Health Technology Assessment 2004; Vol. 8: No. 3

The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling

R Garside, K Stein, K Wyatt, A Round and A Price

February 2004

Health Technology Assessment
NHS R&D HTA Programme

How to obtain copies of this and other HTA Programme reports.
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of *HTA on CD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.

The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling

R Garside,[1*] K Stein,[1] K Wyatt,[2] A Round[1] and A Price[3]

[1] Peninsular Technology Assessment Group, Peninsula Medical School, Universities of Exeter and Plymouth, UK
[2] Research and Development Support Group, Peninsula Medical School, Universities of Exeter and Plymouth, UK
[3] Southampton Health Technology Assessment Centre, University of Southampton, UK

* Corresponding author

Declared competing interests of authors: none

Published February 2004

This report should be referenced as follows:

Garside R, Stein K, Wyatt K, Round A, Price A. The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling. *Health Technol Assess* 2004;**8**(3).

Health Technology Assessment is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE.

NHS R&D HTA Programme

The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

The research reported in this monograph was commissioned by the HTA Programme on behalf of the National Institute for Clinical Excellence (NICE). Technology assessment reports are completed in a limited time to inform the appraisal and guidance development processes managed by NICE. The review brings together evidence on key aspects of the use of the technology concerned. However, appraisal and guidance produced by NICE are informed by a wide range of sources.

The research reported in this monograph was funded as project number 01/61/01.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme, NICE or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for any recommendations made by the authors.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The editors and publisher have tried to ensure the accuracy of this report but do not accept liability for damages or losses arising from material published in this report.

ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

T

Abstract

The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling

R Garside,[1*] K Stein,[1] K Wyatt,[2] A Round[1] and A Price[3]

[1] Peninsular Technology Assessment Group, Peninsula Medical School, Universities of Exeter and Plymouth, UK
[2] Research and Development Support Group, Peninsula Medical School, Universities of Exeter and Plymouth, UK
[3] Southampton Health Technology Assessment Centre, University of Southampton, UK
* Corresponding author

Objectives: To estimate the clinical effectiveness and cost-effectiveness of microwave endometrial ablation (MEA) and thermal balloon endometrial ablation (TBEA) for heavy menstrual bleeding (HMB), compared with the existing (first-generation) endometrial ablation (EA) techniques of transcervical resection (TCRE) and rollerball (RB) ablation, and hysterectomy.
Data sources: Electronic databases, bibliographies of articles, and also experts in the field and relevant industry bodies were asked to provide information.
Review methods: A detailed search strategy was carried out to identify systematic reviews and controlled trials of MEA and TBEA versus first-generation techniques for EA. 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. A deterministic Markov model was developed to assess cost-effectiveness. Data for the model were taken from a range of sources.
Results: The systematic review of first-generation EA techniques versus hysterectomy found that EA offered an alternative to hysterectomy for HMB, with fewer complications and a shorter recovery period. Satisfaction and effectiveness were high for both MEA and TBEA. Costs were lower with EA although the difference narrows over time. Second-generation EA techniques are an alternative treatment to first-generation techniques for HMB, and 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. Using the model to assess cost-effectiveness, costs were very slightly higher for MEA when compared to TBEA, and differences in quality-adjusted life-years (QALYs) were negligible. For MEA compared with transcervical resection of the endometrium (TCRE) and RB ablation, costs were slightly lower with MEA and MEA accrued very slightly more QALYs. Compared with hysterectomy, MEA costs less and accrues slightly fewer QALYs. For TBEA compared with TCRE and RB ablation, costs were lower with TBEA and TBEA accrued slightly more QALYs. Compared with hysterectomy, TBEA costs moderately less and accrues moderately fewer QALYs.
Conclusions: Overall, there were few significant differences between the outcomes of first- and second-generation techniques including bleeding, satisfaction and QoL measures and repeat surgery rates. Second-generation techniques had significantly shorter operating and theatre times and there appear to be fewer serious perioperative adverse effects with second-generation techniques and postoperative effects are similar. Compared with hysterectomy, TCRE and RB 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 retreatment leads this difference to decrease over time. Satisfaction with hysterectomy is initially higher, but there is no significant difference after 2 years. The economic model suggests that second-generation techniques are more cost-effective than first-generation techniques of EA for HMB. Both TBEA and MEA appear to be less costly than hysterectomy, although the latter results in more QALYs. Further research is suggested to make direct comparisons of the cost-effectiveness of second-generation EA techniques, to carry out longer term follow-up for all methods of EA in RCTs, and to develop more sophisticated modelling studies. Further research is also recommended into HMB to establish health-state utility values, its surgical treatment, convalescence, complications of treatment, symptoms and patient satisfaction.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

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 that destroys tissues through cutting or electrocoagulation. The patient's body forms part of the circuit.

Dysmenorrhoea Painful periods.

Electrocautery Cauterisation of tissue using an electric current to generate the heat. Cauterisation 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 – postendometrial 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 fibre-optic technology that allows direct visualisation 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 that allows visualisation through the use of fibre optics.

Leiomyomas Fibroids.

continued

Glossary *continued*

Menopause Cessation of menstruation, usually around age 50 years.

Meno-metrorrhagia Frequent, excessive menstrual bleeding.

Menorrhagia Heavy menstrual bleeding, clinically defined as more than 80 ml of blood per cycle, but more usually defined subjectively by the woman.

Menstruation The cyclic, physiological discharge of blood and mucosal tissues through the vagina from the non-pregnant uterus. It is under hormonal control and recurs at approximately 4-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 sterilisation syndrome In previously sterilised women accumulation of the blood in the Fallopian tubes, which may cause severe pelvic pain.

Premenstrual syndrome A combination of emotional and physical features that 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.

List of abbreviations

ANCOVA	analysis of covariance
ANOVA	analysis of variance
BMI	body mass index
CI	confidence interval
D&C	dilation and curettage
DUB	dysfunctional uterine bleeding
DVT	deep vein thrombosis
EA	endometrial ablation
FDA	Food and Drug Administration (USA)
GA	general anaesthetic
GI	gastrointestinal
GnRH	gonadotrophin-releasing hormone
HES	Hospital Episode Statistics
HMB	heavy menstrual bleeding
HTA	hydrotherm ablator
ICER	incremental cost-effectiveness ratio
ITT	intention-to-treat
IUD	intrauterine device
IUS	intrauterine system
LA	local anaesthetic
LHRH	luteinising hormone-releasing hormone
LNG	levonorgestrel
LTFU	lost to follow-up
MEA	microwave endometrial ablation
MRC	Medical Research Council
MRI	magnetic resonance imaging
NICE	National Institute for Clinical Excellence
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
PBAC	pictorial blood loss assessment chart
PID	pelvic inflammatory disease
PMS	premenstrual syndrome
QALY	quality-adjusted life-year
QoL	quality of life
RB	rollerball
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	randomised controlled trial
RR	relative risk
SD	standard deviation
SE	standard error
SF-36	Short Form with 36 Items
TBEA	thermal balloon endometrial ablation
TCRE	transcervical resection of the endometrium
TTO	time trade-off
TVS	transvaginal ultrasound (sonography)
UTI	urinary tract infection

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Objective

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

Description of proposed service

The technologies examined in this review are MEA and TBEA for the treatment of HMB. Both of these, also referred to as second-generation EA techniques, aim to destroy the endometrial lining of the uterus, thereby reducing or eliminating menstrual bleeding. To achieve endometrial destruction, TBEA uses a balloon catheter in which hot water is circulated for a prescribed amount of time. MA 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.

Epidemiology and background

HMB (or menorrhagia) is defined as the cyclical loss of more than 80 ml of blood over several consecutive cycles. HMB is a common complaint for which one in 20 women aged 30–49 years consult their general practitioner each year (approximately 1.5 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. Danazol, gestrinone and gonadotrophin-releasing hormone (GnRH) analogues may be used as second-line medical treatment. Current surgical interventions include hysterectomy or minimally invasive procedures such as TCRE and RB ablation.

Over 51,000 hysterectomies were performed in the public sector in England in 1999–2000. In about half of these cases, HMB would have been the presenting complaint, and in half of these, the uterus would have been normal. In 1998–9 more than 16,000 admissions for EA were recorded.

This report assesses the effectiveness and cost-effectiveness of MEA and TBEA compared with specific existing surgical techniques for HMB, that is, first-generation EA techniques [by resection (TCRE) and/or RB] and hysterectomy.

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 EA. 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 HMB (2002), were included.

Two randomised controlled trials (RCTs) of MEA and eight trials of TBEA versus first-generation techniques were included. These trials include a total of 1561 women, with sample sizes ranging from 20 to 322 (median 143). Two of the TBEA trials were non-RCTs and the rest were RCTs.

The quality of the trials was variable. The MEA trials included more participants than TBEA trials and were of higher quality and applicability to the UK. Two TBEA studies were not randomised; controls in one were women who underwent first-generation EA at the same institution, and in the other two consecutive cohorts were compared. 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 an endometrial pre-thinning agent in both intervention and control groups. Of the TBEA trials, two gave a dilation and curettage (D&C) immediately prior to the operation in both arms of the trial, two gave GnRH analogues to women in both arms of the trial and one gave no pretreatment to those undergoing TBEA, and GnRH to those in the control group. One gave D&C to women undergoing TBEA, and GnRH to women undergoing TCRE.

Only one MEA and three TBEA studies reported undertaking a sample size calculation. One of these (TBEA) did not recruit sufficient participants to meet requirements. Loss to follow-up was between 0 and 46% (median 3.5%) – the highest figure at 5 years of follow-up (TBEA versus RB). Of the six studies that reported some loss to follow-up, two reported using intention-to-treat (ITT) analysis, although one appears to have used different denominators for some variables. One study does not report loss to follow-up, but does not appear to have data on all recruited women. 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 three TBEA studies and low in one MEA and two TBEA studies. Main outcome measures were measured independently in eight cases and were uncertain in two TBEA studies.

Summary of benefits

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

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

The included studies of MEA and TBEA did not show a significant difference between amenorrhoea rates after first-generation compared with second-generation techniques. Only one study showed a first-generation technique (RB) to be significantly superior for the outcome of amenorrhoea measured at 2 years. 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%) and the amenorrhoea rates in the MEA trials were also higher for the control group. No comparison between MEA and TBEA should be inferred on the basis of amenorrhoea rates between second-generation techniques alone as there were similar differences between control groups across trials. No significant differences between first- and second-generation techniques of EA were shown for any other measure of bleeding.

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

Differences in patient satisfaction reported between first- and second-generation EA techniques were not significant. One study used the Short Form with 36 Items to measure quality of life (QoL) 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 with first-generation EA techniques, second-generation techniques resulted in significantly shorter operating and theatre times, but not in postoperative length of stay or recovery time.

Perioperative and postoperative adverse effects were few with both first- and second-generation techniques, but there were fewer serious perioperative adverse effects with MEA and none with TBEA compared with first-generation techniques. Postoperative adverse effect 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.

Costs

Costs of technologies were estimated for 2002. The costs of TBEA and MEA were similar at £1273 and £1295 per procedure, respectively. Methods used to calculate costs may not have been sufficiently sensitive to measure such small apparent differences with precision. The cost of second-generation ablation is slightly less than combined TCRE and RB ablation at £1614 but slightly more than RB at £1191. Abdominal hysterectomy costs £2275.

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 with TBEA, costs were very slightly higher for MEA (£1448 versus £1324 per woman), and differences in quality-adjusted life-years (QALYs) were negligible (8360.70 versus 8360.77 for the whole cohort). For MEA compared with TCRE and RB ablation, costs were slightly lower with MEA (£1448 versus £1732 TCRE, £1752 RB and £1785 TCRE/RB combined) and MEA accrued very slightly more QALYs (8.361 versus 8.357 TCRE, 8.360 RB and 8.358 TCRE/RB). Compared with hysterectomy, MEA costs less (£1448 versus £2320) and accrues slightly fewer QALYs (8.361 versus 8.774).

For TBEA compared with TCRE and RB ablation, costs were lower with TBEA (£1324 versus £1732 TCRE, £1752 RB and £1785 TCRE/RB combined) and TBEA accrued slightly more QALYs (8.361 versus 8.357 TCRE, 8.360 RB and 8.358 TCRE/RB). Compared with hysterectomy, TBEA costs moderately less (£1324 versus £2320) and accrues moderately less QALYs (8.361 versus 8.774).

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 EA, in other words, women who were 'well'. To a lesser extent, recurrence of HMB and the cost of the procedures were also important in the analysis.

Limitations of the calculations

Given the paucity of data about utility values for the health states relating to HMB, EA and post-convalescence, accurate estimates of costs per QALY are difficult to ascertain. As absolute costs and QALYs for MEA and TBEA are very similar, small changes in inputs relating to aspects of the procedure that affect costs can lead to large changes in the model outputs. There must, therefore, be considerable uncertainty about the precision of these results. In particular, we are not confident that available data are significantly robust to support comparison between second-generation techniques.

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 (>12 cm) and those with uterine pathology or abnormalities. This may account for as many as 60% of women with HMB, although estimates are uncertain.

Notes on the generalisability of the findings

Of the 10 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 study (of MEA) 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 HMB 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 that this group is unlikely, currently, to be treated by EA in the UK.

Conclusions

Both MEA and TBEA techniques appear to offer effective alternatives in the surgical treatment of women with HMB.

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 effects 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 the 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. 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 EA is within the range considered by decision-makers to represent acceptable value for money.

Need for further research

- Head-to-head comparisons of second-generation EA 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, in addition to checking whether longer term complications are an issue.
- More sophisticated modelling studies may improve estimates of cost-effectiveness, taking into account population heterogeneity, and would permit exploration of issues relevant to implementation such as waiting times and detailed budget impact.
- Given the importance of the utility values in determining the cost-effectiveness of treatments for HMB, further research to establish utilities for the states of HMB, its surgical treatment, convalescence and complications of treatment would be valuable.
- Future studies of HMB should use validated QoL measures and established modes of measuring patient satisfaction both with the procedure and with the outcomes.
- Further research into the effect of the constellation of symptoms associated with menstruation (such as pain, bloating and breast tenderness) 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 EA should be further investigated, including different operators (non-consultant medical staff and specialist nurses) and different settings (office versus operating theatre).

Chapter 1

Aim of the review

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

Chapter 2
Background

Description of underlying health problem

HMB (menorrhagia) affects many women. One in 20 women aged 30–49 years consults her general practitioner (GP) with this complaint each year, approximately 1.5 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 that may have physical, emotional and social impacts in addition to 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 one-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 50–60 ml per cycle will lead to a negative iron balance for most women.[4]

Defining menorrhagia

Menorrhagia is objectively defined as the loss of more than 80 ml of blood per cycle over several consecutive cycles.[5] However, objective measurement is difficult and several studies have shown that between 35 and 60% of women who present with the complaint of HMB 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 HMB, associated problems and their impact are discussed further in the section 'Measurement of blood loss' below.

Causes of HMB

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

Studies examining the efficacy of drug treatments in women with HMB 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 in the Royal College of Obstetricians and Gynaecologists (RCOG) guidelines that women should be examined by transvaginal ultrasound (sonography) (TVS) or hysteroscopy for polyps or fibroids.[13] A large prospective study in Italy of 793 women referred for HMB who had a uterus <12 cm found pathology in 57%, leaving 43% of women with no identifiable cause for their heavy bleeding.[14] However, a UK randomised controlled trial (RCT) of 370 women randomised to receive hysteroscopy examination or endometrial biopsy alone found pathology in only 20% of women.[15]

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.

TABLE 1 *Possible causes of HMB and associated factors*[10]

Anatomical	Biochemical	Endocrine	Haematological	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

IUD, intrauterine device.

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[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 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). This technique is now more widely used than the alkaline haematin 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 that 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 HMB

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, whereas 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 HMB and controls who considered their blood loss to be 'normal'. Only 36% of women presenting with the complaint of HMB had their condition objectively verified and 14% of the controls had blood loss in excess of 80 ml 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 HMB do not have objectively measured blood loss of 80 ml 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 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 HMB in general practice found that over half described themselves as having painful periods in addition to HMB.[3]

The definition of HMB, 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 HMB whereas 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.

Measuring the impact of HMB

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

- **Condition-specific scales** These have the advantage of incorporating attributes of QoL that 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 importance to sufferers and reflect their experience and concerns).
- **Generic scales** These have the advantage of allowing comparison between conditions of

impact on QoL. 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 QoL.

- **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 that can be used in cost–utility analyses.

A recent systematic review of QoL measures used in studies of HMB 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 QoL measure appraisal tools, broadly assessing face validity and measurement properties. The authors, Clark and colleagues, conclude that measurement scales in HMB perform better in relation to measurement properties than face validity and that improved condition-specific measures are required to assess the impact of HMB on QoL.[25]

Condition-specific scales

Two condition-specific outcome measures have been developed for women with HMB: 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 QoL 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 QoL have been used in HMB: the Short Form with 36 Items (SF-36), Nottingham Health Profile, health status structured history and single global item. The SF-36 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 QoL.[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 QoL in women with HMB has been determined in a population of women presenting with HMB in a study by Jenkinson and colleagues.[28] Although the authors commented that it was a "feasible" means of looking at quality of life, responding to changes over time, they subsequently suggested that the SF-36 may have some problems when applied to this group of women.[29] In interviews with 49 women with HMB who had completed the SF-36, Jenkinson and colleagues 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 HMB with 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 HMB group, especially for general health perception and mental health scales.

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

Preference-based measures

Clark and colleagues report the use of the EQ5D in two intervention studies as a measure of QoL in HMB. 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 QoL (visual analogue scale). Both studies on HMB used the visual analogue scale for global QoL rating.

Table 2 below shows the baseline ratings for QoL in women with HMB, compared to those in a range of other conditions, measured using a range of approaches to obtain a utility estimate. These values are taken from the website http://www.healthpriorities.uci.edu.

The value of 0.55 for menorrhagia in *Table 2* 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 [standard error (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 QoL 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

TABLE 2 *Examples of utility values for HMB and other health states*

Health state	Utility	Source	How value obtained
Menorrhagia	0.55	Sculpher[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 and Smith[33]	Clinician judgement
Breast cancer chemotherapy after surgery, minor toxicity	0.9	Hillner and Smith[33]	Clinician judgement
Breast cancer after surgery, first recurrence	0.7	Hillner and Smith[33]	Clinician judgement
Breast cancer after surgery, after first recurrence	0.85	Hillner and Smith[33]	Clinician judgement
Breast cancer after surgery, second recurrence	0.5	Hillner and Smith[33]	Clinician judgement
Breast cancer after surgery, after second recurrence	0.7	Hillner and Smith[33]	Clinician judgement
Endometrial cancer	0.9	Hillner *et al*.[34]	Clinical judgement
	0.95	Carter *et al*.[32]	Standard gamble – clinical experts
Myocardial infarction, chest pain	0.67	Tsevat *et al*.[35]	Patient rating scale
Lower third molar extraction, mild postoperative pain	0.7011	Brickley *et al*.[36]	Patient rating scale
Lower third molar extraction, moderate postoperative pain	0.4262	Brickley *et al*.[36]	Patient rating scale
Lower third molar extraction, severe postoperative 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

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 that 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 HMB. It is not a measure of the impact of HMB, but is discussed here alongside other outcome measures in HMB.

"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 healthcare. One study reviewed by Crow and colleagues,[40] showed improvements in health resulted in higher satisfaction, although 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 EA. 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 that 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 QoL.

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 EA, 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 EA 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.

Current service provision

Treatment for HMB aims to improve QoL 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 RCOG. It is recommended by the RCOG that women with HMB should receive hysteroscopy and/or TVS to examine for uterine pathology. In addition, endometrial biopsy may be required to diagnose carcinoma or hyperplasia. Dilation and curettage (D&C) is no longer considered the best way to assess abnormal bleeding.[13]

Drug therapy

For women presenting with HMB, 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 guidelines, if treatment is required, HMB 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 (NSAID)] are considered effective treatments in the initial management of HMB.[5] A meta-analysis of seven studies found that tranexamic acid reduced menstrual blood loss by 47%.[21] A meta-analysis of 10 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 in addition to treatments for HMB may benefit from combined oral contraceptives (COCs) or the progesterone [levonorgestrel (LNG)] releasing intrauterine device (IUD) [LNG intrauterine system (IUS), marketed as Mirena™]. This was originally designed as a contraceptive device but has been licensed for use in HMB 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 HMB, a recent UK survey of primary care prescribing showed that 35% of treatment prescriptions for HMB 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 HMB: general practice management, referral patterns and rates of hysterectomy.[13]

Surgical treatment

If drug therapy is not effective, surgical interventions, including EA 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 transcervical resection of the endometrium (TCRE) in secondary care, of 94 women randomised to receive medical treatment, only 10% remained in this arm after 5 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 EA 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 HMB

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 HMB. In 1998–9, there were 16,219 admissions for EA. Hysterectomy and ablation have a large place in private practice, although no numbers are available for operations performed. 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 HMB. In reality, diffusion has not been straightforward. A study of English hospital admission data between 1989–90 and 1995–6 concluded that EA was not replacing hysterectomy.[45] However, since then numbers of EAs 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 NN, University of Wales, Cardiff: personal communication, 2002).

Figure 1 plots HES codes Q08 and Q09 combined for hysterectomy and Q16 and Q17 combined for EA.

Although there appears to be a trend toward increased ablation and decreased hysterectomy, these figures may mask more complex local variations. A recent study[46] in the USA examined the diffusion of EA using State Inpatient and Ambulatory Surgery Databases of the Healthcare Cost and Utilization Project in six states for 1990–7. Whereas 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 to rather than a replacement therapy for HMB. It is possible that the availability of EA may decrease the threshold for surgical treatment.

Hysterectomy

Hysterectomy is the only treatment for HMB that 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 years.[47] In about half of all hysterectomies,

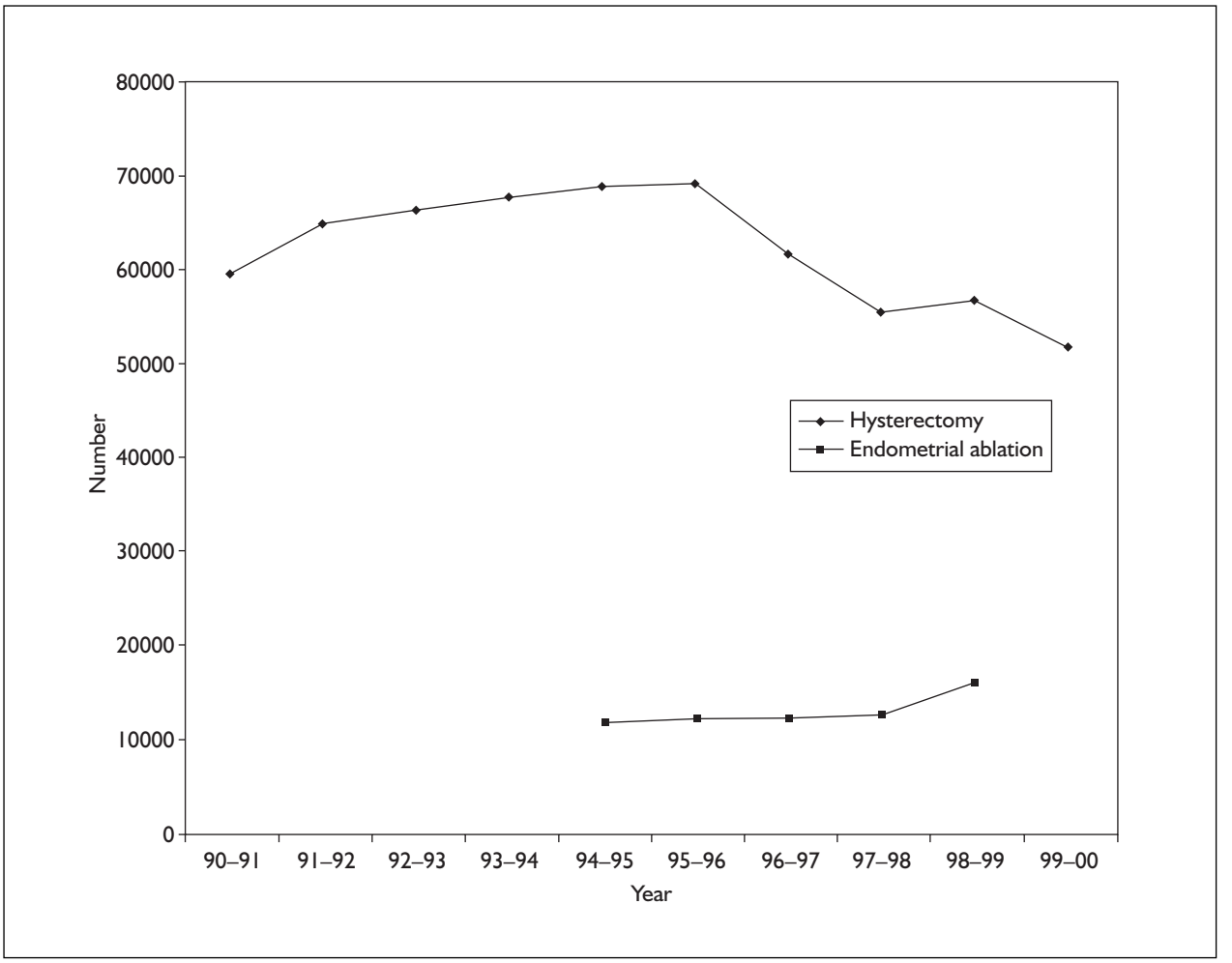


FIGURE 1 *Number of hysterectomies and EA operations in England*

HMB is the presenting complaint and in half of hysterectomies performed for HMB, 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 4–6 weeks. One in 30 women suffer perioperative adverse events (*Table 3*). Postoperative 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]

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 in the long term, women who have undergone hysterectomy may suffer increased risk of some symptoms such as urinary incontinence,[50]

TABLE 3 *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	Respiratory/heart complications
UTI	Anaesthetic	DVT
	GI obstruction/ileus	
	Diarrhoea	

UTI, urinary tract infection; GI, gastrointestinal; DVT, deep vein thrombosis.
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.

vasomotor symptoms and some psychological symptoms compared with their peers.[51] However, in clinical studies, satisfaction with hysterectomy is reportedly very high.[52]

First-generation EA techniques

Since the 1980s, more conservative surgical interventions have been developed as alternatives to hysterectomy. The three most commonly used methods are TCRE, RB and laser ablation, collectively known as 'first-generation' EA techniques. All first-generation techniques require direct visualisation 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 assessment report, TCRE and RB methods are the first-generation comparators for the technologies of interest as these are the most commonly used methods in the UK.

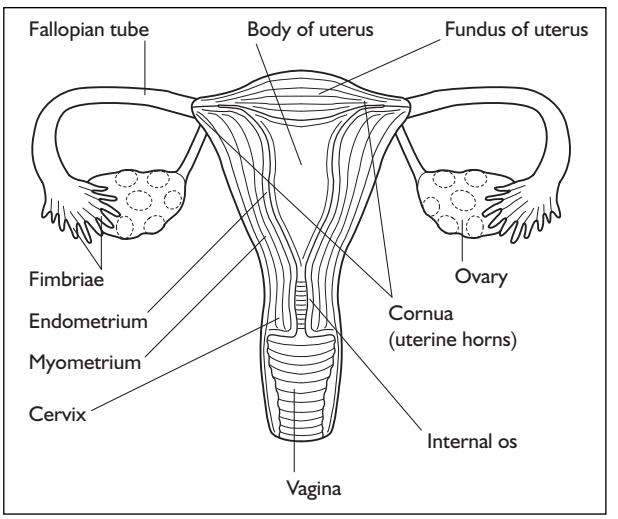


FIGURE 2 *The female reproductive system. © 2002, www.mydr.com.au (Medimedia Australia) (adapted)*

All methods of endometrial destruction aim to destroy the inner lining of the uterus (endometrium) (see *Figures 2* and *3*). 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. EA is not a contraceptive and pre-menopausal women need to continue to use contraception as pregnancies after EA have been reported.

In order to minimise the depth of endometrial lining, thinning agents, such as danazol or gonadotrophin-releasing hormone (GnRH) analogues 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, although both agents produce satisfactory results.[55] Although it is possible to undertake first-generation EA 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 (*Figure 4*) requires a rigid or flexible hysteroscope with a fibre-optic 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 a 0–30° 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

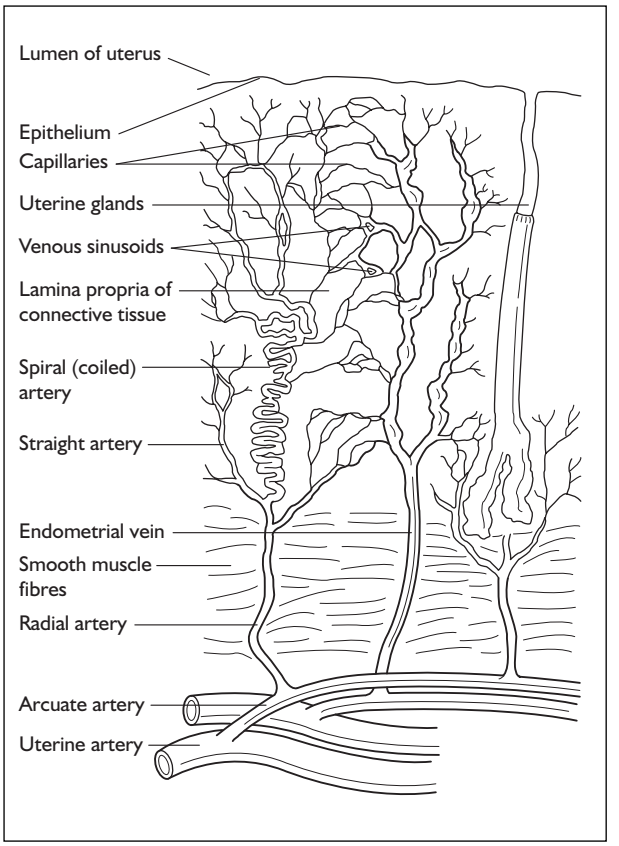


FIGURE 3 *Section through the endometrium. Modified from Human anatomy, Marieb EN, Mallatt J, © 2001 by Pearson Education Inc. Reprinted by permission of Pearson Education, Inc.*

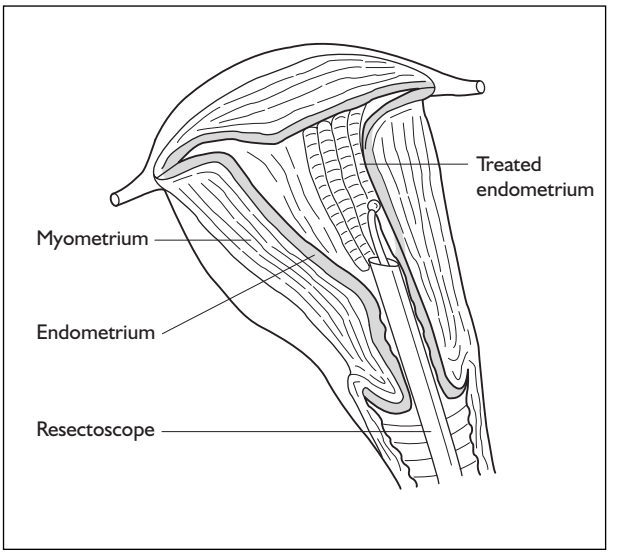


FIGURE 4 *Transcervical resection. From www.gynalternatives.com/ablation.htm, by permission of P Indman*

lining. TCRE provides good samples of endometrium for biopsy. TCRE may also be used for the removal of fibroids, usually those not larger than 2 cm. The operation takes 13–45 minutes[52] and may be done as a day-case procedure.

The RB technique also requires visualisation and irrigation using a resectoscope. A RB 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 RB fits better in the thin-walled uterine horns and lessens the chance of perforation, some surgeons use a combination of cutting loop and RB equipment in the same ablation procedure. As no 'chips' of removed endometrium are generated with RB coagulation, there may be better visibility through the hysteroscope than with TCRE. RB also results in fewer operative adverse effects.[54] In the UK, it is usual for TCRE to be supplemented by RB 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 RB 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 an 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 postoperative, are shown in *Table 4*.

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 (>12 cm).

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

1. Amenorrhoea cannot be guaranteed, and its occurrence depends on technique, operator

TABLE 4 *Adverse effects with first-generation EA techniques*

Very common (>1/10)	Common (>1/100, <1/10)	Uncommon (>1/1000, <1/100)
–	Haemorrhage Uterine perforation Sepsis Pyrexia Fluid overload	Death Pregnancy Cardiovascular/respiratory Visceral burn Blood transfusion Haematoma GI obstruction/ileus Laparotomy
Calculated from Overton *et al*.[54] and Lethaby and Hickey.[9]		

experience and the nature of any associated pathology.
2. Most patients will ultimately be satisfied with the procedure.
3. Further ablation or hysterectomy will be required by some women.

Choosing treatment for HMB

Given the range of treatments for HMB, 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 and speed of return to normal activities. Research has found that about one-third of women have a strong treatment preference.[59] These women are likely to be older, in social class I or II, to 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 Medical Research Council (MRC) study of 2547 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 years) and lowest in those with the most educated women (12% by age 52 years), although this gap appears to be lessening over time.[60]

Patient preferences for treatment for HMB may be affected by a knowledge of treatment options. In a study of 425 women attending their GP for HMB, 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 HMB, some women will find a treatment acceptable if it reduces bleeding symptoms, without amenorrhoea. A study of over 100 women who had undergone EA 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 HMB 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, and 18% thought that conservation of the uterus was most important, showing that individuals have different priorities for treatment.

Description of new intervention

Second-generation EA techniques

Since the 1990s, several new methods of EA have been developed. These are often referred to as second-generation techniques. They do not require direct visualisation 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 vaporising 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 visualisation of the uterine cavity and require no distension fluid.

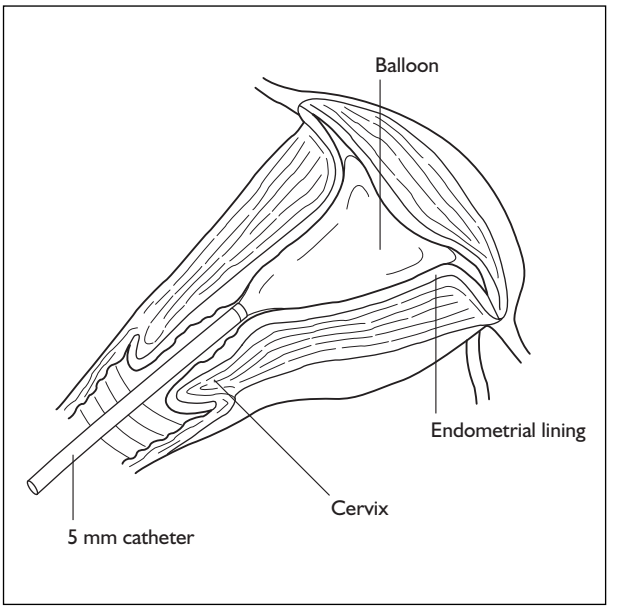


FIGURE 5 *Thermal balloon ablation. Modified from Gynaecology, 3rd ed, Shaw RW, Soutter P, Stanton SL, © 2002, with permission from Elsevier.*

MEA

The MEA technique was developed in Bath, England, in 1993. The microwave frequency (9.2 GHz) was chosen to ensure that tissue penetration was no more than 6 mm. An 8-mm 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 is 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 is measured. The microwave probe is inserted until the tip reaches the fundus. Graduated centimetre 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 2–3 minutes.[64] Following the procedure, analgesia is provided as required. A watery discharge for about 3 weeks is usual.[65]

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

TBEA

The TBEA relies on transfer of heat from heated liquid within a balloon that is inserted into the uterine cavity (see *Figure 5*). Several devices are available including Thermachoice™ and Cavaterm™. All systems involve an electronic controller, a single-use latex or silicone balloon catheter (5 mm) that 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

TABLE 5 *Contraindications for the three second-generation methods of EA*

Contraindication	Microwave	Cavaterm	Thermachoice
Uterine cavity size (cm)	>14	>10	>12
Pervious surgery or trauma leading to uterine wall thickness of at least 8 mm	✓	–	–
Previous classical 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 EA	✓	✓	✓
Active pelvic inflammatory infection	✓	✓	–
Undiagnosed vaginal bleeding	✓	✓	–
Known or suspected endometrial carcinoma	✓	✓	✓
Gross abnormalities such as myomas that prevent the 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 <6 cm in length	–	✓	–

The wording used in this table has been taken from information provided by the manufacturer of each device. Where a dash is present, this indicates that the contraindication was not explicitly stated by the manufacturer.

where the uterine cavity is >10 cm from the internal os to the fundus, and Thermachoice when the cavity is >12 cm 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 at 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 cauterisation of the endometrium. NSAIDs are given postoperatively. The treated lining sloughs off over the following week to 10 days.

The process is similar for the Cavaterm device, with some differences in detail. The cervix is dilated to about 6 mm. After insertion, a silicone balloon is filled with sterile 5% glucose solution to a pressure of 230–240 mmHg. The liquid is heated at 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. NSAIDs are given to reduce perioperative cramping.

Prognostic factors for the failure of TBEA, based on a study of 130 women who underwent TBEA with Thermachoice in The Netherlands, are younger age, retroverted uterus, pretreatment endometrial thickness of at least 4 mm and duration of menstruation.[66]

Adverse effects with second-generation EA devices

Adverse effects 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 in *Table 5*, which shows the manufacturers' descriptions of contraindications for the Microsulis microwave device and the two types of thermal balloon, Cavaterm and Thermachoice.

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 anaesthetic (GA) and LA.[67] Sixty-two women (63%) expressed a preference and were about equally divided between preferring GA and preferring LA. The remainder were randomised. The procedure was considered acceptable under GA 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 GA owing to dilation difficulties ($n = 3$), equipment failure ($n = 1$) and in one case due to identifying a submucosal fibroid that required GA for removal. The trial found that the operation time was not reduced in the randomised arms, but was in the preference groups (19 versus 25 minutes).[67]

If LA 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 2: Background

- HMB is a common complaint among women aged 30–49 years.
- 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 (>80 ml 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 QoL, 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 RB ablation, which rely on considerable surgeon skill and also have associated morbidity and reported mortalities. This report assesses two newer ablation techniques that destroy the endometrial lining through microwave or thermal energy.

Chapter 3
Methods

Methods for reviewing the effectiveness of MEA and TBEA were specified *a priori* and are outlined in the research protocol (Appendix 2).

Research questions

- What is the effectiveness of MEA and TBEA in the treatment of HMB?
- What is the cost-effectiveness of MEA and TBEA in the treatment of HMB?

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 the Acknowledgements (p. 83).

General methods

The methods of the review generally adhered to guidance laid out in the York Centre for Reviews and Dissemination guidelines.

Interventions considered were thermal balloon and microwave methods of EA for HMB.

First-generation methods of EA, TCRE, RB and combined methods are considered as comparators.

In order to provide a more complete picture of surgical management of HMB, information about hysterectomy compared with first-generation methods was examined using an existing systematic review of these treatments, updated with further literature searches.

Assessment of microwave and thermal balloon ablation

Search strategy

Electronic databases were searched for published studies, recently completed and ongoing research. Appendix 3 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.

Inclusion and exclusion criteria

Systematic reviews, RCTs and controlled trials of MEA and TBEA versus TCRE, RB or TCRE and RB 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 by discussion with a third (KS).

Data extraction strategy

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

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*) subgroup analysis, and any assessment of publication bias are provided.
7. A profile summarising 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 ITT analyses are given.

Assessments of the quality of RCTs were performed using quality indicators as given below. Owing 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 (LTFU)
4. whether an ITT 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 EA technique and route of hysterectomy surgery
2. endometrial thinning agents used.

Methods of analysis

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

Economic evaluation

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 HMB who are treated separately by either thermal balloon, microwave, TCRE or RB EA, 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 in *Figure 6*.

The structure of the model is shown in more detail in *Figure 7* (pathway for patients undergoing any type of EA) and *Figure 8* (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 EA. The health states in the EA model are as follows:

- Menorrhagia – all patients in the cohort have preoperative HMB.
- EA – the women undergo EA by MEA, TBEA or resection.
- Complication – following EA, some women will experience complications in the perioperative or immediately postoperative period.

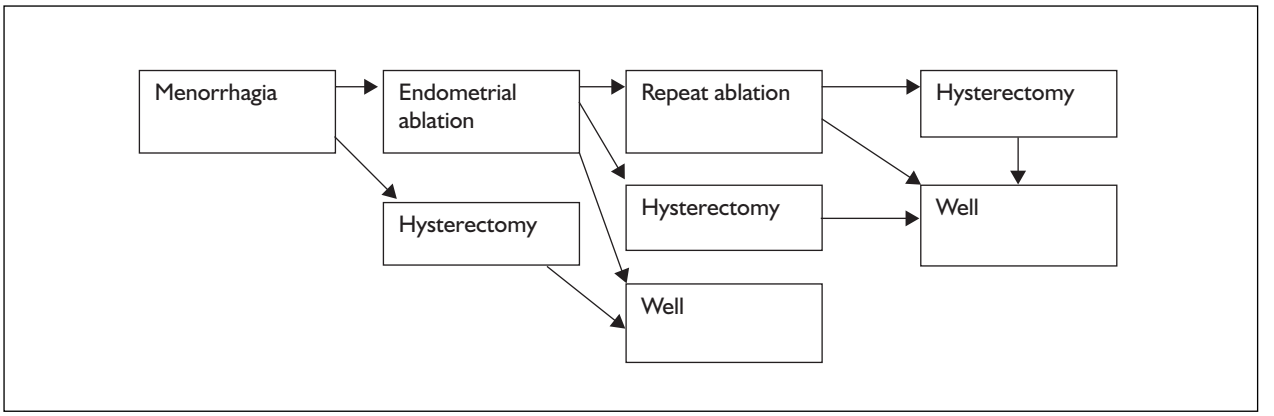


FIGURE 6 *Clinical pathway modelled*

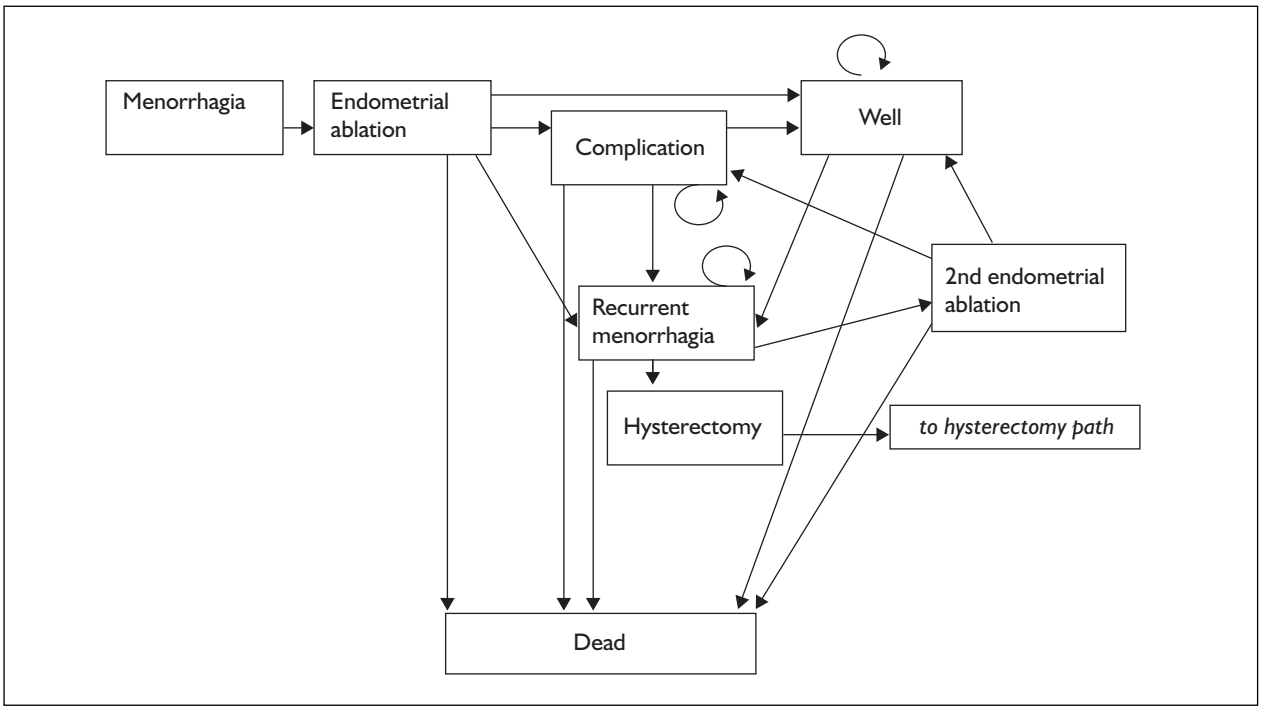


FIGURE 7 *Influence diagram for EA path*

- Well – following EA or complication, women are well.
- Recurrent menorrhagia – following EA, HMB may reoccur (treatment failure) at any time, including immediately postoperatively. Women may stay in this state, or be retreated, or have a hysterectomy.
- Repeat EA – if HMB recurs postoperatively, 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 HMB recurs after the 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 in *Figure 8*.
- Death – it is possible to die from causes other than EA during any health state. At hysterectomy and EA, women may also die as a direct result of the surgical procedure.

The health states in the hysterectomy model (shown in *Figure 8*) are as follows:

- Menorrhagia – all women in the cohort have preoperative HMB.

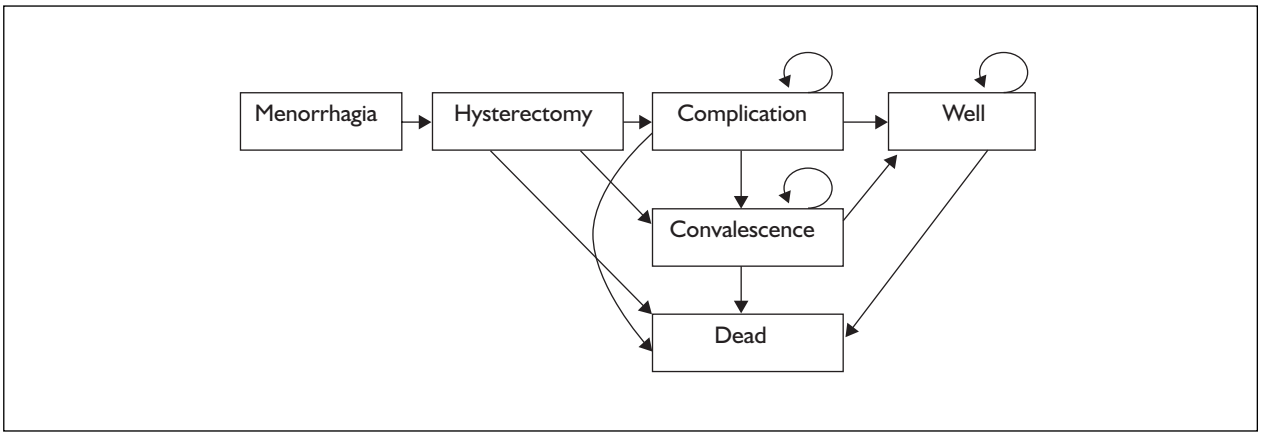


FIGURE 8 *Influence diagram for hysterectomy path*

- Hysterectomy – all women undergo hysterectomy.
- Complication – following hysterectomy, some women will experience complications in the perioperative or immediately postoperative period. The effects of these may last for a median of 1–2 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.

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 EA included in this review (see *Table 6*). The model runs for a total of 10 years. The model assumes that all women become menopausal after 10 years, at age 52 years, which is the average age of menopause in the UK.

Each cycle is 1 month long. In reality, complications following a second-generation ablation may be experienced for less than 1 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 1992–2000 starting at age 42 years 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 perioperative and complications immediately following the procedure are modelled; subjects cannot enter the health state 'complications' from any state except that of the operation.

After an unsuccessful EA treatment, HMB can return at any time (treatment failure), including immediately after the procedure. Recurrent menorrhagia has been assumed to be mostly evident in the first 3 years. This was based on evidence in this assessment (see *Tables 9* and *20*). It was assumed that the total number of women with recurrent menorrhagia counted at each point of follow-up would include both those reporting HMB 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 90% 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. About 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 1 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 *Figures 7* and *8*.
- Costs of each procedure (including cost of equipment, preoperative endometrial thinning, time in theatre, proportion of women undergoing ablation who have GA and LA, 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. First, 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 exceptions to this hierarchy were data for perioperative complications and death. The infrequency of these events means that the small RCTs provide imprecise estimates. Large national audits of hysterectomy and first-generation EA exist – the VALUE and the MISTLETOE studies (see the section 'Adverse effect data from other sources', p. 57). 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 25*. One published cost–utility analysis of surgery for menorrhagia[30] describes utility values that 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 were obtained. A cost per procedure for each type of EA technique and for hysterectomy was 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 procedure includes costs of endometrial thinning agents, anaesthetics, dedicated equipment, operating time and inpatient stay.

Preoperative treatment

It is assumed that once referred to secondary care, all women with HMB will have the cause investigated. The RCOG recommends that women receive a 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 LA or GA. 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 ultrasound 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 4–5 weeks of pre-treatment with thinning agents: oral danazol (200 mg daily) if undergoing LA treatment or the luteinising hormone-releasing hormone (LHRH) analogue Zoladex if undergoing GA.

Surgical procedures

Details for average length of stay in hospital and waiting time for hysterectomy are taken from HES 2000–1 (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 first-generation EA were taken from a systematic review rather than routine NHS statistics which give costs at Healthcare Resource Group level.[9] The HES code for first-generation EA 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 and occlusion of Fallopian tubes) which may distort the actual costs of EA. Instead, the means from the systematic review were used.[52] HES data for 2000–1 were used to obtain waiting times for surgery.[73]

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

Equipment cost
There are two main types of TBEA 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 cost of thermal balloon is the mean cost of the two devices.

Staff costs
It is assumed that all hysterectomy and all first EA techniques are undertaken by a consultant. Staff needed in the operating theatre for a GA 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 versus TBEA
- MEA versus TCRE
- MEA versus TCRE and RB
- MEA versus RB
- MEA versus hysterectomy
- TBEA versus TCRE
- TBEA versus TCRE and RB
- TBEA versus RB
- TBEA versus 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 TBEA and MEA. The sensitivity analysis focused 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 and length of hospital stay
- duration of the model.

Industry submissions

Three submissions from industry were provided to the National Institute for Clinical Excellence (NICE) by manufacturers of thermal balloon and microwave ablation equipment. The submissions were used in a number of ways. First, they were examined for additional information that met the inclusion criteria for the systematic review of effectiveness or the economic model. Second, 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.

Chapter 4
Results

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.

Studies identified

The search for controlled studies including MEA or TBEA identified 216 abstracts. A total of 68 full-text articles were acquired (see Appendix 4 for further details of excluded papers). Fifteen of these were possible controlled studies. A total of 13 trial reports relating to 10 studies were identified as suitable for inclusion.

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 4 for details of inclusion and exclusion)

Included systematic reviews

Eight Cochrane reviews have examined treatments for HMB. Five review the evidence for various medical methods of controlling HMB: oral contraceptives,[76] cyclical progestogens,[77] danazol,[78] NSAIDs[79] and antifibrinolytics.[80] One reviews the evidence for the progesterone-releasing IUD.[81] One examines the use of preoperative thinning agents before hysteroscopic surgery.[55]

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

Quality of included systematic reviews

See Appendix 5 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, ITT 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 (CIs) and by checking the results of statistical tests for heterogeneity.

Dichotomous data were pooled as Peto (fixed effect) odds ratios (ORs) with 95% CI, apart from one outcome (use of LA) 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 (postoperative amenorrhoea) the text data suggested that the difference between the techniques was significant whereas 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 was not reported in either review. Neither review discussed potential biases in the review.

Existing systematic reviews – findings

Details of the data extracted from the existing systematic reviews are given in Appendix 6.

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 1 and 4 years (median 2 years).

The Cochrane review of hysterectomy versus first-generation EA 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 to 0.59) for women undergoing hysterectomy. However, duration of surgery, hospital stay and time to return to work were all shorter following EA [weighted mean difference (WMD) = 23.1 minutes, 95% CI 23.8 to 22.3; WMD 4.0 days, 95% CI 4.9 to 4.8; WMD 4.6 weeks, 95% CI 4.8 to 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 EA. 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 offset by permanent relief from symptoms. Costs were lower for EA but, owing to re-treatment in the EA group, the difference narrows over time with EA costing between 5 and 11% less than hysterectomy at 4 years.

Systematic review of endometrial destruction techniques

The Cochrane review of endometrial destruction techniques[9] identified two RCTs[82,83] of TBEA versus RB. 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 RB, 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 hydrotherm ablator (HTA)] with first-generation techniques.

The studies contained a total of 1595 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 RB group at 12 and 36 months (OR = 0.55, 95% CI 0.31 to 0.99 and OR = 0.5, 95% CI 0.25 to 0.97, respectively) but not at 24 months. Likewise, while additional surgery was significantly more likely in the RB group at 24 months (OR 0.35, 95% CI 0.12 to 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 to 0.8), whereas equipment failure was more likely (OR = 4.07, 95% CI 1.1 to 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 LA (OR = 7.6, 95% CI 1.1 to 52.7) However, equipment failure was more likely in second-generation techniques (OR = 4.1, 95% CI 1.1 to 15.0).

However, as noted above, there are differences in the text and graph figures for some of the findings. Attempts to contact the authors 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 3. The results are described in the next section.

Controlled trials of second-generation EA techniques

A total of 14 publications were found using the search strategy shown in Appendix 3. Three were of MEA[86–88] and 11 were of TBEA.[82–85,89–94] However, two of the MEA papers report on the

same trial at 12 (Cooper and colleagues)[86] and 24 months (Bain and colleagues)[87] 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 (Grainger and colleagues),[84] 36 months (Loffer)[85] and 60 months (Loffer and Graigner)[94] 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 that had been omitted from the original publication.[95] 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 RB ablation that 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, the manufacturers of MEA equipment, provided details of an RCT they conducted as part of their submission to the US Food and Drug Administration (FDA) approval process.[88] Our assessment of this study is based on the information that they supplied.

In summary, two MEA and eight TBEA trials were included in the review although data were taken from all published accounts of these trials. Details of these studies are described below and summarised in *Table 6*, with summary details in Appendix 7.

Most of the included studies are RCTs. Two are non-RCTs. One study, by Gervaise and colleagues[90] (TBEA versus 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. Another by Bongers and colleagues[89] (TBEA versus TCRE) is a prospective cohort comparison of women undergoing EA at one Dutch hospital where all ablations between 1992 and 1994 were TCRE and all after 1995 were TBEA.

Details of trials

Publication date/country and sample size

The studies were published between 1996 and 2002 with recruitment between 1992 and 2001. The TBEA versus RB studies by Romer[83] and Zon-Rabelink[93] did not state the dates of recruitment. The number of women randomised in each trial ranged from 20 to 322 (median 143). A total of 1561 women were included in all trials of second-generation EA techniques.

The MEA versus TCRE/RB study by Cooper and colleagues[86] was based at a single centre in the UK whereas the Microsulis study[88] (MEA versus RB) recruited women from eight sites in the UK and the USA. Bongers and colleagues[89] (TBEA versus TCRE) recruited women from a single centre in The Netherlands. The TBEA versus TCRE study by Gervaise and colleagues[90] recruited women from a single centre in France. Pellicano and colleagues[92] (TBEA versus TCRE/RB) used a single centre in Italy. Soysal and colleagues[91] (TBEA versus RB) recruited women from a single centre in Turkey. The study by Meyer and colleagues[82] (TBEA versus RB) recruited women from multiple centres in the USA and Canada and that by Brun and colleagues[96] (TBEA versus TCRE) from multiple centres in France. The Zon-Rabelink study[93] (TBEA versus 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,[82,85,93] menorrhagia or metrorrhagia,[96] excessive menstrual bleeding,[84] recurrent therapy refractory menorrhagia,[83] menorrhagia unresponsive to medical treatment,[89,92] abnormal uterine bleeding[88] and abnormal menstrual bleeding.[90] Methods of measuring bleeding also varied. The MEA versus TCRE/RB study by Cooper and colleagues[86] included women who self-defined their menstrual loss as heavy. Brun and colleagues[96] (TBEA versus TCRE) used a PBAC score of >80 as an inclusion criterion whereas Meyer and colleagues[82] (TBEA versus RB) and Soysal and colleagues[91] (TBEA versus RB) used a PBAC score of at least 150. The Microsulis study[88] (MEA versus RB) and the Zon-Rabelink study[93] (TBEA versus RB) defined HMB as a score of 185 or more. Gervaise and colleagues[90] (TBEA versus TCRE) quantified HMB through the number of pads used per cycle. No description of how HMB was measured is given by Bongers and colleagues[89] (TBEA versus TCRE), Romer[83] (TBEA versus RB) or Pellicano and colleagues[92] (TBEA versus TCRE/RB).

Participant characteristics

The median average age of the women included in the studies was 42.6 years (range 40.2–46.3) for the intervention arms and 43.2 years (range 40–47.4 years) in the control arms. The Microsulis study[88] (MEA versus RB) and that by

Zon-Rabelink[93] (TBEA versus RB) did not report the ages of participants.

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

All women in the study by Soysal and colleagues[91] (TBEA versus RB) had fibroids of <5 cm diameter. Bongers and colleagues[89] (TBEA versus TCRE), Meyer and colleagues[82] (TBEA versus RB), Gervaise and colleagues[90] (TBEA versus TCRE), Romer[83] (TBEA versus RB) and Pellicano and colleagues[92] (TBEA versus TCRE/RB) excluded women with submucous fibroids from their study. Brun and colleagues[96] (TBEA versus TCRE) only included women with a normal uterus. Zon-Rabelink[93] (TBEA versus RB) did not state whether or not women with fibroids were included.

Only Gervaise and colleagues[90] (TBEA versus 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 and colleagues[86] (MEA versus TCRE/RB) and the studies by Meyer and colleagues[82] (TBEA versus RB) and Brun and colleagues[96] (TBEA versus TCRE) explicitly excluded menopausal women. Bongers and colleagues[89] (TBEA versus TCRE), Soysal and colleagues[91] (TBEA versus RB), Romer[83] (TBEA versus RB), Pellicano and colleagues[92] (TBEA versus TCRE/RB), Zon-Rabelink[93] (TBEA versus RB) and the Microsulis study[88] (MEA versus 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[93] (TBEA) used RB ablation as the comparator whereas the studies by Bongers and colleagues (TBEA), Brun and colleagues (TBEA), Gervaise and colleagues (TBEA), and Soysal and colleagues (TBEA) used TCRE as the control technique.[89–91,96] The control surgery for the trial by Cooper and colleagues[86] (MEA) and Pellicano and colleagues[92] (TBEA) was combined TCRE and RB (TCRE/RB).

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

Soysal and colleagues[91] (TBEA versus RB) and Romer[83] (TBEA versus RB) used 2-monthly injections of a GnRH prior to surgery. Zon-Rabelink[93] (TBEA versus RB) used Zoladex 6 and 2 weeks prior to surgery as pre-thinning agent in both groups. Meyer and colleagues[82] (TBEA versus RB) used a timed 3-minute curettage as pretreatment. Brun and colleagues[96] (TBEA versus TCRE) also performed D&C immediately prior to ablation. Bongers and colleagues[89] (TBEA versus TCRE) used D&C to pretreat those undergoing TBEA and GnRH for 8–12 weeks prior to surgery for TCRE patients. Gervaise and colleagues[90] (TBEA versus TCRE) did not use pre-treatment. Pellicano and colleagues[92] (TBEA versus TCRE/RB) did not use pretreatment in the TBEA group but pretreated those in the control group with GnRH 6 and 2 weeks prior to surgery.

In three trials (Cooper and colleagues,[86] MEA versus TCRE/RB; Gervaise and colleagues,[90] TBEA versus TCRE; and Romer[83] (TBEA versus RB), GA was used for all women in both treatment and control groups. Meyer and colleagues[82] (TBEA versus RB) used LA in 16% of women undergoing RB ablation and 47% of women undergoing TBEA. In the other TBEA trials, LA was used in 38%,[90] 47%[82] and 100%[91] of women undergoing TBEA. In the Microsulis trial[88] (MEA versus RB), 37% of those undergoing MEA and 76% of those undergoing RB ablation had a GA with the remainder having LA or regional anaesthetic. All women undergoing both TBEA and TCRE in the trial by Pellicano and colleagues[92] had a spinal anaesthetic. Bongers and colleagues[89] (TBEA versus TCRE) reported that patients had either spinal anaesthetic or GA but numbers were not reported. Brun and colleagues[96] (TBEA versus TCRE/RB) and Zon-Rabelink[93] (TBEA versus 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 versus 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 versus RB), Bongers and colleagues (TBEA versus TCRE), Romer (TBEA versus RB), Gervaise (TBEA versus TCRE) or Zon-Rabelink (TBEA versus RB) studies.[83,88–90,93]

TABLE 6 *Characteristics of trials reported in all included papers and treatment*

Author/ date/design	No. of patients	Average age (years)	Women with fibroids excluded?	Intervention	Control treat-ment	Pretreatment	Surgeon experience	Anaesthetic	Length of follow-up (months)
Cooper *et al.*, 1999[86] RCT	263	MEA 41.1 (SD 6.7) TCRE/RB 42.0 (SD 8.4)	No	Microwave	TCRE/RB	3.6 mg goserelin 5 weeks prior	At least 50 prior TCREs, at least 5 prior MEAs	100% GA	12
Bain *et al.*, 2002[87] RCT	263	MEA 41.4 (SD 5.4) TCRE/RB 42.2 (SD 5.8)	No	Microwave	TCRE/RB	3.6 mg goserelin 5 weeks prior	At least 50 prior TCREs, at least 5 prior MEAs	GA	24
Microsulis 2002[88] RCT	322	Not stated	No	Microwave	RB	Leuprolide acetate depot 3–5 weeks prior	Not stated	GA: MEA 37% RB 76%	12
Bongers *et al.*, 2000[89] Non-RCT	152	TBEA 42.5 (SD 6.3) TCRE 43.2 (SD 6.4)	Yes	Thermachoice TBEA	TCRE	D&C	Not stated	GA and spinal	24
Brun *et al.*, 2002[96] RCT	51	TBEA 45.5 (±6.0, 35–59) TCRE 46.7 (SD 6.0, 33–46)	Not clear	Cavaterm thermal balloon	TCRE	D&C immediately prior to procedure	Experienced surgeons	Not stated	3
Meyer *et al.*, 1998[82] 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 RB	GA: TBEA 53% RB 84%	12
Grainger *et al.*, 2000[84] RCT	255	Not stated	Yes	Thermachoice thermal balloon	RB	3-minute curettage using 5-mm curette prior to ablation	All experienced in RB and trained in TBEA	Not stated	24
Loffer, 2001[85] RCT	255	Not stated	Yes	Thermachoice thermal balloon	RB	Timed 3-minute suction curettage given to all prior to ablation	All experienced in RB and trained in TBEA	LA, LA with sedation and GA. More GA with RB	36

continued

TABLE 6 *Characteristics of trials reported in all included papers and treatment (cont'd)*

Author/ date/design	No. of patients	Average age (years)	Women with fibroids excluded?	Intervention	Control treat-ment	Pretreatment	Surgeon experience	Anaesthetic	Length of follow-up (months)
Loffer and Grainger, 2002[94] RCT	255	TBEA 40.4 RB 40.9	Yes	Thermachoice thermal balloon	RB	3-minute suction curettage	All experienced in RB and trained in TBEA	Not stated	60
Gervaise *et al.*, 1999[90] Non-RCT	147	TBEA 46.3 (±1.4 34–66 TCRE 47.4 (±0.2) 34–65	Yes	Thermachoice balloon	TCRE	None	Not stated	GA TCRE GA and LA (38%) for TBEA	18
Pellicano *et al.*, 2002[92] 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	24
Romer, 1998[83] RCT	20	TBEA 42 (37–52) RB 40 (37–50)	Yes	Cavaterm balloon	RB	2× monthly injections of GnRH (leuprolide 3.75 mg) operation 2 weeks after injection	Not stated	All GA	9–15
Soysal *et al.*, 2001[91] RCT	96	TBEA 43.6 (±2.5, 40–49) RB 44.3 (±2.6, 40–49)	No, all patients had fibroids	Thermachoice balloon	RB	2× monthly injections of GnRH analogue (3.6 mg goserelin acetate)	One experienced surgeon performed all RB, TBEA by staff surgeons supervised by residents	All RB GA, all TBEA LA	12
Zon-Rabelink, 2001[93] RCT	139	Not stated	Not stated	Thermachoice balloon	RB	Pretreatment with Zoladex 6 and 2 weeks prior to surgery	Not stated	Not stated	24

SD, standard deviation.

Quality assessment of RCTs

The quality of the reports of RCTs is summarised in *Table 7*.

Internal validity

Sample size

The 10 studies included 20,[83] 51,[96] 96,[91] 96,[92] 139,[93] 147,[90] 152,[89] 263,[86] 275[82] and 322[88] women. Sample size calculations were performed in three of the RCTs[82,86,96] and one non-RCT.[89] Sample size calculations were not reported by Microsulis[88] (MEA versus RB), Pellicano and colleagues[92] (TBEA versus TCRE/RB) Soysal and colleagues[91] (TBEA versus RB), Gervaise and colleagues[90] (TBEA versus TCRE), Romer[83] (TBEA versus RB) or Zon-Rabelink[93] (TBEA versus RB).

The trial by Cooper and colleagues[86] (MEA versus 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 RB 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 versus RB), sample size was calculated based on 90% power to detect 20% less effectiveness in the treatment group ($p = 0.05$) based on an 85% response rate for RB. "Effectiveness" is not defined. However, 86% of women undergoing TBEA and 87% of women undergoing RB 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 versus 68% with RB).

The trial by Bongers and colleagues[89] (TBEA versus TCRE) reports that assuming a 9% re-intervention rate after TCRE, a series of 150 patients would be needed to show that balloon ablation is equally effective; 152 women were included in this trial and the re-intervention rate was 20% in the TCRE arm. It should be noted that the sample size calculation appears only in the abstract, and not in the body of the trial report.

The trial by Brun and colleagues[96] (TBEA versus TCRE) based the sample size calculation on 160 patients giving a 90% power ($p = 0.05$) to detect a 15% difference in efficacy. However, only 51 women were actually recruited to the trial.

Selection bias

Allocation to intervention or control arm in the MEA trial by Cooper and colleagues[86] (MEA versus 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 envelopes 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 versus RB) was random, but there was no account of steps taken to conceal allocation. Soysal and colleagues[91] (TBEA versus RB) used computer-generated randomisation and opaque, sealed envelopes for allocation concealment. Pellicano and colleagues[92] (TBEA versus 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[93] (TBEA versus RB) states that women were first stratified by age (over or under 45 years) and parity (nulliparous or parous women) and then randomised with allocation via blind envelopes.

Brun and colleagues[96] (TBEA versus TCRE) used central allocation of patients on a 1:1 basis but the method of randomisation is not described, nor is the allocation concealment method reported. As some data are missing from 24% of patients at baseline, it is not possible to say whether the groups were similar – mean age was similar but the range was greater for women in the TBEA group (TBEA 35–59 years, TCRE 33–46 years).

The Gervaise and colleagues' study[90] (TBEA versus 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 versus 2.4) and containing more women who were post-menopausal (27% versus 7%) than the TBEA group, although the number of pads used per cycle was similar. Higher parity is associated with increased HMB (see the section 'Cause of HMB', p. 3).

The Bongers and colleagues' study[89] (TBEA versus TCRE) was not randomised. The authors report that consecutive women were recruited

prospectively to the trial, with all women attending for EA from 1992 to 1994 undergoing TCRE and all those from 1995 to 1997 undergoing TBEA. Inclusion and exclusion criteria were applied. The baseline characteristics of the two groups are comparable.

The Microsulis trial[88] (MEA versus RB) and the study by Romer[83] (TBEA versus 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 RB ablation are skilled operations, which, like most surgical procedures, are difficult to standardise. The RCTs vary in the extent to which standardisation of procedures are reported.

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

No details of surgeon experience are given in the Microsulis trial[88] (MEA versus RB) and, as this is an eight-centre trial, differences in technique and experience are possible. Indeed, one study centre performed all operations under GA. 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 RB ($p = 0.007$). It is possible that this is related to inexperience with the RB technique. No significant differences in amenorrhoea were shown at the other seven centres.

No details are given about surgeon experience by Bongers and colleagues.[89] Initially, women treated with TBEA were treated for 8 minutes, and this was increased to 16 minutes for the second half of the study. However, looking at the extent of total ablation of the endometrium, the authors examined the possibility that there would be a learning curve with both TCRE and TBEA procedures, leading to improved results over time. This was not seen.

The study by Brun and colleagues[96] (TBEA versus TCRE) recruited from seven centres with each contributing details on 2–12 women. All the surgeons are described as 'experienced' at TCRE although variation is possible, particularly as these were performed to local guidelines at each centre.

In the trial by Meyer and colleagues[82] (TBEA versus RB), it is stated that all surgeons had extensive experience of RB 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[90] (TBEA versus TCRE).

Pellicano and colleagues[92] (TBEA versus TCRE/RB) report that all surgeons were 'proficient' at combined TCRE and RB ablation; 2.7% sorbitol or 0.54% mannitol was used as distension solution.

Romer[83] (TBEA versus RB) and Zon-Rabelink[93] (TBEA versus RB) do not report on the extent of surgeon experience or the operating procedure.

One experienced surgeon performed all the RB ablations in the study by Soysal and colleagues[91] (TBEA versus RB). Glycine was the distension medium and a 3-mm RB 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. Although 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 versus TCRE/RB) reported that 14 patients (5%) were LTFU, nine (7%) in the MEA arm and five (4%) in the TCRE and RB arm. This is fewer than were reported as LTFU at 12 months: 23 (9%) overall, 13 (10%) in the MEA arm and 10 (7%) in the TCRE and RB 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 telephone where necessary. It is stated that ITT analysis is undertaken but some analyses are carried out only on treatment completers followed up.

The Microsulis study[88] (MEA versus RB) reports that 7% of women were LTFU at 12 months, 13 women (6%) in the MEA arm and nine (8%) in the RB arm. All analyses are reported on an ITT basis. In the study by Brun and colleagues[96] (TBEA versus TCRE), one woman (2%) was LTFU at the time of randomisation. No further LTFU was reported at 3 months.

The study by Bongers and colleagues[89] (TBEA versus TCRE) does not report LTFU and states that ITT analysis is undertaken. However the paper provides numbers and percentages for the 'satisfaction' outcomes at 24 months that are not calculated on an ITT basis. This suggests that 37% of TBEA and 38% of TCRE patients may have been LTFU by 24 months. Some other outcomes, such as amenorrhoea rates, only provide percentages so it is not possible to ascertain whether these are calculated on an ITT basis.

In the trial by Meyer and colleagues[82] (TBEA versus RB), 275 patients were randomised but 15 electively withdrew before the procedure was performed. A further four were discovered to be ineligible and 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 3-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 6 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. ITT analysis is not performed. Numbers of the original 275 women allocated to treatment and control arms are only reported in the 3-year follow-up paper; 46% of the recruited participants were LTFU by 60 months. This includes women from two centres that did not provide 5-year follow-up data. Furthermore, in the 5-year paper,[94] patients who had undergone repeat surgery are excluded from calculations of bleeding and pain outcomes.

Gervaise and colleagues[90] (TBEA versus TCRE) reported no LTFU 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 were selected on the basis that follow-up information was available.

Pellicano and colleagues[92] (TBEA versus RB) report 29% LTFU at 2 years.

Romer[83] (TBEA versus RB) had no LTFU of the original 20 women at 12 months.

The study by Soysal and colleagues[91] (TBEA versus RB) lost three patients from the TBEA groups prior to the procedure being performed, but reported no other LTFU at 12 months. These three patients were excluded from analysis.

Two patients were excluded after randomisation by Zon-Rabelink[93] (TBEA versus RB). Both had been allocated to the RB group. One was discovered to have polyps at the time of operative hysteroscopy, and one was discovered to have a PBAC score of <185. Both of these women were excluded from analysis. One further woman, also in the RB group, was LTFU 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 'Quality assessment strategy', p. 17, for the classification of generalisability). All studies except the Microsulis study[88] (MEA versus RB) and Zon-Rabelink[93] (TBEA versus RB) gave details about the patients' characteristics and inclusion and exclusion criteria. However, details of weight or height at baseline were missing from nearly one-quarter of the women recruited by Brun and colleagues[96] (TBEA versus TCRE). In the case of studies with multiple papers (Meyer and colleagues[82] and Cooper and colleagues[86]), good descriptions of patients' characteristics and inclusion criteria were provided in at least one of the study reports. The study by Gervaise and colleagues[90] (TBEA versus TCRE) included women who were post-menopausal but unwilling to discontinue HRT. The results of surgery for these women were not reported separately. The Microsulis study[88] (MEA versus 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 HMB, and post-menopausal women will no longer menstruate. Shorter study follow-up among younger women may underestimate the costs and disbenefits of EA. One trial had a 5-year follow up,[82] four had a

TABLE 7 *Methodological characteristics of included controlled trials*

Author/ date	No. of patients	Adequate allocation to groups?	Blinding?	Comparability of groups?	Same intervention to all patients?	LTFU (%)	Sample size calc.?	ITT?	Generalisability	Main outcome measured independently	Inter-centre variability?	Conflicts of interest?
Cooper *et al.*, 1999[86]	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[88]	322	Uncertain	Uncertain	Uncertain	Uncertain	7%	Uncertain	Yes	Low	Yes	Yes	Yes
Bongers *et al.*, 2000[89]	152	N/A	N/A	Yes	No	Uncertain – maybe 38% at 2 years	Yes	Stated yes, but some data appears to be on evaluable patients	Medium	Yes	Not applicable	None stated
Brun *et al.*, 2002[96]	51	Yes	Uncertain	Uncertain – baseline data missing from 24%	No	2% at randomisation	Yes based on 160 patients	No	Medium	Yes	Not examined	None stated
Meyer *et al.*, 1998[82]	275	Yes	Uncertain	Yes	Yes	12 months 11% 24 months 17% 36 months 22% 60 months 46%	Yes	No. Patients 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

continued

TABLE 7 *Methodological characteristics of included controlled trials (cont'd)*

Author/ date	No. of patients	Adequate allocation to groups?	Blinding?	Comparability of groups?	Same intervention to all patients?	LTFU (%)	Sample size calc.?	ITT?	Generalisability	Main outcome measured independently	Inter-centre variability?	Conflicts of interest?
Gervaise *et al*., 1999[90]	147	No	No	No – 27% of women given TCRE and 7% given TBEA were post-menopausal	Yes	None	No	N/A	Medium	Uncertain	Not applicable	None
Pellicano *et al*., 2002[92]	96	Yes	Uncertain	Yes	Yes	29% at 2 years	No	No	High	Yes		
Romer, 1998[83]	20	Uncertain	Uncertain	Yes	Yes	None	Uncertain	N/A	Low	Uncertain	Not applicable	None
Soysal *et al*., 2001[91]	96	Yes	Uncertain	Yes	Yes	None	No	3 patients allocated to TBEA did not receive treatment and were excluded, no other LTFU	High	Yes	No	None
Zon-Rabelink, 2001[93]	139	Yes	Yes	Uncertain	Yes	2% at 2 years	No	No	Low	Yes	Not stated	None

2-year follow-up,[86,89,92,93] one had an 18-month follow-up,[90] three had a 12-month follow-up[83,88,91] and one had a 3-month follow-up.[96] Romer[83] (TBEA versus RB) followed-up patients for 9–15 months.

Assessment of effectiveness

Reporting of outcomes

Outcome percentages recorded in the following tables are given as reported in the trials and also have been recalculated on an ITT basis where necessary. ITT figures are given in parentheses.

A wide range of outcomes of surgery were reported across the studies and these are shown in *Tables 8–20*. Broadly, the outcomes can be grouped into the following categories:

- bleeding outcomes
- premenstrual syndrome (PMS)-related outcomes
- dysmenorrhoea
- anaemia/haemoglobin outcomes
- satisfaction
- QoL
- operation details
- further surgery
- adverse effects (perioperative and postoperative).

The way in which outcomes were reported differs between studies. For example, some bleeding outcomes use mean PBAC scores, or changes in these, whereas 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 seven of the included studies, and has a consistent definition. *Table 8* shows the rates of postoperative amenorrhoea. Amenorrhoea at 12 months was reported for a median of 45% of women undergoing MEA (range 36–40%) and a median of 15% (range 10–40%) for TBEA. At 12 months, a median of 30% of women undergoing TCRE or RB had amenorrhoea (range 17–46%). The lowest percentage (10%) is found in the TBEA arm of the trial containing women who all had fibroids.[91]

Amenorrhoea at 24 months was experienced by 44% of women undergoing MEA, a median of 17% (range 13–22%) of those undergoing TBEA and by a median of 28% (range 17–43%) of women undergoing TCRE or RB. Only Meyer and colleagues[82] report on longer term follow-up. At 36 months, 12% of women undergoing TBEA and 19% of women undergoing RB had amenorrhoea and at 60 months 14% of women undergoing TBEA and 10% of those undergoing RB were amenorrhagic.

It is not clear from the data supplied by Bongers and colleagues[89] if the stated amenorrhoea rates are based on ITT calculations. Brun and colleagues[96] (TBEA versus TCRE), Pellicano and colleagues[92] (TBEA versus TCRE/RB) and Zon-Rabelink[93] (TBEA versus RB) do not report amenorrhoea.

At 12 months, Meyer and colleagues[82] (TBEA versus RB) reported a statistically significant difference between the TBEA (13%) and RB (22%) groups ($p < 0.05$).

Figure 9 illustrates the findings for amenorrhoea at 12 months for first-generation versus second-generation EA techniques and *Figure 10* shows those at 24 months. The size of the data points indicates the relative size of each study. In most cases the CIs cross the central line, indicating that differences were not statistically significant. The significant difference detected by Meyer and colleagues[82] at 12 months (TBEA versus RB) is not seen in the forest plot because the data have been recalculated here on an ITT basis whereas the original study analysis excluded women LTFU.

At 24 months, only the Meyer[82] and colleagues' study (TBEA versus TCRE) indicates a more favourable outcome for RB. However, there was a loss to follow-up in this trial (17% at 2 years). The study results have not been statistically combined owing to clinical heterogeneity between the trials.

Other recorded outcomes for bleeding are shown in *Tables 9* and *10*. Note that data for 24 months (Meyer and colleagues,[82] TBEA versus RB) were estimated from data presented in graph form in the original study report. Three trials reported postoperative bleeding in terms of spotting, hypomenorrhoea, eumenorrhoea, menorrhagia or metrorrhagia; Romer[83] (TBEA versus RB) at 12 months', Meyer and colleagues[82] (TBEA versus RB) at 24 and 36 months' follow-up, and Gervaise and colleagues[90] (TBEA versus 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 RB were still experiencing menorrhagia. At 60 months, this figure was 2% and 1%, respectively. For further details, see *Table 9*. No trial reported statistically significant differences between the groups for recurrent menorrhagia.

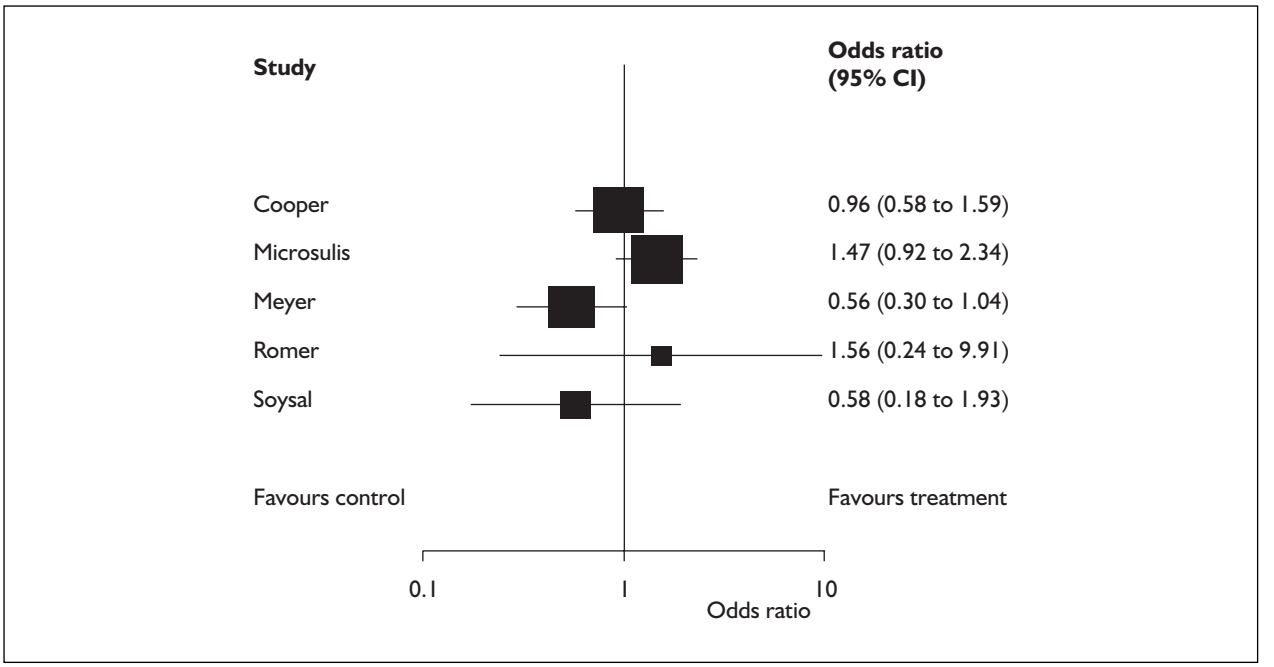


FIGURE 9 *Forest plot of amenorrhoea at 12 months – first-generation versus second-generation EA methods (random effects model, results not pooled)*

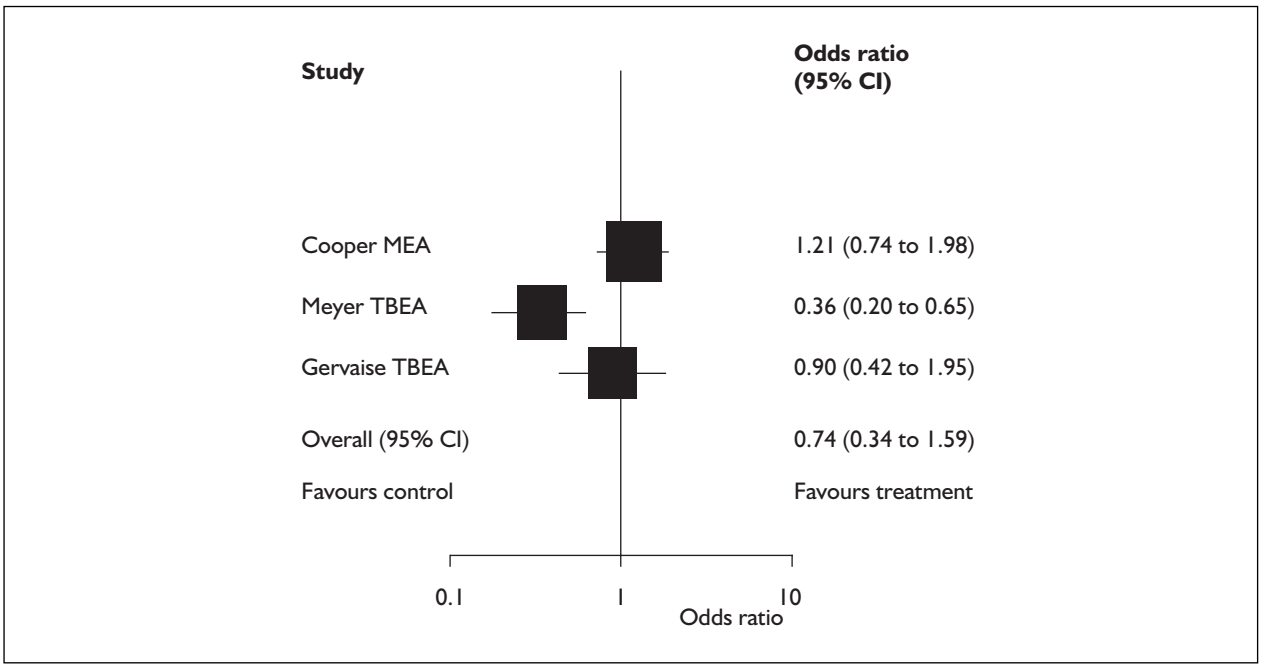


FIGURE 10 *Forest plot of amenorrhoea at 24 months – first-generation versus second-generation EA methods (random effects model, results not pooled)*

Bongers and colleagues[89] (TBEA versus TCRE) report on the number of women undergoing re-intervention surgery who cited menorrhagia or metrorrhagia as a reason, but it is not clear if other women may have also suffered these symptoms but not undergone repeat surgery.

Six trials reported changes in PBAC score. At 12 months Meyer and colleagues[82] (TBEA versus RB) report that 73% of the TBEA and 70% of the RB group had a score of <100 (normal bleeding). More stringently, the Microsulis study[88] (MEA versus RB) uses a PBAC score of <76 to indicate

TABLE 8 *Postoperative amenorrhoea – % (ITT %)*

Author/date	Treatment	Immediate post-op./ 3 months		12 months		24 months		36 months		60 months	
		Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Cooper *et al*., 1999[86]	MEA	–	–	40 (36)	40 (36)	47 (44)	41 (40)	–	–	–	–
Microsulis, 2002[88]	MEA	–	–	55 (55)	46 (46)	–	–	–	–	–	–
Bongers *et al*., 2000[89]	TBEA	17 (–)	36 (–)	15 (–)	22 (–)	13 (–)	17 (–)	–	–	–	–
Brun *et al*., 2002[96]	TBEA	–	–	–	–	–	–	–	–	–	–
Meyer *et al*., 1998[82]	TBEA	–	15 (14)	15 (13)	27 (22)	17 (15)	45 (33)	15 (12)	26 (19)	33 (14)	23 (10)
Gervaise *et al*., 1999[90]	TBEA	25 (25)	38 (38)	–	–	36 (22)	38 (24)	–	–	–	–
Pellicano, *et al*., 2002[92]	TBEA	–	–	–	–	–	–	–	–	–	–
Romer, 1998[83]	TBEA	–	–	40 (40)	31 (30)	–	–	–	–	–	–
Soysal *et al*., 2001[91]	TBEA	–	–	11 (10)	17 (17)	–	–	–	–	–	–
Zon-Rabelink, 2001[93]	TBEA	–	–	–	–	–	–	–	–	–	–

TABLE 9 *Results: type of postoperative bleeding – % (% ITT)*

Author/date	Length of follow-up (months)	Intervention	Spotting	Hypomenorrhoea	Eumenorrhoea	Menorrhagia	Metrorrhagia
Cooper *et al.*, 1999[86]	12	MEA	–	–	–	–	–
		TCRE/RB	–	–	–	–	–
	24	MEA	–	–	–	–	
		TCRE/RB	–	–	–	–	–
Microsulis, 2002[88]	12	MEA	–	–	–	–	–
		RB	–	–	–	–	–
Bongers *et al.*, 2000[89]	24	TBEA	–	–	–	9 (9)[a]	3 (3)[a]
		TCRE	–	–	–	12 (12)[a]	9 (9)[a]
Brun *et al.*, 2002[96]	3	TBEA	–	–	–	–	–
		TCRE	–	–	–	–	–
Meyer *et al.*, 1998[82]	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[90]	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[83]	12	TBEA	–	50 (50)	10 (10)	–	–
		RB	–	60 (60)	10 (10)	–	–
Pellicano *et al.*, 2002[92]	12	TBEA	–	–	–	–	–
		TCRE/RB	–	–	–	–	–
	24	TBEA	–	–	–	–	–
		TCRE/RB	–	–	–	–	–
Soysal *et al.*, 2001[91]	12	TBEA	–	–	–	–	–
		RB	–	–	–	–	–
Zon-Rabelink, 2001[93]	12	TBEA	–	–	–	–	–
		RB	–	–	–	–	–
	24	TBEA	–	–	–	–	–
		RB	–	–	–	–	–

[a] These are minima – women who required repeat surgery for this type of bleeding.

normal bleeding levels and this is reported by 87% of women in the MEA group and 83% of women in the RB group. Soysal and colleagues[91] (TBEA versus RB) report 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 RB group (a mean reduction of 345). At 3 months, Brun and colleagues[96] (TBEA versus TCRE) report a score of 44 (±48) in the TBEA group (a decrease of 413) and a postoperative score of 75 (±78; a decrease of 199) in the TCRE group. In addition, 71% of the TBEA and 79% of the RB group had a bleeding score of <76. (*Table 10*). Zon-Rabelink[93] (TBEA versus RB) does not report actual PBAC scores, but states that these were significantly better for the TBEA group at 2 years ($p = 0.01$), although not at 6 or 12 months. Zon-Rabelink[93] (TBEA versus RB) also reports that there was a significantly greater reduction in bleeding scores ($p = 0.03$) at 2 years for the TBEA group than the RB group, but again does not provide the data. Zon-Rabelink[93] (TBEA versus RB) measures success by a postoperative PBAC score of <185, and 79% of women in the both groups achieved this after 1 year. After 2 years, 78% of women in the TBEA groups and 76% of women in the TCRE group had a score of <185.

Cooper and colleagues[86] (MEA versus 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 10*). 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.[97] 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 versus TCRE/RB) reports bleeding patterns in terms of the length of bleeding (more than 3 days of 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 their usual sanitary protection (at 12 months 11% MEA, 12% TCRE/RB; at 24 months 7% TBEA, 13% TCRE/RB). See *Table 11* for further details. Differences between the groups were not statistically significant.

Pellicano and colleagues[92] (TBEA versus TCRE/RB) report that "bleeding recurred" at 1 year for 5% of women undergoing TBEA and 14% of those undergoing TCRE/RB, and that at 2 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[82,86,88,92] report on postoperative dysmenorrhoea. However, none report using a validated pain score. In the trial by Cooper and colleagues[86] (MEA versus TCRE/RB), 19% of those undergoing MEA and 16% of those undergoing TCRE/RB reported that dysmenorrhoea was unchanged or worse at 12 months postoperation. This was also the case for 17% of MEA and 22% of TCRE/RB groups at 24 months' follow-up (see *Table 12*). In addition, the MEA study by Cooper and colleagues reports a postoperative pain score after 12 months of one for both treatment and control, and at 24 months of zero for MEA and one for TCRE (see *Table 12*).

In the Microsulis trial[88] (MEA versus RB), 31% of women in both trial arms reported postoperative dysmenorrhoea compared with 82 and 80% having preoperative dysmenorrhoea in the MEA and RB arms, respectively. In the trial by Meyer and colleagues,[82] 27% of those treated with TBEA and 20% of those treated with RB ablation reported that dysmenorrhoea was unchanged or worse at 12 months postoperation. At 60 months, Meyer and colleagues report that 13% of women who had undergone TBEA and 9% of those who had undergone RB had moderate to severe dysmenorrhoea. The data for 60 months were estimated from a graph in the original paper and so may be subject to inaccuracy. Pellicano and colleagues[92] report that at 12 months, 2% of women had recurrence of pain in the TBEA group compared with 14% in the TCRE and RB 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 versus RB) also report on pelvic pain that is not related to menses – it is 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 RB group report moderate to severe pain.

Bongers and colleagues[89] (TBEA versus TCRE) report that 4% of women who had TCRE underwent a repeat procedure due to

TABLE 10 *Postoperative PBAC scores – % (% ITT)*

Author/date	Length of follow-up (months)	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[86]	12	MEA	–	–	–	–	–	–	–	3 (0–8)
		TCRE/RB	–	–	–	–	–	–	–	3 (0–10)
	24	MEA	–	–	–	–	–	–	–	1 (0, 7)[a]
		TCRE/RB	–	–	–	–	–	–	–	0 (0, 7)[a]
Microsulis, 2002[88]	12	MEA	–	–	–	87 (87)	–	–	–	–
		RB	–	–	–	83 (83)	–	–	–	–
Bongers *et al.*, 2000[89]	24	TBEA	–	–	–	–	–	–	–	–
		TCRE	–	–	–	–	–	–	–	–
Brun *et al.*, 2002[96]	3	TBEA	44 ± 48	–	–	–	–	–	413 (242)	–
		TCRE	75 ± 78	–	–	–	–	–	199 (157)	–
Meyer *et al.*, 1998[82]	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[90]	1	TBEA	–	–	–	–	–	–	–	–
		TCRE	–	–	–	–	–	–	–	–
	24	TBEA	–	–	–	–	–	–	–	–
		TCRE	–	–	–	–	–	–	–	–
Pellicano *et al.*, 2002[92]	12	TBEA	–	–	–	–	–	–	–	–
		TCRE/RB	–	–	–	–	–	–	–	–
	24	TBEA	–	–	–	–	–	–	–	–
		TCRE/RB	–	–	–	–	–	–	–	–
Romer, 1998[83]	12	TBEA	–	–	–	–	–	–	–	–
		RB	–	–	–	–	–	–	–	–

continued

TABLE 10 *Postoperative PBAC scores – % (% ITT) (cont'd)*

Author/date	Length of followed-up (months)	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)
Soysal *et al.*, 2001[91]	12	TBEA	41.1 ± 29	–	–	75 (71)	–	–	343.2 ± 87	–
		RB	40.2 ± 45	–	–	79 (79)	–	–	345.5 ± 113	–
Zon–Rabelink, 2001[93]	12	TBEA	–	79 (79)	–	–	–	–	–	–
		RB	–	78 (76)	–	–	–	–	–	–
	24	TBEA	–	78 (78)	–	–	–	–	–	–
		RB	–	76 (74)	–	–	–	–	–	–

[a] Median (25th, 75th percentiles).

TABLE 11 *Postoperative bleeding patterns – % (% ITT)*

Author/date	Length of follow-up (months)	Intervention	3–7 days bleeding	>7 days bleeding	>3 days heavy bleeding	2× sanitary protection needed	Menstruation unchanged or worse	Reduction in number of women with anaemia
Cooper *et al.*, 1999[86]	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[88]	12	MEA	–	–	–	–	–	–
		RB	–	–	–	–	–	–
Bongers *et al.*, 2000[89]	24	TBEA	–	–	–	–	–	–
		TCRE	–	–	–	–	–	–
Brun *et al.*, 2002[96]	3	TBEA	–	–	–	–	–	–
		TCRE	–	–	–	–	–	–
Meyer *et al.*, 1998[82]	12	TBEA	–	–	–	–	–	~ 60 (55)
		RB	–	–	–	–	–	~ 60 (49)
	24	TBEA	–	–	–	–	–	–
		RB	–	–	–	–	–	–
	36	TBEA	–	–	–	–	–	–
		RB	–	–	–	–	–	–
Gervaise *et al.*, 1999[90]	1	TBEA	–	–	–	–	–	–
		TCRE	–	–	–	–	–	–
	24	TBEA	–	–	–	–	–	–
		TCRE	–	–	–	–	–	–
Pellicano *et al.*, 2002[92]	12	TBEA	–	–	–	–	2 (5)[a]	–
		TCRE/RB	–	–	–	–	6 (14)[a]	–
	24	TBEA	–	–	–	–	3 (8)[a]	–
		TCRE/RB	–	–	–	–	8 (19)[a]	–
Romer, 1998[83]	12	TBEA	–	–	–	–	–	–
		RB	–	–	–	–	–	–
Soysal *et al.*, 2001[91]	12	TBEA	–	–	–	–	–	–
		RB	–	–	–	–	–	–
Zon–Rabelink, 2001[93]	24	TBEA	–	–	–	–	–	–
		RB	–	–	–	–	–	–

[a] Values for "bleeding recurs".

TABLE 12 *Postoperative menstrual pain – % (% ITT)*

Author/date	Length of follow-up (months)	Intervention	Dysmenorrhoea decreased	Dysmenorrhoea same or worse	Dysmenorrhoea	Pain recurs	Mean pain score: mean, range	Mild dysmenorrhoea	Moderate dysmenorrhoea	Severe dysmenorrhoea
Cooper *et al.*, 1999[86]	12	MEA	–	21 (19)	–	–	1 (0–9)	–	–	–
		TCRE/RB	–	18 (16)	–	–	1 (0–7)	–	–	–
	24	MEA	–	18 (17)	–	–	0 (0, 6)[c]	–	–	–
		TCRE/RB	–	22 (22)	–	–	1 (0, 8)[c]	–	–	–
Microsulis, 2002[88]	12	MEA	–	–	31 (31)	–	–	–	–	–
		RB	–	–	31 (31)	–	–	–	–	–
Bongers *et al.*, 2000[89]	24	TBEA	–	–	0	–	–	–	–	–
		TCRE	–	–	4 (4)[b]	–	–	–	–	–
Brun *et al.*, 2002[96]	3	TBEA	–	–	–	–	–	–	–	–
		TCRE	–	–	–	–	–	–	–	–
Meyer *et al.*, 1998[82]	12	TBEA	70 (64)	30 (27)[a]	–	–	–	–	–	–
		RB	75 (62)	25 (20)[a]	–	–	–	–	–	–
	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[90]	1	TBEA	–	–	–	–	–	–	–	–
		TCRE	–	–	–	–	–	–	–	–
	24	TBEA	–	–	–	–	–	–	–	–
		TCRE	–	–	–	–	–	–	–	–
Pellicano *et al.*, 2002[92]	12	TBEA	–	–	–	1 (2)	–	–	–	–
		TCRE/RB	–	–	–	7 (14)	–	–	–	–
	24	TBEA	–	–	–	2 (4)	–	–	–	–
		TCRE/RB	–	–	–	9 (18)	–	–	–	–

continued

TABLE 12 *Postoperative menstrual pain – % (% ITT) (cont'd)*

Author/date	Length of follow-up (months)	Intervention	Dysmenor-rhoea decreased	Dysmenor-rhoea same or worse	Dysmenor-rhoea	Pain recurs	Mean pain score: mean, range	Mild dysmenor-rhoea	Moderate dysmenor-rhoea	Severe dysmenor-rhoea
Romer, 1998[83]	12	TBEA	–	–	–	–	–	–	–	–
		RB	–	–	–	–	–	–	–	–
Soysal *et al.*, 2001[91]	12	TBEA	–	–	–	–	–	–	–	–
		RB	–	–	–	–	–	–	–	–
Zon-Rabelink, 2001[93]	24	TBEA	–	–	–	–	–	–	–	–
		RB	–	–	–	–	–	–	–	–

[a] Calculated from given categories "Dysmenorrhoea unchanged" and "Dysmenorrhoea increased".
[b] Minimum – women undergoing repeat surgery for this.
[c] Median (25th, 75th percentile).

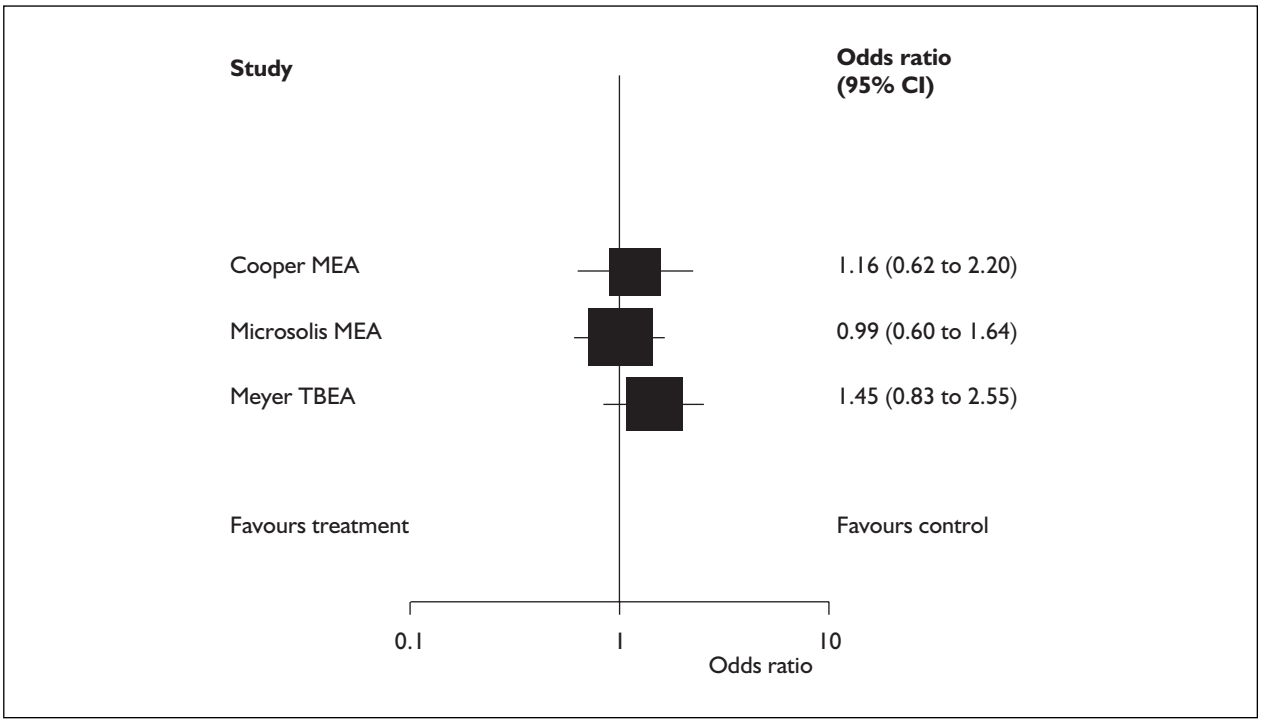


FIGURE 11 *Forest plot of dysmenorrhoea 12 months postoperation second-generation versus first-generation EA (random effects model, results not pooled)*

dysmenorrhoea; however it is not stated whether of not other women suffered dysmenorrhoea who did not opt for further surgery.

Figure 11 shows the dysmenorrhoea rates at 12 months for first-generation versus second-generation EA techniques. The data points have been produced from the numbers describing dysmenorrhoea as the same or worse as pre-operatively. In all cases the CIs cross the central line indicating no statistically significant differences between the groups. Study results have not been combined owing to clinical heterogeneity between the trials.

PMS symptoms

Two studies[82,86] report postoperative PMS symptoms although in different ways. The study by Cooper and colleagues[86] (MEA versus TCRE/RB) reports prevalence of individual symptoms of PMS at 12 months postoperation: bloating, breast discomfort, irritability, headaches and depression (see *Table 13*). There was no statistically significant difference between the groups for any PMS measures. Meyer and colleagues[82] (TBEA versus RB) report the number of women who do not have PMS symptoms at 12, 24 and 36 months postoperation, and the number of women who have moderate or severe PMS at 12 (TBEA 30%, RB 24%) and 24 months (TBEA 25%, RB 22%). There were no statistically significant differences in PMS symptoms between the study arms (*Table 13*).

Satisfaction with treatment

Two studies, Brun and colleagues[96] (TBEA versus TCRE) and Soysal and colleagues[91] (TBEA versus RB), did not report patient satisfaction. The others use slightly different measures of satisfaction.

The study by Cooper and colleagues[86] (MEA versus 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 RB were totally or generally satisfied. Differences between groups were not statistically significant (*Table 14*). 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 versus TCRE/RB) also report that 70% of women in both groups regarded their treatment as effecting a cure or

TABLE 13 *Postoperative PMS symptoms – % (% ITT)*

Author/date	Length of follow-up (months)	Intervention	Bloating	Breast discomfort	Irritability	Headaches	Depression	No PMS	PMS moderate severe
Cooper *et al.*, 1999[86]	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[88]	12	MEA	–	–	–	–	–	–	–
		RB	–	–	–	–	–	–	–
Bongers *et al.*, 2000[89]	24	TBEA	–	–	–	–	–	–	–
		TCRE	–	–	–	–	–	–	–
Brun *et al.*, 2002[96]	3	TBEA	–	–	–	–	–	–	–
		TCRE	–	–	–	–	–	–	–
Meyer *et al.*,1998[82]	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[90]	1	TBEA	–	–	–	–	–	–	–
		TCRE	–	–	–	–	–	–	–
	24	TBEA	–	–	–	–	–	–	–
		TCRE	–	–	–	–	–	–	–
Pellicano *et al.*, 2002[92]	12	TBEA	–	–	–	–	–	–	–
		TCRE/RB	–	–	–	–	–	–	–
	24	TBEA	–	–	–	–	–	–	–
		TCRE/RB	–	–	–	–	–	–	–
Romer, 1998[93]	12	TBEA	–	–	–	–	–	–	–
		RB	–	–	–	–	–	–	–
Soysal *et al.*, 2001[91]	12	TBEA	–	–	–	–	–	–	–
		RB	–	–	–	–	–	–	–
Zon-Rabelink, 2001[93]	24	TBEA	–	–	–	–	–	–	–
		RB	–	–	–	–	–	–	–

TABLE 14 *Satisfaction with treatment and its acceptability – % (% ITT)*

Author/date	Length of follow-up (months)	Intervention	Very/ perfectly satisfied	Satisfied	Not very satisfied no effect	Not satisfied/ complaints it is worse	Excellent	Good	Moderate	Totally or generally satisfied	Cure or acceptable improvement	Treatment acceptable	Menstrual loss acceptable	Recommend treatment?
Cooper *et al.*, 1999[86]	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[88]	12	MEA	–	98 (98)[a]	–	2 (2)	–	–	–	–	–	99 (99)[b]	–	–
		RB	–	99 (99)[a]	–	1 (1)	–	–	–	–	–	100 (100)[b]	–	–
Bongers *et al.*, 2000[89]	3	TBEA	66 (66)	20 (20)	10 (10)	4 (4)	–	–	–	–	–	–	–	–
		TCRE	80 (80)	11 (11)	8 (8)	1 (1)	–	–	–	–	–	–	–	–
	6	TBEA	63 (51)	10 (8)	16 (13)	11 (9)	–	–	–	–	–	–	–	–
		TCRE	57 (52)	7 (7)	35 (32)	1 (1)	–	–	–	–	–	–	–	–
	12	TBEA	63 (52)	13 (10)	10 (8)	14 (12)	–	–	–	–	–	–	–	–
		TCRE	57 (52)	2 (1)	37 (28)	9 (7)	–	–	–	–	–	–	–	–
	24	TBEA	60 (36)	4 (3)	11 (6)	25 (16)	–	–	–	–	–	–	–	–
		TCRE	43 (27)	6 (4)	17 (11)	34 (21)	–	–	–	–	–	–	–	–
Brun *et al.*, 2002[96]	3	TBEA	–	–	–	–	–	–	–	–	–	–	–	–
		TCRE	–	–	–	–	–	–	–	–	–	–	–	–
Meyer *et al.*, 1998[82]	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)	–	–	–	–	–	–	–	–	–	–

continued

TABLE 14 *Satisfaction with treatment and its acceptability – % (% ITT) (cont'd)*

Author/date	Length of follow-up (months)	Intervention	Very/ perfectly satisfied	Satisfied	Not very satisfied no effect	Not satisfied/ complaints it is worse	Excellent	Good	Moderate	Totally or generally satisfied	Cure or acceptable improvement	Treatment acceptable	Menstrual loss acceptable	Recommend treatment?
Gervaise *et al.*, 1999[90]	1	TBEA	–	–	–	–	–	—	–	–	–	–	–	–
		TCRE	–	–	–	–	–	—	–	–	–	–	–	–
	24	TBEA	–	–	–	–	–	–	–	–	–	–	–	–
		TCRE	–	–	–	–	–	–	–	–	–	–	–	–
Pellicano *et al.*, 2002[92]	3	TBEA	–	–	–	–	27 (59)	13 (28)	0	–	–	–	–	–
		TCRE/RB	–	–	–	–	21 (42)	12 (24)	9 (18)	–	–	–	–	–
	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[83]	12	TBEA	–	100 (100)	–	–	–	–	–	–	–	–	–	–
		RB	–	100 (100)	–	–	–	–	–	–	–	–	–	–
Soysal *et al.*, 2001[91]	12	TBEA	–	–	33 (31)	–	–	–	–	–	–	–	–	–
		RB	–	–	39 (39)	–	–	–	–	–	–	–	–	–
Zon-Rabelink, 2001[93]	24	TBEA	–	80 (80)	–	–	–	–	–	–	–	–	–	–
		RB	–	75 (73)	–	–	–	–	–	–	–	–	–	–

[a] "Very satisfied" and "satisfied" combined.
[b] "Acceptance of operation positive".

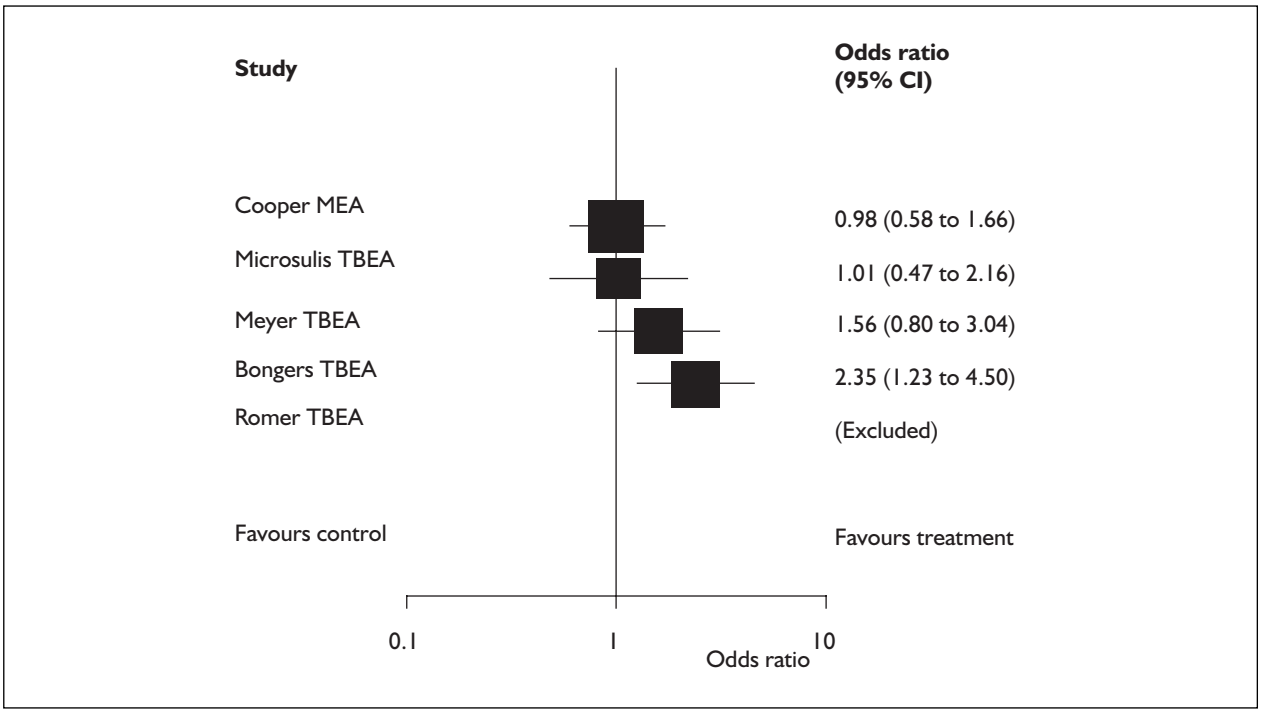


FIGURE 12 *Forest plot of satisfaction at 12 months' follow-up – first-generation versus second-generation EA techniques (random effects model, results not pooled)*

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 14*).

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

Bongers and colleagues[89] (TBEA versus TCRE) rated satisfaction on a four-point scale: "perfectly satisfactory", satisfactory", "no treatment effect" and "complaints worsen". At 12 months they report that 62% of women undergoing TBEA and 53% of those undergoing TCRE were perfectly satisfied or satisfied. At 24 months the figures were 39 and 31%, respectively.

Women in the trial by Meyer and colleagues[82] (TBEA versus RB) were rated as "very satisfied", "satisfied" or "not satisfied" with their treatment at all four follow-up points; 87% 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, the 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 14*). 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[92] (TBEA versus TCRE/RB) found that satisfaction was "excellent" at 12 months for 43% of women undergoing TBEA and 24% of women undergoing TCRE and RB. These figures were 35 and 4%, respectively, at 24 months. Differences between the groups were statistically significant.

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

Soysal and colleagues[91] (TBEA versus RB) report that 31% of those undergoing TBEA and 39% of those undergoing RB 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"

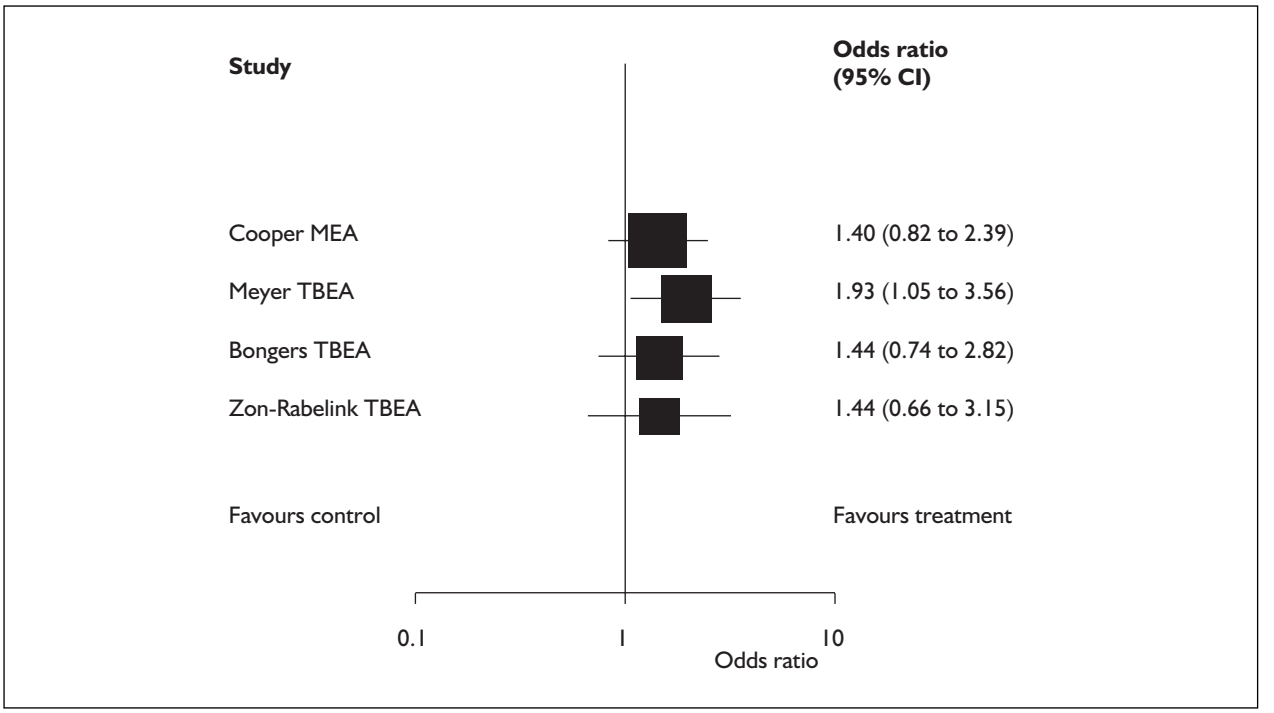


FIGURE 13 *Forest plot of satisfaction at 24 months' follow-up – first-generation versus second-generation EA techniques (random effects model, results not pooled)*

categories, although this is not made clear. Differences between the two techniques were not statistically significant (*Table 14*).

Zon-Rabelink[93] (TBEA versus RB) reports that 80% of women who had undergone TBEA and 75% of those who had undergone RB ablation were satisfied after 2 years. It is not stated how this was measured. This difference was not significant.

Figures 12 and *13* illustrate satisfaction rates at 12 and 24 months for first-generation versus second-generation EA techniques. The data points were produced by combining the categories for "perfectly satisfactory" and "satisfactory" in the study by Bongers and colleagues,[89] "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 12 months, on this dichotomous measure, Bongers and colleagues[89] show a statistically significant effect on satisfaction in favour of TBEA, but this is not seen at 24 months. At 24 months, the Meyer study[82] shows satisfaction to be just significantly in favour of second-generation techniques, but this is not seen at 12 months. Other studies do not detect such a difference. The study results have not been statistically combined owing to clinical heterogeneity between the trials.

QoL

Table 15 shows various aspects of QoL reported in the included studies, of which only two used measures relating to QoL.[82,86] The trial by Cooper and colleagues[86] (MEA versus TCRE/RB) reports that work absence of 2 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 RB still experiencing such work absences at 12 months postoperation.

Meyer and colleagues[82] (TBEA versus RB) report a significant postoperative 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 15*). In addition, whereas two-thirds of women reported that HMB 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 15* for more details.

Only the MEA study by Cooper and colleagues[86] used a QoL instrument validated in HMB, the

TABLE 15 *Pre- and postoperative impact of symptoms on life – % (% ITT)*

Author/date	Length of follow-up (months)	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	
			Preop.	Postop.	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.
Cooper *et al.*, 1999[86]	12	MEA	–	–	36 (36)	3 (3)	–	–	–	–	–	–
		TCRE/RB	–	–	37 (37)	7 (6)	–	–	–	–	–	–
	24	MEA	–	–	–	–	–	–	–	–	–	–
		TCRE/RB	–	–	–	–	–	–	–	–	–	–
Microsulis, 2002[88]	12	MEA	–	–	–	–	–	–	–	–	–	–
		RB	–	–	–	–	–	–	–	–	–	–
Bongers *et al.*, 2000[89]	24	TBEA	–	–	–	–	–	–	–	–	–	–
		TCRE	–	–	–	–	–	–	–	–	–	–
Brun *et al.*, 2002[96]	3	TBEA	–	–	–	–	–	–	–	–	–	–
		TCRE	–	–	–	–	–	–	–	–	–	–
Meyer *et al.*, 1998[82]	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[90]	1	TBEA	–	–	–	–	–	–	–	–	–	–
		TCRE	–	–	–	–	–	–	–	–	–	–
	24	TBEA	–	–	–	–	–	–	–	–	–	–
		TCRE	–	–	–	–	–	–	–	–	–	–
Pellicano *et al.*, 2002[92]	3	TBEA	–	–	–	–	–	–	–	–	–	–
		TCRE/RB	–	–	–	–	–	–	–	–	–	–
	12	TBEA	–	–	–	–	–	–	–	–	–	–
		TCRE/RB	–	–	–	–	–	–	–	–	–	–
	24	TBEA	–	–	–	–	–	–	–	–	–	–
		RB	–	–	–	–	–	–	–	–	–	–
Romer, 1998[83]	12	TBEA	–	–	–	–	–	–	–	–	–	–
		RB	–	–	–	–	–	–	–	–	–	–
Soysal *et al.*, 2001[91]	12	TBEA	–	–	–	–	–	–	–	–	–	–
		RB	–	–	–	–	–	–	–	–	–	–
Zon-Rabelink, 2001[93]	24	TBEA	–	–	–	–	–	–	–	–	–	–
		RB	–	–	–	–	–	–	–	–	–	–

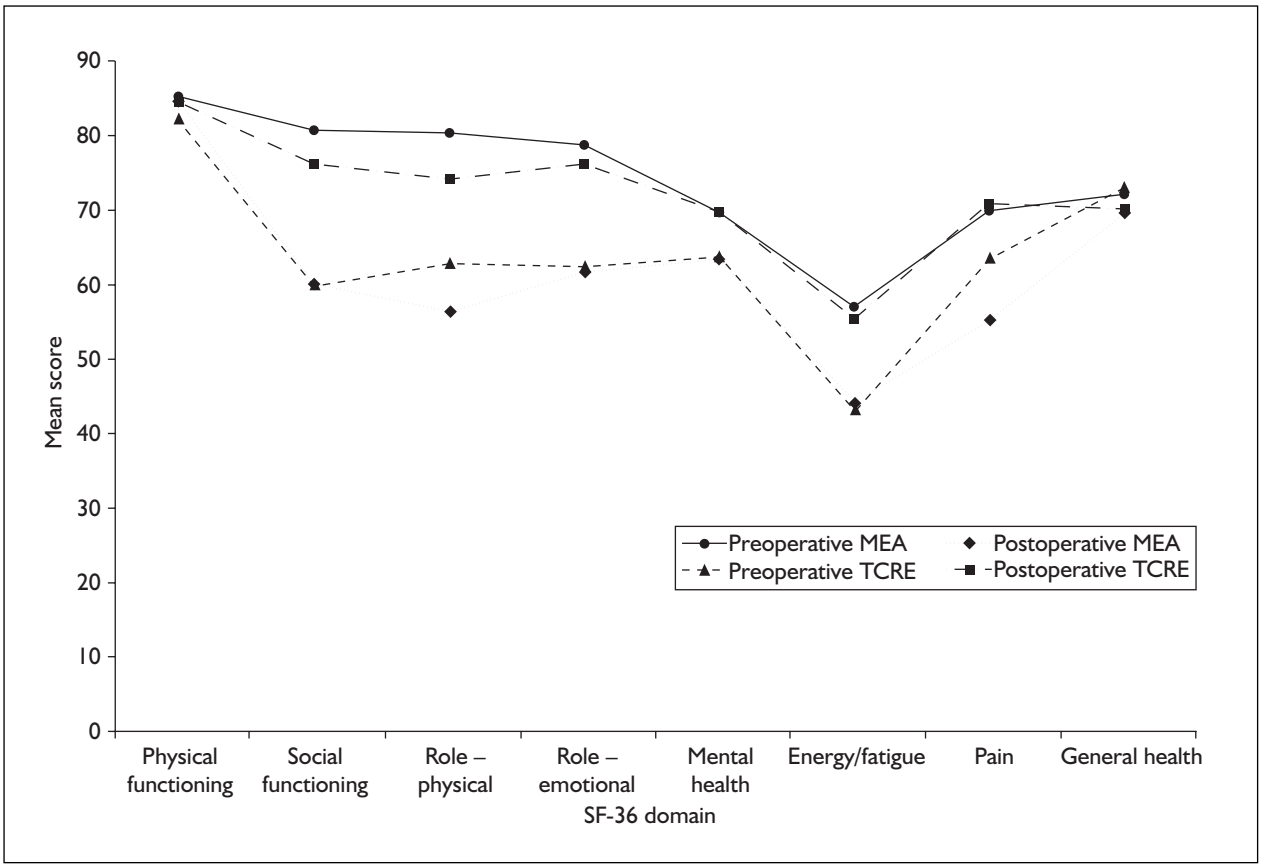


FIGURE 14 *Mean SF-36 scores pre- and postoperation from Cooper* et al.*, 1999*[86]

TABLE 16 *Data used in* Figure 14*: SF-36 scores*

Item	Preop. MEA	Change postop. MEA	Postop. MEA	Preop. 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

SF-36 (see *Figure 14* and *Table 16*). 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 covariance showed that the only difference between the groups was on physical role, in which there was greater improvement with MEA than TCRE.

Operation details

Table 17 reports the results for duration of operations. Two studies[82,90] report on the percentage of operations that took <30 minutes to perform. For TBEA this was 65–100% and for TCRE and RB 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 RB procedures took >50 minutes (difference significant, $p < 0.05$).

TABLE 17 *Operation details*

Author/date	Intervention	<30 minutes % (% ITT)	>50 minutes % (% ITT)	Mean (SD) operating time (minutes)	Mean (SD) theatre time (minutes)	Mean (SD) post-operative stay	Fully recovered in 4 weeks: % (% ITT)	Return to normal domestic activities (days)	Return to work (days)	Resumption of sexual activity (days)
Cooper *et al.*, 1999[86]	MEA	–	–	11.4 (10.5)	20.9 (11.3)	13.4 (17.6) hours	72 (67)	–	–	–
	TCRE/RB	–	–	15.0 (7.2)	26.2 (8.7)	16.7 (21.2) hours	66 (61)	–	–	–
Microsulis, 2002[88]	MEA	–	–	3.45 (1.02)[a]	41.7 (25.4)[b]	–	–	–	–	–
	RB	–	–	20.26 (15.6)[a]	50.0 (23.0)[b]	–	–	–	–	–
Bongers *et al.*, 2000[89]	TBEA	–	–	–	–	–	–	–	–	–
	TCRE	–	–	–	–	–	–	–	–	–
Brun *et al.*, 2002[96]	TBEA	–	–	–	–	–	–	–	–	–
	TCRE	–	–	–	–	–	–	–	–	–
Meyer *et al.*, 1998[82]	TBEA	71 (65)	2 (2)	–	–	–	–	–	–	–
	RB	27 (24)	18 (14)	–	–	–	–	–	–	–
Gervaise *et al.*, 1999[90]	TBEA	100 (100)	–	20.3	–	–	–	–	–	–
	TCRE	53 (53)	–	44.8	–	–	–	–	–	–
Pellicano *et al.*, 2002[92]	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[83]	TBEA	–	–	–	–	–	–	–	–	–
	RB	–	–	–	–	–	–	–	–	–
Soysal *et al.*, 2001[91]	TBEA	–	–	11.5 (±0.8)	–	–	–	–	–	–
	RB	–	–	37.3 (±7.5)	–	–	–	–	–	–
Zon-Rabelink, 2001[93]	TBEA	–	–	–	–	–	–	–	–	–
	RB	–	–	–	–	–	–	–	–	–

[a] Given as "anaesthetic time" and excluding one centre whose patients all had GA.
[b] Given as "treatment time".

Mean operating time is reported in four studies, although the approaches to measurement varied.[86,90–92] A mean theatre time is also given by Cooper and colleagues[86] (MEA versus 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 versus TCRE) as operating time is what Cooper and colleagues refer to as theatre time (see *Table 17*). For TCRE and RB, mean operating time ranges from 15.0 to 44.8 minutes (median 37.3 minutes) The Microsulis study[88] (MEA versus RB) reports an "anaesthetic time" of 41.7 minutes for MEA and 50 minutes for RB and a "treatment time" of 3.45 minutes for MEA and 20.26 minutes for RB.

Differences between procedure times were significant in all studies at the $p = 0.0001$ level for Cooper and colleagues[86] (MEA versus TCRE/RB) and Soysal and colleagues[91] (TBEA versus RB), at 0.009 for the Microsulis study (MEA versus RB) and at the 0.05 level for the study by Gervaise and colleagues[90] (TBEA versus TCRE). Zon-Rabelink[93] (TBEA versus RB) reports that the mean operating time for TBEA was significantly shorter than that for RB ($p < 0.001$) but does not provide the data.

Cooper and colleagues[86] (MEA versus TCRE/RB) also report on the mean postoperative stay and the percentage of women who were fully recovered in 4 weeks. Differences between the groups were not statistically significant.

Bongers and colleagues[89] (TBEA versus TCRE), Brun and colleagues[96] (TBEA versus RB) and Romer[83] (TBEA versus RB) do not give operating times.

Adverse effects

The Microsulis study,[88] Brun and colleagues[96] and Romer[83] did not report adverse effects of treatment. *Tables 18* and *19* show intraoperative and postoperative adverse effects reported in the other trials.

Only the trial by Cooper and colleagues[86] (MEA versus 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] and the TBEA trials by Brun and colleagues[96] reported any intraoperative adverse effects with second-generation techniques; in each trial one women was affected. Adverse effects were reported in 1% of MEAs (one blunt uterine perforation) by Cooper and colleagues[86] and in 3% of TBEA procedures (one cervical burn) by Brun and colleagues.[96] TCRE and RB operations resulted in between 0 and 27% (median 5%) intraoperative adverse effects; these included fluid overload, cervical laceration, uterine perforation and haemorrhage (*Table 18*).

Zon-Rabelink[93] (TBEA versus TCRE) does not give the numbers of adverse effects occurring, but lists those experienced by women in the RB group. He also states that significantly more postoperative pain relief was required by women who had undergone TBEA than those who had undergone RB ($p = 0.01$), but does not give data.

The recording of postoperative adverse effects may be affected both by length of follow-up and LTFU. 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[82,90] 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,[92] one woman each in the TBEA and TCRE/RB group (3%) was reported to have CIN grade one at 2 years postablation procedure. This is the only trial reporting the outcomes of postoperative cervical smears.

Zon-Rabelink[93] (TBEA versus RB) reports that there were no complaints in 95% of women who had undergone TBEA and 97% of women who had undergone RB ablation at 6 weeks of follow-up.

Haemorrhage and pain are not reported in all trials. Haemorrhage was reported after 2% of TBEA procedures as reported by Brun and colleagues[96] and after 0–12% of TCRE/RB procedures.

Three studies of TBEA report postoperative endometritis, occurring in 0–4% (median 2%) after TBEA and 1–4% (median 2%) after TCRE and RB. Two studies[82,91] report postoperative haematometra, after 0–2% of TBA procedures and 1–4% of RB procedures. In addition, one study[82] reports a single case of UTI in the TBEA group and postablation sterilisation syndrome in the RB group (*Table 18*).

TABLE 18 *Intraoperative adverse effects – number (%)*

Author/date	Intervention	ITT (no. reported on)	Procedure abandoned	Equipment failure	Total intraoperative	Fluid overload	Cervical laceration/ burn	Uterine perforation/ laceration	Haemorrhage	Electrolyte imbalance
Cooper *et al.*, 1999[86]	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[88]	MEA	215 (215)	–	–	–	–	–	–	–	–
	RB	107 (107)	–	–	–	–	–	–	–	–
Bongers *et al.*, 2000[89]	TBEA	77	8 (10)	–	0	0	–	–	–	–
	TCRE	75	13 (17)	–	21 (27)	20 (26)[b]	–	1 (1)	–	–
Brun *et al.*, 2002[96]	TBEA	21 (21)[a]	–	–	1 (3)	–	1 (3)	–	–	–
	TCRE	29 (29)[a]	–	–	0	–	–	–	–	–
Meyer *et al.*, 1998[82]	TBEA	134 (125)	–	–	0	0	0	0	0	–
	RB	126 (114)	–	–	4 (3)	2 (1)	1 (1)	1 (1)	0	–
Gervaise *et al.*, 1999[90]	TBEA	73 (73)	–	–	0	0	0	0	0	–
	TCRE	74 (74)	–	–	0	0	0	0	0	–
Pellicano *et al.*, 2002[92]	TBEA	40 (46)	–	–	0	0	0	0	0	–
	TCRE/RB	42 (50)	–	–	8 (19)	5 (12)	1 (2)	2 (5)[c]	0	–
Romer, 1998[83]	TBEA	10 (10)	–	–	–	–	–	–	–	–
	RB	10 (10)	–	–	–	–	–	–	–	–
Soysal *et al.*, 2001[91]	TBEA	48 (45)	–	–	0	0	0	0	0	–
	RB	48 (48)	–	–	5 (10)	2 (4)	1 (2)	0	0	–
Zon-Rabelink, 2001[93]	TBEA	77 (77)	–	–	0	0	0	0	0	0
	RB	62 (60)	–	–	–	No	Yes	Yes	No	Yes

[a] The patient from the Brun *et al.* study was in fact LTFU, but it is not stated to which group this woman was allocated so ITT is not possible.
[b] 3 (4%) >2000 ml intravasation, 20 (26%) >1000 ml intravasation.
[c] Both of these patients had an emergency conversion to hysterectomy at the time of the procedure owing to uterine perforation.

TABLE 19 *Postoperative adverse effects – number (%)*

Author/date	Length of follow-up (months)	Intervention	Total post-operative (cumulative)	Endo-metritis	UTI	Haema-tometra	Urinary inconti-nence	Fever	Haem-orrhage	Pain	Sympto-matic hydro-salpinx	Preg-nancy	CIN grade I
Cooper *et al.*, 1999[86]	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[88]	12	MEA, *n* = 215	–	–	–	–	–	–	–	–	–	–	–
		RB, *n* = 107	–	–	–	–	–	–	–	–	–	–	–
Bongers *et al.*, 2000[89]	24	TBEA, *n* = 77	–	–	–	–	–	–	–	–	–	–	–
		TCRE, *n* = 75	–	–	–	–	–	–	–	–	–	–	–
Brun *et al.*, 2002[96]	3	TBEA, *n* = 29	–	–	–	–	–	–	–	–	–	–	–
		TCRE, *n* = 21	–	–	–	–	–	–	–	–	–	–	–
Meyer *et al.*, 1998[82]	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 *et al.*, 1999[90]	24	TBEA, *n* = 44	1 (2)	0	–	–	–	–	–	–	–	1 (2)	
		TCRE, *n* = 47	2 (4)	2 (4)	–	–	–	–	–	–	–	0	–
Pellicano *et al.*, 2002[92]	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[83]	12	TBEA, *n* = 10	–	–	–	–	–		–	–	–	–	–
		RB, *n* = 10	–	–	–	–	–		–	–	–	–	–
Soysal *et al.*, 2001[91]	12	TBEA, *n* = 45	3 (7)	2 (4)	–	1 (2)	–		–	–	–	–	–
		RB, *n* = 48	3 (6)	1 (2)	–	2 (4)	–		–	–	–	–	–
Zon-Rabelink, 2001[93]	12	TBEA, *n* = 77	–	–	–	–	–	–	–	–	–	–	–
		RB, *n* = 60	–	–	–	–	–	–	–	–	–	–	–

In addition, Pellicano *et al.*[92] report postoperational vaginal bleeding for a mean of 7.8 days (±1) in the TCRE groups and 5.2 days (±1.8) in the TVBEA group. Visual analogue score (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 7 days, TCRE 0, TBEA 0

TABLE 20 *Repeat surgery – number (%) [ITT %]*

Author/date	Length of follow-up (months)	Intervention	Total repeat surgery	Hysterectomy	TCRE	Other ablation
Cooper *et al.*, 1999[86]	12	MEA, *n* = 116	9 (9) [8]	8 (7) [6][a]	1 (1) [1][b]	1 (1) [1]
		TCRE/RB, *n* = 124	11 (9) [8]	11 (9) [8][a]	–	0[c]
	24	MEA, *n* = 120	–	–	–	–
		TCRE/RB, *n* = 129	–	–	–	–
Microsulis, 2002[88]	12	MEA, *n* = 215	1 (<1) [<1]	1 (<1) [<1]	0	0
		RB, *n* = 107	1 (1) [1]	1 (1) [1]	0	0
Bongers *et al.*, 2000[89]	12	TBEA, *n* = 77?	8 (10) [10]	8 (10) [10]	–	–
		TCRE, *n* = 75?	16 (21) [21]	12 (16) [16]	4 (5) [5]	–
	24	TBEA, *n* = 77?	9 (12) [12]	9 (12) [12]	–	–
		TCRE, *n* = 75?	19 (36) [36]	15 (20) [20]	4 (5) [5]	–
Brun *et al.*, 2002[96]	3	TBEA, *n* = 21	–	–	–	–
		TCRE, *n* = 29	–	–	–	–
Meyer *et al.*, 1998[82]	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[d] (16) [7]	7 (11) [5]	2 (3) [1]	–
Gervaise *et al.*, 1999[90]	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[92]	12	TBEA, *n* = 37	2 (5) [4][e]	–	–	–
		TCRE/RB, *n* = 38	4 (10) [8]	–	–	–
	24	TBEA, *n* = 35	2 (6) [4]	–	–	–
		TCRE/RB, *n* = 33	5 (15) [10]	–	–	–
Romer, 1998[83]	12	TBEA, *n* = 10	0	–	–	–
		RB, *n* = 10	0	–	–	–
Soysal *et al.*, 2001[91]	12	TBEA, *n* = 45	4 (9) [8]	4 (9) [8]	–	–
		RB, *n* = 48	4 (8) [8]	4 (8) [8]	–	–
Zon-Rabelink, 2001[93]	24	TBEA, *n* = 77	–	–	–	–
		RB, *n* = 60	–	–	–	–

[a] In addition, 1 woman allocated to each group had hysterectomy as primary procedure.
[b] In addition, 4 women had a TCRE as a primary procedure instead of MEA, owing to equipment failure.
[c] 1 woman had MEA as her primary procedure having been allocated to TCRE group.
[d] Includes 1 D&C.
[e] In addition, 2 women in the TBEA group underwent hysterectomy at the time of the primary procedure (see *Table 18*).

Postablation-tubal sterilisation 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[98] found an incidence of symptomatic cornual hematometra of 10% ($n = 5$) on examination with ultrasound and magnetic resonance imaging (MRI). Of these, two (4%) had cornual hematometra and three (6%) had postablation tubal sterilisation syndrome.

Table 20 shows the percentage of women who subsequently underwent a repeat procedure of EA or hysterectomy at different follow-up times. In order to report the most conservative success rate, percentages based on the number of women

TABLE 21 *Immediate complications reported in the MISTLETOE study – number (%)*

Complication	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)

available for follow-up are reported in the text, and shown in the table in parentheses. Data were on an ITT 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 versus TCRE/RB) reported one (1%) TCRE procedure in the intervention arm. Meyer and colleagues[82] (TBEA versus RB) reported one RB procedure in the intervention arm at 36 months. Neither of these studies had repeat TCRE/RB in the control arm. By contrast, Bongers and colleagues[89] (TBEA versus TCRE) reports four (5%) repeat TCREs in the control arm and none in the TBEA arm by 24 months. At 60 months' follow-up, Meyer and colleagues[82] reported that two women in each of the intervention (TBEA 3%) and control arm (RB 3%) had undergone repeat ablation.

At 24 months, Gervaise and colleagues[90] (TBEA versus TCRE) report that five (7%) patients in the control arm had a repeat TCRE.

Hysterectomy

By 12 months, <1–10% (median 6%) of women had had hysterectomy following initial second-generation ablation. At 24 months, this was the case for 8–12% (median 10%) of women. At 36 months, Meyer and colleagues[82] (TBEA versus 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, 2–16% (median 8%) had also undergone hysterectomy at 12 months. At 24 months, the figure was 1–20% (median 8%), and at 36 months' follow-up 14% had also had a hysterectomy. Meyer and colleagues[82] (TBEA versus RB) report that 14% of women initially undergoing RB ablation had also had a hysterectomy, as had 11% of women at 60 months.

Pellicano and colleagues[92] (TBEA versus TCRE/RB) only report a total repeat surgery figure, that is, not divided by type of procedure. By 12 months, 5% of women undergoing TBEA and 10% of women undergoing TCRE and RB 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[93] reports the percentage of women who had had "intervention therapy" at 2 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.

Adverse effect data from other sources

Large observational studies provide the most comprehensive information about adverse effects, especially where events are rare. The MISTLETOE study[54,101] (Minimally Invasive Surgical Techniques – Laser, Endothermal or Endoscopic) collected data on 10,686 cases of EA from 300 UK NHS hospitals from April 1993 to October 1994. These included 4291 cases of combined techniques (TCRE with loop and RB), 3776 of loop (TCRE) and 650 of RB ablation that will be reported here. MISTLETOE also reports on 1792 laser, 140 radiofrequency and 36 cryoablation treatments that are not reported here. Overall rates have been recalculated to included TCRE and RB only.

Immediate complications are shown in *Table 21*. The data refer to the number of complications. Some women experienced more than one complication.

TABLE 22 *Adverse effects in primary and repeat first-generation ablations*[70]

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

TABLE 23 *Adverse effects of MEA in 1433 cases*[72]

Type	Adverse effect	No.	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

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

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

The MISTLETOE paper reports 10 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 3 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 perioperative 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 with 2.05% of primary ablation ($p = 0.006$). Actual figures are shown in *Table 22*.

No national audit of second-generation techniques has been undertaken. However, a prospective series of 1433 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 23*.

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 1 year;[101] 12 months' data were available for 163 women. No intraoperative complications were reported. Minor postoperative ablations were reported as one case of cystitis, six cases of febrile morbidity (diagnosed as low-grade endometritis), two haematometra and one hospitalisation for pain. The minor complication rate was therefore 3% (30/1000).

A 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 in *Table 24*.

TABLE 24 *Complications with TBEA reported by Rogerson and Duffy*[71]

Intraoperative complication	Incidence (%) (*n* = 5859)	Rate/1000
Haemorrhage	0.03	0.003
Uterine perforation	0.17	0.017
Cardiovascular system/respiratory complication	0.02	0.002
Visceral burn	0.02	0.002
Equipment failure	0.2	0.02
Total (excluding equipment failure)	0.23	0.023

Caution should be exercised when 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 4: Effectiveness

- Two systematic reviews and 10 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 eight of TBEA and the comparators were either TCRE or RB or combined technique.
- Overall, there were few significant differences between the outcomes of first- and second-generation techniques including bleeding, satisfaction and QoL measures and repeat surgery rates. Significant differences were reported most often by Pellicano and colleagues, which was a relatively poor quality study.
- Second-generation techniques had significantly shorter operating and theatre times.
- There appear to be fewer perioperative adverse effects with second-generation techniques and postoperative 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 with hysterectomy, TCRE and RB 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 retreatment leads this difference to decrease over time. Satisfaction with hysterectomy is initially higher, but there is no significant difference after 2 years.

Economic evaluation of microwave and thermal balloon ablation

Assumptions used in the model

Table 25 shows the assumptions for transition probabilities between states, costs of procedures, discounting and utilities used in the model and their source. Many of these values may be subject to uncertainty, for example the utility values used have been taken from the only published cost–utility study found to have elicited values from women with menorrhagia. However, as discussed in the section 'Measuring the impact of HMB' (p. 4), these values may be problematic. We have addressed such uncertainty through sensitivity analysis (see *Table 33*). Similarly, estimates of re-intervention rates are hampered by short-term follow-up and the different ways in which different studies report postoperative bleeding. Again, sensitivity analysis has been performed to explore the impact of uncertainty in these parameters.

Costs

Details of resource use that informed the calculation of costs in the model are shown in *Table 26*. As seen in *Table 17*, the operating and theatre times are not clearly reported in the trials included in this review. Operating times have therefore been examined in sensitivity analysis (see *Table 33*) as this is likely to impact on the overall estimated costs. Costs of managing complications have not been included and this is a limitation of the model. This may underestimate the actual costs of procedures, hysterectomy in particular.

Costs of the equipment for microwave and thermal balloon ablation are shown in *Table 27*. 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, the list price is £375 per treatment.

TABLE 25 *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 years 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, 2001[73] Table 5, Q07	UK data set
Complications after TCRE + RB	0.0398	MISTLETOE study[54]	Large UK observational study
Death after TCRE + RB (direct cause)	0.0002	MISTLETOE study[54]	Large UK observational study
Complications after RB	0.0200	MISTLETOE study[54]	Large UK observational study
Death after RB (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 24*	European survey of complications in 5800 women
Death after TBEA (direct cause)	0	Adverse effect evidence in this report (*Tables 17* and *86*)	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-operative)[90]	Controlled trial. Only data available for immediate postoperative failure rates
TBEA treatment failure years 2 and 3	0.1	See *Table 20*	RCTs in this assessment
Proportion of women with recurrent menorrhagia who undergo hysterectomy	0.6	5-year follow-up of 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 of 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 RB ablation	Twice the rate after 1st ablation	Maclean-Fraser *et al.*, [70] 2002 and professional estimate	Comparative case series study of primary and repeat ablations. Only data on complications after repeat ablation

continued

TABLE 25 *Assumptions used in the model (cont'd)*

Assumptions	Value	Source	Justification for source
Death after repeat TCRE/RB ablation	0.0003	MISTLETOE study[54]	Large UK audit
First-year return of menorrhagia post-TCRE/RB	0.11	Effectiveness data median at 12 months (*Table 9*)	RCT data, best available evidence
Second- and third-year return of menorrhagia following TCRE/RB	0.1	Effectiveness data median at 24 months (*Table 9*) plus repeat surgery rate (*Table 20*)	RCT data, best available evidence
First-year return of menorrhagia post-TBEA/MEA	0.11	Effectiveness data median at 12 months (*Table 9*)	RCT data, best available evidence
Second- and third-year return of menorrhagia following TBEA/MEA	0.1	Effectiveness data median at 24 months (*Table 9*) plus repeat surgery rate (*Table 20*)	RCT data, best available evidence
Discount rates			
Costs	6%	NICE	As recommended by NICE
Benefits	1.5%	NICE	As recommended by NICE
Health state utilities			
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	Sculpher, 1998[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	Sculpher, 1998[30]	Median value based on interviews with 60 women with menorrhagia
MEA/convalescence after MEA	0.85	Sculpher, 1998[30]	Convalescent states postablation assumed to be the same for all types of ablation. Based on the Sculpher score for TCRE[30]
TBEA/convalescence after TBEA	0.85	Sculpher, 1998[30]	Convalescent states postablation assumed to be the same for all types of ablation. Based on the Sculpher score for TCRE[30]
TCRE and RB/convalescence after TCRE and RB	0.85	Sculpher, 1998[30]	Median value based on interviews with 60 women with menorrhagia

TABLE 26 *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 *Table 5*, Q07	UK data set
Duration of surgery	59 minutes	Lethaby *et al.*, 2000[52]	Good quality systematic review
% under GA	100%	Assumed	
1st-generation EA			
Waiting time – mean (median)	79 (45) days	HES, 2001,[73] *Table 5*, Q17	UK data set
Length of stay – weighted mean	2.0 days	Lethaby *et al.*, 2000[52]	Good-quality systematic review
Day cases	60%	HES, 2001,[73] *Table 5*, Q17	UK data set
Duration of surgery – TCRE	40.9 minutes	Median from effectiveness data in this report (*Table 17*)	RCT data – best available evidence
Duration of surgery – RB	50 minutes	Effectiveness data in this report (*Table 17*)	RCT data – best available evidence
Duration of surgery – TCRE/RB	31.6 minutes	Median from Effectiveness data in this report (*Table 17*)	RCT data – best available evidence
% under GA	78	Lethaby and Hickey, 2002[9]	Systematic review
2nd-generation EA			
Waiting time – mean (median)	80 (50) days	HES, 2001,[73] *Table 5*, Q16	UK data set
Length of stay – mean (median)	1.6 (1) days	HES, 2001,[73] *Table 5*, Q16	UK data set
Day cases	65%	HES, 2001,[73] *Table 5*, Q16	UK data set
Duration of surgery – MEA	31.3 minutes	Effectiveness data for theatre in this report (*Table 17*)	Median from RCT data – best available evidence
Duration of surgery – TBEA	18.6 minutes	Effectiveness data for theatre in this report (*Table 17*)	Median from RCT data – best available evidence
% under GA	52	Bain *et al.*, 2001[67]	Partially randomised study of LA versus GA among 98 women in the UK

Fifty-one UK centres operate this arrangement in all, of which six are in Scotland (information supplied by Microsulis Medical). However, the costs may be subject to other types of arrangement and this uncertainty has been addressed through sensitivity analysis (see *Table 33*).

Staff costs are shown in *Table 28*, costs of GA and LA in *Table 29* and total procedure costs in *Table 30*.

TABLE 27 *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; manufacturer informs that owing to various discounts, £335 is the UK average price
Thermachoice cost of surgical	290	Per patient	Manufacturer	Calculated from cost given in Euros
Microwave				
MEA system	39950		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.

TABLE 28 *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 29 *Costs of anaesthesia, ward costs*

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

TABLE 30 *Total procedure costs*

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

TABLE 31 *Summary of cost–utility analysis for MEA at 10 years*

Procedure	Total cost (£)	Total QALYs	Incremental cost	Incremental QALY vs MEA	ICER (£/QALY)
MEA – baseline	1448470	8360.70	–	–	–
TBEA	1323925	8360.77	124545	–0.06	TBEA dominates
TCRE	1731734	8357.03	–283264	3.67	MEA dominates
TCRE + RB	1785045	8357.99	–336574	–2.71	MEA dominates
RB	1752359	8359.92	–303889	0.78	MEA dominates
Hysterectomy	2320512	8774.34	–872042	–413.63	2108

QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio.

TABLE 32 *Summary of cost–utility analysis for TBEA at 10 years*

Procedure	Total cost (£)	Total QALYs	Incremental cost	Incremental QALYs	ICER (£/QALY)
TBEA – baseline	1323925	8360.77	–	–	–
MEA	1448470	8360.70	–124545	0.06	TBEA dominates
TCRE	1731734	8357.03	–407809	3.73	TBEA dominates
TCRE + RB	1785045	8357.99	–461119	2.78	TBEA dominates
RB	1752359	8359.92	–428434	0.85	TBEA dominates
Hysterectomy	2320512	8774.34	–996587	–413.57	2410

Baseline results

The total costs for the modelled cohort of 1000 women over 10 years are presented. *Table 31* shows the cost-effectiveness of MEA compared with each of the other procedures and *Table 32* shows the cost-effectiveness of TBEA compared with each of the other procedures.

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

Compared with MEA, TBEA costs slightly less and accrues very slightly more QALYs. Compared with TCRE, TCRE combined with RB, and RB alone, TBEA costs less and accrues more QALYs. Compared with hysterectomy, TBEA costs less and accrues fewer QALYs.

Although TBEA is seen to dominate MEA, in reality absolute differences in both cost and QALYs are small and are necessarily based on an inferred comparison. It is possible that the methods used to calculate costs are not sensitive enough to identify such small differences accurately.

Sensitivity analyses

Sensitivity analysis was used to assess the effect of altering input values; this is particularly important where the accuracy of initial inputs is uncertain.

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 33*. Each variable was varied independently.

In order to investigate the sensitivity of the model to these various parameters, graphs showing the ICER for TBEA and MEA versus each other, first-generation EA and hysterectomy are shown in Appendix 8.

In comparing TBEA and MEA head to head, relatively small changes have greater effect, in some cases changing the direction of effect. This suggests that the initial findings should be treated with caution, particularly as we have had to rely on inferred comparison for these interventions. Cost associated with each procedure and the procedure time of each procedure were important. In addition, the model is sensitive to aspects that affect the total QALYs accrued, such as relative percentage of women having complications, length of complications and death rate.

Compared with 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)

TABLE 33 *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 report, *Table 25*	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, *Tables 18* and *19*	Based on RCTs – best available evidence
Death following TBEA – direct cause	0–0.0003	Values for EA reported in this report, *Table 25*	Minimum and maximum death rates reported for all procedures included in this review
Proportion of complications lasting more than 1 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 9*)	RCT data
Second- and third-year return of menorrhagia post-TBEA/MEA	0.05–0.2	Total return of menorrhagia at 3 years 21–51% (*Tables 9* and *20*)	Menorrhagia assumed to include all 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 (£)			
LA	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

continued

TABLE 33 *Inputs varied in sensitivity analyses (cont'd)*

Assumptions	Values used in sensitivity analyses	Source	Justification for source
Length of hospital stay	0.5–1.0	Lower level clinician opinion, upper level from HES UK average	Input from clinical experience and national data
Procedure time	20–42 minutes	This report, *Table 17*	Lowest and highest recorded theatre times
Equipment costs MEA	187–562	Author's assumption	Cost ±50%
Equipment costs TBEA	158–474	Authors' assumption	Cost ±50%
Model			
Duration of model	3–10 years	Authors' assumption	

- 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 postablation
- cost of equipment per treatment
- procedure time
- percentage of operations performed under LA
- length for which the model is run
- death rate as direct result of treatment.

The model is highly sensitive to

- utility value for 'well' postablation.

For MEA versus 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 that 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 4: 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 the relative cost-effectiveness.
- Both TBEA and MEA appear to be less costly than hysterectomy, although the latter results in more QALYs.

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
- cost minimisation 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 in Appendix 8.

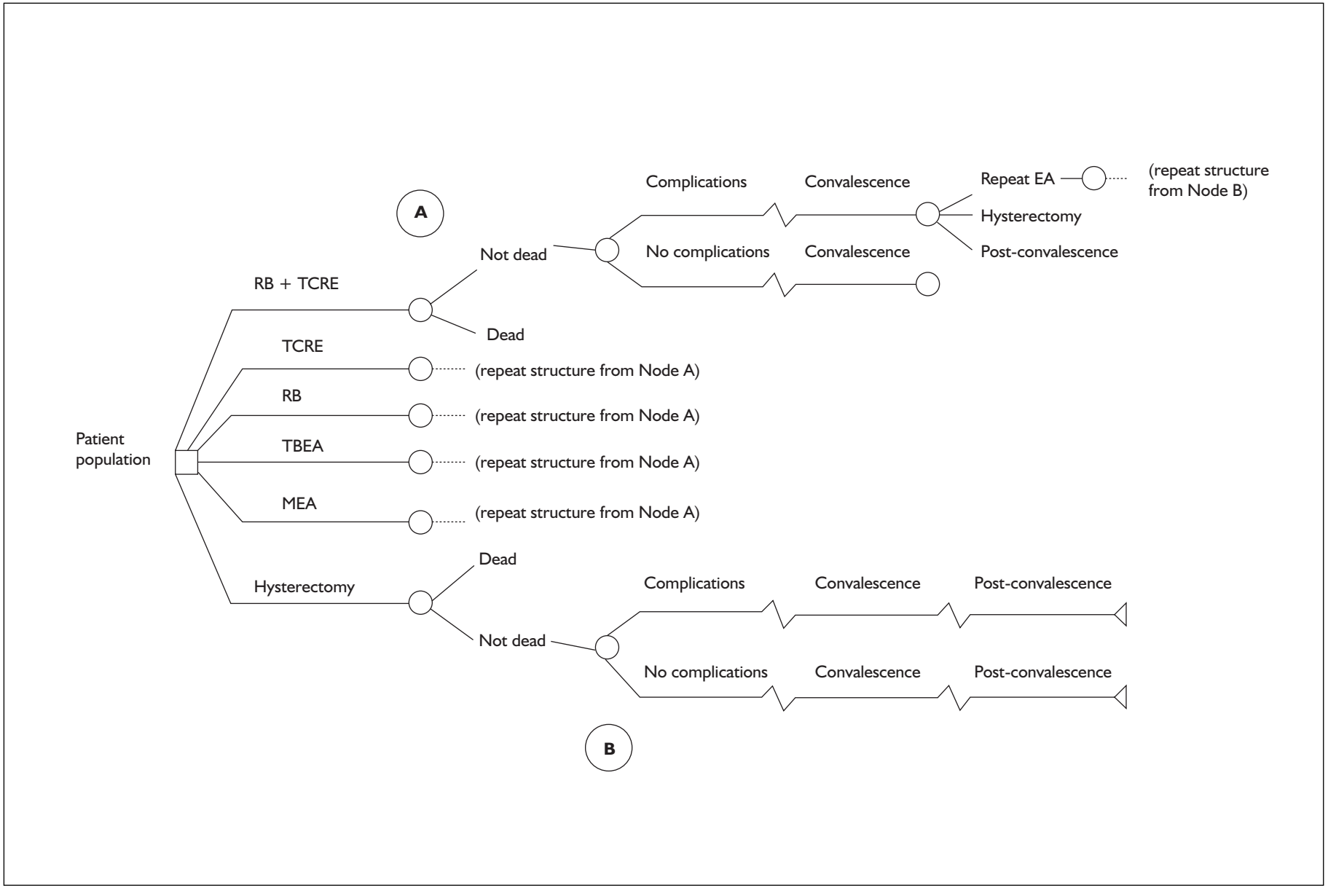


FIGURE 15 *Microsulis model structure*

TABLE 34 *Total discounted costs and QALYs by procedure and cost-effectiveness at 5 years: Microsulis model*

Procedure	Total costs (£)	Total QALYs	Incremental costs (vs MEA) (£)	Incremental QALY (vs MEA)	ICER (MEA)
MEA	1238	3.76	–	–	–
TBEA	1611	2.97	373	–0.79	Dominated
RB	1550	3.54	312	–0.21	Dominated
RB + TCRE	1441	3.48	203	–0.28	Dominated
TCRE	2032	3.56	793	–0.20	Dominated
Hysterectomy	2728	4.08	1489	0.32	£4594

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 (*Figure 15*), 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 5-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 + RB whereas for other ablation techniques the original option is repeated (i.e. TCRE, TCRE + RB, RB 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.

The Microsulis submission concludes that MEA is a cost-saving treatment. Total discounted costs at 5 years are estimated at £1238. Cost savings of 14–55% over other treatments are estimated. Total discounted costs and QALYs according to the Microsulis model are shown in *Table 34*.

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 + RB, 0.74 following RB, 0.79 following MEA and 0.57 following TBEA. Methods of calculating these values are described in Appendix 9. 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 HMB 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 EA techniques suggests that 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 HMB 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 from £2000 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, and therefore the cost-effectiveness levels of MEA and TBEA are not dissimilar.

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, and 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 electroresection (n = 50) and vaginal hysterectomy (n = 50). Limited methodological details are reported and it is therefore difficult to determine 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 (€2799 versus €1424 and €1508, 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 following:

- the methods of calculating resource consumption are not reported
- the completeness of resource use ascertainment and how missing data were handled are not reported
- 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 in 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 EA 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, although 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 with one in each of the ablation techniques. The number of follow-up visits seems high, particularly for vaginal hysterectomy. If the number of follow-

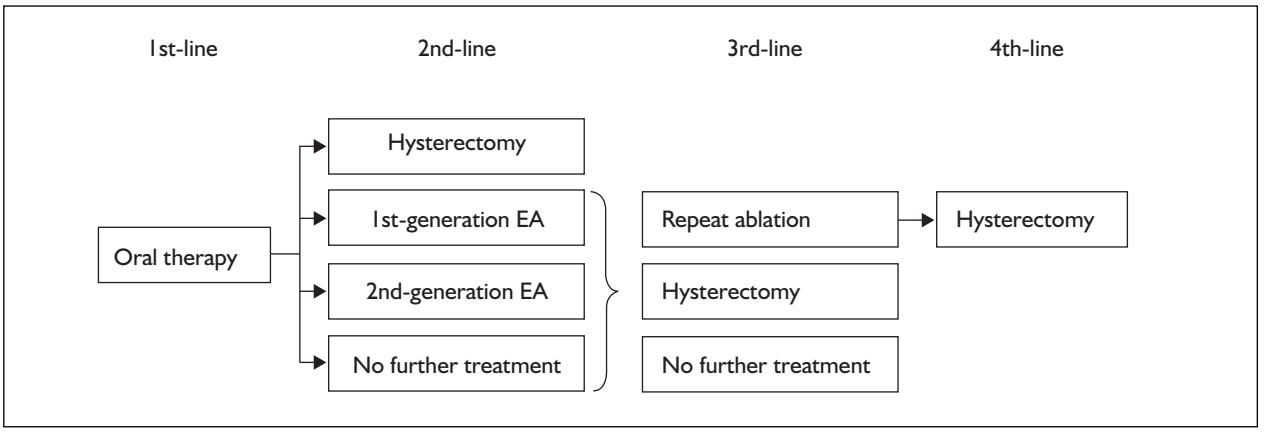


FIGURE 16 *Flow chart of treatment pathway considered in the Cavaterm model*

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 with TCRE and hysterectomy at 3 years. It has been appraised using the framework by Drummond and colleagues[75] and this is shown in Appendix 8. The analysis reports the following outcomes:

- **Cost per additional case of amenorrhoea**. The ICERs for TCRE and hysterectomy, compared with Thermachoice TBEA, are €1736 and €1378, respectively.
- **Cost per additional case of eumenorrhoea or less**. The ICERs for TCRE and hysterectomy, compared with Thermachoice TBEA, are €19,789 and €16,751, respectively.
- **Cost per reintervention case avoided**. Thermachoice TBEA dominates TCRE. The ICER for hysterectomy, compared with Thermachoice, is estimated as €16,994.
- **Cost per additional satisfied patient**. The ICERs for TCRE and hysterectomy, compared with 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, for example, adverse effects 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.

Cavaterm model

The Cavaterm model is a decision-tree model with a 3-year time horizon. The comparisons are between hysterectomy and first-generation and second-generation EA. Use of the two types of TBEA equipment is 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 9.

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 2000) from over 30 trials will "override anomalies and experimental differences" and that this approach is preferable to restricting effectiveness data to that reported from RCTs. This position is open to debate: the quality of a meta-analysis depends on the quality of the studies that 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, although the probability of a type II error remains.

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 1 year, whereas Thermachoice is successful in only 83.3% of cases, based on a weighted mean of data up to 3 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 versus £828 for Thermachoice, £865 for first-generation EA and £2050 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 £1910. 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 HMB. This is not a realistic scenario given the evidence for patient preferences in a proportion of women seeking treatment for HMB.

Comparison between cost-effectiveness analyses

The four models included in the NICE appraisal process for EA 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 3 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.

Table 35 highlights some of the key differences between the modelling studies of EA. Appendix 10 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 €1 = £0.635 based on conversion rate in December 2002.

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 EA is less resource intensive than hysterectomy. There is therefore a potential for resource savings arising from more

TABLE 35 *Comparison between four economic analyses of EA 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	£2096	£2644	£2050	£1777
TCRE	£1110	£1129	£593	£958
Cavaterm	£826	£712	£584	–
Thermachoice	£826	£712	£905	£904
MEA	£942	£674	£793	–
Probability of hysterectomy:				
After TBEA	0.248 (year 5)	0.321 (year 5)	–	0.077 (year 3 Thermachoice) 0.0595 (year 3 Cavaterm)
After MEA	0.248 (year 5)	0.208 (year 5)	–	0.0252
After RB	0.248 (year 5)	0.368 (year 5)	–	0.065–0.195
Utility values:				
Convalescence after TBEA	0.8	0.76	N/A	N/A
Convalescence after MEA	0.8	0.76		
Convalescence after TCRE or RB or TCRE + RB	0.8	0.76		
Convalescence after hysterectomy	0.63	0.74		
Post-convalescence after TBEA	0.9	0.57		
Post-convalescence after MEA	0.9	0.79		
Post-convalescence after TCRE or RB or TCRE + RB	0.9	0.73/0.74		
Post-convalescence after hysterectomy	0.95	0.86		
Utility in menorrhagia	0.55	0.5		

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

Based on the available evidence, second-generation EA techniques appear to offer advantages over first-generation techniques in terms of value for money to the NHS. 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 4: Cost-effectiveness information supplied by industry

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

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 HMB may follow any treatment path. However, the impact of second-generation EA 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 and avoidance of major surgery.
- The number of women with HMB who are eligible for each treatment (for example, larger and abnormal uteri are a contraindication for TBEA and 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/RB ablation and the number of centres that have second-generation ablation equipment).

There are currently nearly 26,000 hysterectomies in the UK for HMB and a further 16,000 EAs, of which about 2000 are second-generation techniques (see the section 'Surgical treatment', p. 8). *Table 36* below shows the effects of changing the balance of the current 42,000 surgical procedures for women with HMB. The cost of first-generation EA is the cost of TCRE combined with RB 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 is equally divided between TBEA and MEA.

If hysterectomies were replaced by EA, overall costs would be reduced. If half were replaced by first-generation techniques, costs would be reduced by £13,546,000 (*Table 37*). 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 38*).

If all first-generation techniques were replaced by second-generation techniques, a saving of £2,002,000 would be made (*Table 39*).

If all hysterectomies were replaced by EA, cost savings would be £28,951,000 if half went to first-generation techniques and the remaining half were equally split between second-generation

TABLE 36 *Estimate of current costs to the NHS of surgical procedures for HMB*

Procedure	Cost per procedure (£)	No. of procedures	Total cost (£)
Hysterectomy	2069	26000	53794000
TCRE/RB	1027	14000	14378000
MEA	942	1000	942000
TBEA	826	1000	826000
Total			**69940000**

techniques (*Table 40*), and £32,812,000 if all were replaced by second-generation techniques (*Table 41*). It is unlikely, however, that all hysterectomies for HMB could be replaced by EA as some women will prefer this treatment or it will be the only available option.

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

TABLE 37 *Costs to NHS if half of current hysterectomies were replaced by first-generation EA*

Procedure	Cost per procedure (£)	No. of procedures	Total cost (£)
Hysterectomy	2069	13000	26897000
TCRE/RB	1027	27000	27729000
MEA	942	1000	942000
TBEA	826	1000	826000
Total			**56394000**

TABLE 38 *Costs to the NHS if half of current hysterectomies were replaced by second-generation EA*

Procedure	Cost per procedure (£)	No. of procedures	Total cost (£)
Hysterectomy	2069	13000	26897000
TCRE/RB	1027	14000	14378000
MEA	942	7500	7065000
TBEA	826	7500	6195000
Total			**54535000**

TABLE 39 *Costs to the NHS if first-generation techniques were replaced by second-generation techniques*

Procedure	Cost per procedure (£)	No. of procedures	Total cost (£)
Hysterectomy	2069	26000	53794000
TCRE/RB	1027	0	0
MEA	942	8000	7536000
TBEA	826	8000	6608000
Total			**67938000**

TABLE 40 *Costs to the NHS if all hysterectomies were replaced by EA*

Procedure	Cost per procedure (£)	No. of procedures	Total cost (£)
Hysterectomy	2069	0	0
TCRE/RB	1027	27000	27729000
MEA	942	7500	7065000
TBEA	826	7500	6195000
Total			**40989000**

TABLE 41 *Costs to the NHS if all hysterectomies were replaced by second-generation EA*

Procedure	Cost per procedure (£)	No. of procedures	Total cost (£)
Hysterectomy	2069	0	0
TCRE/RB	1027	0	0
MEA	942	21000	19782000
TBEA	826	21000	17346000
Total			**37128000**

Chapter 5
Discussion

Main results

HMB is a common condition that 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 HMB. However, it is more expensive than newer alternatives, is a more complex procedure and may result in more serious complications. Although 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.

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 RCTs. However, there are no studies comparing MEA or TBEA to hysterectomy, so effectiveness and cost-effectiveness compared with hysterectomy have had to be inferred through indirect comparison. A good-quality systematic review of first-generation techniques compared with hysterectomy showed that hysterectomy was more effective (as measured by improvement in HMB and patient satisfaction), but was associated with greater consumption of healthcare resources and more adverse effects. 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 10 studies comparing MEA (two studies) and TBEA (eight studies) with first-generation ablation techniques. Duration of follow-up was limited (range 3–60 months, median 24 months). One trial included 5-year follow-up but with 46% LTFU. Overall, the quality of the RCTs 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 greater applicability to the UK.

The included studies of MEA and TBEA did not show a significant difference between amenorrhoea rates after first-generation compared with second-generation techniques. Only one study showed a first-generation technique (RB) to be significantly superior to a second-generation technique (TBEA) for the outcome of amenorrhoea measured at 2 years, although this study had much loss to follow-up. The median proportion of women with the outcome of amenorrhoea appears higher among those treated with MEA (46%) than those with TBEA (14%), although the ranges overlap (MEA 36–55%, TBEA 10–40%) and the amenorrhoea rates in the MEA trials were also higher for the control group. No differences in amount or pattern of continuing menstrual loss were shown in studies that examined these outcomes. No differences were demonstrated for dysmenorrhoea or PMS symptoms in the included studies.

Patient satisfaction is reported in eight of the 10 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 most of the comparisons. Two studies show a significant difference in satisfaction favouring TBEA over control when categories of satisfaction are collapsed into a dichotomous variable (satisfied/not satisfied). However, in both cases this was seen only at one point of follow-up and not all follow-up points (at 12 months but not at 24 months, for example). One of these studies was not randomised and the other was not of high quality.

One study each of MEA and TBEA investigated effects on QoL. One MEA study, by Cooper and colleagues,[86] used the SF-36 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[82] investigated QoL using a global question of impact and found no significant difference between TBEA and RB. Both first- and second-generation ablation techniques have a positive impact on ability to work/pursue normal activities, although neither study that examined this outcome showed a difference between techniques.

All studies reporting operating time 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[86]) 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 (Cooper K, Aberdeen Royal Infirmary: personal communication, 2002).

The adverse effect profiles of second- and first-generation ablation techniques reported in RCTs are similar at around 3–4% overall. Adverse effects include uterine perforation, haemorrhage, pain, haematometra, post-tubal sterilisation syndrome, endometritis and pregnancy. Second-generation techniques were associated with fewer intraoperative complications in the RCTs (1 versus 5% for MEA versus TCRE and 0 versus 3% for TBEA versus RB) and are not prone to the problem of fluid overload – a potentially serious complication possible with hysteroscopic techniques. The small size of RCTs limits statistical power to demonstrate whether such differences are significant. Two large uncontrolled observational studies of MEA and TBEA provide 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 RB in the trial by Meyer and colleagues[82] had had repeat surgery by 5 years of follow-up. This figure is based on the most conservative estimate of success – ITT figures are 11 and 7%, respectively. Most women who needed further surgery had hysterectomy. Adverse effect rates in repeat ablations may be higher than when ablation is the primary procedure.

Costs and cost-effectiveness

The costs of MEA and TBEA procedures are similar, although the methods used to assess these costs 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 with £826 for TBEA. Compared with combined TCRE and RB, 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. Operation time is important and the data available were unclear, but this was examined in sensitivity analysis.

The cost-effectiveness analysis necessarily depends on inferred 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 slightly less costly and very slightly more effective than MEA at 10 years, although differences in costs and utilities are very small and subject to considerable uncertainty. Both second-generation techniques similarly dominate TCRE, RB and TCRE/RB combined. Hysterectomy yields additional benefits for additional cost, with cost–utility ratios of around £2400 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 suggests that these results should be treated with great caution and may be insufficiently robust to guide highly specific policy decisions.

Assumptions, limitations and uncertainties

Quality of studies

The quality of the studies was variable, as discussed in the section ‘Quality assessment of RCTs’ (p. 29). This may limit the validity of the findings. In addition, the included studies contained varied populations – women with menorrhagia as measured in different ways,

inclusion or exclusion of women with fibroids, the inclusion of women who were postmenopausal in one study and two studies that did not give details about the included population. The comparator was either TCRE alone, RB alone or TCRE and RB combined, and these procedures may not have been consistent among the patients in the control groups of some studies. RB and TCRE are known to have different adverse effect rates, as shown in the MISTLETOE study (*Table 21*). 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 as a thinning agent for all participants. However, the TBEA trials vary in their approach to prethinning of the endometrium. While no chemical prethinning is advised by the manufacturers, two trials used GnRH in both arms of the study. Three used a preoperative D&C for both arms, two did not report any prethinning and one used a prethinning agent only in the control arm. It is not known what effect prethinning has on the effectiveness of second-generation EA. A systematic review of prethinning agents in first-generation EA found that prethinning improved the 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 the section 'Measurement of blood loss' (p. 3), outcome measurement in HMB is problematic. It is not clear which outcome should be considered as the most important in assessing the success of EA 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 the section 'Measurement of blood loss' (p. 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 HMB but subjectively regard their bleeding as unacceptably heavy are likely to be less satisfied with their treatment for HMB.[17] Those trials included in this review that have stringently measured HMB as an inclusion criterion 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[86] used self-defined HMB as an entry criterion, which mirrors clinical practice in the UK. Those trials using the PBAC method of measuring HMB have different levels for inclusion of women, as well as for defining success of treatment.

As the major effect of HMB on sufferers is decreased QoL, this is an important outcome measure. Of the included studies, only Cooper and colleagues[86] used a recognised QoL 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 HMB has been questioned (see the section 'Measuring the impact of HMB', p. 4). A range of surrogate measures of impact on QoL, 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 eight of TBEA were identified that 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 HMB. Therefore, longer term rates of recurrent HMB, 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 HMB as a group will also have more psychological symptoms than women of the same age without HMB. 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 LA 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 EA 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 TTO method in interviews with 60 women who had been referred to secondary care by their GP and had uncomplicated HMB. 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.[30] This seems low (see *Table 2* for examples of utility values for other health states). A mean value of 0.5 using the TTO 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 HMB, 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 QoL on a daily basis but for which the worst effects are episodic. In addition, for HMB, 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 HMB may be particularly difficult to interpret. After hysterectomy, there is no possibility of HMB 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, in addition to having some longer term adverse effects such as urinary incontinence. An ablation procedure cannot guarantee amenorrhoea, and there is the possibility of recurrent HMB. In the cost–utility analysis by Sculpher,[30] women rated the 'well' state following hysterectomy more highly than that following EA (median 0.95 versus 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 HMB 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 GP. For example, women who strongly prefer amenorrhoea as an outcome, or who have severe associated menstrual symptomatology (severe PMS, for example) may not be suitable candidates for EA techniques but be better treated with hysterectomy, whereas those preferring to avoid a GA may be better suited to second-generation EA techniques. Other aspects of EA that 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]

TBEA is not suitable for women with larger uterine cavities (>10–12 cm) or those with uterine pathology or abnormalities, who will need to choose another method of treatment. Pathology may account for 20–60% of women with HMB[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 >12 cm 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 that require training and experience. Not all consultants are therefore currently able to perform them.

Need for further research

- Head-to-head comparisons of second-generation EA 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, in addition to checking whether longer term complications are an issue.
- More sophisticated modelling studies may improve estimates of cost-effectiveness, taking into account population heterogeneity, and would permit exploration of issues relevant to implementation such as waiting times and detailed budget impact.
- Given the importance of the utility values in determining the cost-effectiveness of treatments for HMB, further research to establish utilities for the states of HMB, its surgical treatment, convalescence and complications of treatment would be valuable.
- Future studies of HMB should use validated QoL measures and established modes of measuring patient satisfaction both with the procedure and with the outcomes.
- Further research into the effect of the constellation of symptoms associated with menstruation (such as pain, bloating and breast tenderness) 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 EA should be further investigated, including different operators (non-consultant medical staff and specialist nurses) and different settings (office versus operating theatre).

Chapter 6
Conclusions

Both MEA and TBEA techniques appear to offer effective alternatives in the surgical treatment of women with HMB.

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 effects 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 the 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. 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 EA 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.

Acknowledgements

Thanks are due to Dr Hakan Brodin for his advice on the health economics sections of this report and to those who provided useful comments through peer review. Liz Hodson, who obtained the papers used in this report, is also thanked.

Expert advisory panel

Mr N Amso, Senior Lecturer, Consultant Gynaecologist, University Hospital of Wales, Cardiff; Dr S Bhattacharya, Senior Lecturer (Honorary Consultant), Aberdeen Maternity Hospital; Dr K Cooper, Consultant Gynaecologist, Aberdeen Royal Infirmary; Mr N Liversedge, Consultant Gynaecologist, Royal Devon and Exeter Hospital; Dr M-A Lumsden, Reader, Royal Infirmary, Glasgow; Mr NC Sharp, Consultant Gynaecologist, Royal United Hospital, Bath.

Declared competing interests of the expert advisory 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.

Contributions of authors

Ruth Garside drafted the protocol and final report, assessed studies for inclusion, extracted data, populated the economic model and undertook sensitivity analyses. Ken Stein undertook project management, contributed to the writing of the report, critiqued the industry submissions and provided editorial comment of the report and the model. Ali Round designed the economic model and provided comment on drafts of the report. Katrina Wyatt assessed studies for inclusion and extracted data, contributed to writing the report and provided editorial comment on drafts of the report. Alison Price commented on the protocol, carried out all searches and applied inclusion criteria and provided editorial comment on the draft report.

References

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-patient 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. *Fam Pract* 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, Anderson ABN, Turnbull AC. Study of menstrual blood loss. *Br J Obstet Gynaecol* 1980;**87**:603–9.
7. Fraser IS, McCarron G, Markham R. 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. Oxford: Update Software.
10. Kochli OR. Endometrial ablation in the year 2000 – do we have more methods than indications? *Contrib Gynecol Obstet* 2000;**20**:91–120.
11. Turnbull AC, Rees MC. Gestrinone in the treatment of menorrhagia. *Br J Obstet Gynaecol* 1990;**97**:713–15.
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 management 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 patients 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. Determination 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 PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol* 1990;**97**: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, Dimmock PW, Walker TJ, O'Brien PMS. 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, Grenman S, Kivelä A, Kujansuu E, *et al*. Combined laboratory and diary method for objective assessment of menstrual blood loss. *Acta Obstet Gynecol Scand* 1998;**77**:201–4.
23. Royal College of Obstetricians and Gynaecologists. 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. *Qual Life Res* 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. *Int J Technol Assess 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 breast cancer in the elderly: a health outcome-based approach. *Med Decis Making* 1998;**18**:213–19.

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. Decision analysis 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, *et al*. The measurement of satisfaction with health care: implications for practice from a systematic review of the literature. *Health Technol Assess* 2002;**6**(32).

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. *Int J Technol Assess Health Care* 1995;**11**:456–71.

42. Prentice, A. AMES study. Presented at the Joint BSGE/RCOG conference, Conservative surgery for menorrhagia, London, 17 September 2002.

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. Hospital episode statistics 2000–1. London: Office for National Statistics; 2002.

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 Technol 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 hysterectomy 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 review. *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* 2002;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, editors. Endometrial ablation. Edinburgh: Churchill Livingstone; 1993, pp. 133–42.

57. Davis JA, Miller CD. Fluid infusion during hysteroscopic surgery. In Lewis BV, Magos AL, editors. Endometrial ablation, Edinburgh: Churchill Livingstone; 1993, pp. 41–56.

58. Garry R. Evidence and techniques in endometrial ablation: consensus. *Gynaecol Endosc* 2002;**11**:5–17.

59. Coulter A, Peto V, Doll H. Patients' preferences and general practitioners' decisions in the treatment of menstrual disorders. *Fam Pract* 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 Expect* 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. *Gynaecol Endosc* 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 England and Wales Females 1998–2000. London: The Government Actuary Department; 2002.

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. Rogerson L, Duffy S. A European survey of the complications of a uterine thermal balloon system in 5800 women. *Gynaecol Endosc* 2002;**11**:171.

72. Parkin DE. Microwave endometrial ablation (MEA™): a safe technique? Complication data from a prospective series of 1400 cases. *Gynaecol Endosc* 2000;**9**:385–8.

73. Department of Health. Hospital episode statistics 2000–1. London: Office for National Statistics; 2002.

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. *Cochrane Library* 2002;**4**.

77. Lethaby A, Irvine G, Cameron IM. Cyclical progestogens for heavy menstrual bleeding (Cochrane review). *Cochrane Library* 2002;**4**. Oxford: Update Software.

78. Beaumont H, Augood C, Duckitt K, Lethaby A. Danazol for heavy menstrual bleeding (Cochrane review). *Cochrane Library* 2002;**4**. Oxford: Update Software.

79. Lethaby A, Augood C, Duckitt K. Nonsteroidal anti-inflammatory drugs for heavy menstrual bleeding (Cochrane review). *Cochrane Library* 2002;**4**. Oxford: Update Software.

80. Lethaby A, Farquhar C, Cooke I. Antifibrinolytics for heavy menstrual bleeding (Cochrane review). *Cochrane Database Syst Rev* 2002. Oxford: Update Software.

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. Oxford: Update Software.

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. *Zentralbl Gynakol* 1998;**120**:511–14.

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. Microwave endometrial ablation. FDA trial. Coral Springs, FL: Microsulis Americas; 2002.

89. Bongers MY, Mol BW, Dijkhuizen FP, Brolmann HA. Is balloon ablation as effective as endometrial electroresection in the treatment of menorrhagia? *J Laparoendosc Adv Surg Tech A* 2000;**10**:85–92.

90. 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. *Hum Reprod* 1999;**14**:2743–7.

91. Soysal ME, Soysal SK, Vicdan K. Thermal balloon ablation in myoma-induced menorrhagia under local anesthesia. *Gynecol Obstet Invest* 2001; **51**:128–33.

92. 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.

93. Zon-Rabelink I. Rollerball versus Thermachoice. 10th Congress of the European Society for Gynaecological Endoscopy, Proceedings 2001; 11–14.

94. 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.

95. Loffer FD. Three-year comparison of thermal balloon rollerball ablation in treatment of menorrhagia (vol 8, pg 48, 2001). *J Am Assoc Gynecol Laparosc* 2001;**8**:330.

96. Brun JL, *et al*. French randomised comparative multicentre study of Cavaterm™ versus resection in patients with meorrhagia: interim results. Morges, Switzerland: Wallsten Medical SA; 2002.

97. 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.

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

Appendix 1

Pictorial blood loss assessment chart

An assessment chart is illustrated in *Figure 17*.

Name: Ann Other

Day start: 1 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								

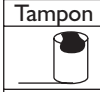
Tampon	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
	||	|			||	|		
		||	|||	||				
		|||| |	||||					
Clots/ flooding								
Pain								

FIGURE 17 *Pictorial blood loss assessment chart. From Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart.* Br J Obstet Gynaecol *1990;**97**:734–9, reproduced with permission of the authors.*

Appendix 2

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, UK.
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 are the effectiveness and cost-effectiveness of MEA and TBEA techniques for HMB compared with transcervical resection and RB ablation and hysterectomy?

Clarification of the research question and scope

HMB (menorrhagia) can have a major impact on women's lives. Objective menorrhagia is defined as total blood loss of more than 80 ml 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 20 women aged 30–49 years 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 years (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]

In 2000–1, 51,858 hysterectomies were performed, 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 postoperative complications and, in some cases, significant emotional implications. Since the 1980s, 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, RB and laser ablation require direct visualisation 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 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 offset by longer operating time, longer recovery period and higher rates of postoperative 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 MEA and TBEA) have fewer complications than resection. Whereas older style EA 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

MEA uses high-frequency microwave energy to heat and destroy the endometrium rapidly. Microwaves at a frequency of around 9 GHz are used and these are absorbed by the endometrial tissue to a depth of 3 mm. The heat that is generated is conducted deeper into the endometrium so that tissue is destroyed to a maximum depth of 5–6 mm, aiming at sufficient EA 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 GA or LA. 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 8 minutes, causing thermal ablation of the endometrial lining. Either LA or GA 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 EA, comparing types of EA or preparatory techniques used during EA. Thirteen of these are RCTs of MEA or TBEA versus first-generation techniques. However, there is likely to be repeat reporting of the same trials among these references.

Scope

All RCTs and non-RCTs of MEA or TBEA versus any removal and ablation of endometrium (by resection or RB) or hysterectomy will be included. Head-to-head comparisons of MEA and TBEA 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 were recruited from family planning clinics, primary care or specialist clinics.

Inclusion criteria

Studies including premenopausal 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:

- postmenopausal bleeding (>1 year from the last period)
- irregular menses and intermenstrual bleeding (metrorrhagia)
- pathological causes of menorrhagia (e.g. uterine cancer)
- iatrogenic causes of menorrhagia (e.g. IUD).

Interventions

ME or TBEA versus any removal and ablation of endometrium (including TCRE and EA by electrocautery or laser) or hysterectomy (by open abdominal, vaginal or laparoscopic routes).

Outcomes

- **QoL**: women's perceived change in QoL
- **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 and 4

- **requirement for further surgery for menstrual symptoms**: at years after surgery 1, 2, 3 and 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 RB 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 that describe trials of MEA or TBEA techniques versus other EA 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
- RCTs
- controlled clinical trials.

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. Owing 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 LTFU.
4. Whether ITT analysis is performed.
5. Whether a power calculation was done.
6. Timing, duration and location of the study.

Study participants:

1. Age and any other recorded characteristics of women in studies.

2. Inclusion criteria.
3. Exclusion criteria.

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

Outcomes:
1. Methods used to evaluate women's satisfaction and QoL 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 QoL, costs and cost-effectiveness and/or QALYs
QoL 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 RB 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:	30 July 2002
Finalised protocol:	20 August 2002
Progress report:	13 November 2002
Draft final report:	22 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.

References

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. *Br 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, Anderson ABN, Turnbull AC. Study of menstrual blood loss. *Br J Obstet Gynaecol* 1980;**87**:603–9.
5. Fraser IS, McCarron G, Markham R. A preliminary study of factors influencing perception of menstrual blood loss volume. *Am J Obstet Gynecol* 1984;**149**:788–93.
6. Wyatt KM, Dimmock PW, Walker TJ, O'Brien PMS. 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.

Appendix 3

Search strategy

Two separate searches were undertaken for this project. One searched specifically for research evidence on MEA and TBEA for all years, the other looked for research comparing hysterectomy with the first-generation EA techniques of RB 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–August 2002)

(((‘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–August 2002)

((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/RB) versus hysterectomy (from 1999 to August 2002)

Cochrane Library (Issue 3, 2002) (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–August 2002)

(((‘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–July 2002)

((((‘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 4 December 2002 to cover the intervening months from August to November 2002 before the report was drafted.

Appendix 4
Excluded studies

Excluded studies are illustrated in *Figure 18*.

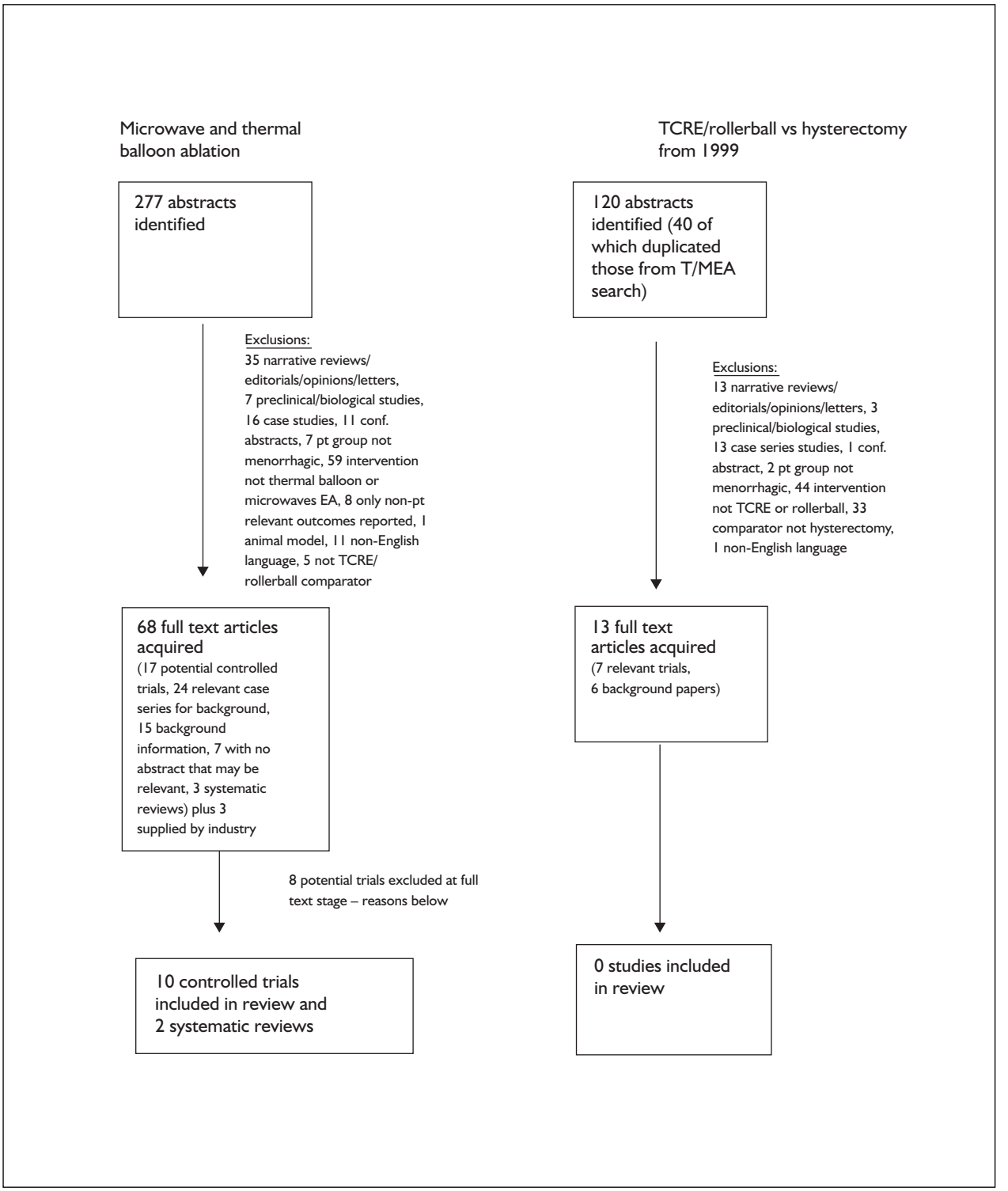


FIGURE 18 *Excluded studies*

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™ thermal balloon. *9th International Menopause Society World Congress on the Menopause* 1999;315–20	Abstract only
Loffer FD, Grainger D, Kung RC, Stabinsky SA. Endometrial ablation for the treatment of menorrhagia: a randomised trial comparing uterine balloon therapy with rollerball. *Acta Obstet Gynecol Scand* 1997;**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 Annu Congress of Int Soc for Gynecol Endoscopy/10th Annu in Mtg of Australian Gynaecological Endoscopy Soc,* 16–19 April 2000;140	Abstract only
Romer T. The treatment of recurrent menorrhagia – Cavaterm-balloon-coagulation versus RB-endometrial ablation – a prospective randomised comparative study. *Zentralbl Gynakol* 1998;**120**:511–14	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 *Obstet gynecol* 1998; **92**:1057	Letter

Studies supplied by industry, exclusions

Study	Reason for exclusion at full-text stage
Hawe J, Abbott J, Hunter D, Phillips G, Garry R. Pre-publication copy of a double blind randomised controlled trial comparing the Cavaterm endometrial ablation system with the Nd:YAG laser for the treatment of dysfunctional uterine bleeding. *Br J Obstet Gynaecol,* in press	Wrong comparator

Appendix 5

Included systematic reviews – QUOROM checklist

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

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 EA techniques but is not explicit in stating that clinical effectiveness or cost-effectiveness is to be evaluated
Search strategy	Databases 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 detail 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 rationale 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 that 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 follow-up 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-squared tests
Quantitative data synthesis	Dichotomous data expressed as Peto OR 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, although in fact all outcomes use fixed-effect models. Where only medians and ranges were available, the median was regarded as identical with the mean and estimate of SD calculated from the range (range × 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 follow-up 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. The study addresses the problem of heterogeneity between the studies. Sensitivity analyses were performed as a result of this; it is stated that there was 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.[9] Endometrial destruction techniques for heavy menstrual bleeding

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

Yes – Cochrane Review.

2. Abstract: Uses a structured format?

Yes – organised as:

Background	Outlines the clinic problem
Objectives	Expresses the clinical question explicitly
Search strategy	The databases searched and other search methods are listed
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% CIs are given
Reviewers' conclusions	Main results given

3. Introduction

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

4. Methods

Searching	Details of databases searched given, search terms listed, registers searched listed, hand searching listed
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 ORs 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 LA). No subgroup 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 first-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, whereas the graph does not.	*6. Discussion* The discussion summarises key findings. Internal and external validity (e.g. 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.

Appendix 6

Included systematic reviews

Reference and design	Research question and search strategy	Inclusion and quality criteria
• *Author:* Lethaby *et al.*, 2002[52] • *Study topic:* EA and hysterectomy for HMB	• *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, PsycLIT 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, total abdominal hysterectomy, subtotal abdominal hysterectomy, laparoscopic hysterectomy, transcervical resection of the endometrium, TCRE, endometrial, laser ablation	Inclusion criteria: • *Study design:* RCTs • *Interventions:* Resection, RB, 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 QoL (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 LTFU, 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 hysterectomy. Outcomes – methods used to measure blood loss, to evaluate resource and patient costs and to evaluated participant satisfaction and change in QoL 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:* 5 RCTs, total of 752 participants
- *Quality of included studies:* 4 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 was 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 follow-up, 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 resources 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 (including point estimates, CI,* p *values, etc.): Satisfaction*: at 1 year odds of satisfaction higher with hysterectomy (Peto OR 0.46, 95% CI 0.24 to 0.88; $p = 0.02$), at 2 years (OR = 0.31, 95% CI 0.16 to 0.59; $p = 0.00$). However, no difference at 3 (OR 0.32, 95% CI 0.08 to 1.37; $p = 0.12$) and 4 years (OR 0.52 to 95% CI 0.21 to 1.26; $p = 0.15$).

  Improvement in MBL: At 1 year odds of greater proportion with improved MB favoured hysterectomy (OR 0.12, 95% CI 0.06 to 0.25), at 2 years no difference (OR 0.10, 95% CI 0.00 to 5.41, $p = 0.3$); at 4 years no difference (OR 0.15, 95% CI 0.01 to 2.38, $p = 0.18$). ORs at 2 and 4 years based on 1 study.

  QoL: GR inventory scores (based on 1 study) no difference at 1 year [WMD 0.000 (95% CI –1.750 to 1.750, $p = 0.00$)].

  All the following SF-36 scores at 2 years – Role limitation (physical), no difference (WMD –1.426, 95% CI –10.310 to 7.458, $p = 0.8$); role limitation (emotional), no difference (WMD –7.272, 95% CI –15.741 to 1.196, $p = 0.09$); social functioning higher scores with hysterectomy (WMD –7.182, 95% CI –12.387 to –1.97, $p = 0.01$); mental health, no difference (–2.935, 95% CI –7.386 to –1.516, $p = 0.20$); energy, no difference (WMD –5.026, 95% CI –10.373 to 0.322, $p = 0.07$); pain, better with hysterectomy (WMD –8.709, 95% CI –15.034 to –2.38, $p = 0.01$); general health perception, better with hysterectomy (WMD –6.697, 95% CI –12.203, to –1.19, $p = 0.02$); physical functioning, no difference (WMD –2.756, 95% CI –7.188 to 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 to 3.286, $p = 0.18$), at 2 years (1 study), no difference (WMD –1.5000, 95% CI –6.287 to 3287, $p = 0.50$).

continued

Results (*cont'd*)

SSR score 2 years after surgery (1 study), no difference (WMD –3.700, 95%CI –11.169 to 3.769, $p = 0.30$).

Total HAD score 2 years after surgery (1 study), no difference (WMD 1.500, 95% CI –1.329 to 4.319, $p = 0.30$), anxiety HAD scores 2 and 4 years after surgery, no difference (WMD 0.669, 95% CI –0.302 to 1.641, $p = 0.18$); depression HAD scores 2 and 4 years after surgery, no difference (WMD 0.002, 95% CI –0.092 to 0.096, $p = 1.00$).

The following 4 measures each based on 1 study: proportion with improvement in QoL at 2 years, no difference (1 study) (OR 0.54, 95% CI 0.15 to 1.98, $p = 0.40$); proportion with improvement in general health at 1 year, better for hysterectomy (OR 0.26, 95% CI 0.11 to 0.63); proportion with improvement in general health 4 years after surgery, no difference (0.36, 95% CI 0.13 to 1.01, $p = 0.05$); proportion with improved symptoms at 1 year, no difference (OR 0.43 95% CI 0.15 to 1.28, $p = 0.13$).

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

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

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

- *Adverse effects*
  Immediate:
  Sepsis fewer with TCRE/ablation (OR 0.16, 95% CI 0.10 to 0.24, $p = 0.00$); haemorrhage, no difference (OR 0.59, 95% CI 0.20 to 1.74, $p = 0.30$); blood transfusion, fewer with TCRE/ablation (OR 0.22, 95% CI 0.08 to 0.57, $p = 0.00$); urinary retention, fewer with TCRE/ablation (OR 0.13, 95% CI 0.04 to 0.44, $p = 0.00$); anaemia (1 study), fewer with TCRE/ablation (OR 0.12, 95% CI 0.03 to 0.43, $p = 0.00$); pyrexia (1 study), fewer with TCRE/ablation (OR 0.12, 95% CI 0.06 to 0.27, $p = 0.00$); vault haematoma, fewer with TCRE/ablation (OR 0.14, 95% CI 0.06 to 0.34, $p = 0.00$); wound haematoma (1 study), fewer with TCRE/ablation (OR 0.11, 95% CI 0.04 to 0.32, $p = 0.00$); anaesthetic, no difference (1 study) (OR 0.12, 95% CI 0.01 to 1.99, $p = 0.14$); fluid overload, more likely with TCRE/ablation (OR 5.57, 95% CI 1.82 to 17.12, $p = 0.00$); perforation (1study), no difference (OR 6.85, 95% CI 0.14 to 346.18, $p = 0.30$), GI obstruction, ileus (1 study), no difference (OR 0.47, 95% CI 0.05 to 4.57, $p = 0.50$); laparotomy (1 study), no difference (OR 0.33, 95% CI 0.05 to 2.41, $p = 0.30$); cautery of hypergranulation, fewer with TCRE/ablation (OR 0.12, 95% CI 0.02 to 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
  Adverse effects after discharge:
  Sepsis (1 study), fewer with TCRE/ablation (OR 0.19, 95% CI 0.08 to 0.47, $p = 0.00$); haematoma, no difference (OR 0.55, 95% CI 0.13 to 2.4, $p = 0.4$); diarrhoea (1 study), no difference (OR 0.13, 95% CI 0.00 to 6.68, $p = 0.3$); haemorrhage (1 study), no difference (OR 7.24, 95% CI 0.14 to 365.04, $p = 0.3$)
- *Further surgery for HMB*
  Within 1 year, more likely with TCRE/ablation (OR 7.33, 95% CI 4.18 to 12.86, $p = 0.00$).
  At 2 years, more likely with TCRE/ablation (OR 7.5, 95% CI 4.20 to 13.42, $p = 0.00$).
  At 3 years (1 study), more likely with TCRE/ablation (OR 4.45, 95% CI 1.78 to 11.15, $p = 0.00$).
  At 4 years (1 study), more likely with TCRE/ablation (OR 9.84, 95% CI 4.93 to 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 patients and controls?:* None reported
- *Appropriate analysis?*: Yes
- *Funding?:* None stated

GR, Golombok Rust Inventory of Marital State; HAD, hospital Anxiety and Depression Scale; MB, menstral bleeding; MBL, menstral blood loss; SSR, Sabbatsberg Sexual Rating Scale.

continued

Reference and design	Research question and search strategy	Inclusion and quality criteria
• *Authors:* Lethaby and Hickey, 2002[a] • *Study topic:* EA techniques for HMB	• *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 6-monthly searches of the Trials Register for the Menstrual Disorders and Subfertility Cochrane Group (most recent 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 was undertaken. Experts, manufacturers and authors were also contacted	*Inclusion criteria* • *Study design:* RCT and comparative studies • *Interventions:* TCRE, laser, RB, saline irrigation, microwave, radiofrequency, heated balloon, photodynamic therapy, cryoablation and any other endometrial destruction techniques compared with 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, LTFU, 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

continued

Results

- *Quantity of included studies:* 8 studies, 1595 participants
- *Quality of included studies:* All had parallel group design, 3 multicentre. 5 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-outs in final analysis. 2 studies did not report power calculations. Five had funding from large pharmaceutical companies
- *Combined treatment effect (including point estimates, CI, p values, etc.):* Significant differences only shown below – all other outcomes no significant differences

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

  Vaporising electrode versus TCRE – Odds of 'difficult' surgery higher with TCRE (OR = 0.25, 95% CI 0.09 to 0.73, $p = 0.01$); with TCRE fluid deficit greater (WMD = 258 ml, 95% CI 173.9 to 342.1, $p = 0.00$); duration of surgery longer with TCRE (WMD = 1.5 minutes, 95% CI 0.35 to 2.65, $p = 0.01$)

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

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

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

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

  2nd- versus 1st-generation techniques overall – 1st generation takes longer (WMD = –10.6, 95% CI –18.6 to –2.5, $p = 0.01$) and has better chance of amenorrhoea at 12 months (OR = 0.76, 95% CI 0.6 to 1.0, $p = 0.04$). More chance of equipment failure with 2nd generation (OR 4.1, 95% CI 1.1 to 14.9, $p = 0.03$) and LA (OR = 7.6, 95% CI 1.1 to 52.7, $p = 0.04$). *NB: text and graph data disagree*
- *Adverse effects:* 2nd generation techniques less likely to have cervical lacerations (OR = 0.08, 95% CI 0.01 to 0.49, $p = 0.01$), hematometra (OR = 0.14, 95% CI 0.04 to 0.57, $p = 0.01$), haemorrhage (OR = 0.14, 95% CI 0.02 to 0.80, $p = 0.03$). 1st-generation techniques less likely to have nausea and vomiting (OR = 2.94, 95% CI 1.52 to 5.70, $p = 0.00$)
- *Assessment of heterogeneity:* Significant heterogeneity found when comparing 1st- and 2nd-generation techniques overall for use of LA 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 <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- and 2nd-generation techniques combined

General comments

- *Generalisability:* High
- *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 patients and controls?:* Not stated
- *Appropriate analysis?:* Yes
- *Funding?:* None stated

Appendix 7

Included controlled study details

Reference and design	Intervention	Subjects	Outcome measures
• *Author:* Cooper *et al.*, 1999[86] • *Study design:* RCT • *Recruitment dates:* Sept. 1996–Feb. 1998 • *Setting:* Single UK gynaecological outpatient dept	• *Treatment:* MEA. Control TCRE by combination electrocautery technique – fundus and cornual regions ablated with RB • *Surgeon experience:* 2 surgeons with at least 50 prior TCREs, MEA training and at least 5 MEAs • *Surgery pretreatment:* 3.6 mg goserelin 5 weeks prior to op. • *Type of anaesthesia:* 100% GA	• *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 week pregnancy or less, gave informed consent • *Exclusion criteria:* Histopathological abnormalities of endometrium • *Participant characteristics:* Mean age, MEA 41.1 years (SD 6.7), TCRE 41.0 years (SD 8.4). Described their periods as heavy – 83 (65%) MEA, 80 (60%) TCRE. 60% in both arms had the problem for 3+ years, fibroids >2 cm 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

	MEA		TCRE		
Results:	**preop. (*n* = 129)**	**postop. (*n* = 116)**	**preop. (*n* = 134)**	**postop. (*n* = 124)**	**95% CI for difference (*p*)**
• *Symptoms*					
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)
2× 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)

continued

	preop. (*n* = 116)	postop. (*n* = 116)	preop. (*n* = 124)	postop. (*n* = 124)	95% CI (ANCOVA *p*)
• *SF-36 score, mean (SD)*					
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)

	MEA (*n* = 116)	TCRE (*n* = 124)	95% CI (*p*)
• *Satisfaction*			
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 (0.8)
• *Operation details*	(*n* = 129)	(*n* = 134)	
Mean operating time (minutes) (SD)	11.4 (10.5)	15.0 (7.2)	–5.7 to 1.4 (0.001)
Mean theatre time (minutes) (SD)	20.9 (11.3)	26.2 (8.7)	–7.7 to 2.8 (<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 postop. 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 weeks*	(*n* = 121)	(*n* = 124)	
	87 (72%)	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 gynaecological 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-squared 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 provided equipment and financial support to one author

DUB, dysfunctional uterine bleeding; ANCOVA, analysis of convariance.

Reference and design	Intervention	Subjects	Outcome measures
• *Authors:* Bain *et al.*, 2002[87] • *Study design:* RCT • *Recruitment dates:* Not stated • *Setting:* One UK hospital obstetric and gynaecological department	• *Treatment:* Microwave EA TCRE control using RB at the fundus and cornual areas • *Surgeon experience:* Two surgeons each with 50 TCRE experience, training and 5 MEAs • *Surgery pretreatment:* Subcutaneous goserelin 3.6 mg 5 weeks before operation • *Type of anaesthesia:* GA	• *Total number of patients:* 263 (129 MEA, 134 TCRE) • *Indication for surgery:* Referred by gynaecological dept for EA • *Inclusion criteria:* Benign endometrial histological sample within 6 months, uterine size ≥ 10 week 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 years (SD 5.4), TCRE mean age 42.2 years (SD 5.8). For baseline SF-36 measures see below. TCRE had significant ($p = 0.03$) 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. SF-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 follow-up at 12 and 24 months

Results:	MEA ($n = 120$) preop.	MEA ($n = 120$) postop.	TCRE ($n = 129$) preop.	TCRE ($n = 129$) postop.	95% CI for difference (p)
• *Symptoms*					
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 to 1.3% ($p = 0.33$)
Dysmenorrhoea	84 (70%)	22 (18%) – same/worse	83 (64%)	29 (22%) – same/worse	–14 to 5% ($p = 0.78$)
2× or more sanitary protection	103 (86%)	9 (14%)	109 (84%)	17 (22%)	–13 to 2% ($p = 0.36$)
Mean bleeding score	28.1 (SD 9.4)	Median – 1 (0,6 25th, 75th percentile)	27.8 (SD 9.1)	Median 3 (0,10 25th, 75th percentile)	–1 to 0 ($p = 0.06$)
Mean pain score	18.9 (SD 11.4)	0 (0,7 25th, 75th percentile)	16.4 (SD 12.4)	1 (0, 8 25th, 75th percentile)	0 to 0 ($p = 0.22$)
Unchanged or heavier	–	8 (7%)		14 (11%)	–11 to 3% ($p = 0.10$)
amenorrhoea	–	57 (47%)		53 (41%)	–9 to 15% ($p = 0.19$)

	($n = 120$) postop.	($n = 120$) Change in score	($n = 129$) postop.	($n = 129$) Change in score	95% CI (p)
• *QoL* *SF-36 score* *Mean (SD)*					
Physical functioning	83.9 (19.8)	2.3 (21.3)[a]	82.5 (22.9)	0.9 (20.4)	–3.8, 6.6 (0.28)
Social functioning	59.9 (22.6)	10.1 (27.5)[b]	60.4 (22.8)	6.2 (23.7)[c]	–2.5,10.3 (0.33)
Role – physical	56.1 (43.1)	18.5 (53.7)[b]	63.7 (41.4)	6.1 (43.8)	–0.2,24.6 (0.06)
Role – emotional	61.3 (42.3)	17.8 (47.5)[b]	63.0 (42.9)	4.2 (40.1)[a]	–3.6, 23.5 (0.17)
Metal health	63.3 (18.8)	6.0 (21.6)[c]	63.3 (20.8)	4.1 (19.8)[c]	–3.3, 6.9 (0.44)
Energy/fatigue	43.6 (22.6)	11.4 (25.1)[b]	43.3 (24.4)	11.8 (22.6)[b]	–6.4, 5.5 (0.90)
Pain	55.7 (28.3)	13.5 (31.7)[b]	63.4 (26.0)	3.0 (29.8)	2.9, 18.2 (0.02)
General health	70.2 (21.6)	0.0 (24.4) (change from baseline significant)	73.0 (19.2)	–2.9 (19.0)	–2.5, 8.4 (0.29)

continued

Results:	MEA (n = 120) preop.	MEA (n = 120) postop.	TCRE (n = 129) preop.	TCRE (n = 129) postop.	95% CI for difference (p)
• *Satisfaction*					
Completely or generally satisfied		79%		67%	7 to 22 (0.02)
Recommend to friend		90%		90%	
Menstrual loss acceptable		96%		88%	0.6 to 14 (0.03)
• *Further surgery*					
Hysterectomy rate		11.60%		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 numbered envelopes showing 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?* Yes
- *Loss to follow-up?:* Yes: 249/263 LTFU at 2 years
- *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 non-parametric continuous variables. Independent nominal data were analysed using chi-squared or Fischer's exact test. Paired categorical data that were related or consisted of dichotomous variables were analysed with Wilcoxon's signed rank test and McNemar's 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

n/s, not significant.
[a] $p < 0.05$.
[b] $p < 0.001$.
[c] $p < 0.01$.

Reference and design	Intervention	Subjects	Outcome measures
• *Authors:* Microsulis, 2002[88] • *Study design:* RCT • *Recruitment dates:* April 2000 – Sept. 2001 • *Setting:* 8 sites in UK and USA	• *Treatment:* MEA RB • *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%, i.v. sedation 62%, regional <1%, sedation plus regional 1% RB, GA 76%, i.v. sedation 18%, regional 4%, sedation plus regional 2% At the centre excluded from above calculation. all women had GA	• *Total number of patients:* 322 (215 MEA, 107 RB) • *Indication for surgery:* abnormal uterine bleeding • *Inclusion criteria:* PBAC >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:* PBAC diary (baseline assessed though 1–3 months data collection, postop., 0 = amenorrhoea, treatment success <75), QoL by SF-36 • *Length of follow-up:* 12 months

	Intervention MEA (n = 215)		**Comparison RB (n = 107)**		
Results:	**preop.**	**postop.**	**preop.**	**postop.**	***p***
• *Symptoms*					
Success (PBAC <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 preop. 0.767 postop.
Success with fibroids		(n = 31)		(n = 26)	
	–	28 (90%)	–	23 (88%)	1.00
Amenorrhoea with fibroids	–	19 (61%)	–	10 (38%)	0.113
Success BMI >30 kg/m^2		(n = 60)		(n = 22)	
	–	58 (97%)	–	18 (82%)	0.042
Reason for treatment failure:		(n = 179)		(n = 92)	
Intermenstrual bleeding		0		1 (1%)	–
PBAC >75		4 (2%)	–	7 (8%)	–
Pt dissatisfaction		0		1 (1%)	–
• *QoL – SF-36*	(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	N/s
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

continued

	Intervention MEA (n = 215)		Comparison RB (n = 107)		
Results:	**preop.**	**postop.**	**preop.**	**postop.**	***p***
• *Operation details:*		(n = 209)		(n = 106)	
Anaesthesia time		39.26 (SD 25.44)		47.10 (SD 23.4)	0.007
Anaesthesia time (excluding the study with all GA)		41.67 (SD 26.21)		50 (SD 22.96)	0.009
Treatment time		3.45 (SD 1.02)		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 not stated
- *Power calculation?:* None stated
- *All patients given same intervention?:* Not stated. All receive same pretreatment
- *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 >30 kg/m^2

General comments

- *Generalisability:* Low. Few details of patient characteristics given and no exclusion criteria given
- *Main outcome measured independently:* Yes
- *Inter-centre variability:* Amenorrhoea rates between centres were assessed and showed a significant difference between treatments in only 1 of 8 studies. One study gave all patients GA and data about anaesthetic are provided with and without 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

BMI, body mass index.

Reference and design	Intervention	Subjects	Outcome measures
• *Authors:* Bongers *et al.*, 2000[89] • *Study design:* Prospective cohort study comparing TBEA and TCRE • *Recruitment dates:* All women undergoing TCRE in 1992–4, TBEA 1995–7 • *Setting:* General teaching hospital in The Netherlands	• *Treatment:* TBEA (Thermachoice) TCRE • *Surgeon experience:* Not stated • *Surgery pretreatment:* TCRE group GnRH for 8–12 weeks. TBEA D&C prior to procedure • *Type of anaesthesia:* GA or spinal anaesthetic	• *Total number of patients:* 152 (77 TBEA; 75 TCRE) • *Indication for surgery:* Menorrhagia unresponsive to medical treatment • *Inclusion criteria:* Patient decided on EA, eligible results of hysteroscopy and endometrial sampling • *Exclusion criteria:* Uterus sounded >12 cm, a separate uterus, submucous fibroids, intrauterine adhesions. • *Participant characteristics:* *TBEA:* Age 42.5 years (SD 6.3) Loss of clots 0 (0–10) Total endometrial thickness 8 (3–37) Uterine length 8.8 (SD 1.1) *TCRE:* Age 43.2 years (SD 6.4) Loss of clots 4 (0–10) Total endometrial thickness 8.5 (1–32) Uterine length 8.1 (SD 1.5)	• *Primary and secondary outcome measures used:* Surgical re-intervention Duration of menstruation, dysmenorrhoea, patients' satisfaction at 3, 6, 12 and 24 months. • *Method of assessing outcomes:* During a 20-minute outpatient visit. Satisfaction on a 4-point scale – perfectly satisfactory, satisfactory, no treatment effect, complaints worsened • *Length of follow-up:* 24 months

Results:	Intervention TBEA (n = 77) preop.	Intervention TBEA (n = 77) postop.	Comparison TCRE (n = 75) preop.	Comparison TCRE (n = 75) postop.	95% CI for difference (p)
• *Symptoms*					
Dysmenorrhoea	–	–	–	3 (4%)[a]	
None	38/77		31/75		No difference in baseline groups
Mild	28/77		30/75		
Moderate	1/77		2/75		
Severe	1/77		0		
Unknown	9/77		12/75		
Mean duration of menstruation days (range)	8 (1–30)		8 (2–25)		TCRE shorter at 3 months (p = 0.01) No difference detected at 6, 12 or 24 months
• *Bleeding patterns*					
Amenorrhoea	–				
3 months		17%		36%	
6 months		15%		22%	
12 months		16%		26%	
24 months		13%		17%	
Hypomenorrhoea	68/77	–	65/75	–	
Polymenorrhoea	2/77	–	0/75	–	
Metrorrhagia	7/77	2 (3%)[a]	10/75	7 (9%)[a]	
Menorrhagia	–	7 (9%)[a]	–	9 (12%)[a]	
• *QoL*					

continued

Results:	Intervention MEA (n = 215) preop.	Intervention MEA (n = 215) postop.	Comparison RB (n = 107) preop.	Comparison RB (n = 107) postop.	p
• *Satisfaction*					
Perfectly satisfied:					
3 months		51 (66%)		60 (80%)	No differences between the groups, however, significant interaction between changes over time – satisfaction decreased (p = 0.001) and decrease stronger in TCRE than TBEA
6 months		39 (63%)		39 (57%)	
12 months		40 (63%)		30 (52%)	
24 months		28 (60%)		20 (43%)	
Satisfied:					
3 months		15 (20%)		8 (11%)	
6 months		6 (10%)		5 (7%)	
12 months		8 (13%)		1 (2%)	
24 months		2 (4%)		3 (6%)	
No treatment effect:					
3 months		8 (10%)		6 (8%)	
6 months		10 (16%)		24 (35%)	
12 months		6 (10%)		21 (37%)	
24 months		5 (11%)		8 (17%)	
Complaints worsened:					
3 months		3 (4%)		1 (1%)	
6 months		7 (11%)		1 (1%)	
12 months		9 (14%)		5 (9%)	
24 months		12 (25%)		16 (34%)	
• *Operation details*					
Procedure abandoned		8 (10%) (converted to TCRE)		13 (17%) (9 no distention, 4 technical problems)	RR 1.7 (95% CI 0.73 to 3.8)
Learning curve effect		None		None	
• *Further surgery*					
Year 1 TCRE		–		4 (5%)	
Year 1 Hysterectomy		8 (10%)		12 (16%)	
Year 2 TCRE		–		4 (5%)	
Year 2 Hysterectomy		9 (12%)		15 (20%)	
3 year cumulative re-intervention rate		13%		26%	p = 0.11 RR 0.36 (95% CI 0.05 to 2.5)
• *Adverse effects*		–		Perforation 1 (hysterectomy next day) >2000 ml intravasation 3 (4%) >1000 ml intravasation 20 (26%)	

Methodological comments

- *Prospective?:* Yes
- *Consecutive patients enrolled?:* Yes for TCRE, uncertain for TBEA
- *Method of randomisation:* None
- *Power calculation?:* Yes – assuming a 9% re-intervention rate after TCRE, a series of 150 patients would be needed to show balloon ablation was equally effective. Note: this is only stated in the abstract, not in the body of the text
- *All patients given same intervention?:* Uncertain – likely that other aspects of care changed over time. In the first half of the study, women undergoing TBEA were treated for 8 minutes, whereas those in the second half were treated for 16 minutes
- *Loss to follow-up?:* Uncertain – this is not stated but TBEA group has no satisfaction data for 29 patients (38%) at 24 months, TCRE for 28 (37%)
- *Method of data analysis:* Differences in baseline tested using chi-squared or Student's t-test. Tested for learning curve effect by looking at the number of totally ablated endometrium at cases 1–20, 2–21, 3–22, etc. Analysis on ITT basis (although see data above – not all outcomes are reported as ITT, and some outcomes only percentages are given, making it impossible to calculate ITT). Kaplan–Meier curves constructed for re-interventions and compared using log-rank test. RR for re-intervention calculated using Cox regression analysis, univariate and multivariate. Repeated measures if variance (ANOVA) was used to establish time effects, treatment effect and time by treatment effect. For repeated measure data, patients with missing measurements included if they had data for at least 2 data points. Differences considered significant at $p < 0.05$ level. Student's t-test used to examine differences between groups at specific times

General comments

- *Generalisability:* Moderate
- *Main outcome measured independently:* Yes
- *Inter-centre variability:* N/A
- *Conflicts of interest:* None stated

RR, relative risk; ANOVA, analysis of variance.

[a] These are postoperative symptoms leading to surgical re-intervention.

Reference and design	Intervention	Subjects	Outcome measures
• *Authors:* Brun *et al.*, 2002[96] • *Study design:* RCT • *Recruitment dates:* Aug. 1999–Oct 2001 • *Setting:* 7 centres in France	• *Treatment:* TBEA (Cavaterm) Control TCRE • *Surgeon experience:* TCRE experienced surgeons • *Surgery pretreatment:* Conventional D&C performed just before operation start • *Type of anaesthesia:* Not stated	• *Total number of patients:* 51 randomised (29 Cavaterm, 21 TCRE, 1 LTFU) • *Indication for surgery:* Menorrhagia or menometrorrhagia (>80 PBAC) • *Inclusion criteria:* Normal uterus, no wish for future pregnancy, no clinical suspicious malignancy • *Exclusion criteria:* Menopause • *Participant characteristics:* TBEA: mean age 45.5 years (SD 6.04, range 35–59), mean weight 69 kg (SD 16.1, range 43–105), mean height 164 cm (SD 5.6, range 153–175) *TCRE:* mean age years 46.7 (SD 6.0, range 33–46), mean weight 68.6 kg (SD 20.9, range 42–111), mean height 160.9 cm (SD 5.6, range 145–168)	• *Primary and secondary outcome measures used:* Bleeding status, satisfaction, adverse effects • *Method of assessing outcomes:* Bleeding recording card based on Higham and Janssen (PBAC). Patient assessed own condition at follow-up, satisfaction rated as 'excellent, good, moderate or bad' • *Length of follow-up:* 3 months

Results:	TBEA preop. *n* = 29	TBEA postop.	TCRE preop. *n* = 21	TCRE postop.	95% CI for difference
• *Symptoms*					
Menorrhagia	13 (45%)		12 (57%)		
Meno-metrorrhagia	14 (48%)		7 (33%)		
Metrorrhagia	2 (7%)		2 (10%)		
Bleeding score		At 3 months		At 3 months	
Mean (SD)	459 (237)	44 (48)	273 (107)	75 (78)	
Median (range)	365 (132–1000)	33 (0–154)	266 (81–467)	64 (0–259)	
Mean change (SD) (95% CI)		–413 (242) (–284, –542)		–199 (157) (–107, –289)	In both groups significantly change from baseline ($p < 0.001$)
• *QoL*	–	–	–	–	–
• *Satisfaction*					
Excellent		12 (41%)		8 (38%)	
Good		15 (52%)		11 (52%)	
Moderate		2 (7%)		2 (9%)	
• *Operation details*					
• *Further surgery*		–		–	
• *Adverse effects*					
Burns in the cervical channel		1 (3%)		0	

Methodological comments
- *Prospective?:* Yes
- *Consecutive patients enrolled?:* Unclear
- *Method of randomisation:* 1:1 randomisation done centrally (does this tally with 29:21 patients in the 2 groups?)
- *Power calculation?:* 80 patients per treatment arm needed for a 15% difference in efficacy with a power of 90% at the 5% significance level. This study reports on <30 patients per arm as many patients preferred TBEA and refused to be randomised
- *All patients given same intervention?:* No – TCRE performed to local protocols, RB adjunct was used as a complement therapy for some
- *Loss to follow-up?:* 1 lost at randomisation prior to treatment – not stated from which group
- *Method of data analysis:* Not ITT and cannot be calculated. Continuous data analysed by *t*-tests. Fisher's exact probability test used to analyse non-parametric data. Patient characteristics data missing from 5/29 and 7/21 (24%)

General comments
- *Generalisability:* Moderate – 24% of patients did not have baseline characteristics of weight and height recorded
- *Main outcome measured independently:* Semi
- *Inter-centre variability:* Not assessed. Centres recruited 3–13 women
- *Conflicts of interest:* None stated

Reference and design	Intervention	Subjects	Outcome measures
• Authors: Gervaise *et al.*, 1999[90] • *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 pretreatment:* None • *Type of anaesthesia:* LA used where medically necessary, or desired by patient in TBEA group – 28 (38%)	• *Total number of patients:* 147 (73 BEA, 74 TCRE) • *Indication for surgery:* Abnormal uterine bleeding • *Inclusion criteria:* 40+ years, excessive menstrual blood loss (as measured by no. of pads/cycle), premenopausal women had to have failed medical therapy (progestins) or be unwilling to continue with them, postmenopausal women were not willing to discontinue HRT • *Exclusion criteria:* Fibroids, polyps, premalignant lesions, uterine cavity >12 cm, those wishing to retain fertility • *Participant characteristics:* TBEA: Age 46.3 ± 1.3 years (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 years (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 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

	TBEA		**TCRE**		
Results:	***n* = 73 Immediate preop.**	***n* = 44 24 months postop.**	***n* = 74 Immediate preop.**	***n* = 47 24 months postop.**	***p***
At 24 months					
• *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*	–	–	–	–	–

continued

• *Operation details*			
Mean operating time	20.3 minutes	44.8 minutes	<0.05
% cases complete in 30 minutes	100%	52.60%	<0.05
• *Further surgery*			
TCRE	0	1	
Hysterectomy	7	5	
• *Adverse effects*			
Perioperative	0	0	
Endometritis	0	2	
Pregnancy (miscarried)	1	0	

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-squared. Student's *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
• Authors: Meyer *et al.*, 1998[82] • *Study design:* RCT • *Recruitment dates:* Jan.–Sept. 1996 • *Setting:* 12 centres in USA and Canada	• *Treatment:* Thermachoice thermal balloon Control – RB • *Surgeon experience:* All had "extensive experience of RB EA" • *Surgery pretreatment:* None • *Type of anaesthesia:* GA TBA 53%, RB 84%	• *Total number of patients:* 275 • *Indication for surgery:* Menorrhagia • *Inclusion criteria:* Aged 30+ years, 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 and 10 cm, no further desire for childbearing, willing to continue with contraception for 3 years postablation • *Exclusion criteria:* Women with submucous myomas or suspected genital tract infection or malignancy, those who had undergone previous EA • *Participant characteristics:* mean (SD) range: TBEA – Age 40.2 years (4.9) 30–51; BMI 24.0 (6.5) 14.4–52.7; age at onset of menorrhagia 29.6 years (9.7) 10.0-47.0; years with menorrhagia 9.9 (8.5) 0.5–37.0; uterine cavity 8.6 cm (1.1) 4.0–10.0. RB – Age 40.9 years (5.2) 29–50; BMI 22.9 (5.5) 15.7–39.6; age at onset of menorrhagia 29.8 years (9.6) 11.0–49.0; years 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 – scores of >150 for menorrhagia. Examination at 3, 6 and 12 months • *Length of follow-up:* 12 months

	Intervention TBEA		Comparison RB		
Results:	**preop. (*n* = 128)**	**postop. (*n* = 125)**	**preop. (*n* = 117)**	**postop. (*n* = 114)**	***p***
(*n* = 245 – completed 6-month follow-up)					
• *Symptoms*					
PMS	115 (89.8%)		106 (90.6%)		
PMS moderate/severe	101 (78.6%)[a]	41 (32.8%)	90 (76.6%)[a]	33 (29.0%)[a]	<0.05 prepost both arms
Dysmenorrhoea	22 (17.2%)	Decreased 88 (70.4%)	19 (16.2%)	Decreased 86 (75.4%)	Differences between arms, >0.05
Mild	52 (40.6%)	Same	37 (31.6%)	Same	
Moderate	45 (35.2%)	31(24.8%)		26(22.8%)	
Severe		Increased 6 (4.8%)	54 (46.2%)	Increased 2 (1.8%)	<0.05
Amenorrhoea (12 months)	–	19 (15.2%)	–	31 (27.2%)	
Mean diary score	552.5	–	570.5	–	
% decreased by	–	107 (85.5%)	–	104 (91.7%)[a]	
<100 at 12 months (normal)	–	100 (80.2%)	–	96 (84.3%)[a]	

continued

	Intervention TBEA		Comparison RB		
Results:	**preop. (*n* = 128)**	**postop. (*n* = 125)**	**preop. (*n* = 117)**	**postop. (*n* = 114)**	***p***
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 (~60%)		~68 (~60%)	
Menorrhagia has severe impact	At least 90 (70%+)[a]	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%)	
• *Operational details*					
Procedure time					
<30 min		89 (71.0%)		33 (28.6%)	<0.05
>50 min		3 (2.3%)		20 (18.0%)	
• *Further surgery*					
Prior to 1 year 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 RB, 108 evaluable patients needed to detect if TBEA is more than 20% less effective than RB (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 RB and 4 TBEA patients LTFU or withdrew
- *Method of data analysis:* Paired *t*-tests, chi-squared 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

[a] 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 [a] 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 have been excluded without comment (changing the denominator) causing this anomaly.

Reference and design	Intervention	Subjects	Outcome measures
• *Authors:* Grainger *et al.*, 2000[84] • *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 – RB electrosurgical ablation • *Surgeon experience:* All experienced in RB and trained in balloon ablation • *Surgery pretreatment:* No drug pretreatment. 3-minute curettage using 5 mm curette prior to ablation • *Type of anaesthesia:* Not stated	• *Total number of patients:* 255 • *Indication for surgery:* Excessive menstrual bleeding • *Inclusion criteria:* Aged 30+ years, premenopausal, documented history of 3 months' HMB (measured by pictorial diary system as 80 ml or more), uterine cavity between 6 and 10 cm, no further fertility desired, continue current contraception for 3 years • *Exclusion criteria:* Women with submucous myomas, suspected genital tract infection or malignancy, history of EA • *Participant characteristics:* None stated	• *Primary and secondary outcome measures used:* Amount of uterine bleeding, effect on QoL. Secondary complications and adverse effects • *Method of assessing outcomes:* Pictorial diary system for bleeding, questionnaire for other menstrual symptoms, impact on life and satisfaction with treatment. Adverse effects documented and recorded. • *Length of follow-up:* 48 months. Following-up telephone contact at 24 h, examined at 1 week, 3 and 6 months, 1 and 2 years

	Thermal Balloon			RB			
Results:	**preop. (*n* = 131)**	**postop. (*n* = 122) 1 yr**	**2 yr**	**preop. (*n* = 124)**	**postop. (*n* = 105) 1 yr**	**2 yr**	**95% CI for difference**
• *Symptoms*							
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 1 year decreased by 85.5%			At 1 year decreased by 91.7%		n/s
		postop. yr 1	**postop. yr 2**		**postop. yr 1**	**postop. yr 2**	
• *Satisfaction*		85.60%	105 (86.1%)		86.70%	91 (86.7%)	n/s
Very satisfied		10.40%	12 (9.8%)		12.40%	12 (11.4%)	n/s
Not satisfied		4%	5 (4.1%)		0.90%	2 (1.9%)	n/s
Recommend procedure			119 (97.5%)			103 (99%)	n/s
		Age (years)			**Age (years)**		
Menstrual symptoms at 2 years		<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
• *Further surgery*	4 (3%)			11 (8.9%)			
• *Adverse effects*	1 (0.8%) pregnancy 2.5 years after ablation						

continued

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 RB, 108 evaluable patients 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 year 227/255 on study at 2 years
- *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 year is definitely not ITT [no PMS at 1 year (n = 34) 27.2% at 2 years (n = 35) (29.2%) TBEA; no PMS at 1 year (n = 32) 28.1%, at 2 years (n = 37) 35.2% (RB)]

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
• *Authors:* Loffer, 2001[85] • *Study design:* RCT • *Recruitment dates:* Jan.–Sept. 1996 • *Setting:* 12 US and 2 Canadian university and private practice sites.	• *Treatment:* TBEA • *Surgeon experience:* All investigators were experienced in RB and trained in TBEA • *Surgery pretreatment:* No drugs used. Timed 3-minute suction curettage given to all prior to ablation • *Type of anaesthesia:* LA, LA with sedation and GA. GA more frequent with RB	• *Total number of patients:* 275 enrolled. 255 treated under protocol (131 TBEA, 124 RB). At 3 years data available for TBEA 114 and RB 100 • *Indication for surgery:* Menorrhagia • *Inclusion criteria:* Aged 30+ years, 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, 4–10 cm sound, no desire for further fertility, willing to continue for 3 years 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:* Patients 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 h. Examined at 1 week, 2, 6 and 12 months. Interviewed at 2 and 3 years

	TBEA		**RB**		
Results:	**preop.**	**postop. at 3 years (*n* = 114)**	**preop.**	**postop. at 3 years (*n* = 99)**	**95% CI difference**
• *Symptoms*					
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%)[a]	2 (1.8%)	108 (78.6%)[a]	2 (2.0%)	
Moderate impact	38 (28.1%)[a]	9 (7.9%)	28 (20.5%)[a]	8 (8.0%)	
Minor impact	2 (1.6%)[a]	103 (90.3%)	1 (0.9%)[a]	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%)	

continued

• *Satisfaction*		
	(*n* = 114)	(*n* = 100)
Very satisfied or satisfied	109 (95.6%)	97 (94%)
• *Further surgery*	(*n* = 114)	(*n* = 99)
	9 (7.9%)	14 (14%)
	(1 repeat EA,	hysterectomies
	8 hysterectomies)	
• *Adverse effects*	0	2 (1.6%)
		Fluid overload (Perioperative)
		1 (0.8%) cervical laceration
Postoperative	3 (2.3%)	1 (0.8%) each endometritis,
	possible endometritis	hematometra, postablation
	1 (0.8%) UTI	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 RB 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 patients 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 years, 17 from the TBEA and 24 from the RB group were LTFU
- *Method of data analysis:* ITT not performed

General comments

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

[a] 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 [a] 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 have been excluded without comment (changing the denominator) causing this anomaly.

Reference and design	Intervention	Subjects	Outcome measures
• *Authors:* Loffer and Grainger, 2002[94] • *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 – RB • *Surgeon experience:* All experienced with RB ablation and trained in TBEA • *Surgery pretreatment:* 3-minute suction curettage • *Type of anaesthesia:* Not stated	• *Total number of patients:* 255 treated (131 TBEA, 124 RB), 147 (76 TBEA, 71 RB) follow-up 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 anatomical abnormalities • *Patient characteristics:* At study recruitment mean age TBEA 40.4 years, RB 40.9 years. At 5-year follow-up mean age TBEA 45.7, RB 46.1 year. 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 telephone 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 years) • *Length of follow-up:* 5 years (±3 months)

Results:	**TBEA at 3 years (*n* = 14)**	**TBEA at 5 years (*n* = 61)**	**RB at 3 years (*n* = 98)**	**RB at 5 years (*n* = 61)**	***p***
• *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%)	0.87
• *Satisfaction*					
Satisfied with procedure		57 (93%)		61 (100)	
Of those who had a further procedure – satisfied (*n* = 25)	22 (88%)				

continued

Results:	**TBEA at 5 years (*n* = 61)**	**RB at 5 years (*n* = 61)**	***p***
• *Further surgery*			
Between year 3 and year 5 follow-up:			
Hysterectomy	13	7	
Repeat ablation	2	2	
D&C	0	1	
At 5 years follow-up:			
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, years of menorrhagia, sound measurement, procedure duration, age and BMI. No characteristic strongly predicted treatment outcome

  Note that 6/14 patients reporting amenorrhoea at 5 years were over 50 and/or experiencing hot flushes

  Data for dysmenorrhoea have been extracted from presented graph; data in the text do not concur with the graph – indicating much less moderate to severe dysmenorrhoea than shown

General comments

- *Generalisability:* Moderate – baseline characteristics not provided although they are reported in other papers relating to this trial
- *Main outcome measured independently:* Uncertain
- *Inter-centre variability:* None stated
- *Conflicts of interest:* Supported in part by Gynaecare

Reference and design	Intervention	Subjects	Outcome measures
• *Authors:* Pellicano *et al.*, 2002[92] • *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 pretreatment:* TCRE group depot GnRH (Enantone 3.75) 6 and 2 weeks before surgery. No pretreatment 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 <100 kg, not desiring pregnancy, uterine size <12 weeks, documented history of at least 3 months' failed medical treatment, documented evidence of normal endometrial histological 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 28.3 kg/m^2 (SD 1.4), mean parity 1.8 (SD 1.0), mean uterine dimensions 315 mL (SD 43), duration of symptoms 3.3years (±1.1). TBEA: mean age 42.6 (SD 4.4), mean BMI 29.8 kg/m^2 (SD 1.9), mean parity 1.9 (SD ±0.7), mean uterine dimensions 295 ml (SD 58), duration of symptoms 3.5 years (±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 from 1 (no pain) to 5 (intolerable pain) and at discharge. Postoperatively, asked to record for 1 week pain, vaginal bleeding and return to normal activities, to intercourse, to sexual activity and to work Follow-up at 3 months, 1 year and 2 years, patients asked for pain and bleeding symptoms and given a questionnaire for satisfaction measured by 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

continued

	TCRE/RB (n = 42)		TBEA (n = 40)		
Results:	**preop.**	**postop.**	**preop.**	**postop.**	***p***
• Symptoms					
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 3 months		1 (2%)		0	
Pain recurs at 1 year (n = 38, 37)		7 (18%)		1 (3%)	0.01
Pain recurs at 2 years (n = 33, 35)		9 (27%)		2 (6%)	0.01
Bleeding recurs					
At 3 months		3 (7%)		1 (3%)	
At 1 year (n = 38, 37)		6 (16%)		2 (5%)	0.01
At 2 years (n = 33, 35)		8 (24%)		3 (9%)	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 months (n = 42, 40)					
Excellent		21 (50%)		27 (67%)	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%)	0.001
Good		12 (32%)		10 (27%)	
Moderate		10 (26%)		5 (13%)	
No improvement		4 (10%)		2 (5%)	
At 2 years (n = 33, 35)					
Excellent		2 (6%)		16 (46%)	0.001
Good		18 (54%)		12 (34%)	
Moderate		3 (9%)		5 (14%)	
No improvement		10 (30%)		2 (6%)	
• *Operation details*					
Operative time (minutes) (SD)		37 (±6)		24 (±4)	0.01
Intraoperative blood loss (ml) (SD)		89 (±38)		7.2 (±2.8)	0.01
Discharge time (days) (SD)		1.3 (0.6)		1.0 (0.4)	n/s
• *Further surgery*					
Reoperation rate:					
3 months		0		0	ns
1 year (n = 38, 37)		4 (10%)		2 (5%)	0.01
2 years (n = 33, 35)		5 (15%)		2 (6%)	0.01

continued

	TCRE/RB (n = 42)		TBEA (n = 40)		
Results:	**preop.**	**postop.**	**preop.**	**postop.**	***p***
• *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
Postoperative					
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)	0.01
Pain at 3 days (VAS)		0.5 (±0.2)		0.4 (±0.1)	n/s
Pain at 7 days (VAS)		0		0	n/s
Urinary incontinence at 2 years (n = 33, 35)		3 (9%)		2 (6%)	
CIN grade 1 (year 2)		1 (3%)		1 (3%)	
Postoperative vaginal bleeding (days)		7.8 (±1)		5.2 (±1.8)	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 1 year (7%) and 9 TCRE and 5 BEA LTFU at 2 years (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's *t*-test for unpaired data, preoperative basal differences using Students *t*-test for paired data. Chi-squared test used for postoperative 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

Reference and design	Intervention	Subjects	Outcome measures
• *Authors:* Romer, 1998[83] • *Study design:* Prospective RCT • *Recruitment dates:* Not given • *Setting:* Not given	• *Treatment:* Thermal balloon (Cavaterm) vs RB ablation • *Surgeon experience:* Not given • *Surgery pretreatment:* 2× 4 weekly injections of GnRH (leuprolide 3.75 mg) operation performed 2 weeks after injection • *Type of anaesthesia:* GA for both interventions	• *Total number of patients:* 20 (10 intervention, 10 control) • *Indication for surgery:* Recurrent therapy refractory menorrhagia (not assessed) • *Inclusion criteria:* Menorrhagia • *Exclusion criteria:* Internal uterine cavity length 10 cm, incomplete family planning, intrauterine abnormalities, myomas, glandular–cystic, adenomyosis hyperplasia, carcinoma • *Participant characteristics:* Age, RB 40 (35–50) years, TBEA 42 (37–52) years; hormone therapy attempts, RB 3 (2–5), TBEA 3 (1–6); curettage, RB 2.5 (2–4), TBEA 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
	preop.	postop.	preop.	postop.	
• Symptoms					
• Bleeding patterns					
Amenorrhoea		4 (40%)		3 (30%)	Dichotomous data presented
Hypomenorrhoea		5 (50%)		6 (6%)	
Eumenorrhoea		1 (10%)		1 (1%)	
Hypermenorrhoea		0		0	
• *QoL*	Not reported				
• *Satisfaction*	All patients satisfied with treatment outcome				No CI given
• *Operation details*	–				
• *Further surgery*	No treatment failures reported at 9–15 months				
• *Adverse effects*	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
• *Authors:* Soysal *et al.*, 2001[91] • Study design: RCT • *Recruitment dates:* Sept. 1997–Feb. 1999 • *Setting:* University medical centre in Turkey	• *Treatment:* TBEA Control – RB ablation, glycine distention medium • *Surgeon experience:* RB performed by one experienced surgeon, TBEA by staff surgeons or supervised residents • *Surgery pretreatment:* Two monthly injections of depot GnRH analogue (3.6 mg goserelin acetate) • Type of anaesthesia: All TBEA LA, all RB GA	• *Total number of patients:* 96 (48 TBEA, 48 RB) • *Indication for surgery:* Myoma-induced menorrhagia • *Inclusion criteria:* Age 40+ years, completed childbearing, PBAC documented menorrhagia, myomatous uterus diagnosed by ultrasound examination, uterine size 12 weeks or less, at clinical evaluation or 380 ml or less at ultrasound or a myoma less than 5 cm diameter. All patients had a physical exam., diagnostic hysteroscopy, suction biopsy and cervical smear • *Exclusion criteria:* Active PID, any submucous myoma larger than 3 cm or with <50% intramural extension shown in high-resolution or in diagnostic hysteroscopy • *Participant characteristics:* mean (range) TBEA – age 43.6 ± 2.5 years (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); RB – age 44.3 ± 2.6 years (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 preoperatively and at 12 months. Operating time (from insertion of operating tool to removal), intraoperative complications, postoperative pain score recorded 12 h 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

	TBEA (*n* = 45)		**RB (*n* = 48)**		
Results:	**preop.**	**postop.**	**preop.**	**postop.**	***p***
• *Symptoms*					
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	n/s
Mean increase in Hb (g/dl)		2.7 ± 1.9		3.0 ± 1.6	n/s
Amenorrhoea		5		8	n/s
PBAC <76		75%		79%	n/s
• *QoL*	–	–	–	–	–

continued

• *Satisfaction*			
Not very satisfied	33%	39%	n/s
• *Operation details*			
Operation time (minutes)	11.5 ± 0.8	37.3 ± 7.5	0.0001
• *Further surgery*			
Hysterectomy	4	4	n/s
• *Adverse effects*			
Linear pain score at 12 h	3.1 ± 1.7	3.2 ± 2.1	n/s
Intraoperatively:			
Fluid overload	–	2	0.05
Haemorrhage	–	2	
Cervical injury	–	1	
Postoperative:			
Haematoma	1	2	n/s
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 patients recruited, 3 patients 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:* N/A
- Conflicts of interest: None stated

PID, pelvic inflammatory disease.

Reference and design	Intervention	Subjects	Outcome measures
• *Authors:* Zon-Rabelink, 2001[93] • *Study design:* RCT • *Recruitment dates:* Not stated • *Setting:* The Netherlands. Number of centres not given	• *Treatment:* TBEA, Control RB • *Surgeon experience:* Not stated • *Surgery pretreatment:* All patients pretreated 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 RB 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 preoperative 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

	TBEA (*n* = 77)		**RB (*n* = 60)**		
Results:	**preop.**	**postop.**	**preop.**	**postop.**	***p***
• *Symptoms*					
PBAC		Lower		Higher	0.01 at 2 years but n/s at 6 and 12 months
Menstrual reduction		More		Less	0.03 at 2 years
Success (PBAC <185) year 1		79% (95% CI 68 to 88%)		79% (95% CI 66 to 88%)	
Success (PBAC <185) year 2		78% (95% CI 67 to 87%)		76% (95% CI 63 to 86%)	
• *QoL*		–		–	–
• *Satisfaction*					
At 2 years		80%		75%	0.53
• *Operation details*					
Mean operation time		Shorter		Longer	0.001
Postoperative pain medication		More		Less	0.01
• *Further surgery*					
At 2 years		17%		15%	
• *Adverse effects*					
Intraoperative complications		None		Perforation of uterus, laceration of cervix, electrolyte dis-balance, suspicion of perforation	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 (<45 or >45 years) 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

Appendix 8

Graphs showing sensitivity analyses for MEA and TBEA

Sensitivity analyses are illustrated in *Figures 19–27*.

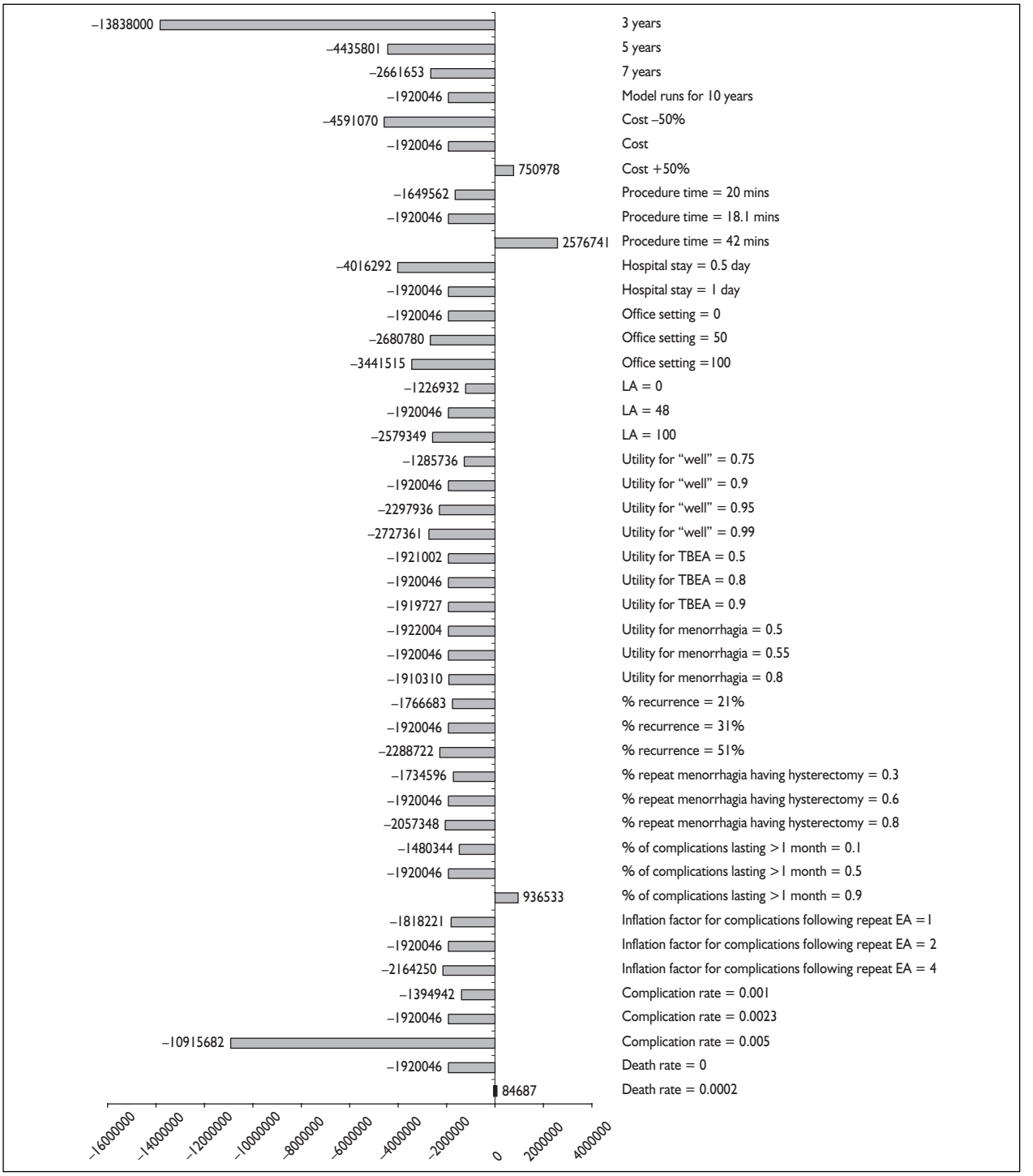


FIGURE 19 *Sensitivity analysis: cost per QALY for TBEA versus MEA*

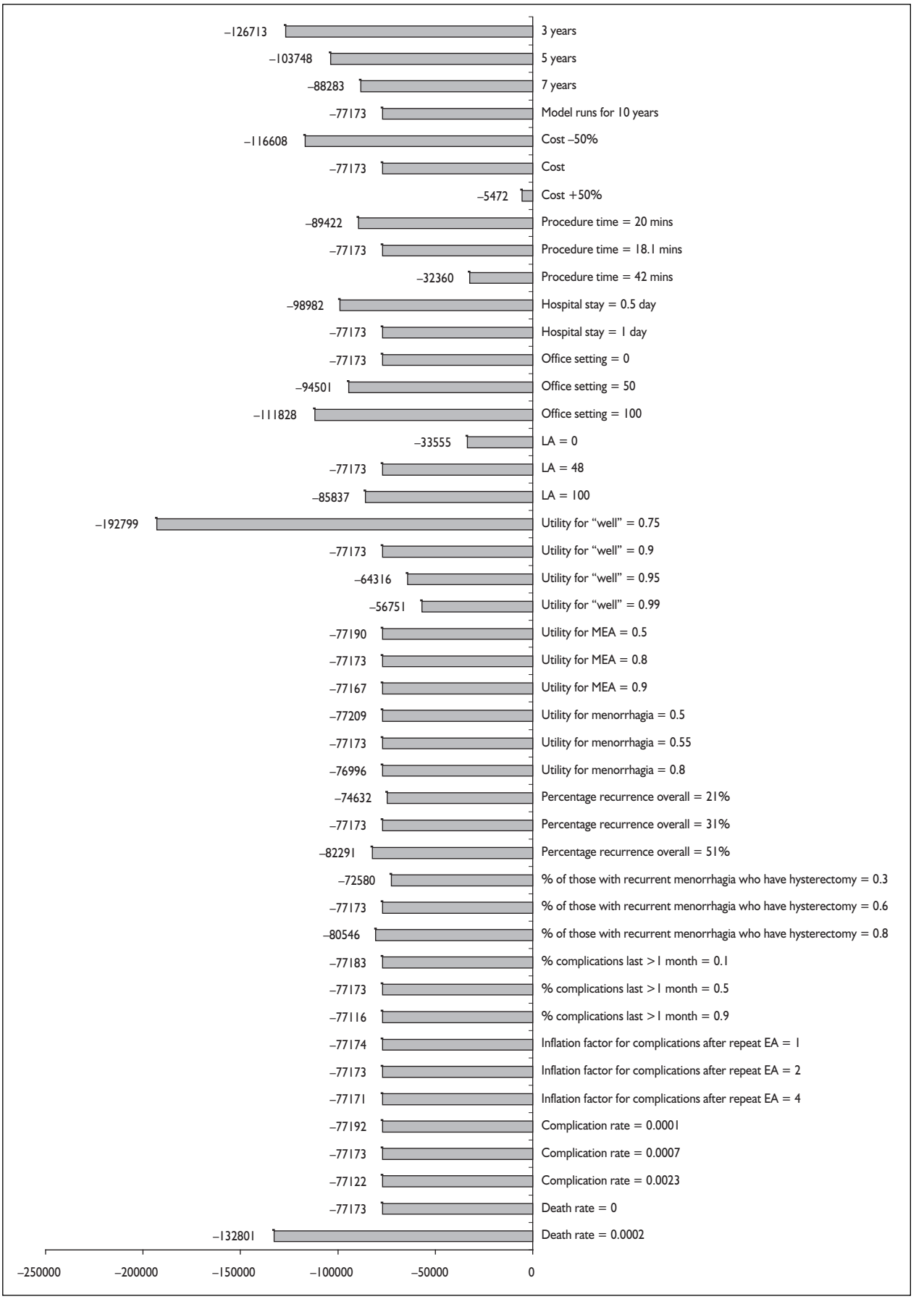


FIGURE 20 *Sensitivity analysis: cost per QALY MEA versus TCRE*

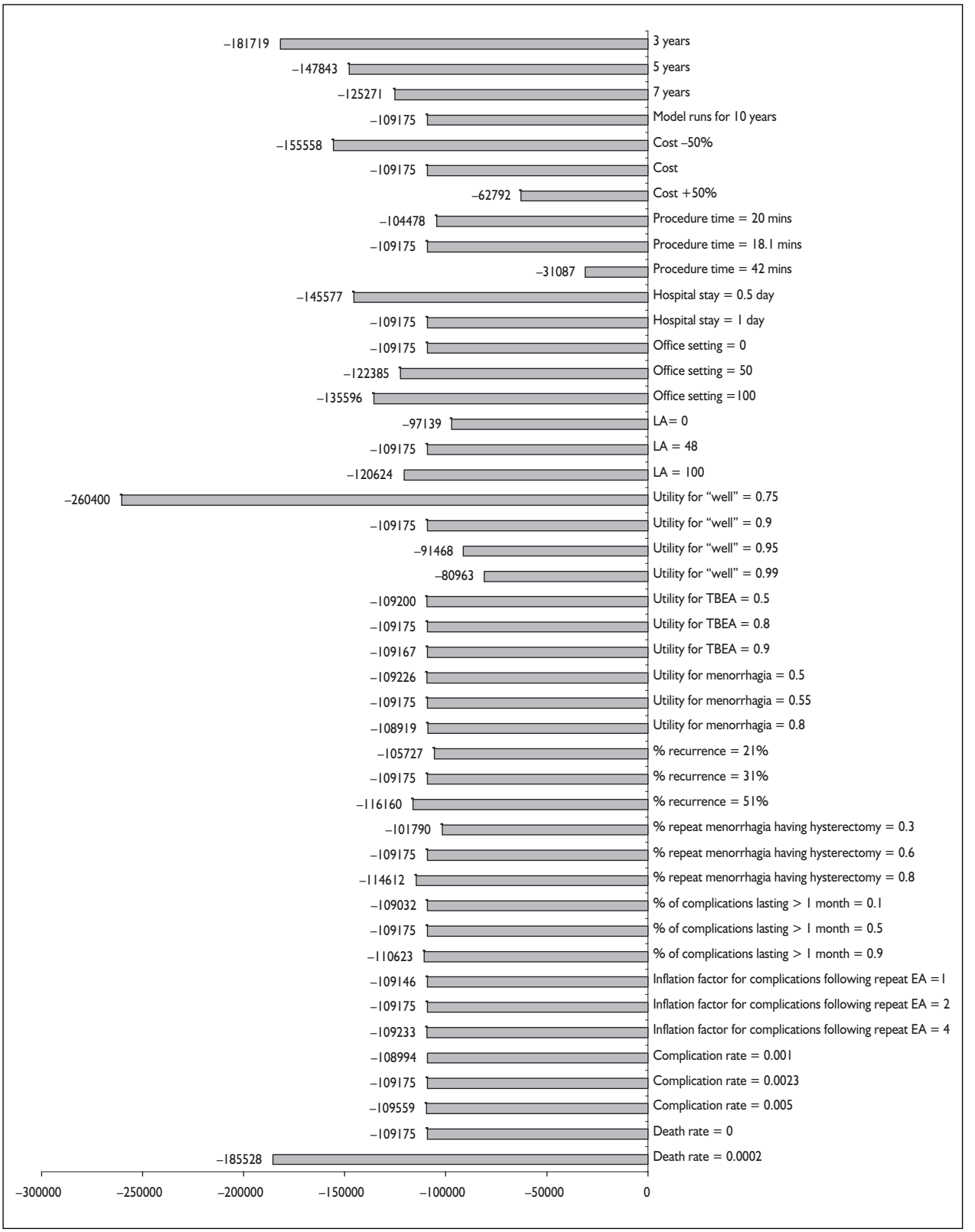


FIGURE 21 *Sensitivity analysis: cost per QALY TBEA versus TCRE*

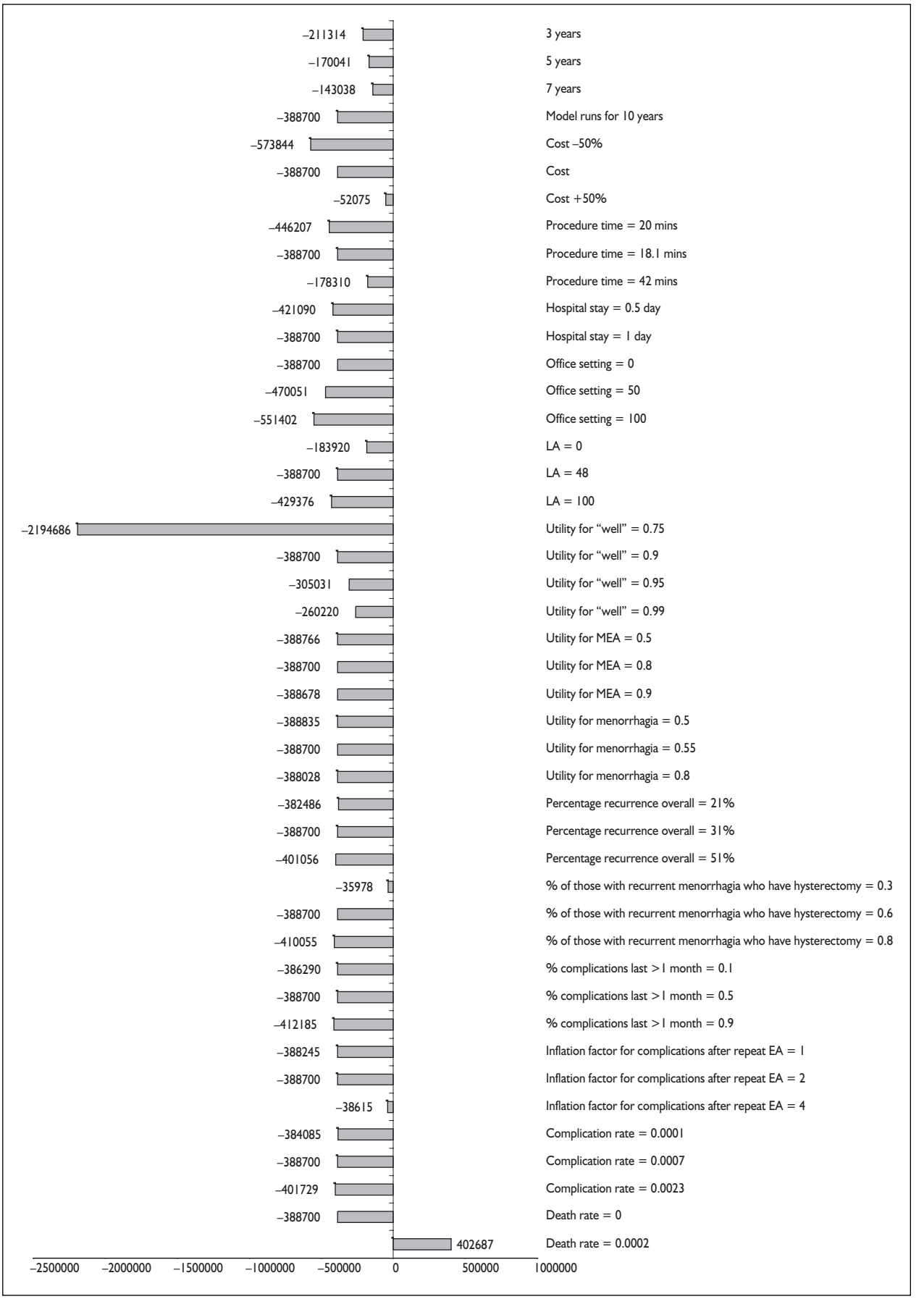


FIGURE 22 *Sensitivity analysis: cost per QALY MEA versus RB ablation*

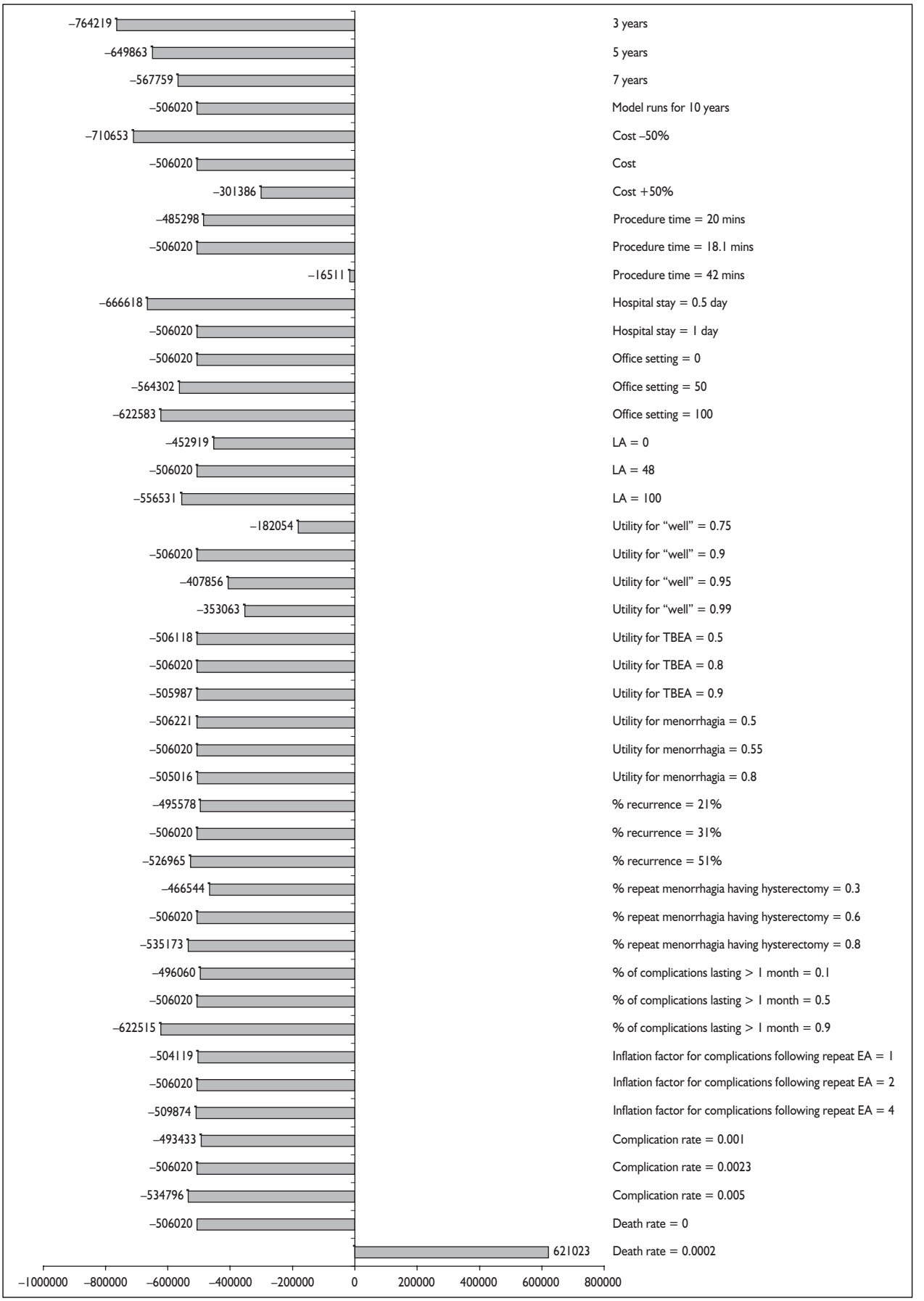


FIGURE 23 *Sensitivity analysis: cost per QALY TBEA versus RB ablation*

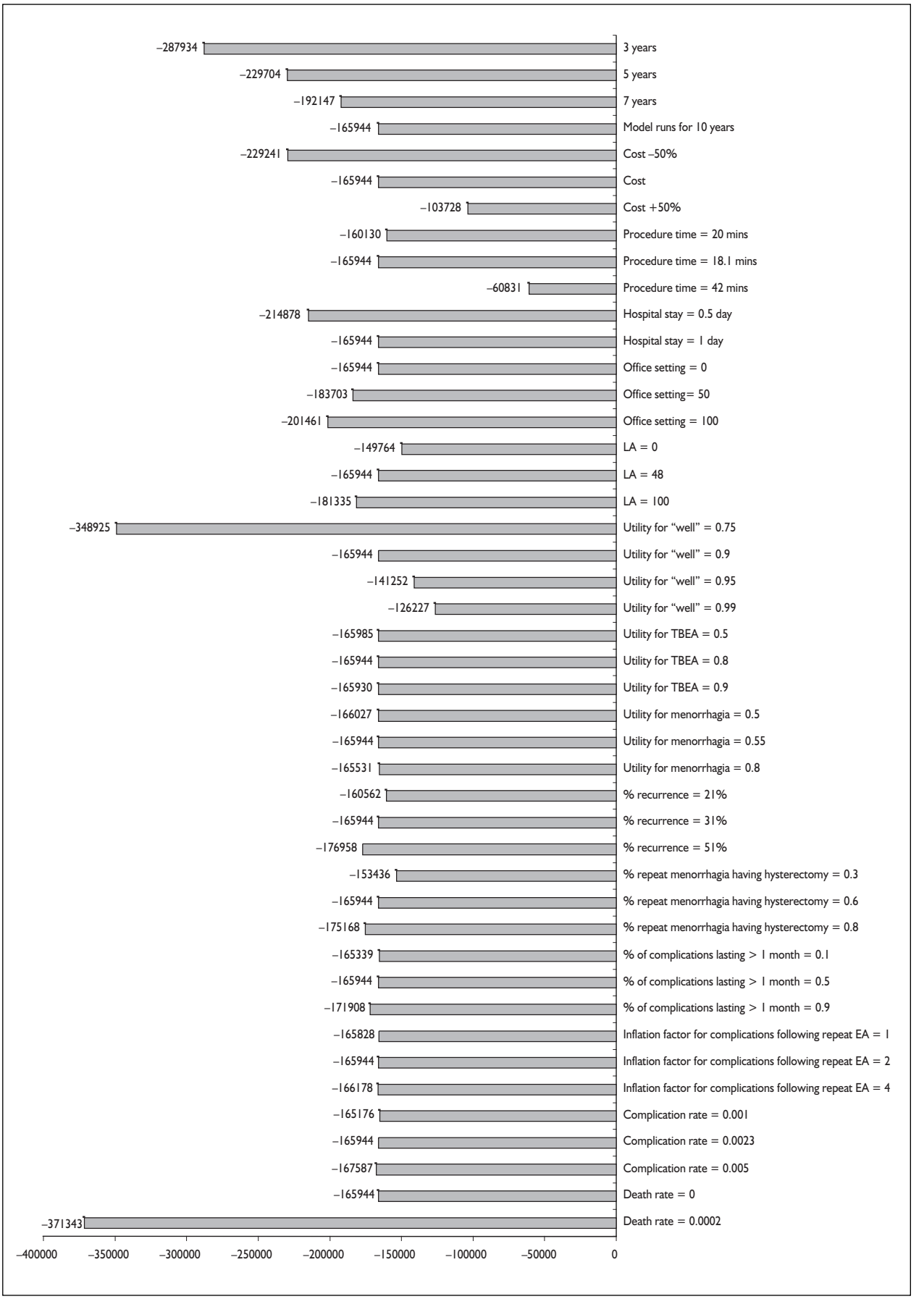


FIGURE 24 *Sensitivity analysis: TBEA versus combined TCRE and RB ablation*

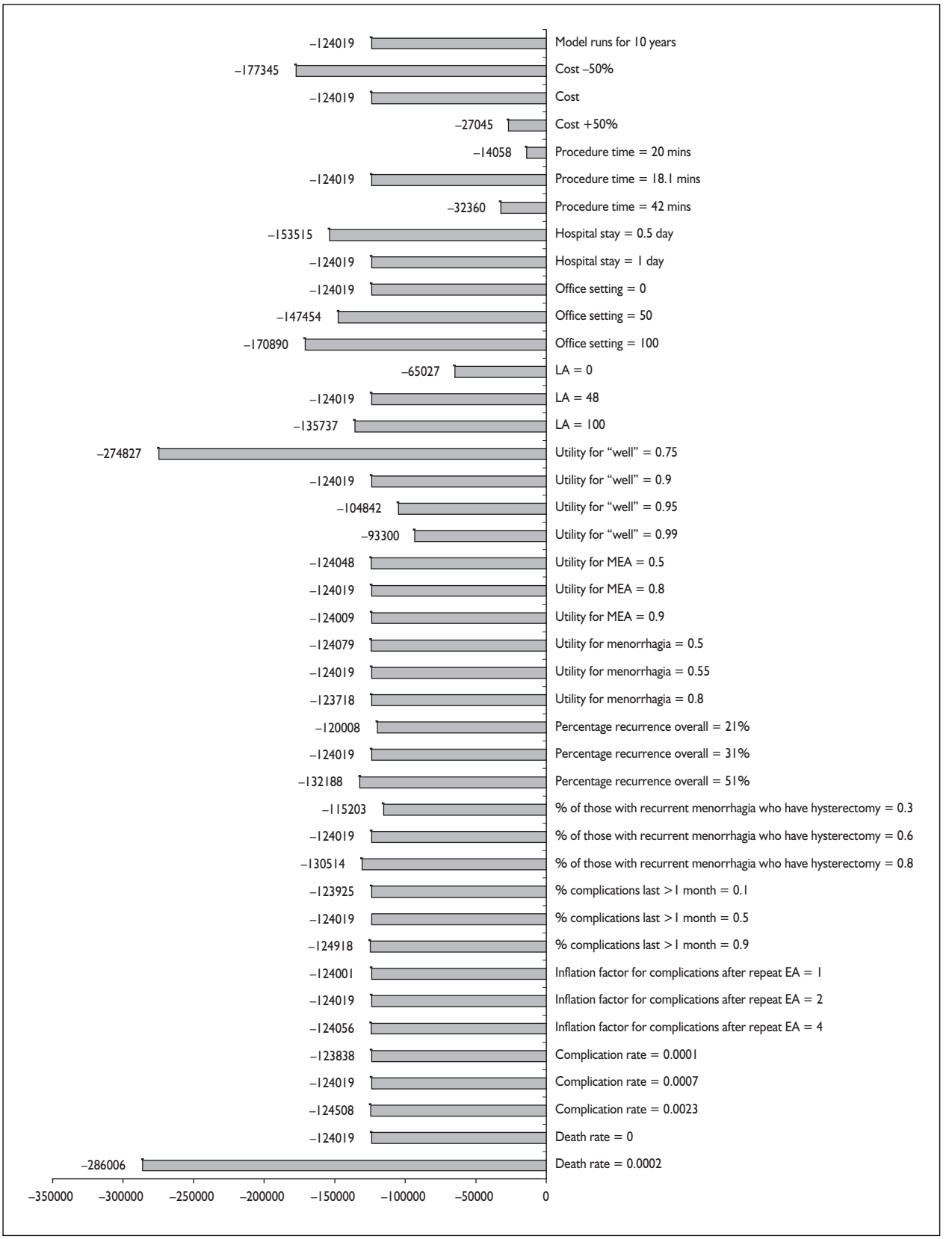


FIGURE 25 *Sensitivity analysis: MEA versus combined TCRE and RB ablation*

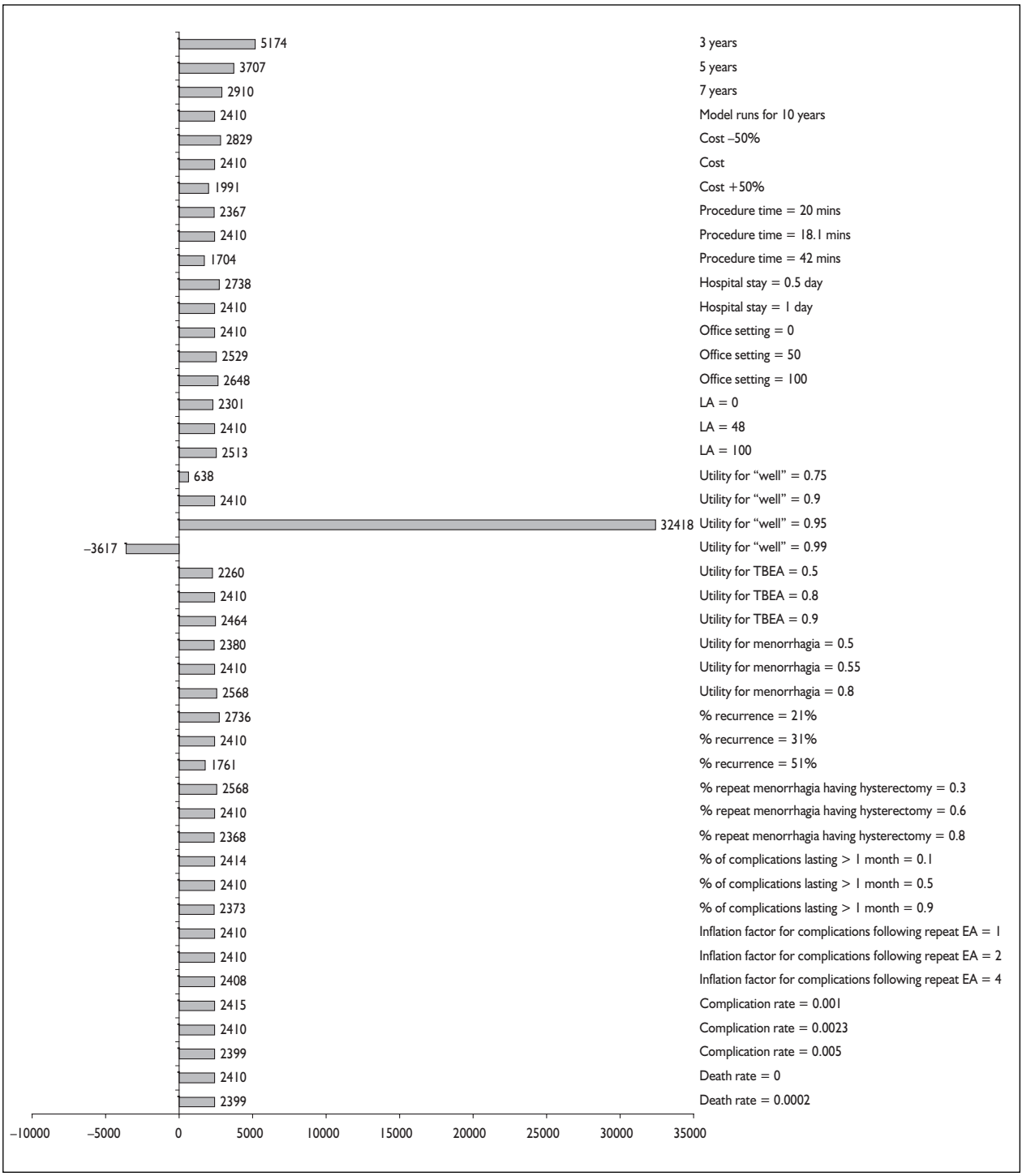


FIGURE 26 *Sensitivity analysis: cost per QALY for TBEA versus hysterectomy*

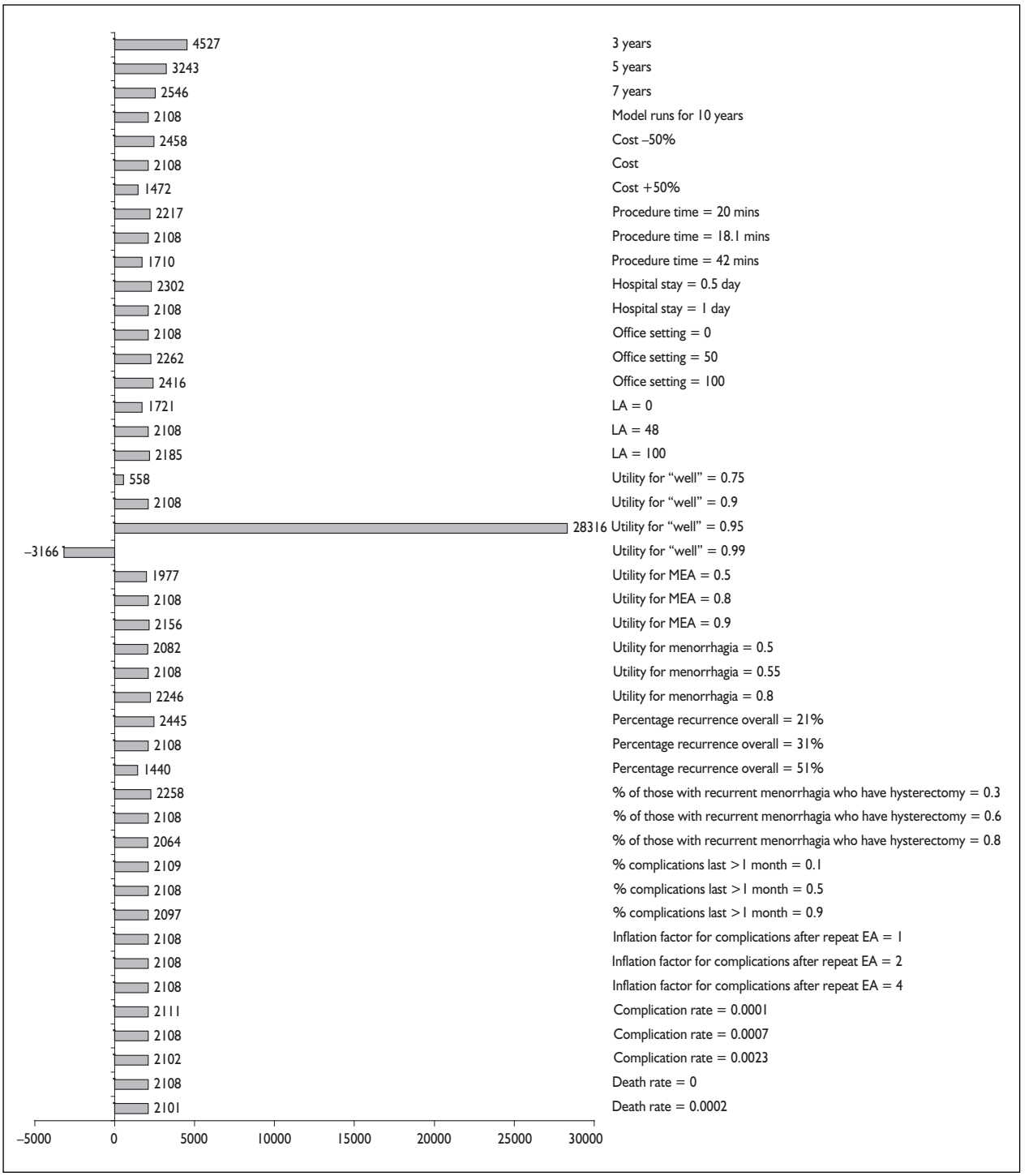


FIGURE 27 *Sensitivity analysis: cost per QALY MEA versus hysterectomy*

Appendix 9

Quality assessment of industry-submitted economic analyses

Assessment of economic model supplied by Microsulis Medical (based on the 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, RB ablation, RB 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, postoperative, menorrhagia, further surgery and hysterectomy). Stage 2 is slightly different for women having MEA than with the other ablation methods, as those with recurrent menorrhagia have a TCRE/RB 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 5 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 5.
5. Cycle length (if relevant)	
If relevant, is the cycle length used in the model stated.	Not relevant.
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 1, 2 and 3 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 1 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. Owing to the similarity of descriptions for convalescence with TCRE being 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 pounds sterling. Theatre overhead costs are calculated from information received from a single Scottish NHS trust. 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 come 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 RB 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 LA in an office setting and 67% of the remaining women had LA in an operating theatre. Although 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 RB ablation had LA. This will underestimate the cost of MEA and TBEA compared with 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 owing to the relatively low

	level of amenorrhoea with TBEA and therefore biases in favour of 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 Monte Carlo simulation.
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-related estimates 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.

Quality assessment of economic analysis supplied by makers of Thermachoice (using the Drummond framework)

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 3-year time horizon is taken, which may underestimate re-intervention rates and bias the analysis in favour of EA.
Was a comprehensive description of competing alternatives given?	Competing alternatives are described, although some aspects of care are not included in the comparison.

Was the effectiveness of the programme or services established?	Effectiveness data are taken from the report of 3-year follow-up in the Meyer trial. Estimates for effects are not calculated on an ITT basis and no account is taken of the precision of results. For example, the difference in amenorrhoea between thermal balloon and TCRE was not statistically significant.
Were all important costs and consequences identified?	No.
Were costs and consequences measured accurately in appropriate units?	Costing study was acknowledged as not being comprehensive, focusing on surgical component. Outcome measurement in relation to EA is discussed elsewhere in this assessment report.
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.
Were costs and consequences adjusted for differential timing?	No, although time horizon is short (3 years).
Was an incremental analysis performed?	Yes.
Was allowance made for uncertainty in the estimates of costs and consequences?	No – a major shortcoming of the analysis.
Did the presentation and discussion of results include all issues of concern to users?	No. The analysis is acknowledged to be limited.

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

1. Structure

Is there a clear statement of the decision problem, the context and the perspective?	The comparisons are clearly stated. The perspective is not well 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 3 years is justified as the extent of current data from RCTs. However, a longer timeframe 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 – 3 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 10 years later and failure rates may be time dependent, it is likely that the 3-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 12 months. 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 owing 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 EA

	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 EA 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-related estimates 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.

Appendix 10

Parameters used in the industry and PenTAG economic models

Parameter	PenTAG value	Microsulis value	Thermachoice value	Cavaterm value
Procedure cost hysterectomy	2096	2644	1778[a]	2050
Procedure cost TCRE	1110	1129	958	593
Procedure cost RB	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 × 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 RB (£)	–	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 1	0.088	0.016	–	–
Probability of hysterectomy following MEA at year 1	0.088	0.078	–	–
Probability of hysterectomy following RB at year 1	0.088	0.015	–	–
Probability of hysterectomy following RB + TCRE at year 1	0.088	0.11	–	–
Probability of hysterectomy following resection at year 1	0.088	0.11	–	–
Probability of hysterectomy following balloon ablation at year 5	0.248	0.321	–	0.077 Thermachoice 0.0595 Cavaterm
Probability of hysterectomy following MEA	0.248	0.208	–	0.0252
Probability of hysterectomy following RB	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 failure following MEA	0	–	–	0.0168
Probability of stopping treatment after failure following TBEA	0	–	–	0.021 Thermachoice 0.073 Cavaterm
Probability of stopping treatment after failure following 1st-generation EA	0	–	–	0.005–0.015
Proportion of patients receiving LA (vs GA; RB, RB + TCRE, resection)	0	0.14	–	0.0.001–0.025

[a] Vaginal hysterectomy.

continued

Parameter	PenTAG value	Microsulis value	Thermachoice value	Cavaterm value
Proportion of patients receiving LA (vs GA; 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 RB	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 RB ablation (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 1	0.11	0	–	–
Probability of RB+TCRE following MEA at year 1	–	0.009	–	–
Probability of repeat surgery following RB at year 1	0.11	0	–	–
Probability of repeat surgery following RB+TCRE at year 1	0.11	0.029	–	–
Probability of repeat surgery following resection at year 1	0.11	0.11	–	–
Probability of repeat surgery following balloon ablation at year 5	0.31	0.011	–	–
Probability of RB + TCRE following MEA at year 5	0.31	0.046	–	–
Probability of repeat surgery following RB at year 5	0.31	0.000	–	–
Probability of repeat surgery following RB +TCRE at year 5	0.31	0.317	–	–
Probability of repeat surgery following resection at year 1	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		–	–
Duration of complications from hysterectomy (years)	80% for 2 months	4.7/365.25	–	–
Duration of convalescence following hysterectomy (years)	8/52	11.6/52	–	–
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 RB ablation (years)	1 month	0.7/365.25	–	–
Duration of convalescence following RB 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 × utility in convalescence following hysterectomy	–	–
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	–	–

continued

Parameter	PenTAG value	Microsulis value	Thermachoice value	Cavaterm value
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 RB ablation (<1)	0.8	0.76	–	–
Utility in post-convalescence following RB 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

[d] Vaginal hysterectomy.

Health Technology Assessment Programme

Prioritisation Strategy Group

Members

Chair,
Professor Tom Walley, Director, NHS HTA Programme & Professor of Clinical Pharmacology, University of Liverpool

Professor Bruce Campbell, Consultant Vascular & General Surgeon, Royal Devon & Exeter Hospital

Professor Shah Ebrahim, Professor in Epidemiology of Ageing, University of Bristol

Dr John Reynolds, Clinical Director, Acute General Medicine SDU, Radcliffe Hospital, Oxford

Dr Ron Zimmern, Director, Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

HTA Commissioning Board

Members

Programme Director,
Professor Tom Walley, Director, NHS HTA Programme & Professor of Clinical Pharmacology, University of Liverpool

Chair,
Professor Shah Ebrahim, Professor in Epidemiology of Ageing, Department of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road, Bristol

Deputy Chair,
Professor Jenny Hewison, Professor of Health Care Psychology, Academic Unit of Psychiatry and Behavioural Sciences, University of Leeds School of Medicine, Leeds

Professor Douglas Altman, Professor of Statistics in Medicine, Centre for Statistics in Medicine, Oxford University, Institute of Health Sciences, Cancer Research UK Medical Statistics Group, Headington, Oxford

Professor John Bond, Professor of Health Services Research, Centre for Health Services Research, University of Newcastle, School of Health Sciences, Newcastle upon Tyne

Professor John Brazier, Director of Health Economics, Sheffield Health Economics Group, School of Health & Related Research, University of Sheffield, ScHARR Regent Court, Sheffield

Dr Andrew Briggs, Public Health Career Scientist, Health Economics Research Centre, University of Oxford, Institute of Health Sciences, Oxford

Dr Christine Clark, Medical Writer & Consultant Pharmacist, Cloudside, Rossendale, Lancs
and
Principal Research Fellow, Clinical Therapeutics in the School of Pharmacy, Bradford University, Bradford

Professor Nicky Cullum, Director of Centre for Evidence Based Nursing, Department of Health Sciences, University of York, Research Section, Seebohm Rowntree Building, Heslington, York

Dr Andrew Farmer, Senior Lecturer in General Practice, Department of Primary Health Care, University of Oxford, Institute of Health Sciences, Headington, Oxford

Professor Fiona J Gilbert, Professor of Radiology, Department of Radiology, University of Aberdeen, Lilian Sutton Building, Foresterhill, Aberdeen

Professor Adrian Grant, Director, Health Services Research Unit, University of Aberdeen, Drew Kay Wing, Polwarth Building, Foresterhill, Aberdeen

Professor Alastair Gray, Director, Health Economics Research Centre, University of Oxford, Institute of Health Sciences, Headington, Oxford

Professor Mark Haggard, Director, MRC ESS Team, CBU Elsworth House, Addenbrooke's Hospital, Cambridge

Professor F D Richard Hobbs, Professor of Primary Care & General Practice, Department of Primary Care & General Practice, University of Birmingham, Primary Care and Clinical Sciences Building, Edgbaston, Birmingham

Professor Peter Jones, Head of Department, University Department of Psychiatry, University of Cambridge, Addenbrooke's Hospital, Cambridge

Professor Sallie Lamb, Research Professor in Physiotherapy/Co-Director, Interdisciplinary Research Centre in Health, Coventry University, Coventry

Dr Donna Lamping, Senior Lecturer, Health Services Research Unit, Public Health and Policy, London School of Hygiene and Tropical Medicine, London

Professor David Neal, Professor of Surgical Oncology, Oncology Centre, Addenbrooke's Hospital, Cambridge

Professor Tim Peters, Professor of Primary Care Health Services Research, Division of Primary Health Care, University of Bristol, Cotham House, Cotham Hill, Bristol

Professor Ian Roberts, Professor of Epidemiology & Public Health, Intervention Research Unit, London School of Hygiene and Tropical Medicine, London

Professor Peter Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh, Western General Hospital NHS Trust, Bramwell Dott Building, Edinburgh

Professor Martin Severs, Professor in Elderly Health Care, Portsmouth Institute of Medicine, Health & Social Care, St George's Building, Portsmouth

Dr Jonathan Shapiro, Senior Fellow, Health Services Management Centre, Park House, Birmingham

Current and past membership details of all HTA 'committees' are available from the HTA website (www.ncchta.org)

Diagnostic Technologies & Screening Panel

Members

Chair,
Dr Ron Zimmern, Director of the Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

Dr Paul Cockcroft, Consultant Medical Microbiologist/ Laboratory Director, Public Health Laboratory, St Mary's Hospital, Portsmouth

Professor Adrian K Dixon, Professor of Radiology, Addenbrooke's Hospital, Cambridge

Dr David Elliman, Consultant in Community Child Health, London

Dr Andrew Farmer, Senior Lecturer in General Practice, Institute of Health Sciences, University of Oxford

Dr Karen N Foster, Clinical Lecturer, Dept of General Practice & Primary Care, University of Aberdeen

Professor Jane Franklyn, Professor of Medicine, University of Birmingham

Professor Antony J Franks, Deputy Medical Director, The Leeds Teaching Hospitals NHS Trust

Mr Tam Fry, Honorary Chairman, Child Growth Foundation, London

Dr Susanne M Ludgate, Medical Director, Medical Devices Agency, London

Dr William Rosenberg, Senior Lecturer and Consultant in Medicine, University of Southampton

Dr Susan Schonfield, CPHM Specialised Services Commissioning, Croydon Primary Care Trust

Dr Margaret Somerville, Director of Public Health, Teignbridge Primary Care Trust, Devon

Mr Tony Tester, Chief Officer, South Bedfordshire Community Health Council, Luton

Dr Andrew Walker, Senior Lecturer in Health Economics, University of Glasgow

Professor Martin J Whittle, Head of Division of Reproductive & Child Health, University of Birmingham

Dr Dennis Wright, Consultant Biochemist & Clinical Director, Pathology & The Kennedy Galton Centre, Northwick Park & St Mark's Hospitals, Harrow

Pharmaceuticals Panel

Members

Chair,
Dr John Reynolds, Clinical Director, Acute General Medicine SDU, Oxford Radcliffe Hospital

Professor Tony Avery, Professor of Primary Health Care, University of Nottingham

Professor Iain T Cameron, Professor of Obstetrics & Gynaecology, University of Southampton

Mr Peter Cardy, Chief Executive, Macmillan Cancer Relief, London

Dr Christopher Cates, GP and Cochrane Editor, Bushey Health Centre, Bushey, Herts.

Mr Charles Dobson, Special Projects Adviser, Department of Health

Dr Robin Ferner, Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Dr Karen A Fitzgerald, Pharmaceutical Adviser, Bro Taf Health Authority, Cardiff

Professor Alastair Gray, Professor of Health Economics, Institute of Health Sciences, University of Oxford

Mrs Sharon Hart, Managing Editor, *Drug & Therapeutics Bulletin*, London

Dr Christine Hine, Consultant in Public Health Medicine, Bristol South & West Primary Care Trust

Professor Robert Peveler, Professor of Liaison Psychiatry, Royal South Hants Hospital, Southampton

Dr Frances Rotblat, CPMP Delegate, Medicines Control Agency, London

Mrs Katrina Simister, New Products Manager, National Prescribing Centre, Liverpool

Dr Ken Stein, Senior Lecturer in Public Health, University of Exeter

Professor Terence Stephenson, Professor of Child Health, University of Nottingham

Dr Richard Tiner, Medical Director, Association of the British Pharmaceutical Industry, London

Professor Dame Jenifer Wilson-Barnett, Head of Florence Nightingale School of Nursing & Midwifery, King's College, London

Therapeutic Procedures Panel

Members

Chair,
Professor Bruce Campbell,
Consultant Vascular and General Surgeon, Royal Devon & Exeter Hospital

Dr Mahmood Adil, Head of Clinical Support & Health Protection, Directorate of Health and Social Care (North), Department of Health, Manchester

Professor John Bond, Head of Centre for Health Services Research, University of Newcastle upon Tyne

Mr Michael Clancy, Consultant in A & E Medicine, Southampton General Hospital

Dr Carl E Counsell, Senior Lecturer in Neurology, University of Aberdeen

Dr Keith Dodd, Consultant Paediatrician, Derbyshire Children's Hospital, Derby

Professor Gene Feder, Professor of Primary Care R&D, Barts & the London, Queen Mary's School of Medicine and Dentistry, University of London

Ms Bec Hanley, Freelance Consumer Advocate, Hurstpierpoint, West Sussex

Professor Alan Horwich, Director of Clinical R&D, The Institute of Cancer Research, London

Dr Phillip Leech, Principal Medical Officer for Primary Care, Department of Health, London

Mr George Levvy, Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay, Professor of Psychiatry for the Elderly, University of Leicester

Dr Mike McGovern, Senior Medical Officer, Heart Team, Department of Health, London

Dr John C Pounsford, Consultant Physician, North Bristol NHS Trust

Professor Mark Sculpher, Professor of Health Economics, Institute for Research in the Social Services, University of York

Dr L David Smith, Consultant Cardiologist, Royal Devon & Exeter Hospital

Professor Norman Waugh, Professor of Public Health, University of Aberdeen

Expert Advisory Network

Members

Mr Gordon Aylward,
Chief Executive,
Association of British Health-Care Industries, London

Ms Judith Brodie,
Head of Cancer Support Service, Cancer BACUP, London

Mr Shaun Brogan,
Chief Executive, Ridgeway Primary Care Group, Aylesbury, Bucks

Ms Tracy Bury,
Project Manager, World Confederation for Physical Therapy, London

Mr John A Cairns,
Professor of Health Economics, Health Economics Research Unit, University of Aberdeen

Professor Howard Stephen Cuckle,
Professor of Reproductive Epidemiology, Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds

Professor Nicky Cullum,
Director of Centre for Evidence Based Nursing, University of York

Dr Katherine Darton,
Information Unit, MIND – The Mental Health Charity, London

Professor Carol Dezateux,
Professor of Paediatric Epidemiology, London

Professor Martin Eccles,
Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle upon Tyne

Professor Pam Enderby,
Professor of Community Rehabilitation, Institute of General Practice and Primary Care, University of Sheffield

Mr Leonard R Fenwick,
Chief Executive, Newcastle upon Tyne Hospitals NHS Trust

Professor David Field,
Professor of Neonatal Medicine, Child Health, The Leicester Royal Infirmary NHS Trust

Mrs Gillian Fletcher,
Antenatal Teacher & Tutor and President, National Childbirth Trust, Henfield, West Sussex

Ms Grace Gibbs,
Deputy Chief Executive, Director for Nursing, Midwifery & Clinical Support Servs., West Middlesex University Hospital, Isleworth, Middlesex

Dr Neville Goodman,
Consultant Anaesthetist, Southmead Hospital, Bristol

Professor Robert E Hawkins,
CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor F D Richard Hobbs,
Professor of Primary Care & General Practice, Department of Primary Care & General Practice, University of Birmingham

Professor Allen Hutchinson,
Director of Public Health & Deputy Dean of ScHARR, Department of Public Health, University of Sheffield

Professor Rajan Madhok,
Medical Director & Director of Public Health, Directorate of Clinical Strategy & Public Health, North & East Yorkshire & Northern Lincolnshire Health Authority, York

Professor David Mant,
Professor of General Practice, Department of Primary Care, University of Oxford

Professor Alexander Markham,
Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Dr Chris McCall,
General Practitioner, The Hadleigh Practice, Castle Mullen, Dorset

Professor Alistair McGuire,
Professor of Health Economics, London School of Economics

Dr Peter Moore,
Freelance Science Writer, Ashtead, Surrey

Dr Andrew Mortimore,
Consultant in Public Health Medicine, Southampton City Primary Care Trust

Dr Sue Moss,
Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton, Surrey

Professor Jon Nicholl,
Director of Medical Care Research Unit, School of Health and Related Research, University of Sheffield

Mrs Julietta Patnick,
National Co-ordinator, NHS Cancer Screening Programmes, Sheffield

Professor Chris Price,
Visiting Chair – Oxford, Clinical Research, Bayer Diagnostics Europe, Cirencester

Ms Marianne Rigge,
Director, College of Health, London

Professor Sarah Stewart-Brown,
Director HSRU/Honorary Consultant in PH Medicine, Department of Public Health, University of Oxford

Professor Ala Szczepura,
Professor of Health Service Research, Centre for Health Services Studies, University of Warwick

Dr Ross Taylor,
Senior Lecturer, Department of General Practice and Primary Care, University of Aberdeen

Mrs Joan Webster,
Consumer member, HTA – Expert Advisory Network

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

ISSN 1366-5278