The only other cost-utility analysis also found their model very sensitive to utility values and there is uncertainty around this value.*

5.7 Impact on NHS budget

The economic models supplied by this assessment team and by industry assess the relative cost per QALY of each treatment, assuming that a woman with heavy menstrual bleeding may follow any treatment path. However, the impact of second generation endometrial ablation techniques on the NHS budget will depend on a number of factors such as:

- Women's preferences for different treatments offered, which will depend on an individual's desire for such aspects as amenorrhoea as an outcome, avoidance of major surgery etc.

- Number of women with HMB who are eligible for each treatment (for example, larger and abnormal uteri are a contraindication for TBEA, thin Caesarean scars are a contraindication for MEA)
- The existing diffusion of the technologies in the UK (for example, the number of surgeons performing TCRE/rollerball ablation, the number of centres that have second generation ablation equipment).

There are currently nearly 26,000 hysterectomies in the UK for heavy menstrual bleeding and a further 16,000 endometrial ablations, of which about 2,000 are second generation techniques (See Section 3.2.2 page 23). Table 35 below shows the effects of changing the balance of the current 42,000 surgical procedures for women with heavy menstrual bleeding. The cost of first generation EA is the cost of TCRE combined with rollerball as this is the most usual technique in the UK and the cost of hysterectomy is based on abdominal hysterectomy as this accounts for 80% of hysterectomies undertaken in the UK. Initial costs have been calculated assuming second generation ablation in equally divided between TBEA and MEA.

Table 35: Estimate of Current Cost to the NHS of surgical procedures for HMB

Procedure	Cost per procedure (£)	Number of procedures	Total costs (£)
Hysterectomy	2,069	26,000	53,794,000
TCRE / rollerball	1,027	14,000	14,378,000
MEA	942	1,000	942,000
TBEA	826	1,000	826,000
			69,940,000

If hysterectomies were replaced by endometrial ablation, overall costs would be reduced. If half were replaced by first generation techniques, costs would be reduced by £13,546,000 (Table 36). If half of all hysterectomies were replaced by second generation techniques (equally split between the technologies) costs would be reduced by £15,405,000 (Table 37).

Table 36: Costs to NHS if half hysterectomies were replaced by first generation EA

Procedure	Cost per procedure (£)	Number of procedures	Total costs (£)
Hysterectomy	2,069	13,000	26,897,000
TCRE / rollerball	1,027	27,000	27,729,000
MEA	942	1,000	942,000
TBEA	826	1,000	826,000
			56,394,000

Table 37: Costs to the NHS if half current hysterectomies were replaced by second generation EA

Procedure	Cost per procedure (£)	Number of procedures	Total costs (£)
Hysterectomy	2.069	13,000	26,897,000
TCRE / rollerball	1.027	14,000	14,378,000
MEA	942	7,500	7,065,000
TBEA	826	7,500	6,195,000
			54,535,000

If all first generation techniques were replaced by second generation techniques, a saving of £2,002,000 would be made (Table 38).

Table 38: Costs to the NHS if first generation techniques replaced by second generation techniques

Procedure	Cost per procedure (£)	Number of procedures	Total costs (£)
Hysterectomy	2,069	26,000	53,794,000
TCRE / rollerball	1,027	0	0
MEA	942	8,000	7,536,000
TBEA	826	8,000	6,608,000
			67,938,000

If all hysterectomies were replaced by endometrial ablation, cost savings would be £28,951,000 if half went to first generation techniques and the remaining half were equally split between second generation techniques (Table 39), and £32,812,000 if all were replaced by second generation techniques (Table 40). It is however, unlikely that all hysterectomies for heavy menstrual bleeding could be replaced by EA as some women will prefer this treatment or it will be the only available option.

Table 39: Costs to NHS if all hysterectomies were replaced by EA

Procedure	Cost per procedure (£)	Number of procedures	Total costs (£)
Hysterectomy	2,069	0	0
TCRE / rollerball	1,027	27,000	27,729,000
MEA	942	7,500	7,065,000
TBEA	826	7,500	6,195,000
			40,989,000

Table 40: Costs to the NHS if all hysterectomies were replaced by second generation EA

Procedure	Cost per procedure (£)	Number of procedures	Total costs (£)
Hysterectomy	2,069	0	0
TCRE / rollerball	1,027	0	0
MEA	942	21,000	19,782,000
TBEA	826	21,000	17,346,000
			37,128,000

The largest cost savings are therefore to be made through replacing some hysterectomies for HMB with endometrial ablation. Whilst replacing current levels of first generation ablation with second generation ablation techniques also results in savings, these are less.

6 DISCUSSION

6.1 Main results

Heavy menstrual bleeding (HMB) is a common condition which results in a considerable burden of ill health among women. Surgical intervention is frequently sought following failure of medical intervention, and a range of options are now available.

Hysterectomy is an established and effective treatment for heavy menstrual bleeding. However it is more expensive than newer alternatives, is a more complex procedure and may result in more serious complications. While the guarantee of amenorrhoea as a treatment outcome may be preferred by some women, this may not compensate others for having to undergo major surgery with its associated risks and recovery time or for the loss of their womb. Because of this, new minimally invasive surgical techniques have been developed.

6.1.1 Clinical Effectiveness

In this assessment we have carried out a systematic review of the effectiveness of MEA and TBEA against first generation EA and hysterectomy. This included nine trials, of which eight were randomised controlled trials. However, there are no studies comparing MEA or TBEA to hysterectomy so effectiveness and cost-effectiveness compared to hysterectomy has had to be inferred through indirect comparison. A good quality systematic review of first generation techniques compared to hysterectomy showed that hysterectomy was more effective (as measured by improvement in heavy menstrual bleeding and patient satisfaction) but was associated with greater consumption of health care resources and more adverse events. Satisfaction rates and effectiveness with first generation techniques and hysterectomy were high and the reviewers concluded that first generation techniques are an alternative surgical treatment for HMB.

The systematic review carried out for this assessment included nine studies comparing MEA (two studies) and TBEA (seven studies) to first generation ablation techniques. Duration of follow up has been limited (range 3-60 months, median 24). One trial included five year follow up but with 46% loss to follow up. Overall, the quality of the randomised controlled trials is moderate, and limited by the impossibility of blinding operators and subjects. All studies have some methodological limitations. The trials of MEA included more participants than those of TBEA and were of higher quality and applicability to the UK.

Only one study showed a first generation technique (TCRE) to be significantly superior for the outcome of amenorrhoea measured at one year, and this difference was not found to be superior using intent to treat analysis. Methodological details of this study are limited. No significant difference in amenorrhoea at two years was shown in the randomised trials. More women undergoing MEA become amenorrhagic than those undergoing TBEA, although the ranges overlap. No differences in amount or pattern of continuing menstrual loss were shown in studies which examined these outcomes. No differences were demonstrated for dysmenorrhoea or pre-menstrual symptoms in the included studies.

Patient satisfaction is reported in seven of the nine included studies and was high in all cases, despite differences in methods of outcome measurement, and showed no difference in satisfaction with different technologies in almost all of the comparisons. Only one study shows a significant difference in satisfaction, at two years, favouring rollerball over TBEA

when categories of satisfaction are collapsed into a dichotomous variable (satisfied/not satisfied).

One study each of MEA and TBEA investigated effects on quality of life. One MEA study, by Cooper and colleagues, used the SF36 outcome measure and showed improvements across the majority of domains for both MEA and TCRE over baseline. Only one comparison between groups was significant in an analysis of covariance: physical role was significantly improved in the TCRE group compared with the MEA group. The clinical significance of this isolated finding is uncertain. Meyer and colleagues investigated quality of life using a global question of impact and found no significant difference between TBEA and rollerball. Both first and second generation ablation techniques have a positive impact on ability to work/pursue normal activities, though neither study which examined this outcome showed a difference between techniques.

All studies showed that second generation techniques require significantly less operating or theatre time than first generation techniques. Differences in approaches to defining the time of interest make interpretation of the results difficult and preclude pooling the results of individual studies. Whether the difference in time to complete the procedure would be sufficient to permit staff redeployment for other purposes is possible but not certain. No differences in length of hospital stay have been shown. Equipment failure was reported in only one trial (Cooper and colleagues) and was significantly more frequent with MEA (9%) than TCRE (2%). However, this trial used a prototype machine and the same centre has since undertaken nearly 1000 further MEA treatments with no further equipment failure (Personal communication, K. Cooper).

The adverse effect profiles of second and first generation ablation techniques reported in RCTs are similar at around 3-4% overall. Adverse events include uterine perforation, haemorrhage, pain, haematometra, post-tubal sterilization syndrome, endometritis and pregnancy. Second generation techniques were associated with fewer intraoperative complications in the RCTs (1% vs 5% for MEA vs TCRE and 0% vs 3% for TBEA vs rollerball) and are not prone to the problem of fluid overload. The small size of RCTs limits statistical power to demonstrate whether such differences are significant. Two large uncontrolled observational studies of MEA and TBEA provides further evidence for low rates of complications.

Repeat surgery rates provide some indication of treatment failure. Reoperation rates appear to increase with time. In the longest duration study, 25% of the group allocated to TBEA and 16% of those allocated to rollerball in the trial by Meyer and colleagues had had repeat surgery by five years of follow up. This figure is based on the most conservative estimate of success – intent to treat figures are 11% and 7% respectively. Most women who needed further surgery had hysterectomy. Adverse event rates in repeat ablations may be higher than when ablation is the primary procedure.

6.1.2 Costs and cost effectiveness

The costs of MEA and TBEA procedures are similar, although the methods used to assess them may not be sensitive enough to measure such a small difference precisely. MEA was found to be slightly more expensive at £942 per treatment compared to £826 for TBEA. Compared to combined TCRE and rollerball, which is the most common type of first generation EA in the UK, both methods are cheaper, by £85 for MEA and by £201 for TBEA per treatment.

The cost effectiveness analysis necessarily depends on indirect comparisons - between MEA and TBEA and between both second generation techniques and hysterectomy. Such

comparisons are prone to bias and confounding and should be viewed with caution. However, in the absence of direct evidence, such analyses are deemed necessary by decision-makers. The cost utility analysis carried out for this assessment suggests that TBEA may be less costly and slightly more effective than MEA at 10 years although differences in costs and utilities are small and subject to uncertainty. Both second generation techniques similarly dominate TCRE, rollerball and TCRE/rollerball combined. Hysterectomy yields additional benefits for additional cost, with cost utility ratios of around £2,400 per QALY against both MEA and TBEA. These findings are subject to considerable uncertainty. In particular, the absence of evidence of clinical benefit between second generation options and between first and second generation techniques suggest these results should be treated with great caution and may be insufficiently robust to guide highly specific policy decisions.

6.2 Assumptions, limitations and uncertainties

Quality of Studies

The quality of the studies was variable, as discussed in Section 5.4.1 (page 53). This may limit the validity of the findings. In addition, the included studies contained varied population – women with menorrhagia as measured in different ways, inclusion or exclusion of women with fibroids, the inclusion of women who were post-menopausal in one study as well as two studies which did not give details about the included population. The comparator was either TCRE alone, rollerball alone or TCRE and rollerball combined, and these procedures may not have been consistent among the patients in the control groups of some studies. Rollerball and TCRE are known to have different adverse effects rates as shown in the MISTLETOE study (Table 20, page 87.) As a result no meta-analyses were possible. The study populations and techniques may not reflect clinical practice in the UK.

Both MEA trials use GnRH thinning agent for all participants. However, the TBEA trials vary in their approach to pre-thinning of the endometrium. While no chemical pre-thinning is advised by the manufacturers, two trials used GnRH in both arms of the study. Two used a pre-operative D&C for both arms, two do not report any pre-thinning and one used a pre-thinning agent only in the control arm. It is not known what effect pre-thinning has on the effectiveness of second generation EA. A systematic review of pre-thinning agents in first generation EA found that pre-thinning improved operating conditions for the surgeon and short term clinical outcomes although the effect on amenorrhoea and repeat surgery decreased over time.[55]

Outcome measures

As outlined in Section 3.1.3, (page 17) outcome measurement in heavy menstrual bleeding is problematic. It is not clear which outcome should be considered as the most important in assessing the success of endometrial ablation techniques given preferences for type of treatment and outcome. While amenorrhoea is an objective measure, it is arguably not the most appropriate measure for women who wish treatment to lessen menstrual bleeding but do not necessarily require menstruation to be eliminated. In clinical practice, where women are offered a choice of treatment, women who privilege amenorrhoea as an outcome may prefer to have a hysterectomy from the start.

As detailed in Section 3.1.3, there are a number of methods for measuring actual menstrual blood volume. However, these are rarely used in routine clinical practice and other measures are not used consistently across the studies. Women who do not have clinical heavy menstrual bleeding but subjectively regard their bleeding as unacceptably heavy are likely to be less satisfied with their treatment for heavy menstrual bleeding.[17] Those trials included in this review which have stringently measured heavy menstrual bleeding as an

inclusion criteria for women entering the trial may show higher success rates than will be seen in normal clinical practice. Only the MEA trial by Cooper and colleagues used self-defined HMB as an entry criteria, which mirrors clinical practice in the UK. Those trials using the PBAC method of measuring heavy menstrual bleeding have different levels for inclusion of women, as well as for defining success of treatment.

As the major effect of heavy menstrual bleeding on sufferers is decreased Quality of Life (QoL), this is an important outcome measure. Of the included studies, only Cooper and colleagues[86] used a recognised Quality of Life measure (the SF-36) and no trials used a condition specific measure of QoL. The validity of using generic measures of QoL alone in studies of heavy menstrual bleeding has been questioned (See Section 3.1.4 page 19). A range of surrogate measures of impact on quality of life, such as ability to work outside the home or impact on life have been used. Satisfaction, another important patient relevant outcome measure, is measured on different scales in the studies and no clear reports of the method of obtaining these data are given. It is difficult to draw conclusions from an outcome such as satisfaction which is related both to processes and outcomes of treatment. For both QoL and satisfaction the variety of measures used makes comparison between studies difficult.

Availability of evidence

Only two studies of MEA and seven of TBEA were identified which met the inclusion criteria.

There is also little evidence in the literature for long term follow up of women who have undergone MEA or TBEA for heavy menstrual bleeding. Therefore, longer term rates of recurrent heavy menstrual bleeding, and associated further surgery, are not known. It is also not known what adverse effects may be experienced in the longer term.

There is some evidence that in the long term, women who have undergone hysterectomy (for any indication) may be at increased risk of symptoms such as urinary incontinence,[50] vasomotor symptoms and some psychological symptoms.[51] However, women with heavy menstrual bleeding as a group will also have more psychological symptoms than women of the same age without heavy menstrual bleeding. In addition, in clinical studies, satisfaction with hysterectomy is reportedly very high.[52]

Cost-utility analysis

There is little difference in the costs and utilities for TBEA and MEA, and these are difficult to estimate precisely. In addition, the opportunity costs of freeing senior staff, bed and theatre time if second generation techniques are increasingly done by junior staff and under local anaesthetic have not been examined.

The economic model is very sensitive to the utility values used, especially the value for women who are “well” following recovery from an endometrial ablation procedure or hysterectomy. Little published evidence is available for this leaving the results of the cost-effectiveness model necessarily uncertain. A cost utility study by Sculpher[30] has provided most of the utility values used in this report. Values were obtained using the time-trade off method in interviews with 60 women who had been referred to secondary care by their GP and had uncomplicated heavy menstrual bleeding. Other methods of valuing health states, such as standard gamble or the EQ-5D may have generated different values, and in turn different costs/QALY.

The value for the state of menorrhagia was rated at a median of 0.55 (mean 0.5, SE 0.04) by the women interviewed in the Sculpher study. This seems low (see Table 1, page 20 for examples of utility values for other health states). A mean value of 0.5 using the time trade of method as here, suggests that women would be prepared to trade 50% of their future life

expectancy to avoid it. The range of scores for menorrhagia was zero (as bad as being dead) to 0.95 (where 1.0 is best possible health.) Clearly, even among women suffering from heavy menstrual bleeding, the impact of the condition is valued very differently by different individuals. A single utility value must therefore be regarded as uncertain. In the same study, women were asked to rate their own current health state which had a mean of 0.65 (SE 0.04) and a median of 0.75 (range 0-1.0), much higher than the state of menorrhagia, which the author ascribes to most women not menstruating at the time of the interview. The author acknowledges that there are problems eliciting values for chronic health states that may affect quality of life on a daily basis but for which the worst effects are episodic. In addition, for heavy menstrual bleeding, effects are not life-long, but will disappear at menopause.

Further health states, such as the utility value for post-convalescence ("well") after treatment for heavy menstrual bleeding may be particularly difficult to interpret. After hysterectomy, there is no possibility of heavy menstrual bleeding or other menstrual symptoms returning. Hysterectomy also prevents the possibility of some gynaecological cancers. In contrast, hysterectomy may cause premature ovarian failure and early menopause, as well as having some longer term adverse effects such as urinary incontinence. An ablation procedure cannot guarantee amenorrhoea, and there is the possibility of recurrent heavy menstrual bleeding. In the cost-utility analysis by Sculpher (1998),[30] women rated the "well" state following hysterectomy more highly than that following EA (median 0.95 vs 0.90 respectively). This may be influenced by individual women's preference for a particular treatment. Sculpher suggests that "further analysis is required to explore whether preference based treatment allocation has the potential to be cost-effective."[30]

Subgroups

The suitability of women with a complaint of heavy menstrual bleeding for the different treatments discussed in this assessment is likely to depend both on the woman's expectations and personal requirements (such as family completion or presence of other menstrually related symptoms) and the preference of her doctor. For example, women who strongly prefer amenorrhoea as an outcome, or who have severe associated menstrual symptomatology (severe premenstrual syndrome, for example) may not be suitable candidates for endometrial ablation techniques but be better treated with hysterectomy, while those preferring to avoid general anaesthetic may be better suited to second generation EA techniques. Other aspects of endometrial ablation which are known to appeal to women are the avoidance of major surgery, shorter hospitalisation and quicker return to work.[62] However, as women may desire conflicting aspects of surgery (such as wishing to stop periods but also wanting to avoid hospitalisation) full information about the procedures on offer and careful counselling may be needed.[63]

Thermal balloon ablation is not suitable with women for larger uterine cavities (>10 or 12 cm) or those with uterine pathology or abnormalities, who will need to chose another method of treatment. Pathology may account for 20 - 60% of women with heavy menstrual bleeding[14;15] although the review was unable to obtain information about the percentage of women with HMB with abnormally shaped uterine cavities or those with cavities over 12cm in length.

Practical considerations

Resource savings may be possible with second generation techniques if more junior medical staff or nurse practitioners were able to carry out the procedures. The MEA operations reported by Cooper and colleagues[86] were all performed by experienced registrars rather than consultants. In addition, first generation techniques are skilled operations which require training and experience. Not all consultants are therefore currently able to perform them.

6.3 NEED FOR FURTHER RESEARCH

- Head to head comparisons of second generation endometrial ablation techniques should be considered.

- Longer term follow up for all methods of EA in RCTs will provide better information about failure rates and repeat procedures as well as checking whether longer term complications are an issue.

- Given the importance of the utility values in determining cost-effectiveness of treatments for heavy menstrual bleeding, further research to establish utilities for the states of heavy menstrual bleeding, its surgical treatment, convalescence and complications of treatment would be valuable.

- Future studies of heavy menstrual bleeding should use validated quality of life measures and established modes of measuring patient satisfaction both with the procedure and the outcomes.

- Further research into the effect of the constellation of symptoms associated with menstruation (such as pain, bloating, breast tenderness etc.) and the part that these symptoms play in women's perceptions of bleeding and the effect of its treatment could help to establish which women will find treatment of bleeding alone acceptable.

- Alternative models of care for endometrial ablation should be further investigated, including different operators (non-consultant medical staff and specialist nurses) and different settings (office vs operating theatre).

7 CONCLUSIONS

Both microwave and thermal balloon endometrial ablation techniques appear to offer effective alternatives in the surgical treatment of women with heavy menstrual bleeding.

Second generation techniques are quicker to perform and appear to provide similar outcomes to first generation approaches. First generation techniques are associated with fewer adverse events than hysterectomy and there is evidence in favour of greater safety for second over first generation techniques. In trials between first and second generation techniques, there were very few significant differences in main clinical outcomes.

In essence, there seems to be little discernible difference between second generation techniques on the basis of currently available data, however TBEA may be suitable for fewer women as it has more restrictions on uterine size, abnormality and pathology. Both MEA and TBEA appear to offer similar outcomes to older ablation techniques at similar or lower costs. More patients undergoing MEA are amenorrhagic than those undergoing TBEA, although it is not possible to predict which patients will become amenorrhagic and the differences are small. If amenorrhoea is the preferred outcome, hysterectomy is the most effective technology, but with higher costs. The cost utility ratio for hysterectomy versus endometrial ablation is within the range considered by decision makers to represent acceptable value for money.

The potential exists for reducing costs of ablation further by using non-consultant operators or for increasing access by carrying out ablation in other settings, such as outpatient suites or community hospitals. The impact of such developments cannot currently be estimated with certainty. Finally, the value of increasing the range of treatment choices available to women has not been considered in this health technology assessment but may form an important consideration for decision makers.

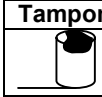
8 APPENDICES

8.1 Appendix 1: Pictorial blood loss assessment chart

Name: Ann Other

Day start: 1st July 2002

Towel	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
	||	|	|		|	|		
		||||	||||	||				
		||	||					
Clots/ flooding		50p x |	1p x 3					
Pain								

Tampon	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
	||	|			||	|		
		||	|||	||				
		|||| |	||||					
Clots/ flooding								
Pain								

From *The Management of Menorrhagia*[13] (p.73)

8.2 Appendix 2: Expert Advisory Panel

Expert panel	
Mr Nazaar Amso, Dept of Obstetrics and Gynaecology University Hospital of Wales Heath Park, Cardiff CF14 4XW	Dr S Bhattacharya MRCOG Dept of Obstetrics and Gynaecology Aberdeen Maternity Hospital Cornhill Road Aberdeen AB25 2ZD
Dr Kevin Cooper MRCOG Consultant gynaecologist Dept of Obstetrics and Gynaecology Aberdeen Royal Infirmary Foresterhill Aberdeen AB25 2ZN	Dr Neil Liversedge Dept of Obstetrics and Gynaecology Royal Devon and Exeter Hospital Barrack Road, Exeter EX2 5DW
Ms Mary -Ann Lumsden Dept of Obstetrics and Gynaecology Queen Elizabeth Building Royal Infirmary 10 Alexandra Parade Glasgow G31 2ER	Mr Nicholas C. Sharp Consultant Gynaecologist Dept of Obstetrics and Gynaecology Royal United Hospital Combe Park, Bath BA1 3NG

Declared conflicts of interest for the Expert Panel:

Dr Nazar Amso has been a principal investigator and first author in the first large observational report of Thermachoice EA (1998) and its follow up (accepted for publication). He has had travel/accommodation expenses paid for by Gynecare in the past when presenting data.

Dr Kevin Cooper has undertaken trials on microwave ablation and has had travel/accommodation to conferences paid for by Microsulis in the past.

Mr Nicholas Sharp is co-inventor of the microwave technology and has a financial interest. Microsulis Medical Ltd have sponsored a Research Fellowship at the Royal United Hospital for the last 7 years and have sponsored conference attendance for Mr Sharp and for the Research Fellows.

8.3 Appendix 3: Research protocol

TECHNOLOGY ASSESSMENTS FOR THE NHS HTA PROGRAMME

FINAL PROTOCOL: MICROWAVE AND THERMAL BALLOON ENDOMETRIAL ABLATION FOR HEAVY MENSTRUAL BLEEDING: A SYSTEMATIC REVIEW

Details of the research team

Correspondence to: Ms. Ruth Garside Research Fellow, Peninsula Technology Assessment Group, Dean Clarke House, Southernhay East, Exeter EX1 1PQ
Dr. Ken Stein, Senior Lecturer in Public Health, Peninsula Technology Assessment Group (LEAD)
Dr Katrina Wyatt, Lecturer in Health Services Research, University of Exeter
Mrs Kim Dalziel. Research Fellow, Peninsula Technology Assessment Group
Dr. Ali Round, Senior Lecturer in Public Health, Peninsula Technology Assessment Group
Ms Alison Price, Information Specialist, Southampton Health Technology Assessment Centre

Full title of research question

What is the effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation techniques for heavy menstrual bleeding compared to transcervical resection and rollerball ablation and hysterectomy ?

Clarification of the research question and scope

Heavy menstrual bleeding (HMB) or menorrhagia can have an major impact on women's lives. Objective menorrhagia is defined as total blood loss of more than 80ml per menstruation over several consecutive cycles.[1] However, since objective measurement is difficult, other subjective methods of estimating blood loss, such as flooding, passing of clots, the numbers of pads or tampons used and haemoglobin levels, are likely to be used in clinical practice. Subjective assessment of a woman's periods and the effect that they have on her lifestyle should be taken into consideration when looking at treatment efficacies for HMB.

Menorrhagia without major pathology is a condition that affects many otherwise healthy women with one in twenty women aged 30 to 49 consulting her GP each year with menorrhagia.[2] First line treatment is usually with drugs, although only 58% of women receive medical therapy before referral to a specialist.[3] Once referred to a gynaecologist, 60% of women with menorrhagia will have a hysterectomy within 5 years. One in five women in the UK have a hysterectomy before the age of 60 (Coulter 1991, in RCOG Guidelines for menorrhagia in secondary care, 1998) and about half of these are for a patient complaint of menorrhagia.[4] It has been estimated that up to half of all women presenting with menorrhagia will have blood loss within the normal range defined by population studies.[5] Hysterectomy is the only operation carried out without a routine assessment of the organ.[6]

51,858 hysterectomies were performed in 2000/01 of which 82% were abdominal and the remainder vaginal.[7] Of these operations at least half might be expected to be performed for menorrhagia.[8]

Hysterectomy is a radical solution for HMB, and there are risks of peri- and post-operative complications and, in some cases, significant emotional implications. Since the 1980s, endometrial ablation (EA) techniques have been developed as alternative, less invasive treatments for menorrhagia. All methods of endometrial destruction aim to destroy the inner lining of the uterus (endometrium). The endometrium is capable of regeneration and techniques must cause necrosis of the endometrial cells in order to suppress menstruation. This includes removing the full thickness of the uterine lining together with the superficial myometrium (underlying muscular layer), and the basal glands thought to be the focus of endometrial growth. First generation techniques such as resection, roller-ball and laser ablation require direct visualization of the endometrium using a hysteroscope.

A Cochrane review comparing endometrial resection and ablation techniques with hysterectomy has been undertaken and was updated in 1999.[9] This review considers five RCTs, four comparing transcervical resection of the endometrium (TCRE) and hysterectomy and one with a three way comparison including laser EA. This will be reviewed and an updated search for relevant RCTs undertaken in order to provide additional information for the appraisal to offer a more complete overview of the ablation techniques and hysterectomy.

The Cochrane review concluded that endometrial destruction offered an alternative surgical treatment for menorrhagia to hysterectomy. Both types of procedure were considered as effective and had high satisfaction rates from women. The permanent relief that hysterectomy offers is off-set by longer operating time, longer recovery period and higher rates of post-operative complications. The initial cost of endometrial destruction is significantly lower than for hysterectomy but, as a proportion of women require further surgery, this cost difference lessens over time.[9]

It has been suggested that newer EA techniques (such as microwave and thermal balloon endometrial ablation) have fewer complications than resection. While older style endometrial ablation techniques require specialist training and require a high level of technical skill, newer methods are regarded as quick and easy to learn.[10]

Technologies to be appraised

Microwave endometrial ablation (MEA) uses high frequency microwave energy to rapidly heat and destroy the endometrium. Microwaves at a frequency of around 9GHz are used and these are absorbed by the endometrial tissue to a depth of 3mm. The heat which is generated is conducted deeper into the endometrium so that tissue is destroyed to a maximum depth of 5-6mm aiming at sufficient endometrial ablation without risk to adjacent organs.

An applicator inserted into the uterine cavity through the dilated cervix delivers the microwaves. The applicator is slowly withdrawn with a sweeping movement to ensure that all of the endometrium is treated. The temperature is monitored and controlled through an external control unit. Treatment takes 5-10 minutes to complete and can be carried out under general or local anaesthetic. Medication is given to minimise cramping during and after the procedure.

Thermal ablation uses a silicone or latex balloon catheter which is inserted into the uterus through the vagina. A sterile liquid is used to inflate the balloon to fit the uterine cavity and is then heated to about 87°C and circulated within the balloon for about eight minutes causing

thermal ablation of the endometrial lining. Either local or general anaesthesia may be used. Medication is given to minimise cramping during and after the procedure.

A preliminary literature review found 52 references relating to RCTs of hysterectomy versus various methods of endometrial ablation, comparing types of EA or preparatory techniques used during EA. Thirteen of these are RCTs of microwave ablation or thermal balloon ablation versus first generation techniques. However, there is likely to be repeat reporting of the same trials among these references.

Scope
All randomised and non-randomised controlled trials of microwave or thermal balloon endometrial ablation versus any removal and ablation of endometrium (by resection or roller-ball,) or hysterectomy will be included. Head to head comparisons of microwave and thermal balloon ablation will be sought. Uncontrolled studies will be excluded.

The existing Cochrane systematic review of endometrial resection and hysterectomy will be reviewed. An updated search to locate any recent RCTs of this comparison will be undertaken.

Population
All women recruited from family planning clinics, primary care or specialist clinics.

Inclusion criteria:
Studies including pre-menopausal women with regular heavy periods measured objectively or subjectively.

Exclusion criteria:
Studies including women with the following criteria will be excluded if these women cannot be separately identified:
- Post menopausal bleeding (>1 year from the last period)
- Irregular menses and intermenstrual bleeding (metrorrhagia)
- Pathological causes of menorrhagia (eg uterine cancer)
- Iatrogenic causes of menorrhagia (eg intra-uterine device)

Interventions
Microwave or thermal balloon endometrial ablation versus any removal and ablation of endometrium (including transcervical resection of the endometrium, and endometrial ablation by electrocautery or laser) or hysterectomy (by open abdominal, vaginal or laparoscopic routes).

Outcomes

- **Quality of life:** Women's perceived change in quality of life.
- **Menstrual bleeding:** Amenorrhoea, objective or subjective assessment of improvement in menstrual blood loss
- **Duration of surgery**
- **Length of hospital stay**
- **Time to return to normal activities / work**
- **Rate of satisfaction:** At years after surgery 1,2,3, 4.

- **Requirement for further surgery for menstrual symptoms:** At years after surgery 1,2,3,4.
- **Adverse events:** Including uterine perforation, bleeding, haematometra, laceration, air embolism, intra-abdominal injury, fluid absorption, infection, cyclical pain, pregnancy and death.
- **Resource use / cost**

Patient Preferences
Information about patient preferences for methods or treatment for menorrhagia will be taken from included studies. We will extract data on the number of women approached to participate, the number taking part and the number who expressed a preference for a particular surgery.

Report methods

The report will include a systematic review of the evidence for clinical effectiveness and cost-effectiveness based on clinical review and cost data from published sources. The review will be undertaken systematically following the general principles outlined in NHS CRD Report 4. The research protocol will be updated as necessary as the research programme progresses. Any changes to the protocol will be reported to NCCHTA and NICE.

Search Strategy and Inclusion Criteria
Searches for clinical efficacy will start with the Cochrane library. Where good quality relevant systematic reviews are found these will form the core of the assessment of effectiveness. Preliminary searches show that a Cochrane review for hysterectomy versus TCRE and rollerball exists and searches for this comparison will be restricted to the years since the existing review was written.

For the main research question, all publications which describe trials of microwave or thermal balloon endometrial ablation techniques versus other endometrial ablation techniques or versus hysterectomy will be obtained using the search strategy described below. Preliminary searches have shown that a Cochrane review of endometrial destruction techniques also exists. Where appropriate, any meta-analyses will be updated.

Only studies with a comparison arm will be considered for inclusion. Where RCT evidence directly addressing the questions of interest and sufficient to reach a conclusion is obtained then non-randomised studies will not be included. If insufficient RCT evidence is available non-randomised studies will be included.

Titles and abstracts will be examined for inclusion by two independent reviewers and disagreement will be resolved by consensus.

Databases:
Electronic databases: including MEDLINE (Silver Platter); PubMed (previous 6 months for latest publications); EMBASE; The Cochrane Library including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, DARE, NHS EED and HTA databases; NRR (National Research Register); Web of Science Proceedings; Current Controlled Trials; Clinical Trials.gov
Bibliographies of included studies will be assessed for relevant studies.
Contacting research groups and industry

Inclusion
- Systematic Reviews

- Randomised Controlled Trials (RCTs)
- Controlled clinical trials (CCTs)

Exclusion
- Animal models
- Preclinical and biological studies
- Narrative reviews, editorials, opinions
- Non controlled studies
- Non English language papers
- Reports published as meeting abstracts only

Review methods

Data extraction strategy
Data will be extracted by one researcher and checked by another.

Quality assessment
Assessments of quality will be performed using the indicators shown below. Due to the nature of the intervention, the presence of blinding of treatment and treatment concealment are not applicable measures of quality except possibly in head to head comparisons.

Trial characteristics:
1. Appropriate method of randomisation of RCTs
2. Blind assessment of outcomes
3. Numbers of women randomised, excluded and lost to follow up.
4. Whether intent to treat analysis is performed
5. Whether a power calculation was done
6. Timing, duration and location of the study

Study participants:
5. Age and any other recorded characteristics of women in studies.
6. Inclusion criteria
7. Exclusion criteria

Interventions used:
3. Type of endometrial ablation technique and route of hysterectomy surgery
4. Endometrial thinning agents used.

Outcomes:
1. Methods used to evaluate women's satisfaction and quality of life post-surgery
2. Methods used to measure menstrual loss
3. Methods used to evaluate resource and patients costs
4. Length of follow up

Methods of analysis/ synthesis
Where appropriate, meta-analysis methods will be employed to estimate a summary measure of effect, otherwise information will be synthesised by narrative methods.

Methods for evaluating quality of life, costs and cost effectiveness and/or QALYS
Quality of life measures, costs for treatments and savings will be taken from published work. Estimates of resource costs from individual trusts or groups of trusts may be used, if time permits, where published data are not available.

If an economic analysis for microwave or thermal ablation already exists we will provide a critique of this. If no economic analysis already exists, a cost effectiveness model will be undertaken of microwave and thermal ablation techniques versus TCRE and rollerball ablation and hysterectomy.

Handling the Industry submission

Where information provided by industry meets our inclusion criteria, this will be included in the review.

Project Management

Timetable
Draft Protocol: 30th July 2002
Finalised protocol: 20th August 2002
Progress report: 13th November 2002
Draft final report: 22nd January 2003

Competing interests
None

External reviewers
A group is currently being formed. This group will act as an expert resource to guide the process of the review. At least two separate experts will be identified as peer reviewers of the completed draft review.

Reference List

1. Royal College of Obstetricians and Gynaecologists. The Initial Management of Menorrhagia. Evidence Based Guidelines No. 1. London: Royal College of Obstetricians and Gynaecologists, 1998.
2. Vessey MP, Villard-Mackintosh L, Mcpherson K, Coulter A, Yeates D. The epidemiology of hysterectomy: findings in a large cohort study. *Brit J Obstet Gynaecol* 1992;99:402-7.
3. Coulter A, Bradlow J, Agass M, Martin-Bates C, Tulloch A. Outcomes of referrals to gynaecology out-patients clinics for menstrual problems: an audit of general practice records. *Br J Obstet Gynaecol* 1991;98:789-96.
4. Chimbira TH AATAC. Study of menstrual blood loss. *Br J Obstet Gynaecol* 1980;87:603-9.
5. Fraser IS MGMR. A preliminary study of factors influencing perception of menstrual blood loss volume. *Am J Obstet Gynecol* 1984;149:788-93.
6. Wyatt KM DPWTOP. Determination of total menstrual blood loss. *Fertil Steril* 2001;76:125-31.
7. Hospital Episode Statistics. London: Department of Health, 2001.
8. Coulter A, Kelland J, Long A, Melville A, O'Meara S, Sculpher M *et al*. The Management of Menorrhagia. *Effective Health Care* 1995;9.
9. Lethaby A, Shepperd S, Cooke I, Farquhar C. Endometrial resection and ablation versus hysterectomy for heavy menstrual bleeding. *Cochrane Database.Syst Rev* 2000.
10. Cooper KG, Bain C, Parkin DE. Comparison of microwave endometrial ablation and transcervical resection of the endometrium for treatment of heavy menstrual loss: a randomised trial. *Lancet* 1999;354:1859-63.

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8.4 Appendix 4: Search Strategy

Two separate searches were undertaken for this project. One searched specifically for research evidence on thermal balloon and microwave endometrial ablation for all years, the other looked for research comparing hysterectomy with the first generation EA techniques of rollerball ablation and TCRE from 1999 onwards to update an existing Cochrane review. The following databases were searched for published studies and recently completed and ongoing research.

Search 1: Microwave and Thermal Balloon endometrial ablation

- Cochrane Library (Issue 3, 2002)

Includes the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, DARE, NHS EED and HTA databases.

#1 (((MENORRHAGIA or BLEEDING) or BLOOD) or MENSTRUAL)
#2 MICROWAVE*
#3 MICROWAVES*.ME
#4 THERMAL OR BALLOON
#5 (ENDOMETRI* near ((ABLAT* or RESECT*) or DESTRUCTION))
#6 DIATHERMY*.ME
#7 BALLOON-DILATATION*.ME
#8 CATHETER-ABLATION*.ME
#9 #2 OR #3 OR #6
#10 #9 AND #5
#11 #4 OR #7 OR #8
#12 #11 AND #5
#13 #10 OR #12

- National Research Register (Issue 2, 2002)

As for the Cochrane Library (above)

- MEDLINE (WebSPIRS) 1966-2002/08

((('Menorrhagia-' / all subheadings in MIME,MJME) or (menorrhagia) or (bleeding or blood or menstrual)) and (((microwave near (endomet* ablat*)) or (explode 'Diathermy-' / all subheadings in MIME,MJME) or (microwave*)) or ((thermal balloon) or (Catheter-Ablation-methods in MIME) or ('Catheter-Ablation' / all subheadings in MIME,MJME) or (Balloon-Dilatation-methods in MJME) or (Catheter-Ablation-methods in MJME) or (thermal near (balloon* or ablat*))))) and ((explode 'Hysterectomy-' / all subheadings in MIME,MJME) or (hysterectom*))

- PubMED (Internet version for recent studies) Last 180 days

endometrial and (ablation or resection or destruction)

- Embase (WebSPIRS) 1980-2002/08

((ENDOMETRI* near ((ABLAT* or RESECT*) or DESTRUCTION)) and ((microwave*) or ('microwave-irradiation' / all subheadings) or ('microwave-radiation' / all subheadings) or ('diathermy-' / all subheadings))) or ((ENDOMETRI* near ((ABLAT* or RESECT*) or DESTRUCTION)) and ((thermal near balloon) or ('balloon-dilatation' / all subheadings) or ('balloon-catheter' / all subheadings) or ('catheter-ablation' / all subheadings)))

- Web of Science Proceedings All years (from 1980)

(endometrial or endometrium) and (ablation or resection or destruction) and (microwave* or thermal balloon)

- Clinical Evidence Issue 7 September 2002

Endometrial and (destruction or resection or ablation)

Search 2: Endometrial ablation (TCRE/Rollerball) vs hysterectomy from 1999 to 08/2002

- Cochrane Library (Issue 3, 2002) Searched from 1999 – August 2002

#1 (((MENORRHAGIA or BLEEDING) or BLOOD) or MENSTRUAL)
#2 HYSTERECTOMY*:ME
#3 HYSTERECTOM*
#4 (ENDOMETRI* near ((ABLAT* or RESECT*) or DESTRUCTION))
#5 ((#2 or #3) or #4)
#6 #1 and #5
#7 #6 Publication date from 1999 to 2002

- National Research Register (Issue 2, 2002)

#1 (ENDOMETRI* NEAR ((ABLAT* OR RESECT*)OR DESTRUCTION))
#2 HYSTERECTOM*
#3 HYSTERECTOMY*.ME
#4 (((MENORRHAGIA OR BLEEDING) OR BLOOD) OR MENSTRUAL)
#5 #1 OR #2 OR #3
#6 #5 AND #4

- MEDLINE (WebSPIRS) 1999-2002/08

((('Menorrhagia-' / all subheadings in MIME,MJME) or (menorrhagia) or (bleeding or blood or menstrual)) and ((explode 'Hysterectomy-' / all subheadings in MIME,MJME) or (hysterectom*) or (endometr* near (ablat* or resect* or destruction)))) and (((((('Menorrhagia-' / all subheadings in MIME,MJME) or (menorrhagia) or (bleeding or blood or menstrual)) and ((explode 'Hysterectomy-' / all subheadings in MIME,MJME) or (hysterectom*) or (endometr* near (ablat* or resect* or destruction)))) and (English in la) and (LA=ENGLISH) and (PT=RANDOMISED-CONTROLLED-TRIAL)) or ((((('Menorrhagia-' / all subheadings in

MIME,MJME) or (menorrhagia) or (bleeding or blood or menstrual)) and ((explode 'Hysterectomy-' / all subheadings in MIME,MJME) or (hysterectom*) or (endometr* near (ablat* or resect* or destruction)))) and (LA=ENGLISH) and (PT=META-ANALYSIS)) or ((systematic near (review or overview)) or meta-anal* or metaanal*) or (random*))

- PubMED (Internet version) Last 180 days

(endometrial or endometrium) and (ablation or resection or destruction)

- Embase (WebSPIRS) 1999-2002/07

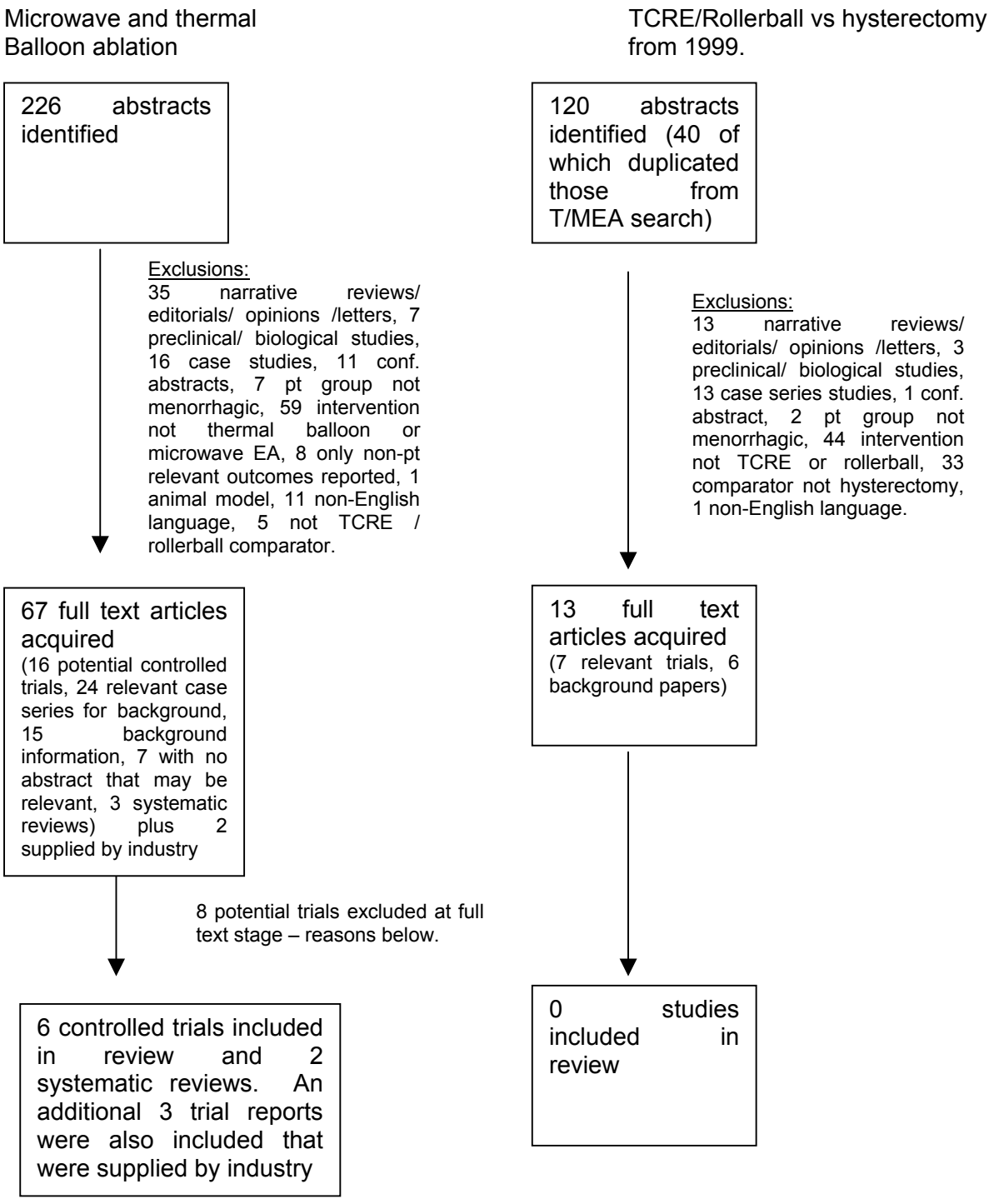
((((('menorrhagia-' / all subheadings) or (menorrhagia or bleeding or blood or menstrual)) and (('endometrium-ablation' / all subheadings) or (endometr* near (ablat* or resection or destruction)) or (explode 'hysterectomy-' / all subheadings) or (hysterectom*))) and (random* or meta-anal* or metaanal* or (systematic* near (review* or overview*)))) and (English in la)

- Web of Science Proceedings 1999-August 2002

(endometrial or endometrium) and (ablation or resection or destruction)

An updated search of Medline and Embase was run for both search strategies on 04/12/2002 to cover the intervening months from 08/2002 to 11/2002 before the report was drafted.

8.5 Appendix 5: Excluded studies



List of excluded studies from search strategy:

Study	Reason for exclusion at full text stage
Uterine balloon to avoid hysterectomy. *J-WOMEN'S-HEALTH* 1997;**6**:401-2.	Opinion piece
Bongers MY, Mol BWJ, Fernandez H, Gervaise A. Thermal balloon ablation versus endometrial resection for treatment of abnormal uterine bleeding. *HUM-REPROD* 2000;**15**:1424-5.	Letters
Garuti G, Cellani F, Colonnelli M, Luerti M. Endometrial thermal ablation to treat dysfunctional menorrhagia; a clinical experience using two different techniques. *ITAL-J-GYNAECOL-OBSTET* 2001;**13**:160-5.	Comparison of HTA and thermal balloon ablation
Genolet PM, Gerber S, De Grandi P, Friberg B, Ahlgren M. Endometrial ablation for dysfunctional uterine bleeding in the perimenopause, clinical results of a multicentre trial with the Cavaterm (TM) thermal balloon. *9Th International Menopause Society World Congress on the Menopause* 1999;315-20.	Abstract only
Loffer;FD-Grainger,D.Kung-RC-Stabinsky. Endometrial Ablation for the Treatment of Menorrhagia: A Randomised Trial Comparing Uterine Balloon Therapy with Rollerball. *Acta Ovbstet Gynecol Scand*; 76: 23	Abstract only
Parkin D. A randomised controlled trial comparing transcervical endometrial resection with microwave endometrial ablation in the treatment of dysfunctional uterine bleeding: 2 year follow up. *9th Ann Congress of Int Soc for Gynecologic Endoscopy/10th Ann Mtg of Australian Gynaecological Endoscopy Soc 16 19 April 2000* 2000;140.	Abstract only
Romer T. The treatment of recurrent menorrhagia - Cavaterm-balloon-coagulation versus roller-ball-endometrial ablation - A prospective randomised comparative study. *ZENTRALBL-GYNAKOL* 1998;**120**:511-4.	Excluded because in German but later included when an English translation was supplied by Wallesten, the makers of Cavaterm.
Wortman,M. Thermal balloon and rollerball ablation to treat menorrhagia: A multicenter comparison ZT OBSTET GYNECOL Obstetrics and gynecology 1998; 92 (6) 1057	Letter

8.6 Appendix 6: Included Systematic Reviews – QUOROM checklist

1. Lethaby et al 2002, Endometrial resection and ablation versus hysterectomy for heavy menstrual bleeding.[52]

1. Title: Identify the report as a systematic review?

Yes – (Cochrane Review)

2. Abstract: Uses a structured format?

Yes. Organised as:

Background	Outlines the clinical problem.
Objectives	The clinical question states that the review will compare endometrial ablation techniques but is not explicit in stating that clinical effectiveness or cost effectiveness are to be evaluated
Search strategy	Data bases and additional sources searched are listed.
Selection criteria	Describes the population, intervention, and study design.
Data collection and analysis	Describes outcomes extracted, methods of data extraction, and quantitative data synthesis in sufficient details to permit replication. Methods for validity assessment not described.
Main results	Characteristics of included trials not reported. Description of findings presented but not point estimates or CIs.
Reviewers' conclusions	Reports the main results.

3. Introduction

Yes. Describes the clinical problem, biological rational for the intervention.

4. Methods

Searching	Databases searched are listed, hand searching listed. No restrictions of publication status, language or year of publication are stated.
Selection	Inclusion criteria are given which include description of included population, intervention study design and outcomes.
Validity assessment	Methodological quality is described in relation to adequate concealment prior to randomisation, power calculations for sample size, ITT analysis and attrition rates. Sensitivity analyses are undertaken.
Data abstraction	Independently by two reviewers. Additional information about trial methodology and results sought from corresponding author of trials where necessary.
Study characteristics	Study design, patient characteristics, intervention details, outcome definitions, length of FU are assessed. Heterogeneity was examined by inspecting the scatter in the data points on the graphs and the overlap in their CI, and by checking the results of chi-square tests.
Quantitative data synthesis	Dichotomous data expressed as Peto odds ratio and 95% CI, meta-analysis using RevMan, continuous data shown as weighted mean

	difference and 95% CI. Stated that fixed approach used unless significant heterogeneity, though in fact all outcomes use fixed effect models. Where only medians and ranges were available, the median was regarded as identical to the mean and estimate of SD calculated from the range (range X 0.95/4). Not clear by what method the studies are weighted in the meta-analysis for continuous outcomes as not stated– it does not appear to be sample size, and is not consistent across outcomes.

5. Results

Trial flow	Not included
Study characteristics	Study design, patient characteristics, intervention details, outcome definitions, length of FU are tabulated
Quantitative data synthesis	Agreement on selection and validity assessment is not reported. Results of meta-analysis presented from RevMan.

6. Discussion

The discussion summarises key findings, clinical inferences based on internal and external validity are not discussed, the results are interpreted based on the total evidence included in the review, potential biases are not discussed. Addresses the problem of heterogeneity between the studies. Sensitivity analyses were performed as a result of this, it is stated that no change in the direction of results although points estimates did change which are not stated. Future research agenda is suggested.

2. Lethaby and Hickey, (2002)Endometrial destruction techniques for heavy menstrual bleeding. [9]

1. Title: Identify the report as a systematic review?

Yes – Cochrane Review

2. Abstract: Uses a structured format?

Yes – organised as below

Background	Outlines the clinic problem.
Objectives	Expresses the clinical question explicitly.
Search strategy	The databases searched are listed as well as other search methods.
Selection criteria	Selection criteria – type of trials, population, intervention and outcomes are listed.
Data collection and analysis	Methods for inclusion, quality assessment and data extraction are described. Methods of data synthesis not described.
Main results	Characteristics of RCTs included and excluded are not described. Point estimates and 95% CI are given.
Reviewers' conclusions	Main results given.

3. Introduction

Yes. Describes the clinical problem, biological rational for the intervention

4. Methods

Searching	Details of databases searched given, search terms listed, registers searched listed, handing searching
Selection	Inclusion and exclusion criteria given. Titles and abstracts screened by one reviewer. Uncertainty at full script stage resolved by discussion with colleague.
Validity assessment	Quality of included trials assessed independently by two reviewers.
Data abstraction	Data extraction performed independently by two reviewers. Additional information about trial methodology and results sought from corresponding author of trials where necessary.
Study characteristics	Study characteristics are described.
Quantitative data synthesis	Dichotomous data expressed as odds ratios with 95% CI meta-analysis with RevMan using Peto-modified Mantel-Haenszel method. Continuous outcomes shown as weighted mean difference with 95% CI. Heterogeneity assessed by inspecting the scatter in the data points on the graphs and the overlap of their CIs, and by checking results of Chi-squared tests. Fixed effects model used unless there was significant heterogeneity (one outcome only – use of local anaesthetic). No sub-group analysis planned. A priori sensitivity analyses planned.

5. Results

Trial flow	Trial flow diagram not included.
Study characteristics	Descriptions for each trial tabulated, including patient characteristics, method of randomisation, inclusion/exclusion criteria, outcomes. Interventions described but not referenced.
Quantitative data synthesis	Agreement on selection and validity assessment is not reported. Results of meta-analysis presented from RevMan. However, in the section comparing all 1st generation and all second generation methods of EA, the figures given in the text and those presented in the graphs differ. In the case of results for amenorrhoea, this leads the text to suggest the difference is significant, whilst the graph does not.

6. Discussion

The discussion summarises key findings. Internal and external validity (eg study differences in actual menstrual blood loss among participants, inclusion of patients who had not failed medical management) are discussed. The results are discussed in the light of total available evidence. Potential biases in the review process are not discussed. Future research agenda is suggested.

8.7 Appendix 7: Included Systematic Reviews

Reference and Design	Research Question and Search strategy	Inclusion and quality criteria
▪ *Author:* Lethaby et al 2002 ▪ *Study topic:* Endometrial ablation and hysterectomy for heavy menstrual bleeding	▪ *Aim:* To determine the effectiveness of endometrial resection and ablation techniques vs. hysterectomy to reduce menstrual blood flow. ▪ *Search strategy (databases searched):* Trial Register of the Cochrane Menstrual Disorders and Subfertility Group, MEDLINE, Embase, Current Contents Biological Abstracts, Social Sciences Index, PsychLIT and CINAHL. Relevant journals were hand searched and citation lists of included trials, conference abstracts and review articles also searched. ▪ *Search terms*: menorrhagia, excessive menstrual blood loss, dysfunctional uterine bleeding, iron deficient anaemia, heavy menstrual bleeding, hysterectomy, vaginal hysterectomy, vaginal hysterectomy, total abdominal hysterectomy, subtotal abdominal hysterectomy, laparoscopic hysterectomy, transcervical resection of the endometrium, TCRE, endometrial, laser ablation	Inclusion criteria: ▪ *Study design:* RCTs ▪ *Interventions:* Resection, rollerball, laser or other ablations of the endometrium ▪ *Population:* Women of reproductive years with regular heavy periods measured either objectively or subjectively. ▪ *Setting:* Primary care, family planning or specialist clinics. ▪ *Outcome measures:* Objective or subjective improvement in menstrual blood loss, women's perceived change in quality of life (recorded in a reproducible and validate format), length of stay in Hospital, time to return to work, duration of surgery, rate of satisfaction at 1, 2, 3, 4 years, mortality. ▪ *Quality criteria:* trial characteristics – method of randomisation, presence of blinding of treatment allocation, quality of allocation concealment, number of women randomised, excluded or lost to FU, whether ITT analysis done, whether power calculation was done, duration timing and location of study. Participant characteristics – age and any other recorded characteristics, other inclusion criteria, exclusion criteria. Interventions – type of Endometrial destruction techniques and route or hystercet0my. Outcomes – methods used to measure blood loss, to evaluate resource and patient costs and to evaluated participant satisfaction and change in quality of life [post surgery. ▪ *Application of methods:* Trials were selected for inclusion by 2 reviewers, assessment of quality was independently assessed by 2 reviewers using forms designed to Cochrane guidelines.

Results

- *Quantity of included studies:* Five RCTs, total of 752 participants.
- *Quality of included studies:* Four out of 5 had an allocation score of A based on adequate concealment prior to allocation. The other gave no indication of method of concealment although randomisation was by sealed envelope. No trial was blinded – patients and surgeons knew what operation what performed. Power calculations were performed for 4/5 studies and analysis was by ITT. 4 studies were single centre and the 5th had 9 UK centres but no imbalances were seen in baseline prognostic factors. Withdrawals after randomisation and prior to surgery were 8%, 2%, 6%, 13% and 3%. At longer FU, additional losses were 9%, 21%, 0%, 39% and 9%. Two trials calculated cost per participant based on resource use. A third summed the average costs of variable resource s and then added a factor of 100% to allow for fixed costs (this method did not permit estimates of variance to be calculated)
- *Combined treatment effect (incl. point estimates, CI, p values etc):* Satisfaction: at 1 year odds of satisfaction higher with Hysterectomy (Peto odds ration 0.46, 95% CI 0.24, 0.88; p=0.02) At 2 years (OR = 0.31, 95% CI 0.16, 0.59; p=0.00) However no difference at 3 (OR 0.32, 95% CI 0.08, 1.37 p=0.12) and 4 years (OR 0.52, 95% CI 0.21, 1.26; p=0.15). Improvement in MBL: At 1yr odds of greater proportion with improved MB favoured hysterectomy (OR 0.12, 95% CI 0.06, 0.25), at 2 yrs no difference (OR 0.10 95% CI 0.00, 5.41, p=0.3); at 4 years no difference (OR 0.15, 95% CI 0.01, 2.38, p=0.18) ORs at 2&4 yrs based on 1 study.

QoL: GR inventory scores (based on 1 study) no difference at 1 yr (WMD 0.000 (95% CI –1.750, 1.750, p= 0.00)

All the following SF36 scores at 2 yrs - Role limitation (physical) No difference (WMD –1.426, 95% CI –10.310, 7.458, p=0.8), Role limitation (emotional) No difference (WMD –7.272, 95% CI –15.741, 1.196, p=0.09), Social functioning higher scores with hysterectomy (WMD –7.182, 95% CI –12.387, -1.97, p=0.01), mental health – no difference (-2.935, 95% CI –7.386, 1.516, p= 0.20), Energy no difference (WMD –5.026, 95% CI –10.373, 0.322, p= 0.07), Pain, better with hysterectomy (WMD –8.709, 95% CI –15.034, -2.38, p= 0.01), General health perception better with hysterectomy (WMD –6.697, 95% CI –12.203, -1.19, p=0.02) Physical functioning no difference (WMD –2.756, 95% CI –7.188, 1.676, p=0.20).

Change in Euroqol score from baseline at 4 months (1 study) No difference (WMD –7.0000 95% CI –17.286, 3.286, p=0.18) at 2 years (1 study) no difference (WMD -1.5000, 95% CI –6.287, 3287, p=0.50).

SSR score at 2 yrs after surgery (1 study) no difference (WMD –3.700, 95%CI –11.169, 3.769, p=0.30)

Total HAD score 2 yrs after surgery (1 study), No difference (WMD 1.500, 95% CI –1.329, 4.319, p=0.30), Anxiety HAD scores 2 and 4 yrs after surgery, No difference (WMD 0.669, 95% CI –0.302, 1.641, p=0.18), Depression HAD scores 2 and 4 yrs after surgery No difference (WMD 0.002, 95% CI –0.092, 0.096, p=1.00)

The following 4 measures each based on 1 study - Proportion with improvement in QoL at 2 yrs No difference (1 study) (OR 0.54, 95% CI 0.15, 1.98, p=0.40)

Proportion with improvement in general health at 1 yr Better for hysterectomy (OR 0.26, 95% CI 0.11, 0.63)

Proportion with improvement in general health 4 yrs after surgery no difference (0.36, 95% CI 0.13, 1.01, p=0.05)

Proportion with improved symptoms at 1 yr No difference (OR 0.43 95% CI 0.15-1.28, p=0.13)

Duration of surgery : Shorter with TCRE/ablation (WMD –23.062, 95% CI –23.799, -22.324, p=0.00)

Duration of hospital stay: Shorter with TCRE/ablation (WMD –4.907, 95% CI 4.948, -4.866, p=0.00)

Time to return to work: Shorter with TCRE/ablation (WMD –4.641 95% CI –4.853, -4.430, p=0.00)

- *Adverse effects*

Immediate:

Sepsis fewer with TCRE/Ablation (OR 0.16, 95% CI 0.10, 0.24, p=0.00), Haemorrhage no difference (OR 0.59, 95% CI 0.20, 1.74, p=0.30), Blood transfusion, fewer with fewer with TCRE/Ablation (OR 0.22, 95% CI 0.08, 0.57, p=0.00), Urinary retention fewer with TCRE/Ablation (OR0.13, 95% CI 0.04, 0.44, p=0.00), Anaemia (1 study) fewer with TCRE/Ablation (OR 0.12, 95% CI 0.03, 0.43, p=0.00), Pyrexia (1 study) fewer with TCRE/Ablation (OR 0.12, 95% CI 0.06, 0.27, p=0.00), Vault haematoma fewer with TCRE/Ablation (OR 0.14, 95% CI 0.06, 0.34, p=0.00), Wound haematoma (1 study) fewer with TCRE/Ablation (OR 0.11, 95% CI 0.04, 0.32, p=0.00), Anaesthetic no difference (1 study) (OR 0.12, 95% CI 0.01, 1.99, p=0.14), Fluid overload, more likely with TCRE/Ablation (OR5.57, 95% CI 1.82, 17.12, p=0.00), Perforation (1study) no difference (OR 6.85, 95% CI 0.14, 346.18, p=0.30), GI obstruction, ileus (1 study) no difference (OR 0.47 95% CI 0.05, 4.57, p=0.50), Laparotomy (1 study) no difference (OR 0.33, 95% CI 0.05, 2.41, p=0.30), cautery of hyper-granulation fewer with TCRE/Ablation (OR 0.12, 95% CI 0.02, 0.94).

- *Assessment of heterogeneity:* Through examining the scatter in data points on graphs and their overlap in CI and by checking the results of chi-squared tests

AEs after discharge:
Sepsis (1 study) fewer with TCRE/Ablation (OR 0.19, 95% CI 0.08, 0.47, p = 0.00), Haematoma No difference (OR 0.55, 95% CI 0.13, 2.4, p=0.4), Diarrhoea (1 study) no difference (OR 0.13, 95% CI 0.00, 6.68, p=0.3), haemorrhage (1 study) no difference (OR 7.24, 95% CI 0.14, 365.04, p=0.3)

- *Further surgery for HMB*

Within one year More likely with TCRE/Ablation (OR 7.33, 95% CI 4.18, 12.86, p=0.00)
At 2 years More likely with TCRE/Ablation (OR 7.5, 95% CI 4.20, 13.42, p=0.00)
At 3 yrs (1 study) more likely with TCRE/ablation (OR 4.45, 95% CI 1.78, 11.15, p=0.00)
At 4 years (1 study) more likely with TCRE/ablation (OR 9.84, 95% CI 4.93, 19.67,, p=0.00)

Methodological comments

- *Search strategy* OK
- *Participants* OK
- *Inclusion/exclusion criteria:* OK
- *Quality assessment of studies:* Good
- *Method of synthesis:* Differences between groups for continuous data outcomes using weighted mean difference. A fixed effects model used unless significant heterogeneity shown, in which case results were confirmed with a random effects model. Median regarded as identical to the mean where this was the only measure available and an estimate of SD calculated from the range. Some outcomes were reported by only one included study.

General comments

- *Generalisability:* High
- *Appropriate outcome measures used?* Yes
- *Any differences in baseline characteristics of pts and controls?* None reported
- *Appropriate analysis?* Yes
- *Funding?* None stated

Reference and Design	Research Question and Search strategy	Inclusion and quality criteria
▪ *Author:* Lethaby, A, Hickey M. 2002 (UK) ▪ *Study topic:* Endometrial ablation techniques for heavy menstrual bleeding	▪ *Aim:* To compare the efficacy, safety and acceptability of methods used to destroy the endometrium to reduce HMB in premenopausal women. ▪ *Search strategy (databases searched):* Regular six monthly searches of the Trials Register for the Menstrual Disorders and Subfertility Cochrane Group (most recent ion July 2001), also MEDLINE (1966-Sept. 2001), EMBASE (1980-Aug. 2001), Current contents (1993- Week 38, 2001), Biological Abstracts (1980 – June 2001), PsychInfo (1967 – Aug. 2001), CINAHL (1982-July 2001) ▪ *Search terms:* menorrhagia, hypermenorrhagia, (excessive) menstrual blood loss, dysfunctional uterine bleeding, iron deficient anaemia, heavy menstrual bleeding, dysfunctional uterine bleeding, transcervical resection of the endometrium, TCRE, endometrial ablation, laser ablation, hysteroscopy, electrosurgery, rollerball, (thermal) balloon, hypertherm(ia), thermotherapy, photodynamic therapy, phototherapy, cryoablation, microwave ablation, radiofrequency, saline irrigation, laser interstitial, Thermachoice, Cavatherm, ELITT, Vesta, Novasure, Microsulis, Cryogen, bipolar. In addition, the National Research Register issue 3, 2001, MRC clinical trials register and NHS CRD were searched using the search terms menorrhagia and endometrial ablation. And hand-searching of journals, conference abstracts and review articles undertaken. Experts, manufacturers and authors were also contacted.	*Inclusion criteria* ▪ *Study design*: RCT and comparative studies ▪ *Interventions:* TCRE, laser, rollerball, saline irrigation, microwave, radiofrequency, heated balloon, photodynamic therapy, cryoablation and any other endometrial destruction techniques compared to each other or grouped into categories (1st or 2nd generation techniques) to reduce HMB. ▪ *Population:* Women of reproductive years with regular heavy periods measured objectively or subjectively. ▪ *Setting:* Primary care, family planning or specialist clinics. ▪ *Outcome measures:* Primary – objective or subjective assessment of improvement in MBL, QoL, Improvement of menstrual symptoms such as amenorrhoea and PMS. Secondary – length of hospital stay, time to return to work, duration of surgery, operative difficulties, rate of satisfaction with procedure, complication rate, resource use/cost, requirement for further surgery for HMB, mortality. ▪ *Quality criteria:* Trial characteristics – Method of randomisation, blinding, quality of allocation concealment, number randomised, excluded, lost to FU, ITT analysis, power calculation included, duration, timing, location of study, source of funding. Study characteristics – age and other recorded characteristics of women, other inclusion criteria, exclusion criteria. Interventions used- type of EA technique. Outcomes – methods used to measure blood loss, to evaluate resource and patient costs and to evaluate satisfaction, change in QoL and menstrual symptoms. ▪ *Application of methods* Data extracted independently by 2 reviewers using forms according to Cochrane guidelines. Authors of 4 trials contacted for further information but only one response received.

Results

- *Quantity of included studies:* Eight studies, 1595 participants
- *Quality of included studies:* All had parallel group design, 3 multicentre. Five had adequate randomisation procedures, 3 did not report if randomisation was concealed. Blinding not reported and unlikely in all. Two trials did not report ITT, 2 had no drop-outs, 4 reported ITT but 2 of these did not in fact include drop-pouts in final analysis. 2 studies did not report power calculations. Five had funding from large pharmaceutical companies.
- *Combined treatment effect (incl. point estimates, CI, p values etc):* Significant differences only shown below – all other outcomes no sig. diffs.

Laser v. TCRE – laser surgery average 9 minutes longer (WMD = 9.15, 95%CI 7.2, 11.1, p=0.00); odds ratio of equipment failure(OR = 6, 95% CI 1.7, 20.9, p=0.01) and fluid overload (OR 5.2, 95% CI 1.5, 18.4, p= 0.01) greater with laser.

Vaporising electrode vs TCRE – Odds of "difficult" surgery higher with TCRE (OR = 0.25, 95% CI 0.09, 0.73, p=0.01); With TCRE fluid deficit greater (WMD = 258mls, 95% CI 173.9, 342.1, p=0.00); duration of surgery longer with TCRE (WMD=1.5mins 95%CI 0.35, 2.65, p=0.01)

Balloon vs Rollerball – With rollerball, amenorrhoea more likely at 12 months (OR 0.55, 95% 0.31, 0.99, p=0.05) and 36 months (OR = 0.5, 95% CI 0.25, 0.97, p=0.04) not sig. different at 24 and 60 months. Greater likelihood of repeat surgery with at 24 months (OR=0.35, 95% CI 0.12, 0.99, p=0.05) but effect not seen at 12 and 36 months FU. At 5 yrs, odds of satisfaction greater with rollerball (OR = 0.13, 95%CI 0.02, 0.94, p=0.04) but not at other years.

Vesta vs TCRE – Duration of procedure longer for TCRE (WMD = 16.2 mins, 95% CI 12.9, 19.6, p=0.00). Women with Vesta more likely to have local anaesthetic (OR = 20.5, 95% CI 10.7, 39.3, p=0.00)

Microwave vs. TCRE – Odds of haemorrhage higher with TCRE (OR = 0.14, 95% CI 0.02, 0.8, p=0.03). Odds equipment failure higher with microwave (OR = 4.07, 95% CI 1.1, 15.0, p=0.03)

HTA vs Rollerball – HTA more likely to have local anaesthetic (OR 2.85, 95% 1.6, 5.1, p=0.00), and less likely to have haematometra (OR = 0.18, 95% CI 0.03, 0.93, p=0.04) but more likely to have abdominal pain at 2 wks (OR 1.85, 95% CI 1.1, 3.1, p=0.02) and less likely to have nausea vomiting after surgery (OR 3.7, 95% CI 1.5, 9.0, p=0.01)

2^{nd} vs 1^{st} generation techniques overall – 1^{st} generation takes longer (WMD = -10.6, CI –18.6, -2.5, p=0.01) and have better chance of amenorrhoea at 12 months (OR = 0.76, 95% CI 0.6, 1.0, p=0.04). More chance of equipment failure with 2^{nd} generation (OR 4.1, 95%CI 1.1, 14.9, p=0.03) and local anaesthetic (OR = 7.6, 95% CI 1.1, 52.7, p=0.04). (*NB- text and graph data disagree)*

- *Adverse effects* 2^{nd} generation less likely to have cervical lacerations (OR = 0.08, 95% CI 0.01, 0.49, p= 0.01) hematometra (OR = 0.14, 95% CI 0.04, 0.57, p= 0.01), haemorrhage (OR = 0.14, 95% CI 0.02, 0.80). 1^{st} generation techniques less likely to have nausea and vomiting (OR = 2.94, 95% CI 1.52, 5.70, p= 0.00)
- *Assessment of heterogeneity:* Significant heterogeneity found when comparing 1^{st} and 2^{nd} generation techniques overall for use of local anaesthetic and time taken for procedure. Random effects model confirmed significant differences between the techniques.

Methodological comments

- *Search strategy* : OK
- *Participants:* OK
- *Inclusion/exclusion criteria*: All methods of ablation were included, in many cases this leads to only one trial for each intervention.
- *Quality assessment of studies:* Good
- *Method of synthesis:* Good – Dichotomous data Outcomes pooled unless ratio of mean to SD less than 1.00 (test of skew), fixed effects except where significant heterogeneity when confirmed through random effects. However, text and graph data are different for the comparison of 1st generation techniques vs 2nd generation techniques combined.

General comments

- *Generalisability:*
- *Appropriate outcome measures used?* Yes – but wide range of outcome measures used in the trials and different measures for items such as satisfaction and QoL. Makes comparison between studies difficult.
- *Any differences in baseline characteristics of pts and controls?* Not stated
- *Appropriate analysis?* Yes
- *Funding?* None stated

8.8 Appendix 8: Included Controlled Study Details

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Cooper et al (1999) ▪ Study design: RCT ▪ *Recruitment dates:* Sept 1996 – Feb 1998. ▪ *Setting:* Single UK gynae. outpatient dept.	▪ *Treatment:* MEA. Control TCRE by combination electrocautery technique – fundus and cornual regions ablated with rollerball. ▪ *Surgeon experience*: 2 surgeons with at least 50 prior TCREs, MEA training and at least 5 MEAs. ▪ *Surgery pre-treatment:* 3.6mg goserelin 5 weeks prior to op. ▪ *Type of anaesthesia:* 100% general	▪ *Total number of patients:* 263 randomised, 129 assigned MEA (123 received), 134 assigned TCRE (132 received). ▪ Indication for surgery: DUB. ▪ *Inclusion criteria:* Premenopausal women, completed their families, uterine size equiv. to 10 wk pregnancy or less, gave informed consent ▪ *Exclusion criteria:* Histopathological abnormalities of endometrium. ▪ *Participant characteristics:* Mean age MEA 41.1 (6.7 SD), TCRE 41.0 (8.4 SD). Described their periods as heavy - 83 (65%) MEA, 80 (60%). 60% in both arms had the problem for 3+ yrs, fibroids >2cm in 14 (11%) MEA, 18 (14%) TCRE.	▪ *Primary and secondary outcome measures used:* Primary – patients' satisfaction with and acceptability of procedures. Secondary effect on menstrual status, health related QoL, operative details and morbidity. ▪ *Method of assessing outcomes:* Patient questionnaire including QoL measure SF-36, operating details reported by surgeon questionnaire. Bleeding and pain score calculated using a five point scale. ▪ *Length of follow up*: 12 months

Results:	**MEA**		**TCRE**		95% CI for difference (p)
▪ *Symptoms*	pre op (n=129)	postop (n=116)	pre op (n=134)	postop(n=124)	
Amenorrhoea	-	46 (40%)	-	49(40%)	-14 to 20 (0.23)
Irregular periods	66 (51%)	-	76 (57%)	-	-
3-7 days bleeding	58 (45%)	49 (42%)	54 (40%)	51 (41%)	-11 to 13 (0.23)
>7 days bleeding	70 (54%)	6 (5%)	80 (60%)	9 (7%)	-17 to 35 (0.23)
>3 days heavy bleeding	88 (69%)	8 (7%)	82 (64%)	7 (6%)	-10 to 31 (0.79)
Dysmenorrhoea	91 (73%)	24 (20%) - same/worse	90 (68%)	22 (18%) – same/worse	-11 to 20 (0.62)
2x sanitary protection	111 (86%)	14 (12%)	113 (84%)	16 (14%)	-17 to 21 (0.98)
Bleeding score	27 (22-36)	3 (0-8)	27 (21-34)	3 (0-10)	-3.2 to1.2 (0.37)
Pain score	19 (11-26)	1 (0-9)	16 (7-25)	1 (0-7)	-2.7 to 1.8 (0.7)
Bloating	107 (87%)	75 (65%)	115 (87%)	63 (51%)	1 to 26 (0.03)
Breast discomfort	94 (76%)	64 (55%)	103 (79%)	61 (49%)	-6 to 18 (0.64)
Irritability	105 (86%)	67 (58%)	117 (87%)	65 (52%)	-6 to 19 (0.4)
Headaches	89 (75%)	56 (48%)	93 (72%)	54 (44%)	-7 to 17 (0.46)
Depression	71 (57%)	42 (36%)	79 (61%)	49 (40%)	-9 to 17 (0.5)
>2 days work absence	46 (36%)	4 (3%)	49 (37%)	8 (7%)	..
Menstruation unchanged or worse	-	9 (8%)	-	11 (9%)	-14 to 26 (0.98)

▪ *SF-36 score Mean (SD)*	preop(n=116)	postop(n=116)	preop(n=124)	postop(n=124)	95% CI (ANCOVA p)
Physical functioning	84.6 (19.2)	0.7 (18.9)	82.2 (23.3)	2.4 (16.8)	-6.4 to 2.9 (0.58)
Social functioning	60.1 (23.0)	20.6 (26.5)	60.1 (22.9)	16.2 (24.4)	-2.1 to 10.9 (0.12)
Role-physical	56.5 (42.2)	23.9 (49.4)	62.9 (41.7)	11.3 (41.7)	-1.0 to 24.3 (0.03)
Role-emotional	61.8 (42.5)	17.0 (48.5)	62.6 (43.2)	13.7 (47.9)	-9.1 to 15.6 (0.38)
Mental health	44.3 (22.6)	6.3 (19.5)	63.8(21.7)	6.0 (22.2)	-4.9 to 5.7 (0.83)
Energy/fatigue	63.6 (18.8)	12.8 (21.7)	43.3 (24.3)	12.1 (23.0)	-4.9 to 6.5 (0.58)
Pain	55.4 (28.2)	14.8 (31.0)	63.7(26.1)	7.2 (31.1)	-0.2 to 15.5 (0.54)
General health	69.7 (21.7)	2.4 (20.3)	73.0 (19.4)	-2.9 (20.0)	- 0.2 to10.5 (0.06)
▪ *Satisfaction*	**MEA** (n=116)		**TCRE** (n=124)		**95% CI (p)**
Totally or generally satisfied	89 (77%)		93 (75%)		-12 to 17 (0.88)
Cure or acceptable improvement	91 (78%)		94 (76%)		-11 to 18 (0.76)
Treatment acceptable	109 (94%)		112 (90%)		-11 to 35 (0.34)
Would recommend treatment	105 (91%)		110 (89%)		-16 to 25 (0.68)
▪ *Operation details*	(n=129)		(n=134)		
Mean operating time, min (SD)	11.4 (10.5)		15.0 (7.2)		-5.7to1.4 (0.001)
Mean theatre time, min (SD)	20.9 (11.3)		26.2 (8.7)		-7.7to2.8 (<0.001)
Procedure abandoned	5 (4%)		5 (4%)		-4 to 5 (0.57)
Equipment failure	11 (9%)		3 (2%)		1 to 12 (0.02)
Mean post-op stay (h) (SD)	13.4 (17.6)		16.7 (21.2)		-8.0 to 1.5 (0.17)
▪ *Further surgery*	10 (8%)		13 (10%)		..
▪ *Adverse effects*	(n=129)		(n=134)		
Blunt perforation	1 (1%)		1 (1%)		…
Haemorrhage	0		5 (4%)		0 to 7 (0.06)
Readmission	4		6		-7 to 3 (0.17)
▪ *Fully recovered within 4 wks*	(n=121) 87 (72%)		(n=124) 82 (66%)		

Methodological comments

- *Prospective?* Yes
- *Consecutive patients enrolled?* Uncertain
- *Method of Randomisation* – Telephone to secretary to open series of sealed, opaque, sequentially numbered envelopes showing treatment code. Sequence predetermined by computer generated random numbers in blocks of 20.
- *Power calculation?* Need 230 women to detect a minimum 15% difference in satisfaction (p=0.05) based on known satisfaction of 78% for TCRE.
- *All patients given same intervention?* Yes
- *Loss to follow up?* Yes 13/129 in MEA, 10/134 LTFU at 12 months. Records checked to find that none of the women LTFU received further gynae surgery in the Region
- *Method of data analysis:* ITT used, however, some baseline characteristics appear not to be ITT, and some figures seem incorrect – maybe differing denominators for missing data? Independent and paired t tests for continuous variables with normal distribution, ANCOVA used to adjust for baseline differences between treatment groups in SF-36 scores. Mann-Whitney U test for ordinal or continuous variables without normal distribution. Chi-sq or Fisher's exact test for independent nominal data, McNemar's and Wilcoxon's ranked-sum tests for paired nominal data . 95% CI calculated for differences in means of normally distributed data.

General comments

- *Generalisability:* High
- *Main outcome measured independently:* Uncertain
- *Inter-centre variability:* Not applicable
- *Conflicts of interest*: Microsulis Medical ltd provided equipment and financial support to one author.

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Bain et al, 2002 ▪ *Study design*: RCT ▪ *Recruitment dates:* Not stated ▪ *Setting:* One UK hospital O&G department.	▪ *Treatment:* Microwave EA TCRE control using rollerball at the fundus and cornual areas. ▪ *Surgeon experience:* Two surgeons each with 50 TCRE experience, training and 5 MEAs. ▪ *Surgery pre-treatment:* Subcutaneous goserelin 3.6mg 5 weeks before operation ▪ *Type of anaesthesia:* General	▪ *Total number of patients:* 263 (129 MEA, 134 TCRE) ▪ *Indication for surgery:* Referred by gynaecological dept. for EA. ▪ *Inclusion criteria:* Benign endometrial histologic sample within 6 months, uterine size >=10wk pregnancy. Women with fibroids and irregular cavities NOT excluded. ▪ *Exclusion criteria:* Perimenopausal (FSH >30 U/L), adnexal pathology, further pregnancy contemplated. ▪ *Participant characteristics:* MEA mean age 41.4 (5,4 SD), TCRE mean age 42.2 (SD5.8). For baseline Short Form 36 measures see below. TCRE had significant (p=.03) higher pain than MEA group at baseline.	▪ *Primary and secondary outcome measures used:* Satisfaction, acceptability of menstrual improvement. QoL, further surgery ▪ *Method of assessing outcomes:* Satisfaction, acceptability of menstrual improvement by direct questioning. Short form 36 for QoL. Subsequent surgery from Hospital database. Bleeding and pain scores obtained using a 5 point scale for each day of period – maximum score 50. ▪ *Length of follow up:* hospital review at 4 months. Mail FU at 12 and 24 months

Results:	**MEA (n=120)**		**TCRE (n=129)**		95% CI for difference
▪ *Symptoms*	preop	postop	pre op	postop	
Irregular periods	60 (50%)	n/s	70 (54%)	n/s	-
>7 days bleeding	64 (53%)	n/s	74 (57%)	n/s	-
>3 days heavy bleeding	81 (67.5%)	2 (2%)	81 (63%)	7 (5%)	-9, 1.3% (p=.33)
Dysmenorrhoea	84 (70%)	22 (18%) - same/worse	83 (64%)	29 (22%) – same/worse	-14, 5% (p=.78)
Double or more sanitary protection	103 (86%)	9 (14%)	109 (84%)	17 (22%)	-13, 2% (p=.36)
Mean Bleeding score	28.1 (9.4 SD)	Median - 1 (0,6 25th, 75th percentile)	27.8 (9.1 SD)	Median 3 (0,10 25th, 75th percentile)	-1, 0 (p=.06)
Mean pain score	18.9 (11.4 SD)	0 (0,7 25th, 75th percentile)	16.4 (12.4 SD)	1 (0, 8 25th, 75th percentile)	0,0 (p=.22)
Unchanged or heavier	-	8 (7%)		14 (11%)	-11, 3%(p=.10)
Amenorrhoea	-	57 (47%)		53 (41%)	-9, 15% (p=.19)
▪ *QoL*	(n=120)	(n=120)	(n=129)	(n=129)	
Short Form 36 (mean and SD)		Change in score		Change in score	95% CI (p)
Physical functioning	83.9 (19.8)	2.3 (21.3)*	82.5 (22.9)	0.9 (20.4)	-3.8, 6.6 (.28)
Social functioning	59.9 (22.6)	10.1 (27.5)+	60.4 (22.8)	6.2 (23.7)#	-2.5,10.3 (.33)
Role-physical	56.1 (43.1)	18.5 (53.7)+	63.7 (41.4)	6.1 (43.8)	-0.2,24.6 (.06)
Role emotional	61.3 (42.3)	17.8 (47.5)+	63.0 (42.9)	4.2 (40.1)*	-3.6, 23.5 (.17)
Metal health	63.3 (18.8)	6.0 (21.6)#	63.3 (20.8)	4.1 (19.8)#	-3.3,6.9 (.44)
Energy/fatigue	43.6 (22.6)	11.4 (25.1)+	43.3 (24.4)	11.8 (22.6)+	-6.4, 5.5 (.90)
Pain	55.7 (28.3)	13.5 (31.7)+	63.4 (26.0)	3.0 (29.8)	2.9, 18.2 (.02)
General Health	70.2 (21.6)	0.0 (24.4) (change from baseline significant *p<.05, +p<.001, #p<.01)	73.0 (19.2)	-2.9 (19.0)	-2.5, 8.4 (.29)

▪ *Satisfaction*			
Completely or generally satisfied	79%	67%	7,22 (p=.02)
Recommend to friend	90%	90%	
Menstrual loss acceptable	96%	88%	0.6, 14 (p=.03)
▪ *Further surgery*			
Hysterectomy rate	11.6%	12.7%	
Laparoscopy plus hysteroscopy	2	2	
Diagnostic hysteroscopy	1	1	
Repeat ablation	0	0	
▪ *Adverse effects*			
Pregnancy	1	0	

Methodological comments

- *Prospective?* Yes
- *Consecutive patients enrolled?* Uncertain
- *Method of Randomisation:* By telephone with secretary opening the next in a series of sealed, opaque, sequentially opened envelope with treatment code, determined by computer generated random number squares.
- *Power calculation?* A sample size of 80% power to detect a 15% absolute difference in treatment satisfaction at a 5% significance level ($p<0.05$).
- *All patients given same intervention?*
- *Loss to follow up?* Yes. 249/263 FU at 2 yrs.
- *Method of data analysis:* Analysis by ITT, continuous variables with normal distribution analysed using independent and paired t tests, Mann-Whitney U test for ordinal or nonparametric continuous variables. Independent nominal data were analysed using chi-sq. or Fischer exact test. Paired categorical data which were related or consisted of dichotomous variable, were analysed with Wilcoxon signed rank test and McNemar test respectively.

General comments

- *Generalisability:* High*:*
- *Inter-centre variability:* Not applicable

Conflicts of interest: Microsulis provided equipment and part time financial support for one author to undertake the research.

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Microsulis 2002 ▪ Study design: RCT ▪ *Recruitment dates:* April 2000 – Sept. 2001 ▪ *Setting:* 8 sites in the UK and USA	▪ *Treatment:* Microwave ablation Rollerball ▪ Surgeon experience: *Not stated* ▪ Surgery pre-treatment: *single leuprolide acetate depot 3-5 weeks prior to procedure.* ▪ *Type of anaesthesia:* At 7 centres (data here with one site removed) - MEA GA 37%, IV sedation 62%, regional <1%, sedation plus regional 1% RB GA 76%, IV sedation 18%, regional 4%, sedation plus regional 2% At the centre excluded form above calculation. all women had GA.	▪ *Total number of patients:* 322 (215 MEA, 107 RB) ▪ Indication for surgery: Abnormal uterine bleeding ▪ *Inclusion criteria:* PBLAC of >185 ▪ *Exclusion criteria:* Not stated ▪ *Participant characteristics:* 22% of patients had fibroids <3cm.	▪ *Primary and secondary outcome measures used:* Patient bleeding Amenorrhoea, duration of treatment time, duration of anaesthetic, anaesthetic type, treatment failure (re-treatment), dysmenorrhoea, QoL, satisfaction and acceptability of treatment, adverse incidents, complications ▪ Method of assessing outcomes: *PBLAC diary (baseline assessed though 1-3 months data collection, post-op, 0=amenorrhoea, treatment success <75), QoL by SF-36* ▪ Length of follow up: 12 months

Results:	**Intervention (n=215)**	**MEA**	**Comparison (n=107)**	**RB**	P-value
▪ *Symptoms*	Preop	postop	pre op	postop	
Success (PBLAC <75)	-	187 (87%)	-	89 (83%)	0.359
Amenorrhoea	-	119 (55%)	-	49 (46%)	0.106
Dysmenorrhoea	176 (82%)	66 (31%)	86 (80%)	33 (31%)	0.841 pre op 0.767 post op
Success with fibroids	-	(n=31) 28 (90%)	-	(n=26) 23 (88%)	1.00
Amenorrhoea with fibroids	-	19 (61%)	-	10 (38%)	0.113
Success BMI >30kg/ m^2	-	(n=60) 58 (97%)	-	(n=22) 18 (82%)	0.042
Reason for treatment failure:		(n=179)		(n=92)	
Intermenstrual bleeding		0		1 (1%)	-
PBLAC >75		4 (2%)		7 (8%)	-
Pt dissatisfaction		0		1 (1%)	-
▪ *QoL – SF36*	(n=208)	(n=193)	(n=102)	(n=97)	
Physical	47.1 +/- 9.22	54.1 +/-6.6	46.5 +/- 8.1	53.6 +/- 6.9	**Not sig.**
Mental	46.5 +/- 11.5	52.2 +/-9.1	46.6 +/- 11.4	51.5 +/-9.7	
▪ *Satisfaction*					
Acceptance of operation positive		194 (99%)		97 (100%)	
Acceptance of operation negative		2 (1%)		0	1.00
Very satisfied/ satisfied		193 (98%)		96 (99%)	
Dissatisfied		3 (2%)		1 (1%)	1.00

▪ *Operation details*	(n=209)	(n=106)	
Anaesthesia time	39.26 (SD 25.44)	47.10 (SD 23.4)	0.007
Anaesthesia time (excl the study with all GA)	41.67 (SD 26.21)	50 (SD22.96)	0.009
Treatment time	3.45 (SD1.02)	20.26 (15.60)	0.000
▪ *Further surgery*			
Repeat ablation	0	0	-
Hysterectomy	1	1	
▪ *Adverse effects*	-	-	-

Methodological comments

- *Prospective?* Not stated
- *Consecutive patients enrolled?* Not stated
- *Method of Randomisation* 2:1 ratio of MEA to RB treatments. Methods of allocation and concealment are not stated.
- *Power calculation?* None stated
- *All patients given same intervention?* Not stated. All receive same pre-treatment
- *Loss to follow up?* 13 (6%) MEA and 9 (8%) RB patients LTFU.
- *Method of data analysis:* ITT data supplied only for amenorrhoea and treatment success measures, otherwise evaluable patient data given only. Subgroup analyses are given for women with and without fibroids, cavity length and BMI >30kg/m^2

General comments

- *Generalisability:* low. Few details of patient characteristics are given and no exclusion criteria are given.
- *Main outcome measured independently:* Yes
- *Inter-centre variability:* Amenorrhoea rates between centres were assessed, and showed a significant difference between treatments in only one of 8 studies. One study gave all patients GA and data about anaesthetic is provided with and without with study included.
- *Conflicts of interest*: Conducted by the manufacturer of MEA as part of their application for FDA approval in the USA. Unpublished, therefore not peer reviewed.

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Gervaise et al 1999 ▪ *Study design:* Controlled study. Controls taken from records of TCRE patients during same time period as the intervention group. ▪ *Recruitment dates:* Nov. 1994-April 1998 ▪ *Setting:* Single centre in France	▪ *Treatment:*. Thermal Balloon ablation (Thermachoice™) TCRE using 1.5% glycine ▪ *Surgeon experience:* Not stated ▪ *Surgery pre-treatment:* None ▪ *Type of anaesthesia:* LA used where medically necessary, or desired by patient in TBEA group – 28 (38%.)	▪ *Total number of patients:* 147 (73BEA, 74TCRE) ▪ Indication for surgery: Abnormal uterine bleeding ▪ *Inclusion criteria:* 40+ yrs, excessive menstrual blood loss (as measured by no. of pads/cycle), pre-menopausal women had to have failed medical therapy (progestins) or unwilling to continue with them, post menopausal women were not willing to discontinue HRT. ▪ *Exclusion criteria:* Fibroids, polyps, premalignant lesions, uterine cavity >12cm, those wishing to retain fertility. ▪ *Participant characteristics:* TBEA: Age 46.3 +/-1.3 (34-66); Menopausal status 5 (6.8%); parity 2.4 +/-0.3 (0-9); Pads/cycle 86 =/-40.4; anteverted: retroverted 59:14; Uterine cavity depth 8.9 =/-0.3 (6-12) TCRE: Age 47.4+/-1.4 (34-65); Menopausal 20 (27%); parity 1.9 =/-0.2 (0-4); Pads/cycle 81 +/-41.7; Anteverted: retroverted 63:11; Uterine cavity 9.1 +/-0.2 (7-12) Differences in parity and menopause significant.	▪ *Primary and secondary outcome measures used:* Amenorrhoea or eumenorrhoea or than hypomenorrhoea. Elimination of dysmenorrhoea. ▪ *Method of assessing outcomes:* Telephone interview. ▪ *Length of follow up:* TBEA median 18.3 +/- 2.7 (range 3-44) months, TCRE median 19.2 +/- 2.3 (range 3-36) months

Results: At 24 months	**TBEA N=73** Immediate postop	**N=44** 24 months Postop	**TCRE N=74** Immediate post op	**N=47** 24 months Postop	**p-values**
▪ *Symptoms*					
Amenorrhoea	18 (24.7%)	16 (36.4%)	28 (37.8%)	18 (38.3%)	n/s
Hypomenorrhoea	16 (21.9%)	7 (15.9%)	23 (31.1%)	13 (27.7%)	n/s
Eumenorrhoea	28 (38.4%)	15 (34.1%)	10 (13.5%)	8 (17.0%)	0.0006
Menorrhagia	8 (11.0%)	4 (9.1%)	9 (12.2%)	7 (14.9%)	n/s
Metrorrhagia	3 (4.1%)	2 (4.5%)	4 (5.4%)	1 (2.1%)	n/s
▪ *QoL*	-	-	-	-	-
▪ *Satisfaction*	-	-	-	-	-

▪ *Operation details* Mean operating time % cases complete in 30 mins ▪ *Further surgery* TCRE Hysterectomy ▪ *Adverse effects* Perioperative Endometritis Pregnancy (miscarried)	 20.3 mins 100% 0 7 0 0 1	 44.8 mins 52.6% 1 5 0 2 0	 P<0.05 P<0.05

Methodological comments

- *Prospective?* Yes for intervention, controls matched retrospectively from records.
- *Consecutive patients enrolled?* Unclear
- *Method of Randomisation* None
- *Power calculation?* None stated
- *All patients given same intervention?* Yes
- *Loss to follow up?* None
- *Method of data analysis:* Significance of the differences between groups in categorical variables tested using chi-square. Students t-test used for continuous variables. Kaplan Meier survival curves for "survival" distributions of treatments, differences tested with Mantel-Cox (log-rank) statistics. Cox-proportional hazards model to analyse possible relationships between event failure and possible covariates and to study prognostic factors.

General comments

- *Generalisability:* High
- *Main outcome measured independently:* Unclear – probably not – telephone interview
- *Inter-centre variability:* N/A
- *Conflicts of interest*: None stated

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Meyer et al 1998 ▪ Study design: *RCT* ▪ *Recruitment dates:* Jan-Sept 1996 ▪ *Setting:* 12 centres in USA and Canada	▪ *Treatment:* Thermachoice™ thermal balloon Control - Rollerball ▪ *Surgeon experience:* All had "extensive experience of rollerball EA" ▪ *Surgery pre-treatment:* None ▪ *Type of anaesthesia:* General TBA 53%, R/ball 84%	▪ *Total number of patients:* 275 ▪ *Indication for surgery:* Menorrhagia ▪ *Inclusion criteria:* Aged 30+, premenopausal, have normal Pap smear and endometrial biopsy within the past 6 months, 3 months documented history of HMB, failed medical therapy, uterine cavity sounded between 4-10cm, no further desire for childbearing, willing to continue with contraception for 3 years post ablation. ▪ *Exclusion criteria:* Women with submucous myomas or suspected genital tract infection or malignancy, those who had undergone previous EA. ▪ *Participant characteristics:* mean(SD) range TB - Age 40.2 (4.9) 30-51, BMI 24.0 (6.5) 14.4-52.7, Age at onset of menorrhagia 29.6 (9.7) 10.0-47.0, Years with menorrhagia 9.9 (8.5) 0.5-37.0, Uterine cavity 8.6cm (1.1) 4.0-10.0. Rollerball – Age 40.9 (5.2) 29-50, BMI 22.9 (5.5) 15.7–39.6, Age at onset of menorrhagia 29.8 (9.6) 11.0-49.0, yrs with menorrhagia 10.0 (8.9) 1.0-35.0, Uterine cavity 8.6 cm (1.2) 4.0-10.5	▪ *Primary and secondary outcome measures used:* Satisfaction, menstrual bleeding, PMS, ability to work outside the home, ▪ *Method of assessing outcomes:* MB measured through pictorial diary system – scored of >150 for menorrhagia. Examination at 3, 6 and 12 months ▪ *Length of follow up:* 12 months

Results: (n=245 – completed 6 month FU)	**Intervention TBEA (n=128) Preop**	**(n=125) postop**	**Comparison R/ball (n=117) pre op**	**(n=114) postop**	95% CI for difference
▪ *Symptoms*					
PMS	115 (89.8%)		106 (90.6%)		
PMS mod/severe	101(78.6%)*	41 (32.8%)	90 (76.6%)*	33 (29.0%)*	(p<.05 pre-post both arms)
Dysmenorrhoea	22 (17.2%)	Decreased		Decreased 86	
Mild	52 (40.6%)	88 (70.4%)	19 (16.2%)	(75.4%)	Diffs between arms p >0.05
Moderate	45 (35.2%)	Same	37 (31.6%)	Same	
Severe		31(24.8%)	54 (46.2%)	26(22.8%)	
		Increased 6 (4.8%)		Increased 2 (1.8%)	P<0.05
Amenorrhoea (12mnths)	-	19 (15.2%)	-	31 (27.2%)	
Mean diary score	552.5	-	570.5	-	
% decreased by	-	107 (85.5%)	-	104 (91.7%)*	
<100 at 12mnth (normal)	-	100 (80.2%)	-	96 (84.3%)*	
Score decreased by 90%	-	77 (61.6%)	-	78 (68.4%)	
>=50% reduction	-	at least 112 (90%+)	-	At least 103 (90%+)	
Haemoglobin values g/dL	12.7 (+/-1.4)		12.5 (+/-1.6)		
Reduction in the number of women with anaemia		75 (approx) (60% approx)		68 (approx) (60% approx)	
Menorrhagia has severe impact on life	At least 90 (70%+)*	4 (3.2%)	At least 82 (70%+)	2 (1.8%)	
▪ *QoL*					
Inability to work outside the home	51 (39.8%)	5 (4.0%)	45 (38.5%)	3 (2.7%)	
▪ *Satisfaction*	(n=125)		(n=114)		
Very satisfied	107 (85.6%)		99 (86.7%)*		
Satisfied	13 (10.4%)		14 (12.4%)*		
Not satisfied	5 (4.0%)		1 (0.9%)		
▪ *Operation details*					
Procedure time					
<30mins	89 (71.0%)*		33 (28.6%)*		p<0.05
>50 mins	3 (2.3%)*		20 (18.0%)*		
▪ *Further surgery*					
Prior to 1yr FU	2 (1.6%)		3 (2.6%)		
▪ *Adverse effects*					
Intraoperative	0		4 (3.2%) (2 fluid overload, 1 cervical lacerations, 1 uterine perforation)		
Post operative					
Endometriosis	3 (2.4%)		1 (0.9%)		
UTI	1 (0.8%)		0		
Hematometra	0		1 (0.9%)		
Symptomatic right hydrosalpinx (post-tubal sterilisation syndrome)	0		1 (0.9%)		

Methodological comments

- *Prospective?* Not stated
- *Consecutive patients enrolled?* Not stated
- *Method of Randomisation* 1:1 allocation by generation of a random numbers table.
- *Power calculation?* Assuming 85% response rate for patients treated with rollerball, 108 evaluable patients needed to detect if thermal balloon is more than 20% less effective than rollerball, (90% power, p=0.05)
- *All patients given same intervention?* Yes.
- *Loss to follow up?* 15 withdrew after randomisation, 5 anaesthetised but not treated for the study (1 had a perforation, 4 found to have an exclusion criteria in theatre). At 12 months 7 r/ball and 4 TBA lost to FU or withdrew.
- *Method of data analysis:* Paired t-tests, chi-square probabilities and a repeated measures analysis of variance used to compare demographics and outcomes. ITT not performed.

General comments

- *Generalisability:* High
- *Main outcome measured independently:* Unclear
- *Inter-centre variability:* Variation not statistically significant.
- *Conflicts of interest*: Dr Loffer has received a stock option from Gynaecare.

* In a number of cases, only percentages, not actual numbers, are provided in the text. Actual numbers have been calculated using this percentage of the number of people reported as followed up (n in the table). In a number of cases, the resultant number is uncertain. For those marked with an asterisk it is not possible to ascertain a whole number of people from the data given. The number provided is the nearest estimate. It is suspected that additional missing data for individual variables has been excluded without comment (changing the denominator) casing this anomaly.

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Grainger et al 2000 ▪ Study design: RCT ▪ *Recruitment dates:* Jan. – Sept. 1996 ▪ *Setting:* 14 University affiliated or private practice centres in USA and Canada	▪ *Treatment:* Thermachoice™ thermal balloon. Control- Rollerball electrosurgical ablation ▪ *Surgeon experience*: All experienced in rollerball and trained in balloon ablation. ▪ *Surgery pre-treatment:* No drug pre treatment. 3 minute curettage using 5mm curette prior to ablation. ▪ *Type of anaesthesia:* Not stated	▪ *Total number of patients:* 255 ▪ Indication for surgery: Excessive menstrual bleeding ▪ *Inclusion criteria:* Aged 30+, premenopausal, documented history of 3 months excessive MB (measured by pictorial diary system as 80ml or more) uterine cavity between 6 and 10 cm, no further fertility desired, continue current contraception for 3 yrs ▪ *Exclusion criteria:* Women with submucous myomas, suspected genital tract infection or malignancy, history of endometrial ablation. ▪ *Participant characteristics:* None stated	▪ *Primary and secondary outcome measures used:* Amount of uterine bleeding, affect on QoL. Secondary complications and AEs. ▪ *Method of assessing outcomes:* Pictorial diary system for bleeding, questionnaire for other menstrual symptoms, impact on life and satisfaction with treatment. AE documented and recorded. ▪ *Length of follow up:* 48 months. FU phone contact at 24 hrs, examined at 1 wk, 3 and 6 months, 1 and 2 yrs.

Results:	**Thermal balloon n=131**	**N=122**	**Rollerball N=124**	**N=105**	95% CI for difference
▪ *Symptoms*	Preop	postop 1Yr 2yr	pre op	Postop 1Yr 2yr	
No PMS	N/s	34 (27.2%) 36 (29.2%)		32 (28.1%) 37 (35.2%)	n/s
PMS moderate or severe	103 (78.6%)	41 (32.8%) 35 (28.6%)	95 (76.6%)	33 (29.0%) 31 (29.5%)	n/s
Unable to work outside home	52 (39.8%)	5 (4.0%) 1 (0.8%)	48 (38.5%)	3 (2.7%) 3 (2.9%)	n/s
Mean menstrual diary score		At 1yr decreased by 85.5%		At 1yr decreased by 91.7%	n/s
Menstrual symptoms at 2 yrs		Age:			
		<40 >40		<40 >40	
Amenorrhoea		13(11%) 8(15%)		19(18%) 26(25%)	n/s
Spotting		18(15%) 13(11%)		23(22%) 14(13%)	n/s
Hypomenorrhoea		44(36%) 55(45%)		43(41%) 31(30%)	n/s
Eumenorrhoea		30(25%) 26(21%)		13(12%) 22(21%)	n/s
Menorrhagia		16(13%) 11(9%)		8(8%) 13(12%)	n/s
▪ *Satisfaction*	Post op Yr1	Post op Yr 2	Postop Yr 1	Postop Yr 2	
Very	85.6%	105 (86.1%)	86.7%	91 (86.7%)	n/s
Satisfied	10.4%	12 (9.8%)	12.4%	12 (11.4%)	n/s
Not	4%	5 (4.1%)	0.9%	2 (1.9%)	n/s
Recommend procedure		119 (97.5%)		103 (99%)	n/s
▪ *Further surgery*	4 (3%)		11 (8.9%)		
▪ *Adverse effects*	1 (0.8%) pregnancy 2.5 yrs after ablation				

Methodological comments

- *Prospective?* Yes
- *Consecutive patients enrolled?* Uncertain
- *Method of Randomisation:* Randomised by blocks in 1:1 allocation.
- *Power calculation?* Assuming an 85% response rate for rollerball, 108 evaluable pts per treatment required to detect if balloon therapy was at least 20% less effective (α =0.05, 90% power)
- *All patients given same intervention?* Yes
- *Loss to follow up?* 16 discontinued before 1 yr (see other pub?) 227/255 on study at 2 yrs.
- *Method of data analysis:* Paired t tests, chi-squared probabilities and a repeated measures analysis of variance to compare demographics and outcomes. For most variables, numbers are not given so it is not possible to check whether ITT has been done, this seems unlikely. One variable at 1 yr is definitely not ITT (No PMS at 1 yr n=34; 27.2%, at 2 yr n=35 (29.2%) TB, Rollerball no PMS at 1 yr n=32 (28.1%), at 2 yr n=37 (35.2%))

General comments

- *Generalisability:* Poor
- *Main outcome measured independently:* Unclear – questionnaires used.
- *Inter-centre variability:* Not examined
- *Conflicts of interest*: Supported by Gynaecare

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Loffer, FD 2001 ▪ Study design: RCT ▪ *Recruitment dates:* Jan.-Sept. 1996 *Setting:* 12 US and 2 Canada University and private practice sites.	▪ *Treatment:* Thermal balloon ablation. ▪ *Surgeon experience*: All investigators were experienced in rollerball and trained in thermal balloon ablation. ▪ *Surgery pre-treatmen*t No drugs used. Timed 3 minute suction curettage given to all prior to ablation. ▪ *Type of anaesthesia:* Local, local with sedation and general. General more frequent with rollerball.	▪ *Total number of patients:* 275 enrolled. 255 treated under protocol. (131 TBA, 124 RB) At 3 yrs data avail. for TBA 114 and RB 100 ▪ *Indication for surgery:* Menorrhagia ▪ *Inclusion criteria:* Aged 30+, premenopausal, normal Pap smear, and endometrial biopsies, at least 3 months documented history of excessive bleeding unresponsive to medical therapy measured by minimum threshold score on daily pictorial record of bleeding, normal uterine cavity, 4-10cm sound, no desire for further fertility, willing to continue for 3 yrs on current contraceptive. ▪ *Exclusion criteria:* Submucous myomas, suspected genital urinary tract infection or malignancy, those with previous ablation. ▪ *Participant characteristics:* None stated	▪ *Primary and secondary outcome measures used:* Pt reported menstrual flow Also menstrual symptoms, adverse effects, impact of menorrhagia on QoL, ▪ *Method of assessing outcomes:* Validated pictorial diary method. *Patient questionnaire* ▪ *Length of follow up:* Telephone contact within 24 hrs. Examined at 1 wk, 2, 6 and 12 months. Interviewed at 2 and 3 years.

Results:	**Thermal balloon**	Postop at 3yrs	**Rollerball**	Postop at 3yrs	95% CI for difference
▪ *Symptoms*	Preop	(n=114)	pre op	(n=99)	
Amenorrhoea		17 (14.9%)		26 (26.3%)	
Spotting		11 (9.6%)		16 (16.2%)	
Hypomenorrhoea		45 (39.5%)		26 (26.3%)	
Eumenorrhoea		33 (29.0%)		25 (25.2%)	
Menorrhagia		8 (7.0%)		6 (6.0%)	
	(n=137)	(n=114)	(n=138)	(n=99)	
No PMS symptoms	12 (8.8%)	36 (31.6%)	12 (8.7%)	37 (37.4%)	
▪ *QoL*	(n=137)	(n=114)	(n=138)	(n=99)	
Menorrhagia having Severe impact on life	96 (70.3%)*	2 (1.8%)	108 (78.6%)*	2 (2.0%)	
Moderate impact	38 (28.1%)*	9 (7.9%)	28 (20.5%)*	8 (8.0%)	
Minor impact	2 (1.6%)*	103 (90.3%)	1 (0.9%)*	89 (90.0%)	
	(n=136)	(n=112)	(n=136)	(n=98)	
Not able to work outside the home	54 (39.7%)	5 (4.5%)	57 (41.9%)	5 (5.1%)	
▪ *Satisfaction*					
		(n=114)		(n=100)	
Very satisfied or Satisfied		109 (95.6%)		97 (94%)	

▪ *Further surgery*	(n=114) 9 (7.9%) (1 repeat EA, 8 hyst.)	(n=99) 14 (14%) hysterectomies	
▪ *Adverse effects* (Perioperative)	0	2 (1.6%) Fluid overload 1 (0.8%) cervical laceration 1 (0.8%) uterine laceration	
Postoperative	3 (2.3%) possible endometritis 1 (0.8%) UTI	1 (0.8%) each endometritis, hematometra, post ablation sterilisation syndrome	

Methodological comments

- *Prospective?* Yes
- *Consecutive patients enrolled?* Uncertain
- *Method of Randomisation:* Using a 1:1 allocation ratio at each centre
- *Power calculation?* Assuming rollerball response rate of 85%, 108 women required in each arm to provide a 0.9 power to detect if the test procedure is at least 20% less effective at preventing menorrhagia ($\alpha = 0.05$).
- *All patients given same intervention?* Yes
- *Loss to follow up?* Yes. 20 pts were randomised and not entered into the study – 11 withdrew voluntarily, 8 were not eligible and 1 RB aborted because of uterine perforation secondary to cervical dilation. At 3 yrs, 17 from thermal balloon and 24 rollerball group were LTFU
- *Method of data analysis:* ITT not performed.

General comments

- *Generalisability:* Low
- *Main outcome measured independently:* No. Using pt completed pictorial diaries.
- *Inter-centre variability:* Not reported
- *Conflicts of interest*: Supported by Gynaecare.

* In a number of cases, only percentages, not actual numbers, are provided in the text. Actual numbers have been calculated using this percentage of the number of people reported as followed up (n in the table). In a number of cases, the resultant number is uncertain. For those marked with an asterisk it is not possible to ascertain a whole number of people from the data given. The number provided is the nearest estimate. It is suspected that additional missing data for individual variables has been excluded without comment (changing the denominator) casing this anomaly.

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Loffer, 2002 ▪ *Study design*: RCT ▪ *Recruitment dates:* 1996-7 *Setting:* 14 North American centres, 12 of which provided data for this 5 year follow up which was not planned in original protocol.	▪ *Treatment:* Thermal Balloon (Thermachoice) Control group – rollerball. ▪ *Surgeon experience*: All experienced with RB ablation and trained in TBEA. ▪ *Surgery pre-treatment:* 3 minute suction curettage. ▪ *Type of anaesthesia:* Not stated.	▪ *Total number of patients:* 255 treated (131 TBEA, 124 RB), 147 (76 TBEA, 71 RB) FU for 5 years but 122 (61 TBEA, 61 RB) analysed for bleeding patterns – those undergoing repeat procedure excluded. ▪ *Indication for surgery*: Menorrhagia ▪ *Inclusion criteria:* Desiring no future fertility. ▪ *Exclusion criteria:* menopause, evidence of cervical or uterine malignancy, uterine anatomic abnormalities. ▪ *Patient characteristics:* At study recruitment mean age TBEA 40.4yrs, RB 40.9. At 5 yr FU mean age TBEA 45.7, RB 46.1. BMI, duration menorrhagia before surgery, uterine size similar between groups.	▪ *Primary and secondary outcome measures used:* Menstrual status, dysmenorrhoea, pelvic pain, satisfaction, additional gynaecological treatments and conditions. ▪ *Method of assessing outcomes:* Patient questionnaire administered by phone by the physician's office. Bleeding status self reported as none, spotting, light, normal or excessive. Severity of dysmenorrhoea and pelvic pain or cramping not associated with menses reported as none, mild, moderate or severe. Success was calculated as the number of women with normal or less bleeding without further procedure (successes) divided by successes plus all known treatment failures (excessive bleeding or repeat procedure at 5 yrs.) ▪ *Length of follow up*: 5 years (+/- 3 months)

Results:	**TBEA at 3 yrs N=114**	**TBEA at 5 yrs N=61**	**RB at 3 yrs N=99**	**RB at 5 yrs N=61**	
▪ *Symptoms*					
Amenorrhoea	17 (15%)	14 (23%)	26 (26%)	20 (33%)	
Spotting	11 (10%)	6 (10%)	16 (16%)	7 (11%)	
Hypomenorrhoea	45 (39%)	23 (38%)	26 (26%)	15 (25%)	
Eumenorrhoea	33 (29%)	15 (25%)	25 (25%)	17 (28%)	
Menorrhagia	8 (7%)	3 (5%)	6 (6%)	2 (3%)	
Dysmenorrhoea:					
None		52%		52%	
Mild		21%		26%	
Moderate		21%		13%	
Severe		5%		8%	
Non menstrual pelvic pain:					
None		42 (69%)		49 (80%)	
Mild		13 (21%)		7 (11%)	
Moderate		3 (5%)		5 (8%)	
Severe		3 (5%)		0	
Success		58/85 (68%)		59/85 (69%)	P=0.87
▪ *Satisfaction*					
Satisfied with procedure		57 (93%)		61 (100)	
Of those who had a further procedure – satisfied (n=25)	22 (88%)				

▪ *Further surgery* Between yr 3 and yr 5 FU:			
Hysterectomy	13	7	
Repeat ablation	2	2	
D&C	0	1	
At 5 years FU:			
Hysterectomy	21	21	
Repeat ablation	3	2	
D&C	0	1	
Reason for hysterectomy:	(n=21)	(n=21)	
Bleeding	9 (43%)	7 (33%)	
Pelvic pain	3 (14%)	10 (48%)	
Bleeding and pelvic pain	5 (24%)	1 (5%)	
Myomas	1 (5%)	1 (5%)	
Ovarian cysts	1 (5%)	0	
Mood swings /depression	0	1 (5%)	
Uterine prolapse	2 (9%)	0	
Endometrial hyperplasia	0	1 (5%)	

Methodological comments

- *Prospective?* Yes
- *Consecutive patients enrolled?* Not stated
- *Method of Randomisation:* 1:1 allocation.
- *Power calculation?* None stated
- *All patients given same intervention?* Yes but techniques may vary between centres.
- *Loss to follow up? 53*/131 (40%) TBEA, 53/124 (43%) RB LTFU. The paper also excludes from analysis of outcomes a further 25 patients (10%) who underwent a repeat procedure between years 3 and 5.
- *Method of data analysis:* Descriptive statistics. Logistic regression performed using a stepwise selection for gravidity, parity, baseline Higham score, uterine position, yrs of menorrhagia, sound measurement, procedure duration, age and BMI. No characteristic strongly predicted treatment outcome.

Note that 6/14 patients reporting amenorrhoea at 5 yrs were over 50 and/or experiencing hot flushes.
Data for dysmenorrhoea have been extracted from presented graph, data in the text does not concur with the graph – indicating much less moderate to severe dysmenorrhoea than shown.

General comments

- *Generalisability:* Moderate – baseline characteristics not provided though are reported in other papers relating tot his trial.
- *Main outcome measured independently:* Uncertain
- *Inter-centre variability:* none stated
- *Conflicts of interest*: Supported in part by Gynecare.

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Pellicano et al 2002 ▪ *Study design:* RCT ▪ *Recruitment dates:* May 1998 – June 1999 ▪ *Setting:* Single centre in Italy	▪ *Treatment:* TBEA (Cavaterm) Control TCRE + RB (2.7% sorbitol and 0.54% mannitol distention solution. RB for corneal area, fundus and isthmus.) ▪ *Surgeon experience:* "Proficient" in TCRE. ▪ *Surgery pre-treatment:* TCRE group depot GnRH (Enantone 3.75) 6 and 2 weeks before surgery. No pre-treatment prior to TBEA. ▪ *Type of anaesthesia:* Spinal anaesthesia.	▪ *Total number of patients:* 96 randomised. (50 TCRE, 46 TBEA) 82 treated (42 TCRE, 40 TBEA) ▪ Indication for surgery: Menorrhagia unresponsive to medical treatment ▪ *Inclusion criteria:* <50 years old, weighing <100kg, not desiring pregnancy, uterine size <12 wks, documented history of at least 3 months failed medical treatment, documented evidence of normal endometrial histologic condition and pap smear within last 12 months. ▪ *Exclusion criteria:* Submucosal fibroids, endometriosis, adnexal masses, uterovaginal prolapse, severe urinary symptoms, severe intercurrent illness. ▪ *Participant characteristics:* TCRE: mean age 43.2 (SD +-3.5), mean BMI 28.3kg/m^2(SD+- 1.4), mean parity 1.8 (SD +-1.0), mean uterine dimensions 315 mL (SD +- 43), duration of symptoms 3.3yrs (+-1.1) TBEA: mean age 42.6 (SD +-4.4), mean BMI 29.8kg/m^2 (SD+- 1.9), mean parity 1.9 (SD +-0.7), mean uterine dimensions 295 mL (SD +-58), duration of symptoms 3.5yrs (+-0.9)	▪ *Primary and secondary outcome measures used:* Satisfaction. Pain, resumption of normal activities, operation details ▪ *Method of assessing outcomes:* Pain during operation on a visual analogue scale 1 (no pain) to 5 (intolerable pain) and at discharge. Post-operatively, asked to record for one week pain, vaginal bleeding and return to normal activities, to intercourse, to sexual activity and to work. FU at 3 months, 1 yr and 2 yrs patients asked for pain and bleeding symptoms and given a questionnaire for satisfaction measured buy the question "How do you think your health state is after the procedure?" (4-point scale excellent, good moderate, no improvement) ▪ Length of follow up: 24 months

Results:	**TCRE/RB N=42**		**TBEA N=40**		95% CI for difference
▪ *Symptoms*	Preop	postop	pre op	postop	
Irregular periods	26 (62%)		24 (60%)		**n/s**
Period >7days	33 (79%)		34 (85%)		**n/s**
Cycle <24 days	30 (71%)		30 (75%)		n/s
Dysmenorrhoea	16 (38%)		17 (43%)		n/s
Premenstrual symptoms	32 (76%)		27 (64%)		n/s
Pelvic pain	9 (21%)		9 (23%)		n/s
Pain recurs at 3m		1 (2%)		0	
Pain recurs at 1 yr (n=38, 37)		7 (18%)		1 (3%)	p<0.01
Pain recurs at 2 yrs (n=33,35)		9 (27%)		2 (6%)	p<0.01
Bleeding recurs					
At 3 mnths		3 (7%)		1 (3%)	
At 1 yr (n=38, 37)		6 (16%)		2 (5%)	p<0.01
At 2 yrs (n=33, 35)		8 (24%)		3 (9%)	p<0.01
▪ *QoL*					
Normal domestic activities (days)		6.2 (+-3.3)		4.1 (+-2.6)	N/s
Return to work (days)		0.9 (+- 0.3)		0.7 (+-0.1)	N/s
Resumption of sexual activity (days)		9.8 (+-0.7)		9.6 (+-0.6)	N/s
▪ *Satisfaction*					
At 3 mth (n=42, 40)					
Excellent		21 (50%)		27 (67%)	P<0.001
Good		12 (29%)		13 (33%)	
Moderate		9 (21%)		0	
No improvement		0		0	
At 1 year (n=38, 37)					
Excellent		12 (32%)		20 (54%)	P<0.001
Good		12 (32%)		10 (27%)	
Moderate		10 (26%)		5 (13%)	
No improvement		4 (10%)		2 (5%)	
At 2 yrs (n=33, 35)					
Excellent		2 (6%)		16 (46%)	P<0.001
Good		18 (54%)		12 (34%)	
Moderate		3 (9%)		5 (14%)	
No improvement		10 (30%)		2 (6%)	

▪ *Operation details*			
Operative time mins (SD)	37 (+-6)	24 (+-4)	P<0.01
Intraoperative blood loss, mL (SD)	89 (+-38)	7.2 (+-2.8)	P<0.01
Discharge time, days (SD)	1.3 (0.6)	1.0 (0.4)	N/s
▪ *Further surgery*			
Reoperation rate:			
3 mnths	0	0	ns
1 yr (n=38, 37)	4 (10%)	2 (5%)	P<0.01
2 yrs (n=33, 35)	5 (15%)	2 (6%)	P<0.01
▪ *Adverse effects*			
Intraoperative:			
Fluid overload	5 (12%)	-	N/s
Cervical tear	1 (2%)	-	N/s
Conversion to hysterectomy (due to severe uterine perforation)	2 (5%)	-	N/s
Postoperative pain:			
VAS (SD)	3.8 (+-0.6)	3.2 (+-0.7)	N/s
Post operative A/E			
Fever	2 (5%)	1 (2.5%)	-
UTI/retention	1 (2%)	0	-
Haemorrhage	4 (10%)	5 (12.5%)	-
Blood transfusions	-	2 (5%)	-
Pain at discharge (VAS)	1.5 (+-0.6)	1.9 (+-0.3)	P<0.01
Pain at 3 days (VAS)	0.5 (+-0.2)	0.4 (+-0.1)	N/s
Pain at 7days (VAS)	0	0	N/s
Urinary incontinence at 2 yrs (n=33, 35)	3 (9%)	2 (6%)	
CIN grade 1 (yr2)	1 (3%)	1 (3%)	
Post-op vaginal bleeding (days)	7.8 (+-1)	5.2 (+-1.8)	P<0.05

Methodological comments

- *Prospective?* Yes
- *Consecutive patients enrolled?* All invited to participate.
- *Method of Randomisation:* Computer generated random number sequence.
- *Power calculation?* No
- *All patients given same intervention?* Yes
- *Loss to follow up?* 105 eligible patients consented, 9 withdrew before randomisation. 96 randomised and 14 refused allocated treatment (8/50 TCRE, 6/46 TBEA, 15%). 4 TCRE and 3 TBEA LTFU at yr 1 (7%) and 9 TCRE and 5 TBEA LTFU at 2 yrs (15%). Total LTFU = 28/96 (29%)
- *Method of data analysis:*

ITT not used. Test for differences in characteristics between the groups using 2-tailed Student t-test for unpaired data, pre-operative basal differences using student t test for paired data. Chi-square test used for post operative details and satisfaction between the groups. Wilcoxon rank sum test for operative times, blood loss, duration of symptoms, discharge time.

General comments

- *Generalisability:* High
- *Main outcome measured independently:* Yes
- *Inter-centre variability:* N/A
- *Conflicts of interest*: Surgical equipment supplied by Wolf Germany and Wallsten Medical SA.

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Romer, 1998 ▪ *Study design:* Prospective RCT ▪ *Recruitment dates:* Not given ▪ *Setting:* Not given	▪ *Treatment:* Thermal balloon (Cavaterm™) vs rollerball ablation ▪ *Surgeon experience:* Not given ▪ *Surgery pre-treatment:* 2X 4 weekly injections of GnRH (leuprolide 3.75mg) operation performed 2 weeks after injection ▪ *Type of anaesthesia:* General for both interventions	▪ *Total number of patients:* 20 ▪ (10 intervention, 10 control) ▪ *Indication for surgery:* Recurrent therapy refractory menorrhagia (not assessed) ▪ *Inclusion criteria:* ▪ *Exclusion criteria:* Internal uterine cavity length 10cm, incomplete family planning, intra-uterine abnormalities, myomas, glandular-cystic, adenomyosis hyperplasia, carcinoma ▪ *Participant characteristics:* RB: Cavaterm™ Age 40 (35-50) 42 (37-52) Horm. Ther. Attempts 3 (2-5) 3 (1-6) Curettage 2.5 (2-4) 2.2 (2-5)	▪ *Primary and secondary outcome measures used:* Satisfaction Bleeding patterns ▪ *Method of assessing outcomes:* Not stated ▪ *Length of follow up:* 9 –15 months

Results:	Intervention		Comparison		95% CI for difference
▪ *Symptoms*	preop	postop	pre op	postop	
▪ *Bleeding patterns* *Amenorrhoea* *Hypomenorrhoea* *Eumenorrhoea* *Hypermenorrhoea*		4 (40%) 5 (50%) 1 (10%) 0		3 (30%) 6 (6%) 1 (1%) 0	Dichotomous data presented
▪ *QoL*	Not reported				
▪ *Satisfaction*	All patients satisfied with treatment outcome				No CI given
▪ *Operation details* ▪ *Further surgery* ▪ *Adverse effects*	- No treatment failures reported at 9-15 months Author does a comparison of pros and cons of each technique but not based on trial data				

Methodological comments

- *Prospective?* Yes
- *Consecutive patients enrolled? Not clear*
- *Method of Randomisation* Not clear
- *Power calculation?* Not stated
- *All patients given same intervention?* 10 given RB: 10 given Cavaterm™
- *Loss to follow up?* None
- *Method of data analysis:* dichotomous data

General comments

- *Generalisability:* Low
- *Main outcome measured independently:* No
- *Inter-centre variability:* N/A
- *Conflicts of interest*: None stated

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Soysal et al 2001 ▪ Study design: RCT ▪ *Recruitment dates:* Sept. 1997 – February 1999 ▪ *Setting:* University medical centre in Turkey.	▪ *Treatment:* Thermal Balloon Ablation Control – Rollerball ablation, glycine distention medium. ▪ *Surgeon experience*: R/B performed by one experienced surgeon, TBEA by staff surgeons or supervised residents ▪ *Surgery pre-treatment:* Two monthly injections of depot GnRH analog (3.6mg goserelin acetate) ▪ *Type of anaesthesia:* All TBEA local anaesthetic, all R/B general.	▪ *Total number of patients:* 96 (48 TBEA, 48 R/B) ▪ *Indication for surgery:* Myoma induced menorrhagia ▪ *Inclusion criteria:* Age 40+, completed childbearing, PBAC documented menorrhagia, myomatous uterus diagnosed by ultrasound examination, uterine size 12 weeks or less, at clinical evaluation or 380ml or less at ultrasound or a myoma less than 5cm diameter. All pts had a physical exam, diagnostic hysteroscopy, suction biopsy and cervical smear. ▪ *Exclusion criteria:* Active PID, any submucous myoma larger than 3cm or with <50% intramural extension shown in high resolution or in diagnostic hysteroscopy. ▪ *Participant characteristics:* mean (range) TBEA – Age 43.6 +/- 2.5 (40-49), parity 2.9 (1-6), PBAC 383.1 +/-97.2 (223-811), Uterine volume, ml at sonography 195+/-24.1(151-245), after GnRH 128 +/-19 (107-149) R/B – Age 44.3 +/-2.6 (40-49), parity 3.1 (1-5), PBAC 387.1 +/-101 (243-759), Uterine volume, ml at sonography 199.2 +/-20, (167-239), after GnRH 132 +/-21 (111-146)	▪ *Primary and secondary outcome measures used:* Blood loss, haemoglobin levels. Operating time, pain post operation, future hysterectomy, amenorrhoea, complications, satisfaction. ▪ *Method of assessing outcomes:* PBAC for blood loss (>150 = menorrhagia) at 3 ,6 and 12 months. Haemoglobin values recorded pre-operatively and at 12 mnths. Operating time (from insertion of operating tool to removal), intraoperative complications, postoperative pain score recorded 12 hrs after surgery using 10 point linear pain score. Success defined as eumenorrhoea or PBAC<76. Satisfaction on a 3 point scale – very satisfied, satisfied and dissatisfied. ▪ *Length of follow up:* 12 MONTHS

Results:	**TBEA n=45**		R/Ball n=48		95% CI for difference
▪ *Symptoms*	Preop	postop	pre op	Postop	
PBAC score	384.3 +/-101	41.1 +/-29	385.6 +/-103	40.2 +/-45	-
Hb g/dl	10.0 +/-1.49	12.8 +/-0.9	9.8 +/- 1.2	12.9 +/-0.9	-
Mean decrease in PBAC		343.2 +/-87		345.5 +/-113	Not sig.
Mean increase in Hb, g/dl		2.7 +/-1.9		3.0 +/-1.6	Not sig.
Amenorrhoea		5		8	Not sig.
PBAC <76		75%		79%	Not sig.
▪ *QoL*	-	-	-	-	-
▪ *Satisfaction*					
Not very satisfied	33%		39%		Not sig.

▪ *Operation details*			
Operation time, min	11.5 +/- 0.8	37.3 +/-7.5	P<0.0001
▪ *Further surgery*			
Hysterectomy	4	4	Not sig.
▪ *Adverse effects*			
Linear pain score at 12 hrs	3.1 +/- 1.7	3.2 +/-2.1	Not sig.
Intraoperatively-			
Fluid overload	-	2	P<0.05
Haemorrhage	-	2	
Cervical injury	-	1	
Postoperative-			
Haematoma	1	2	Not sig.
Endometritis	2	1	

Methodological comments
- *Prospective?* Yes
- *Consecutive patients enrolled?* Uncertain
- *Method of Randomisation:* Computer generated randomisation using opaque, sealed envelopes.
- *Power calculation?* None stated
- *All patients given same intervention?* Yes
- *Loss to follow up?* 96 pts recruited, 3 pts allocated to TBEA lost before procedure, no other LTFU
- *Method of data analysis:* SPSS for tests such as Student's t test for independent samples and paired samples, the Mann-Whitney U test, Fisher's exact test, chi-squared test and others were used. Baseline characteristics give a mean, SD and a range - if the data were believed to be non-parametric, median and range should be given, if not mean and SD would suffice.

General comments
- *Generalisability:* High
- *Main outcome measured independently:* Yes
- *Inter-centre variability:* not applicable
- *Conflicts of interest*: None stated

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* van Zon-Rabelink, 2001 ▪ *Study design*: RCT ▪ *Recruitment dates:* Not stated *Setting:* Netherlands. Number of centres not given.	▪ *Treatment:*. ▪ *Surgeon experience*: Not stated ▪ *Surgery pre-treatment:* All patients pre-treated with zoladex 6 and 2 weeks prior to surgery. ▪ *Type of anaesthesia:* Not stated	▪ *Total number of patients:* 139 (77 TBEA, 62 RB) 2 from rollerball group excluded after randomisation ▪ *Indication for surgery:* Menorrhagia ▪ *Inclusion criteria:* PBAC score >184, DUB according to TVS and hysteroscopy. ▪ *Exclusion criteria:* None stated. ▪ *Patient characteristics:* No differences found in age, parity, uterine cavity, endometrial thickness and Hb and pre-operative FSH levels.	▪ *Primary and secondary outcome measures used:* PBAC score, adverse effects, success rate, QoL ▪ *Method of assessing outcomes*: Success defined as PBAC score <185. Other methods of assessing outcomes not stated. ▪ *Length of follow up*: 24 months.

Results:	**TBEA n=77**	**RB n=60**	
▪ *Symptoms*			
PBAC	Lower	Higher	p=0.01 at 2 yrs but not sig. at 6 and 12 months.
Menstrual reduction	More	Less	p=0.03 2 yrs
Success (PBAC <185) Year 1	79% (95% CI 68-88%)	79% (95% CI 66-88%)	
Success (PBAC <185) Year 2	78% (95% CI 67-87%)	76% (95%CI 63-86%)	
▪ *QoL*	-	-	-
▪ *Satisfaction* At 2 years	80%	75%	P=0.53
▪ *Operation details* Mean operation time	Shorter	Longer	P<0.001
Post-op. pain medication	More	Less	P=0.01
▪ *Further surgery* At 2 years	17%	15%	
▪ *Adverse effects* Intra-operative complications	None	Perforation of uterus, laceration of cervix, Electrolyte dis-balance, Suspicion of perforation	P<0.001
No complaints at 6 weeks	95%	97%	

Methodological comments

- *Prospective?* Not stated
- *Consecutive patients enrolled?* Not stated
- *Method of Randomisation:* Stratified by age (< or > 45) and parity (nulips and parity). Blind envelope allocation.
- *Power calculation?* None stated
- *All patients given same intervention?* Yes.
- *Loss to follow up?* 2 women excluded after being randomised to RB group – one had polyps at operation and one had a PBAC score <185. These women were excluded from analysis. One women in RB arm LTFU.
- *Method of data analysis:* Descriptive. No details given

General comments

- *Generalisability:* Low
- *Main outcome measured independently:* Yes – but success outcome of PBAC <185 is a high score.
- *Inter-centre variability:* Not stated
- *Conflicts of interest*: None stated

8.9 Appendix 9: Graphs showing sensitivity analyses for MEA and TBEA

Figure 18: Sensitivity analysis: Cost per QALY for TBEA vs MEA

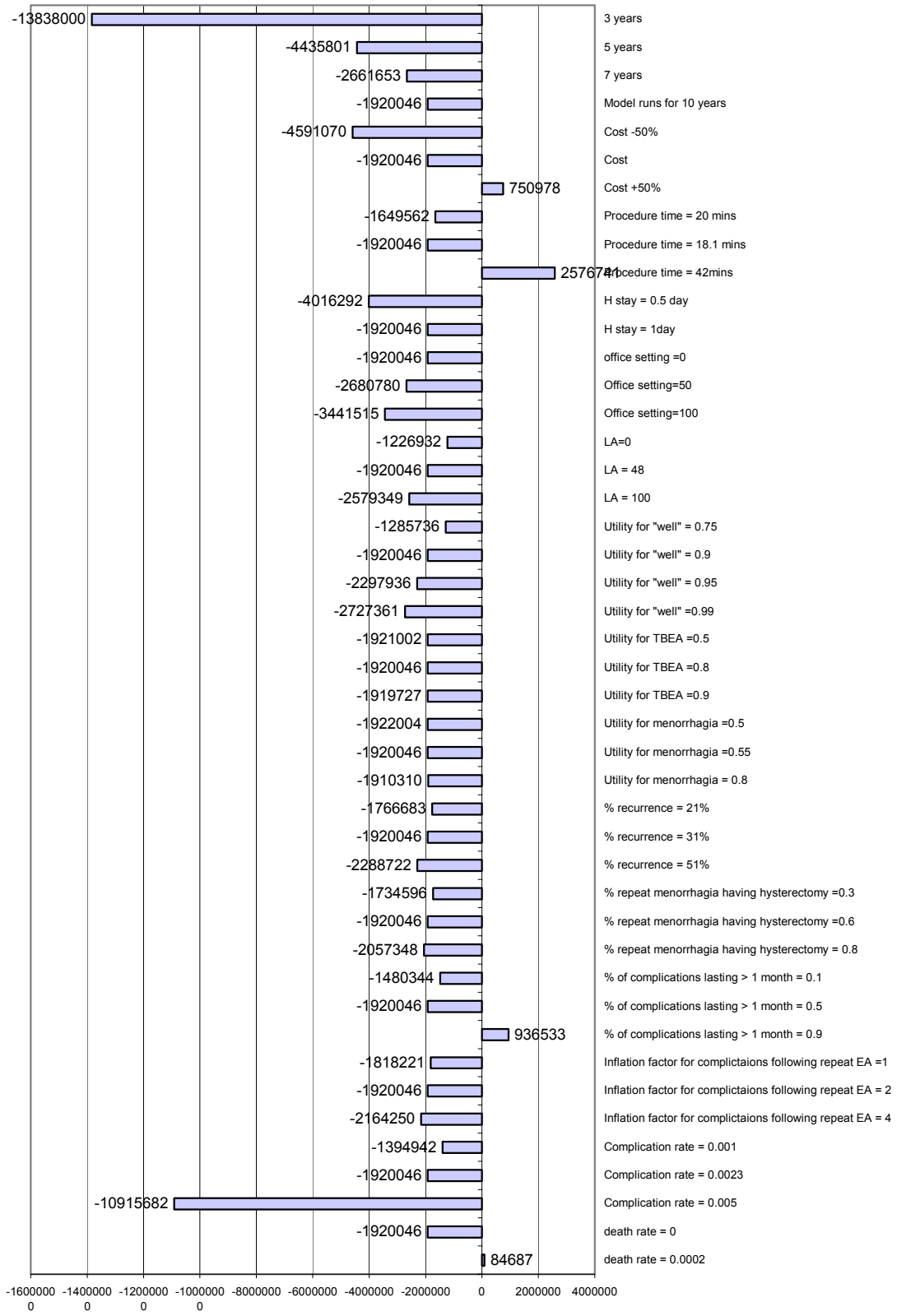


Figure 19: Sensitivity analysis: Cost per QALY MEA vs TCRE

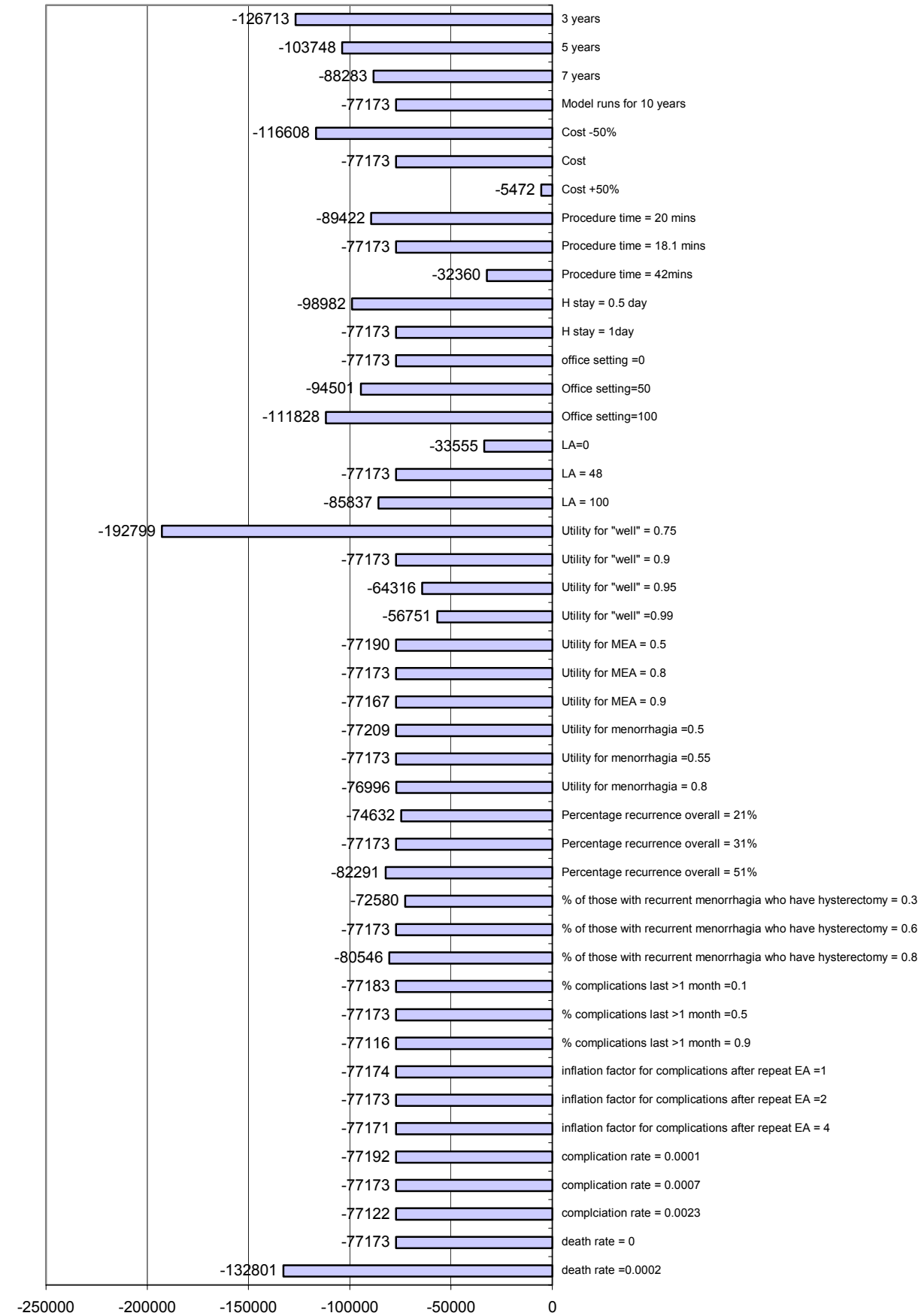


Figure 20: Sensitivity analysis: Cost per QALY TBEA vs TCRE

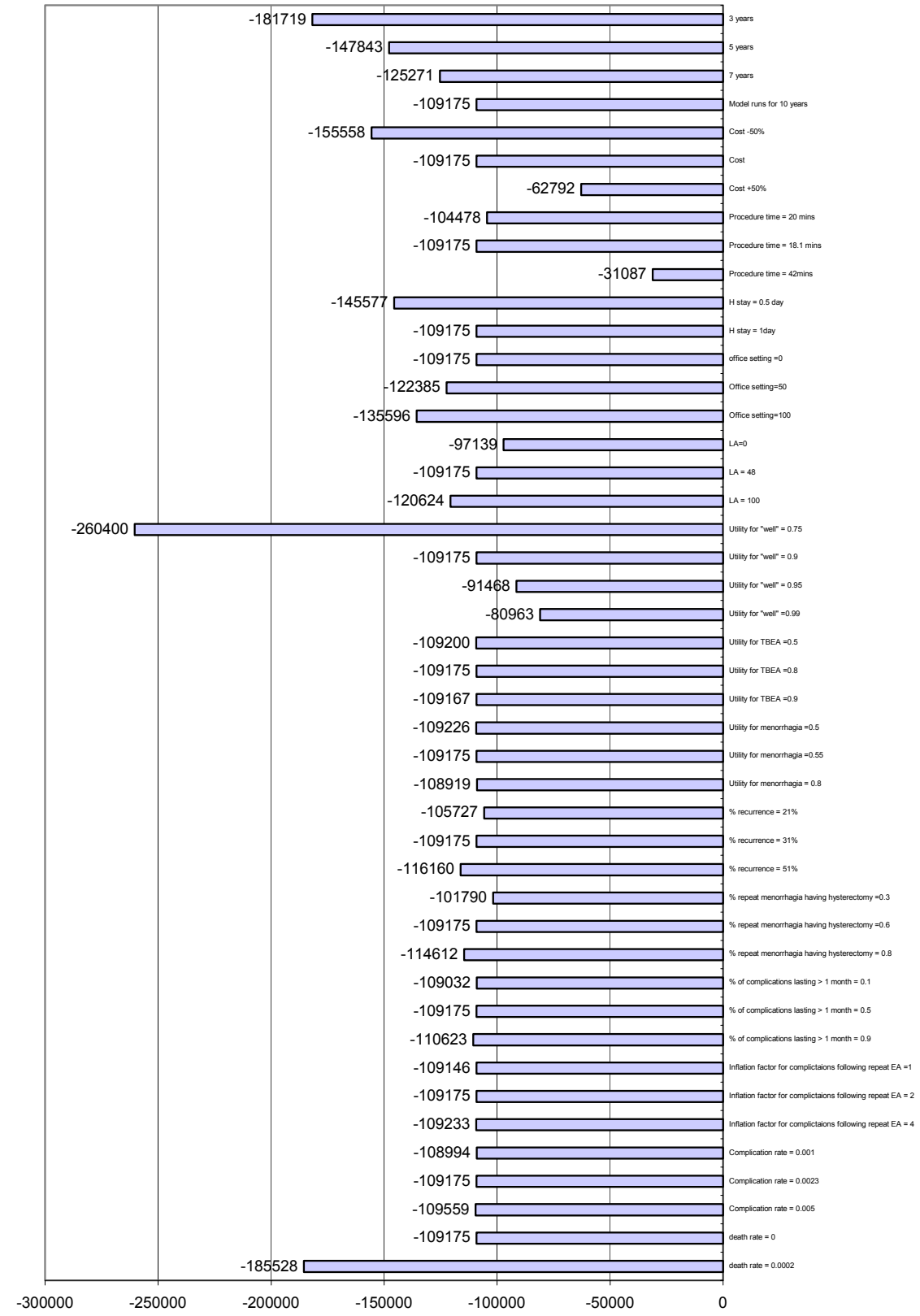


Figure 21: Sensitivity analysis Cost per QALY MEA vs Rollerball

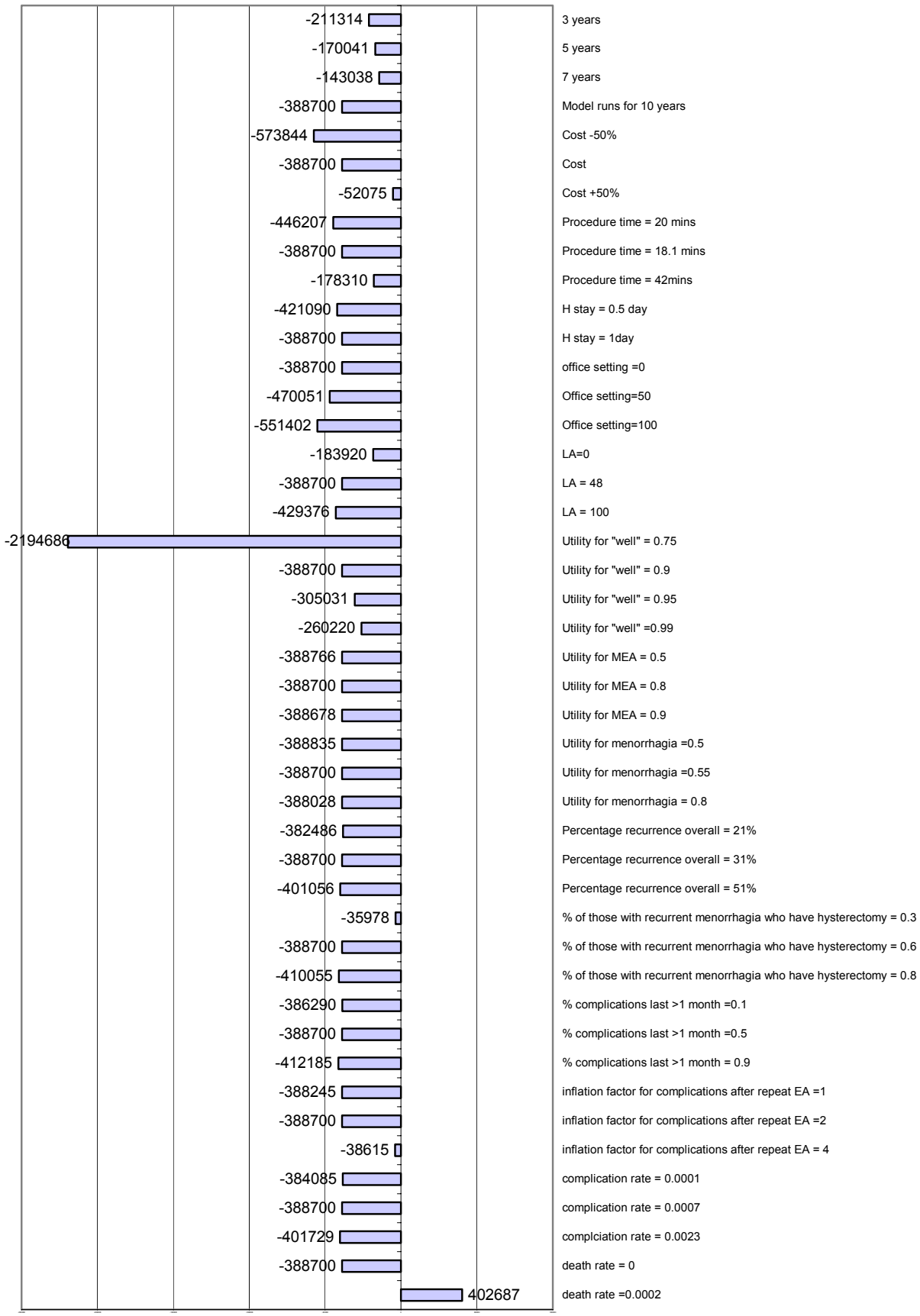


Figure 22: Sensitivity analysis: Cost per QALY TBEA vs rollerball ablation

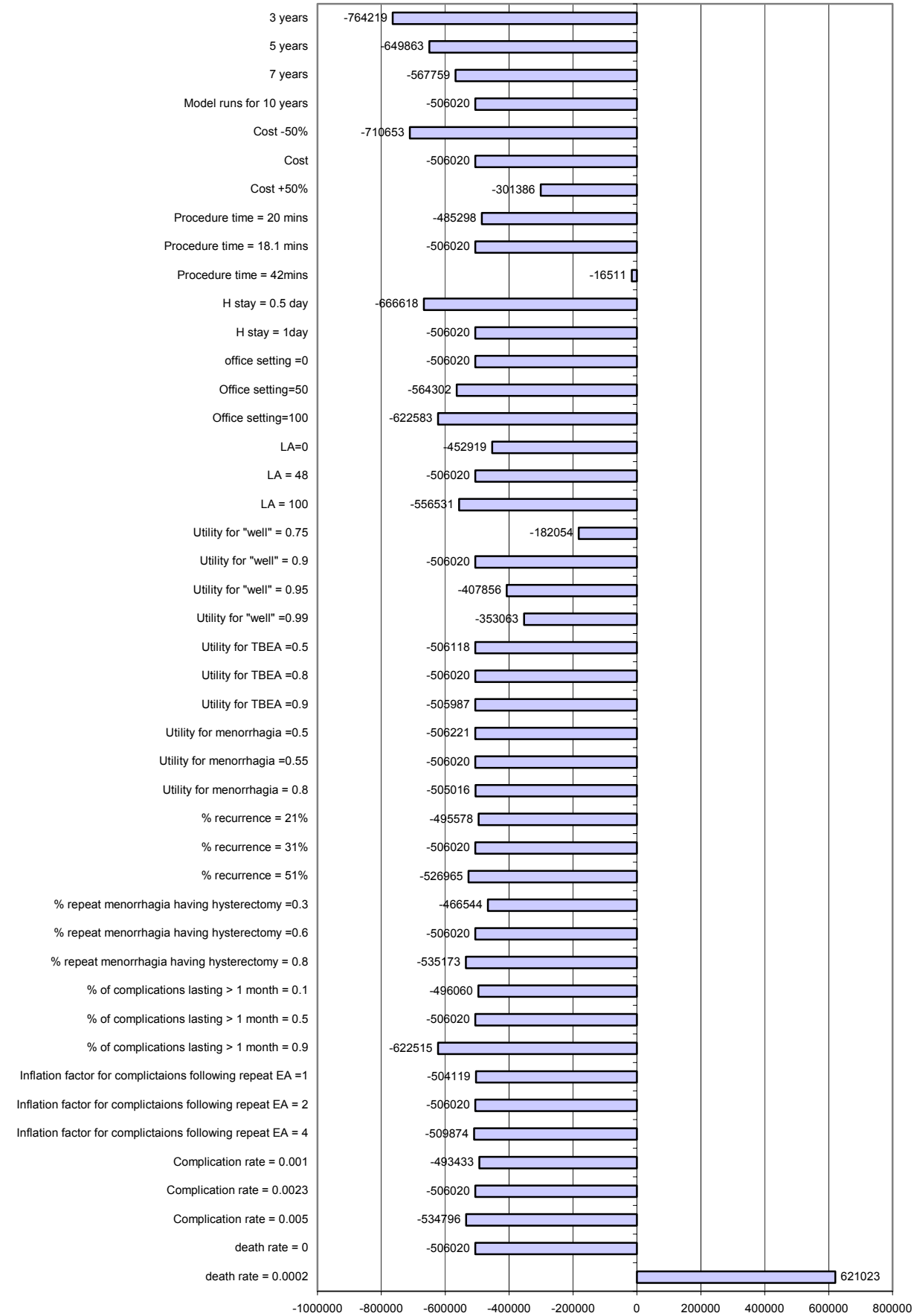


Figure 23: Sensitivity analysis: TBEA versus combined TCRE and rollerball ablation

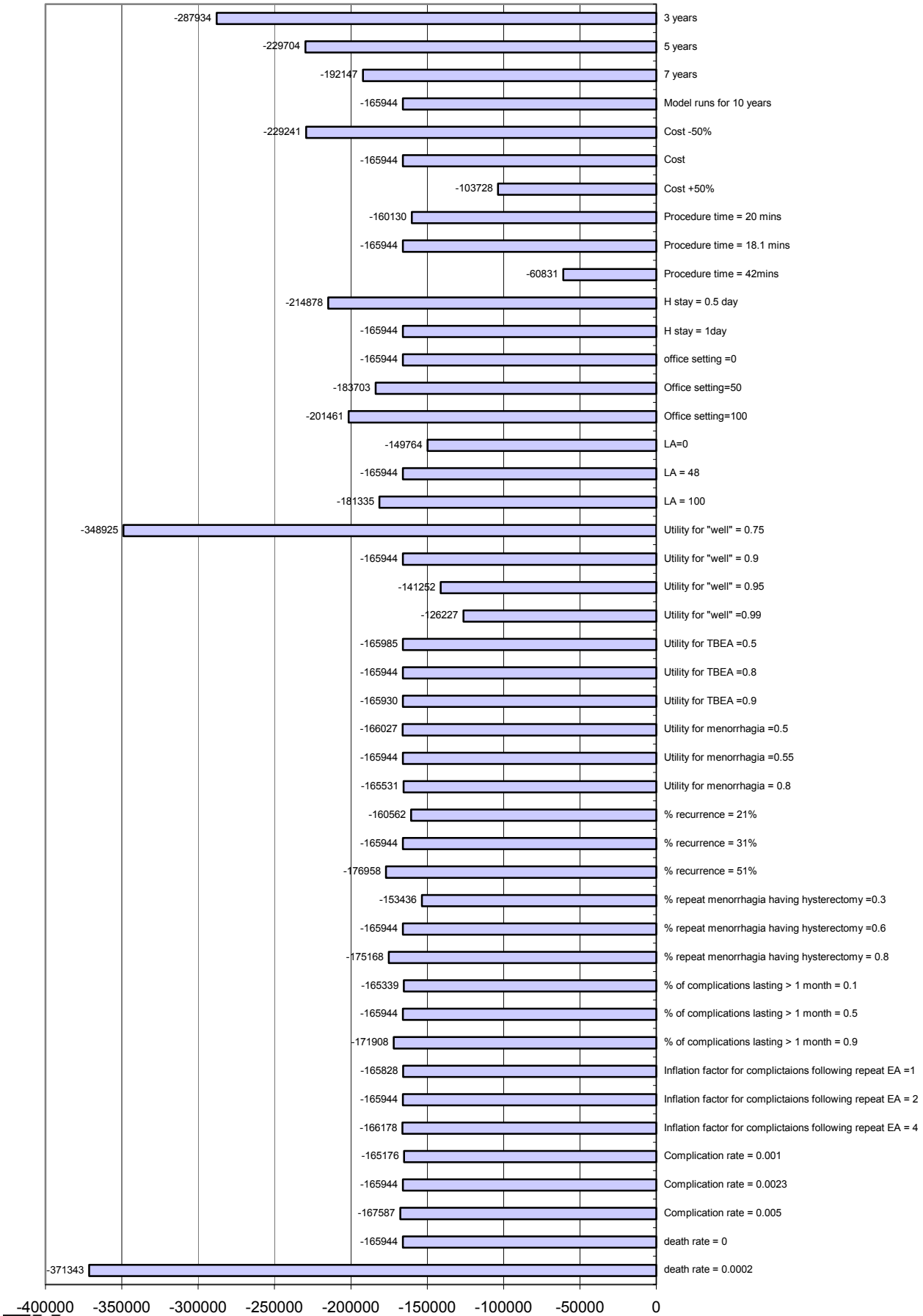


Figure 24: Sensitivity analysis: MEA versus combined TCRE and rollerball ablation

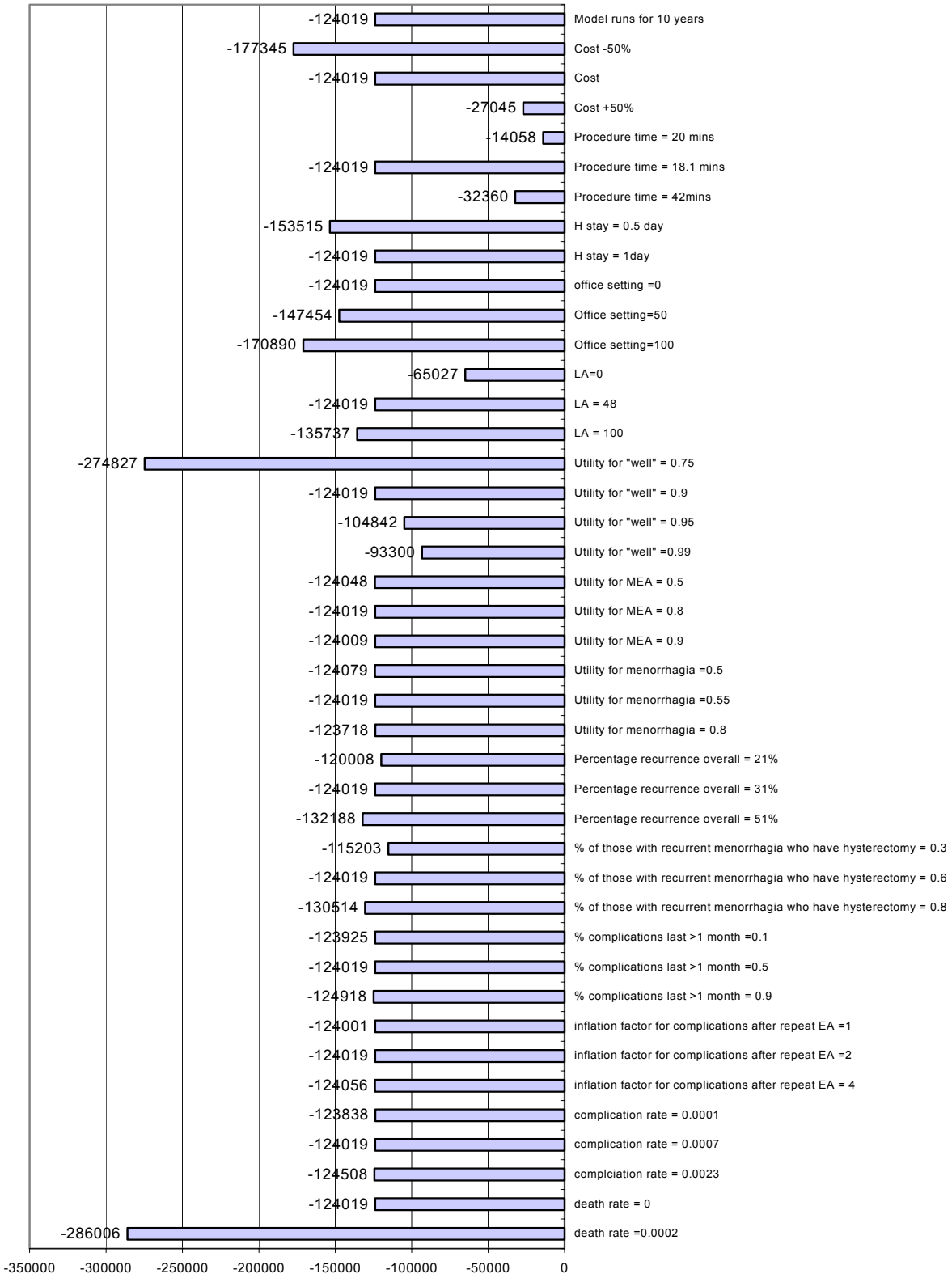


Figure 25: Sensitivity analysis: Cost per QALY for TBEA vs. hysterectomy

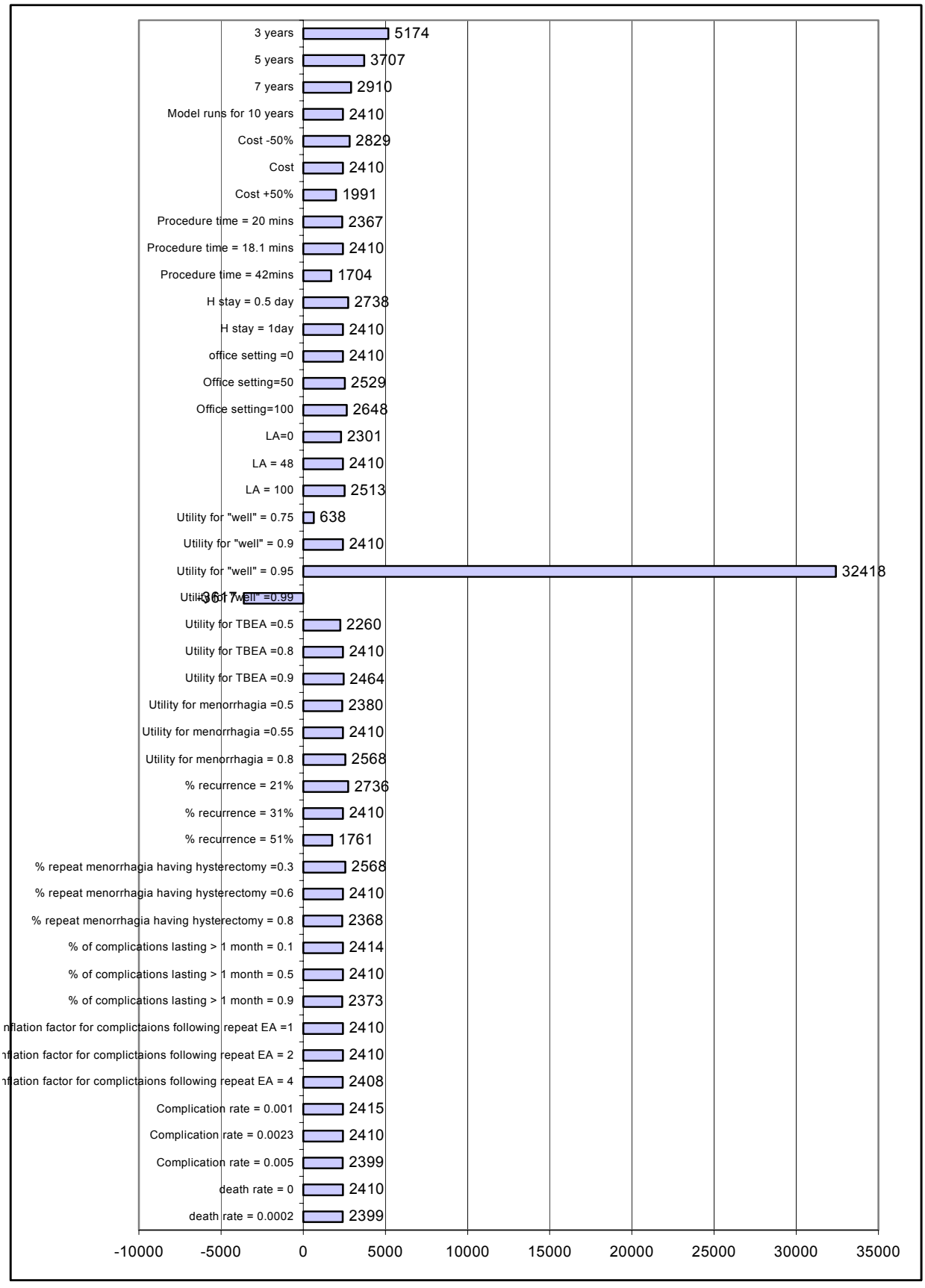
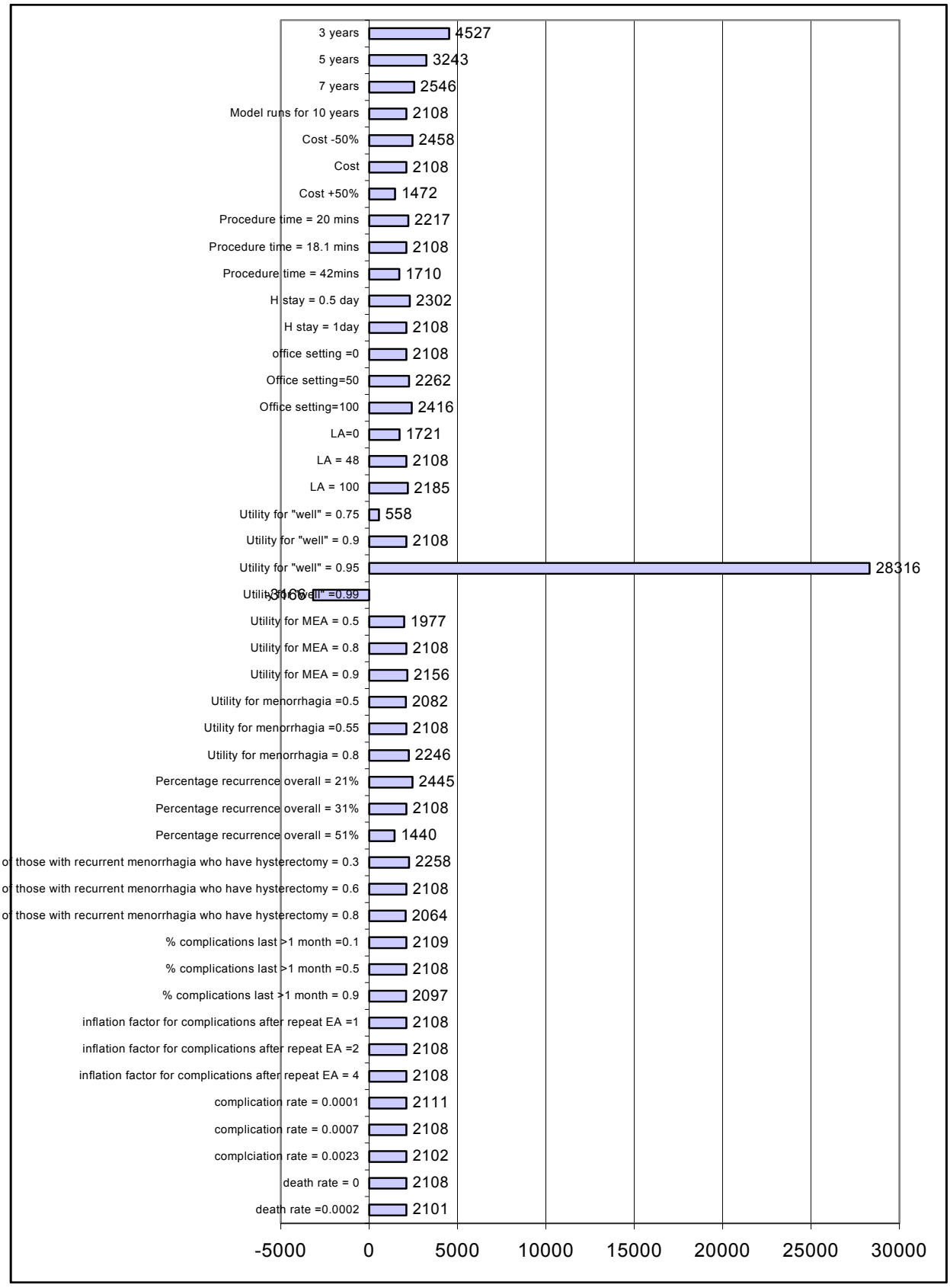


Figure 26: Sensitivity analysis: Cost per QALY MEA vs hysterectomy



8.10 Appendix 10: Quality assessment of industry submitted economic analyses

8.10.1 Assessment of economic model supplied by Microsulis Medical Ltd. (based on Sculpher framework)

1. Structure	
Is there a clear statement of the decision problem, the context and the perspective?	The model aims to determine the costs and consequences of MEA, balloon ablation, rollerball ablation, rollerball with resection, resection only and hysterectomy treatments for menorrhagia in the UK. MEA is the technology appraised and is compared to first and second generation EA techniques. An incremental cost –effectiveness analysis is used to estimate additional costs and benefits of using MEA rather than the other treatments.
Is a theory of the underlying disease detailed?	Background information is provided about menorrhagia and existing surgical treatments.
Are the underlying assumptions involved in the model clearly specified? Are they justified? Are the implications of relaxing these assumptions described?	Assumes probability of further procedures over time follows a logarithmic distribution.
2. Disease states	
Is the chosen model type appropriate for the time dimension of the disease process?	Two stage pathway in a decision tree. Initially, there are nine health states (pre-operation, operation, death, complication, convalescence, post-operative, menorrhagia, further surgery and hysterectomy). Stage Two is slightly different for women having MEA than with the other ablation methods, as those with recurrent menorrhagia have a TCRE/rollerball procedure or hysterectomy, not a repeat procedure
Is a justification of the choice of states within the model provided? If so, does this accord with the theory of disease process?	Not directly but the states do appear to adequately describe the states involved in menorrhagia and its treatment.
Is any empirical evidence provided on the suitability of the states (e.g. sensitivity to change in the underlying disease)?	No evidence is given although the states do appear to map the progress of condition.
Have any important disease states been omitted from the model?	No
3. Options	
Is there a clear statement of the options being evaluated?	Yes, the model evaluates first and second generation EA methods.
Do these appear to cover the range of logical and feasible options?	Yes.
4. Time horizon	
Is the time horizon of the analysis stated?	Yes – model duration is five years.
If so, is this justified in terms of the underlying disease and the effect of interventions?	This time horizon is justified based on the majority of further procedures being undergone by the end of year five.
5. Cycle length (if relevant)	
If relevant, is the cycle length used in the model stated.	N/R
Is justification offered on the choice of cycle length? If so, does the justification relate to the disease process?	No
6. Data identification	
Are the sources of parameter values in the model clearly stated?	Most transition probabilities are from the literature. Cumulative probabilities of repeat resection or hysterectomy at one, two and three years following initial resection were obtained from a life table analysis. The probability of a further procedure within each year

	is a function of the probability of undergoing the procedure at year one and a growth rate corresponding to the time since the initial procedure and follows a logarithmic distribution. Utilities are taken from published literature. Those for menorrhagia, convalescence and post-convalescence for resection and hysterectomy are taken from a published cost utility analysis[30] derived from a time trade of analysis with 60 women with menorrhagia. Due to the similarity of descriptions for convalescence with TCRE were similar to the other methods of ablation, this value was also assigned to them. Resource costs are estimated from the perspective of the NHS in British pounds sterling. Theatre overhead costs are calculated from information received from a single Scottish NHS trusts. Source of staff costs is not stated. Other costs come from Chartered Institute of Public Finance Accountancy (CIPFA) and the Royal Pharmaceutical Society of Great Britain. Operation details are taken from the literature The cost of TBEA equipment is taken from the full list price, plus cost of umbilical cable. All other procedures are assumed to require standard operating equipment which is assumed to be included in the theatre overheads.
Is reasonable empirical justification, from earlier iterations of the model, offered that these data are optimal?	No. Most data comes from the literature The utility values for post-convalescence are calculated as the ratio of "bleeding and pain" scores for each procedure and TCRE. The "bleeding and pain" score was the summation of the proportion of women with amenorrhoea and with dysmenorrhoea at 12 months, based on data in RCTs. This method of calculating a utility score is not sourced or justified. In addition, amenorrhoea may not be the best measure of success as many women do not seek this as a treatment aim. Those who do may be more likely to seek hysterectomy for HMB. The utility calculation gives a low post-convalescence value for TBEA which has relatively low levels of amenorrhoea – 0.57, while the other EA methods range from 0.73 to 0.79 and hysterectomy 0.86. In addition, this utility value of 0.57 for TBEA, 0.73 for RB and TCRE and TCRE alone and 0.74 for rollerball ablation during post-convalescence, is lower than the figure of 0.76 that these methods all receive during convalescence, which is counter-intuitive. It would be expected that utility of convalescence was lower than that for post-convalescence ("well"). There was no indication in the literature to ascertain the duration of recurrent menorrhagia prior to undergoing a repeat procedure. In the base case analysis it was therefore assumed that a woman would have menorrhagia for 50% of the time between the end of convalescence and the time of a further procedure. No justification for this figure is given.
For the first iteration of the model, has satisfactory justification been offered that data are based on a search of all the low-cost data sources (e.g. Medline, DARE, Cochrane library)?	Yes. Medline and Embase were searched for relevant literature. Search limits were RCTs, English language, published after 1994 and human studies.
Are ranges specified for parameters?	Yes.
Is there evidence to suggest selective use of data?	Some. It is assumed that 50% of women undergoing TBEA and MEA received local anaesthetic (LA) in an office setting and an 67% of the remaining women have LA in an operating theatre. Though this latter figure is based in published evidence ,[67] unpublished

	evidence from the same centre has concluded that post-operative pain and nausea make MEA unsuitable as an outpatient, rather than day case, procedure. In addition, the estimation of first generation procedures undertaken under LA is 14%, taken from a UK RCT[102]. However, this may be an underestimate as systematic review[9] evidence showed that 23% of women undergoing rollerball ablation had local anaesthetic. This will underestimate the cost of MEA and TBEA compared to first generation techniques.
If some parameter estimates are based on elicitation of expert opinion, have the methods used for this purpose been adequately described (e.g. inclusion criteria, sample size, elicitation methods)?	Not applicable.
Are the claims made about the model results tempered by the limitations of the data?	The authors discuss limitations of the data available for several parameters.
7. Data incorporation	
For each parameter value, is there clear and reasonable justification of how data have been incorporated into the model?	In the absence of post-convalescence utility values, the value available for resection was multiplied by a factor representing relative severity of bleeding and pain. This was calculated by summing the proportion of women with amenorrhoea and the proportion of women with dysmenorrhoea at 12 months. No reference is given for this technique which gives a value of 0.57 for balloon ablation, and of 0.79 for MEA due to the relatively low level of amenorrhoea with TBEA and therefore biases in favour or MEA. Women experiencing repeat menorrhagia are assumed to spend half the time between with the post-convalescence utility value and half with the value for menorrhagia.
Has a stochastic analysis been undertaken?	Uncertainty has been examined by one- and two-way sensitivity analyses and a Monte Carlo simulation was used to vary all parameter simultaneously. Parameters varied are listed and the range used for each given. Triangular distribution is used in MC.
If so, do the distributions in parameter values reflect second order uncertainty?	Not applicable.
Have appropriate distributions been selected for each parameter?	Not applicable.
Have interval rates been translated into transition probabilities using the appropriate formula?	Not applicable
If appropriate, has a half cycle correction been applied to adjust time-relate estimate in the model?	Not applicable
8. Internal consistency	
Is there a statement about the tests of internal consistency that were undertaken?	No statement is made about tests of internal consistency that were undertaken.
9. External consistency	
Are any relevant studies and/or models identified by the analyst for purpose of comparison?	No.
Have any comparisons of the outputs of the model with independent external sources been reported?	No

If so, are the conclusions justified? Have discrepancies been investigated and explained?	Not applicable.

8.10.2 Quality Assessment of economic analysis supplied by makers of Thermachoice™ (using the Drummond frame work)

1. Was a well-defined question posed in answerable form?	Yes, the comparison is between thermal balloon, TCRE and hysterectomy The viewpoint of the analysis is not stated. Cost data are taken from the French healthcare system and are not comprehensive. A three year time horizon is taken, which may underestimate re-intervention rates and bias the analysis in favour of endometrial ablation.
2. Was a comprehensive description of competing alternatives given?	Competing alternatives are described, though some aspects of care are not included in the comparison.
3. Was the effectiveness of the programme or services established?	Effectiveness data are taken from the report of three year follow up in the Meyer trial. Estimates for effects are not calculated on an intention to treat basis and no account is taken of the precision of results. For example, the difference in amenorrhoea between thermal balloon and TCRE were not statistically significant.
4. Were all important costs and consequences identified?	No.
5. Were costs and consequences measured accurately in appropriate units?	Costing study was acknowledged as not being comprehensive, focussing on surgical component. Outcome measurement in relation to endometrial ablation is discussed elsewhere in this assessment report.
6. Were costs and consequences valued credibly?	Resources were identified and costed in the French healthcare system - some difficulty in extrapolating these to the UK. Base year for costings not stated. Consequences are reasonably maintained in natural units.
7. Were costs and consequences adjusted for differential timing?	No, although time horizon is short (three years).
8. Was an incremental analysis performed?	Yes
1. Was allowance made for uncertainty in the estimates of costs and consequences?	No - a major shortcoming of the analysis.
2. Did the presentation and discussion of results include all issues of concern to users?	No. The analysis is acknowledged to be limited.

8.10.3 Quality assessment of economic analysis supplied by the makers of Cavaterm™ (using Sculpher framework)

Critical appraisal	Cavaterm Model
1. Structure	
Is there a clear statement of	The comparisons are clearly stated. The perspective is not well

the decision problem, the context and the perspective?	defined but is predominantly that of the NHS, and in particular the secondary care sector. However, number of days absent from work is included which incorporates an element of patient or societal perspective.
Is a theory of the underlying disease detailed?	The condition process is described elsewhere in the industry submission to NICE and is relatively simple.
Are the underlying assumptions involved in the model clearly specified? Are they justified?	The treatment pathway is clearly described. The model's baseline is current practice i.e. the proportion of women receiving each of the competing technologies. The current utilisation of different second generation techniques was estimated from expert opinion. *Not justified (methods not stated)* All second ablations are repeats of the original technique. *Justified - unlikely that women will move to another ablation technique and no information on this available.* It is assumed that all women who undergo an unsuccessful second ablation will have hysterectomy. *This will represent a slight overestimate of the number of women eventually undergoing hysterectomy. It is likely that some women will reject hysterectomy for a variety of reasons. This group may have a further ablation or continue with medical treatment. Some will reach the menopause before hysterectomy is carried out. The increase in the number of hysterectomies performed for failure of ablation will bias the model against ablation.*
Are the implications of relaxing these assumptions described?	The sensitivity analysis examines the effect of relaxing assumptions regarding differential effectiveness of second generation technologies, using different sources of effectiveness data and varying other key inputs in one way sensitivity analyses. The impacts of relaxing more fundamental assumptions regarding the treatment pathway are not explored.
2. Disease states	
Is the chosen model type appropriate for the time dimension of the disease process?	The time horizon of three years is justified as the extent of current data from RCTs. However, a longer time frame may be appropriate given the importance of the failure rate and its potential relationship with time beyond this period. The modelling approach does not permit a cost utility analysis. The modelling approach does not allow for the differential timing of events and associated discounting.
Is a justification of the choice of states within the model provided?	Yes
If so, does this accord with the theory of disease process?	Not relevant
Is any empirical evidence provided on the suitability of the states (e.g. sensitivity to change in the underlying disease)?	No
Have any important disease states been omitted from the model?	No
3. Options	
Is there a clear statement of the options being evaluated?	Yes

Do these appear to cover the range of logical and feasible options?	Yes
4. Time horizon	
Is the time horizon of the analysis stated?	Yes - three years
If so, is this justified in terms of the underlying disease and the effect of interventions?	No The average age of women in the RCTs of EA was 42 years. Since the menopause occurs on average around ten years later and failure rates may be time dependent, it is likely that the three year time horizon may have underestimated cumulative failure rate.
5. Data identification	
Are the sources of parameter values in the model clearly stated?	Yes
Is reasonable empirical justification, from earlier iterations of the model, offered that these data are optimal?	No - this is the first iteration of the model
For the first iteration of the model, has satisfactory justification been offered that data are based on a search of all the low-cost data sources (e.g. Medline, DARE, Cochrane library)?	Yes. The model is informed by a review of the effectiveness of the technologies concerned.
Are ranges specified for parameters?	Yes
Is there evidence to suggest selective use of data?	Possibly.
If some parameter estimates are based on elicitation of expert opinion, have the methods used for this purpose been adequately described (e.g. inclusion criteria, sample size, elicitation methods)?	No - as noted above.
Are the claims made about the model results tempered by the limitations of the data?	Not in all cases. The assumption that Cavaterm is more effective than the alternative balloon ablation technology, Thermachoice, is given undue weight given the nature of the underlying empirical data. This comes from an indirect comparison, based on trials carried out on small numbers of women over different follow up times. Failure rates are similar for the two technologies at Some sweeping claims for Cavaterm are made. For example, relating to the complete replacement of existing technologies with Cavaterm and potential impact on operating theatre time and bed days. It is unlikely that such a complete technological transfer would be achieved because (a) some women will have a strong preference for hysterectomy, based on their high valuation of amenorrhoea over eumenorrhoea and (b) not all women with menorrhagia are candidates for balloon ablation due to variation in uterine morphology and pathology. Similar claims are made for the potential impact of Cavaterm use on hospital bed day capacity and the labour market.
6. Data incorporation	
For each parameter value, is there clear and reasonable justification of how data have been incorporated into the model?	Not in all cases. There is limited justification for the choice of one source for data over another. Failure rates are acknowledged to be a key parameter. However, the method for incorporating data is weak, mainly because of the way that primary research has been reported. In the industry submission, data from studies carried out at different times are combined in a meta-

	analysis and compared across the different endometrial ablation technologies. The most appropriate statistical analysis would be a survival analysis, including time to failure as this outcome is likely to be highly time dependent. Such data are lacking, which undermines attempts to compare different endometrial ablation technologies.
Has a stochastic analysis been undertaken?	Yes. The model
If so, do the distributions in parameter values reflect second order uncertainty?	No. A uniform distribution for parameter values is assumed in each case.
Have appropriate distributions been selected for each parameter?	No
Have interval rates been translated into transition probabilities using the appropriate formula?	Not relevant
If appropriate, has a half cycle correction been applied to adjust time-relate estimate in the model?	Not relevant
7. Internal consistency	
Is there a statement about the tests of internal consistency that were undertaken?	No. The model as received does not permit close examination of the underlying calculations being carried out as two key spreadsheets are not included or accessible.
8. External consistency	
Are any relevant studies and/or models identified by the analyst for purpose of comparison?	None were available.
Have any comparisons of the outputs of the model with independent external sources been reported?	No.
If so, are the conclusions justified? Have discrepancies been investigated and explained?	See elsewhere in this assessment report.

8.11 Appendix 11: Parameters used in the industry and PenTAG economic models

Parameter	PenTAG Value	Microsulis Value	Therma-choice Value	Cavaterm Value
Procedure cost hysterectomy	2096	2644	1778*	2050
Procedure cost TCRE	1110	1129	958	593
Procedure cost Rollerball	1190	624	-	593
Procedure cost TCRE/RB	1027	545	-	593
Procedure cost Cavaterm™	826	712	-	584
Procedure cost Thermachoice™	826	712	905	581
Procedure cost MEA	942	674	-	798
Success rate following repeat EA	-	-	-	0.5 x that of primary EA success rate
Mean cost of a complication following balloon ablation (£)	-	770	-	-
Mean cost of a complication following hysterectomy (£)	-	647	-	-
Mean cost of a complication following MEA (£)	-	695	-	-
Mean cost of a complication following RB+TCRE (£)	-	641	-	-
Mean cost of a complication following rollerball (£)	-	408	-	-
Mean cost of a complication following resection (£)	-	614	-	-
Discount rate for benefits (% expressed as decimal)	0.015	0.015	-	-
Discount rate for costs (% expressed as decimal)	0.06	0.06	-	-
Failure rate 1st generation EA	0.31	-	-	0.1-0.3
Failure rate MEA	0.31	-	-	0.12
Failure rate Thermachoice™	0.31	-	-	0.14
Failure rate Cavaterm™	0.31	-	-	0.07
Probability of hysterectomy following balloon ablation at year one	0.088	0.016		-
Probability of hysterectomy following MEA at year one	0.088	0.078		-
Probability of hysterectomy following rollerball at year one	0.088	0.015		-
Probability of hysterectomy following RB+TCRE at year one	0.088	0.11		-
Probability of hysterectomy following resection at year one	0.088	0.11		-
Probability of hysterectomy following balloon ablation at year five	0.248	0.321		0.077 Therma-choice 0.0595 Cavaterm™
Probability of hysterectomy following MEA	0.248	0.208		0.0252
Probability of hysterectomy following rollerball	0.248	0.368		0.065-0.195
Probability of hysterectomy following RB+TCRE	0.248	0.250		0.065-0.195
Probability of hysterectomy following resection	0.248	0.269		0.065-0.195
Probability of stopping treatment after	0	-		0.0168

failure following MEA				
Probability of stopping treatment after failure following TBEA	0	-		0.021 Therma-choice 0.073 Cavaterm™
Probability of stopping treatment after failure following 1st generation EA	0	-		0.005-0.015
Proportion of patients receiving local anaesthetic (vs general anaesthetic; rollerball, RB+TCRE, resection)	0	0.14		0.0.001-0.025
Proportion of patients receiving local anaesthetic (vs general anaesthetic; MEA, balloon ablation)	0.52	0.63		0.4-0.6 TBEA 0.4-0.0 MEA
Proportion of MEAs and balloon ablations performed in office (vs theatre)	0	0.5		-
Probability of a surgical complication of balloon ablation	0.0023	0.032		0.03-0.04
Probability of a surgical complication of hysterectomy	0.	0.129		0.2-0.5
Probability of a surgical complication of MEA	0.0007	0.02		0.07
Probability of a surgical complication of RB+TCRE	0.0606	0.13		0-0.15
Probability of a surgical complication of rollerball	0.02	0.106		0-0.15
Probability of a surgical complication of resection	-	0.111		0-0.15
Time required to perform balloon ablation (minutes)		27.4		20-30
Time required to perform hysterectomy (minutes)		66.5		50-135
Time required to perform MEA (minutes)	21	20.9		20-30
Time required to perform rollerball (minutes)	20	39.6		25-36
Time required to perform RB+TCRE (minutes)	26.2	28.4		25-36
Time required to perform resection (minutes)	-	51.2		25-36
Probability of repeat surgery following balloon ablation at year one	0.11	0		-
Probability of RB+TCRE following MEA at year one	-	0.009		-
Probability of repeat surgery following rollerball at year one	0.11	0		
Probability of repeat surgery following RB+TCRE at year one	0.11	0.029		
Probability of repeat surgery following resection at year one	0.11	0.11		
Probability of repeat surgery following balloon ablation at year five	0.31	0.011		
Probability of RB+TCRE following MEA at year five	0.31	0.046		
Probability of repeat surgery following rollerball at year five	0.31	0.000		
Probability of repeat surgery following RB+TCRE at year five	0.31	0.317		
Probability of repeat surgery following resection at year one	0.11	0.127		
Duration of complications from balloon ablation (years)	<1 month	2.3/365.25		
Duration of convalescence following balloon ablation (years)	< 1 month	Jan-52		
Duration of complications from hysterectomy (years)	80% for 2 months	4.7/365.25		
Duration of convalescence following	8/52	11.6/52		

hysterectomy (years)				
Duration of complications from MEA (years)	< 1 month	1.5/365.25		
Duration of convalescence following MEA (years)	1 month			
Duration of complications from RB+TCRE (years)	1 month	1.7/365.25		
Duration of convalescence following RB+TCRE (years)	1 month	2.3/52		
Duration of complications from rollerball ablation (years)	1 month	0.7/365.25		
Duration of convalescence following rollerball ablation (years)	1 month	2.3/52		
Duration of complications from resection (years)	1 month	1.7/365.25		
Duration of convalescence following resection (years)	1 month	2.3/52		
Utility in convalescence following balloon ablation (<1)	0.8	0.76		
Utility in post convalescence following balloon ablation (<1)	0.9	0.57		
Utility during treatment of complications of hysterectomy (<1)	0.55	0.5*u_hyst_conv		
Utility in convalescence following hysterectomy (<1)	0.63	0.74		
Utility in post convalescence following hysterectomy (<1)	-	0.86		
Utility in convalescence following MEA (<1)	0.8	0.76		
Utility in post convalescence following MEA (<1)	0.9	0.79		
Utility in menorrhagia (<1)	0.55	0.5		
Utility in post convalescence following RB+TCRE (<1)	0.9	0.76		
Utility in convalescence following RB+TCRE (<1)	0.8	0.73		
Utility in convalescence following rollerball ablation (<1)	0.8	0.76		
Utility in post convalescence following rollerball ablation (<1)	0.9	0.74		
Utility in convalescence following resection (<1)	0.8	0.76		
Utility in post convalescence following resection (<1)	0.9	0.73		
Time period of model (years)	10	5		3

8.12 Appendix 12: REFERENCE LIST

1. National Statistics Online. Census 2001. http://www.statistics.gov.uk/census2001/pop2001/england_Wales.asp . 2002.

2. Coulter A, Bradlow J, Agass M, Martin-Bates C, Tulloch A. Outcomes of referrals to gynaecology out-patients clinics for menstrual problems: an audit of general practice records. *Br J Obstet Gynaecol* 1991;**98**:789-96.

3. Coulter A,.Jenkinson C. Quality of life and patient satisfaction following treatment for menorrhagia. *Family Practice* 1994;**11**:394-401.

4. Rybo G. Clinical and experimental studies on menstrual blood loss. *Acta Obstet Gynecol Scand* 1966;**45**:1-23.

5. Royal College of Obstetricians and Gynaecologists. The Initial Management of Menorrhagia. Evidence Based Guidelines No. 1. London: Royal College of Obstetricans and Gynaecologists, 1998.

6. Chimbira TH AATAC. Study of menstrual blood loss. *Br J Obstet Gynaecol* 1980;**87**:603-9.

7. Fraser IS MGMR. A preliminary study of factors influencing perception of menstrual blood loss volume. *Am J Obstet Gynecol* 1984;**149**:788-93.

8. Hallberg L, Hogdahl A., Nilsson L., Rybo G. Menstrual blood loss - a population study. *Acta Obstet Gynecol Scand* 1966;**45**:320-51.

9. Lethaby A,.Hickey M. Endometrial destruction techniques for heavy menstrual bleeding. *Cochrane Database.Syst Rev* 2002;CD001501.

10. Kochli OR. Endometrial ablation in the year 2000--do we have more methods than indications? *Contributions to gynecology and obstetrics* 2000;**20**:91-120.

11. Turnbull AC,.Rees MC. Gestrinone in the treatment of menorrhagia. *Br J Obstet Gynaecol* 1990;**97**:713-5.

12. Andersson JK,.Rybo G. Levonorgestrel-releasing intrauterine device in the treatment of menorrhagia. *Br J Obstet Gynaecol* 1990;**97**:690-4.

13. Royal College of Obstetricians and Gynaecologists. The Managment of menorrhagia in secondary care. Evidence based guidelines No. 5. London: RCOG Press, 1999.

14. Vercellini P, Cortesi I, Oldani S, Morchetta M, De Giorgi O, Crosignani PG. The role of transvaginal ultrasonography in the evaluation of patinets with excessive menstrual bleeding. *Hum Reprod* 1997;**12**:1768-71.

15. Bain C, Parkin DE, Cooper KG. Is outpatient diagnostic hysteroscopy more useful than endometrial biopsy alone for the investigation of abnormal uterine bleeding in unselected premenopausal women? A randomised comparison. *Br J Obstet Gynaecol* 2002;**109**:805-11.

16. Hallberg L,.Nilsson L. Determinatin of menstrual blood loss. *Scand J Clin Lab Invest* 1964;**16**:244-8.

17. Gannon MJ, Day P, Hammadieh N, Johnson N. A new method for measuring menstrual blood loss and its use in screening women before endometrial ablation. *Br J Obstet Gynaecol* 1996; **103**:1029-33.

18. Higham JM, O'Brien PMS, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol* 1990;**907**:734-9.

19. Reid PC, Coker A, Coltart R. Assessment of menstrual blood loss using a pictorial chart: a validation study. *Br J Obstet Gynaecol* 2000;**107**:320-2.

20. Wyatt KM DPWTOP. Determination of total menstrual blood loss. *Fertil Steril* 2001;**76**:125-31.

21. Coulter A, Kelland J, Long A, Melville A, O'Meara S, Sculpher M *et al*. The Management of Menorrhagia. *Effective Health Care* 1995;**9**.

22. Hurskaienen R, Teperi J, Turpeinen U, et al. Combined laboratory and diary method for objective assessment of menstrual blood loss. *Acta Obstet Gynecol Scand* 1998;**77**:201-4.

23. Recommendations arising from the 39th Study group: Disorders of the menstrual cycle. *Disorders of the menstrual cycle*, London: RCOG, 2000.

24. Warner P, Critchley OD, Lumsden MA, Campbell-Brown M, Douglas A, Murray G. Referral for menstrual problems: a cross sectional survey of symptoms, reasons for referral and managment. *BMJ* 2001;**323**:24-8.

25. Clark TJ, Khan KS, Foon R, Pattison H, Bryan S, Gupta JK. Quality of Life instruments in studies of menorrhagia: a systematic review. *Eur J Obstet Gynecol Reprod Biol* 2002;**104**:96-104.

26. Lampling DL, Rowe P, Clarke A, Lethaby A. Development and Validation of the menorrhagia outcomes questionnaire. *Br J Obstet Gynaecol* 1998;**105**:776-9.

27. Shaw RW, Brickley M, Evans L, Edwards M. Perceptions of women on the impact of menorrhagia on their health using multi-attribute utility assessment. *Br J Obstet Gynaecol* 1998;**105**:1155-9.

28. Jenkinson C, Peto V, Coulter A. Measuring change over time: a comparison of results from a global single item of health status and the multi-dimensional SF-36 health status survey questionnaire in patients presenting with menorrhagia. *Quality of Life Research* 1994;**3**:317-21.

29. Jenkinson C, Peto V, Coulter A. Making sense of ambiguity: evaluation in internal reliability and face validity of the SF-36 questionnaire in women presenting with menorrhagia. *Qual Health Care* 1996;**5**:9-12.

30. Sculpher M. A cost-utility analysis of abdominal hysterectomy versus transcervical endometrial resection for the surgical treatment of menorrhagia. *International Journal of Technology Assessment in Health Care* 1998;**14**:302-19.

31. Weinstein MC. Estrogen use in post-menopausal women - costs, risks and benefits. *N Engl J Med* 1980;**303**:308-16.

32. Carter KJ, Ritchey NP, Castro F, Caccamo LP, Kessler E, Erickson BA. Treatment of early stage breat cancer in the elderly: a health outcome-based approach. *Med Decis Making* 1998;**18**:213-9.

33. Hillner BE,.Smith TJ. Efficacy and cost effectiveness of adjuvant chemotherapy in women with node-negative breast cancer: A decision-analysis model. *N Engl J Med* 1991;**324**:160-8.

34. Hillner BE, Hollenberg JP, Pauker SG. Postmenopausal estrogens in prevention of osteoporosis: benefit virtually without risk of cardiovascular effects are considered. *Am J Med* 1986;**80**:1115-27.

35. Tsevat J, Goldman L, Lamas GA, Pfeffer MA, Chapin CC, Connors KF *et al*. Functional status versus utilities in survivors of myocardial infarction. *Med Care* 1991;**29**:1153-9.

36. Brickley M, Kay E, Shepherd JP, Armstrong RA. Dedcision analyisis for lower-third-molar surgery. *Med Decis Making* 1995;**15**:143-51.

37. Weinstein MC, Coley CM, Richter JM. Medical management of gallstones: a cost-effectiveness analysis. *J Gen Intern Med* 1990;**5**:277-84.

38. Bass EB, Steinberg EP, Pitt HA, Saba GP, Lillemoe KD, Kafonek DR. Cost effectiveness of extracorporeal shock-wave lithotripsy versus cholecystectomy for symptomatic gallstones. *Gastroenterology* 1991;**101**:189-99.

39. Dolan P,.Kind P. Inconsistency and health state valuations. *Soc Sci Med* 1996;**42**:609-15.

40. Crow R, Gage H, Hampson S, Hart J, Kimber A, Storey L, and Thomas H. The measurement of satisfaction with health care: implications for practice from a systematic review of the literature. 2002.

41. Coulter A, Kelland J, Peto V, Rees MCP. Treating menorrhagia in primary care: An overview of drug trials and a survey of prescribing practice. *International Journal of Technology Assessment in Health Care* 1995;**11**:456-71.

42. Prentice, A. AMES study. 9-17-2002. Joint BSGE/RCOG conference. Conservative Surgery for Menorrhagia.

43. Cooper KG, Jack SA, Parkin DE, Grant AM. Five-year follow up of women randomised to medical management or transcervical resection of the endometrium for heavy menstrual loss: clinical and quality of life outcomes. *Br J Obstet Gynaecol* 2001;**108**:1222-8.

44. Department of Health. Hosptial Episode Statitistics 2000-01. 2002. London, Office for National Statistics.

45. Bridgman SA,.Dunn KM. Has endometrial ablation replaced hysterectomy for the treatment of dysfunctional uterine bleeding? National figures. *Br J Obstet Gynaecol* 2000;**107**:531-4.

46. Farquhar C, Naoom S, Steiner CA. The impact of endometrial ablation on hysterectomy rates in women with benign uterine conditions in the United States. *Int J Tech Assess Health Care* 2002;**18**:625-34.

47. Vessey MP, Villard-Mackintosh L, Mcpherson K, Coulter A, Yeates D. The epidemiology of hysterectomy: findings in a large cohort study. *Br J Obstet Gynaecol* 1992;**99**:402-7.

48. Maresh MJA, Metcalfe MA, McPherson K, Overton C, Hall V, Hargreaves J *et al*. The VALUE national ysterectomy study: description of the patients and their surgery. *Br J Obstet Gynaecol* 2002;**109**:302-12.

49. Farrell SA,.Kieser K. Sexuality after hysterectomy. *Obstet Gynecol* 2000;**95**:1045-51.

50. Brown JS, Sawaya G, Thorn DH, Grady D. Hysterectomy and urinary incontinence: a systematic reveiw. *Lancet* 2000;**356**:535-9.

51. Kuh D, Wadsworth M, Hardy R. Women's health in midlife: the influence of the menopause, social factors and health in earlier life. *Br J Obstet Gynaecol* 1997;**104**:923-33.

52. Lethaby A, Shepperd S, Cooke I, Farquhar C. Endometrial resection and ablation versus hysterectomy for heavy menstrual bleeding. *Cochrane Database.Syst Rev* 2000;CD000329.

53. Weber AM. Endometrial ablation. *Obstet Gynecol* 2002;**99**:969-70.

54. Overton C, Hargreaves J, Maresh M. A national survey of the complications of endometrial destruction for menstrual disorders: The MISTLETOE study. *Br J Obstet Gynaecol* 1997;**104**:1351-9.

55. Sowter MC, Lethaby A, Singla AA. Pre-operative endometrial thinning agents before endometrial destruction for heavy menstrual bleeding (Cochrane Review). *Cochrane Database.Syst Rev* 2002;CD001124.

56. Vancaillie TG. Electrocoagulation of the endometrium. In Lewis BV, Magos AL, eds. *Endometrial Ablation*, pp 133-42. Edinburgh: Churchill Livingstone, 1993.

57. Davis JA, Miller CD. Fluid infusion during hysteroscopic surgery. In Lewis BV, Magos AL, eds. *Endometrial Ablation*, pp 41-56. Edinburgh: Churchill Livingstone, 1993.

58. Garry R. Evidence and techniques in endometrial ablation: Consensus. *Gynaecological Endoscopy* 2002;**11**:5-17.

59. Coulter A, Peto V, Doll H. Patients' preferences and general practitioners' decisions in the treatment of menstrual disorders. *Family Practice* 1994;**11**:67-74.

60. Marshall S, Hardy RJ, Kuh D. Socioeconomic variation in hysterectomy up to age 52: national, population based, prospective cohort study. *BMJ* 2000;**320**:1579.

61. Cooper KG, Grant AM, Garratt AM. The impact of using a partially randomised patient preference design when evaluating alternative managements for heavy menstrual bleeding. *Br J Obstet Gynaecol* 1997;**104**:1367-73.

62. Nagele F, Rubinger T, Magos A. Why do women choose endometrial ablation rather than hysterectomy? *Fertil Steril* 1998;**69**:1063-6.

63. Sculpher M, Dwyer N, Browning J, Horsley S, Cullimore J. A survey of women's preferences regarding alternative surgical treatments for menorrhagia. *Health Expectations* 1998;**1**:96-105.

64. Sharp NC, Cronin N, Feldberg I, Evans M, Hodgson D, Ellis S. Microwaves for menorrhagia: A new fast technique for endometrial ablation. *Lancet* 1995;**346**:1003-4.

65. Hodgson DA, Feldberg IB, Sharp N, Cronin N, Evans M, Hirschowitz L. Microwave endometrial ablation: development, clinical trials and outcomes at three years. *Br J Obstet Gynaecol* 1999;**106**:684-94.

66. Bongers MY, Mol B-WJ, Brolmann H-AM. Prognostic factors for the success of thermal balloon ablation in the treatment of menorrhagia. *Obstet Gynecol* 2002;**99**:1060-6.

67. Bain C, Cooper KG, Parkin DE. A partially randomized patient preference trial of microwave endometrial ablation using local anaesthesia and intravenous sedation or general anaesthesia: A pilot study. *Gynaecological Endoscopy* 2001;**10**:223-8.

68. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF *et al*. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. *Lancet* 1999;**354**:1896-900.

69. The Government Actuary Department. Interim Life Tables- expectation of life for Engalnd and Wales Females 1998-2000. 2002. London, The Government Actuary Department.

70. MacLean-Fraser E, Penava D, Vilos GA. Perioperative complication rates of primary and repeat hysteroscopic endometrial ablations. *J Am Assoc Gynecol Laparosc.* 2002;**9**:175-7.

71. Rogersen, L. and Duffy, S. A European survey of the complications of a uetrine thermal balloon system in 5800 women (unpublished). 2002.

72. Parkin DE. Microwave endometrial ablation (MEA^{TM}): A safe technique? Complication data from a prospective series of 1400 cases. *Gynaecological Endoscopy* 2000;**9**:385-8.

73. Hosptial Episode Statistics. London: Department of Health, 2001.

74. Sculpher M, Fenwick E, Claxton K. Assessing quality in decision analytic cost-effectiveness models: A suggested framework and example of application. *Pharmacoeconomics* 2000;**17**:461-77.

75. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. Oxford: Oxford University Press, 1997.

76. Iyer V, Farquhar C, Jepson R. Oral contraception pills for heavy menstrual bleeding. *The Cochrane Library* 2002;**4**.

77. Lethaby A, Irvine G, Cameron IM. Cyclical progestogens for heavy menstrual bleeding (Cochrane Review). *The Cochrane Library* 2002;**4**.

78. Beaumont H, Augood C, Duckitt K, Lethaby A. Danazol for heavy menstrual bleeding (Cochrane Review). *Cochrane Library* 2002;**4**.

79. Lethaby A, Augood C, Duckitt K. nonsteroidal anti-inflammatrory drugs for heavy menstrual bleeding (Cochrane Review). *The Cochrane Library* 2002;**4**.

80. Lethaby A, Farquhar C, Cooke I. Antifibrinolytics for heavy menstrual bleeding (Cochrane Review). *Cochrane Database.Syst Rev* 2002.

81. Lethaby AE, Cooke I, Rees M. Progesterone/progestogen releasing intrauterine systems versus either placebo or any other medication for heavy menstrual bleeding. *Cochrane Database.Syst Rev* 2000;CD002126.

82. Meyer WR, Walsh BW, Grainger DA, Peacock LM, Loffer FD, Steege JF. Thermal balloon and rollerball ablation to treat menorrhagia: a multicenter comparison. *Obstet Gynecol* 1998;**92**:98-103.

83. Romer T. Therapy of recurrent menorrhagia--Cavaterm balloon coagulation versus roller-ball endometrium coagulation--a prospective randomized comparative study. *Zentralblatt fur Gynakologie* 1998;**120**:511-4.

84. Grainger DA, Tjaden BL, Rowland C, Meyer WR. Thermal balloon and rollerball ablation to treat menorrhagia: two-year results of a multicenter, prospective, randomized, clinical trial. *J Am Assoc Gynecol Laparosc.* 2000;**7**:175-9.

85. Loffer FD. Three-year comparison of thermal balloon and rollerball ablation in treatment of menorrhagia. *J Am Assoc Gynecol Laparosc.* 2001;**8**:48-54.

86. Cooper KG, Bain C, Parkin DE. Comparison of microwave endometrial ablation and transcervical resection of the endometrium for treatment of heavy menstrual loss: a randomised trial. *Lancet* 1999;**354**:1859-63.

87. Bain C, Cooper KG, Parkin DE. Microwave endometrial ablation versus endometrial resection: a randomized controlled trial. *Obstet Gynecol* 2002;**99**:983-7.

88. Microsulis Americas Inc. Microwave endometrial ablation FDA trial. 2002.

89. Gervaise A, Fernandez H, Capella-Allouc S, Taylor S, La Vieille S, Hamou J *et al*. Thermal balloon ablation versus endometrial resection for the treatment of abnormal uterine bleeding. *Human Reproduction* 1999;**14**:2743-7.

90. Soysal M.E., Soysal, S-K, and V, K-. Thermal balloon ablation in myoma-induced menorrhagia under local anesthesia. *Gynecol Obstet Invest* 2001;**51**:128-33.

91. Pellicano M, Guida M, Acunzo G, Cirillo D, Bifulco G, Nappi C. Hysteroscopic transcervical endometrial resection versus thermal destruction for menorrhagia: a prospective randomized trial on satisfaction rate. *Am J Obstet Gynecol* 2002;**187**:545-50.

92. Zon-Rabelink I. Rollerball versus Thermachoice. *10Th Congress of the European Society for Gynaecological Endoscopy, Proceedings* 2001;11-4.

93. Loffer FD,.Grainger D. Five-year follow-up of patients participating in a randomized trial of uterine balloon therapy versus rollerball ablation for treatment of menorrhagia. *J Am Assoc Gynecol Laparosc.* 2002;**9**:429-35.

94. Loffer FD. Three-year comparison of thermal balloon rollerball ablation in treatment of menorrhagia (vol 8, pg 48, 2001). *Journal of the American Association of Gynecologic Laparoscopists* 2001;**8**:330.

95. Confidential data from Wallsten Medical 2002.

96. Pinion SB, Parkin DE, Abramovich DR, Naji A, Alexander DA, Russell IT *et al*. Randomised trial of hysterectomy, endometrial laser ablation, and transcervical endometrial resection for dysfunctional uterine bleeding. *BMJ* 1994;**309**:979-83.

97. Pellicano M, Guida M, Acunzo G, Cirillo D, Bifulco G, Nappi C. Hysteroscopic transcervical endometrial resection versus thermal destruction for menorrhagia: A prospective randomised trial on satisfaction rate. *Am J Obstet Gynecol* 2002;**187**:545-50.

98. Bae IH, Pagedas AC, Perkins HE, Bae DS. Postablation-tubal sterilization syndrome. *J Am Assoc Gynecol Laparosc.* 1996;**3**:435-8.

99. McCausland AM,.McCausland VM. Frequency of symptomatic cornual hematometra and postablation tubal sterilization syndrome after total rollerball endometrial ablation: a 10-year follow-up. *Am J Obstet Gynecol* 2002;**186**:1274-80.

100. Overton C, Hargreaves J, Maresh M. A national survey of the complications of endometrial destruction for menstrual disorders: The MISTLETOE study. *Contemp Rev Obstet Gynaecol* 1998;**10**:209-16.

101. Amso NN, Stabinsky SA, McFaul P, Blanc B, Pendley L, Neuwirth R. Uterine thermal balloon therapy for the treatment of menorrhagia: the first 300 patients from a multi-centre study. International Collaborative Uterine Thermal Balloon Working Group. *Br J Obstet Gynaecol* 1998;**105**:517-23.

102. O'Connor H, Broadbent JA, Magos AL, McPherson K. Medical Research Council randomised trial of endometrial resection versus hysterectomy in management of menorrhagia. *Lancet* 1997;**349**:897-901.