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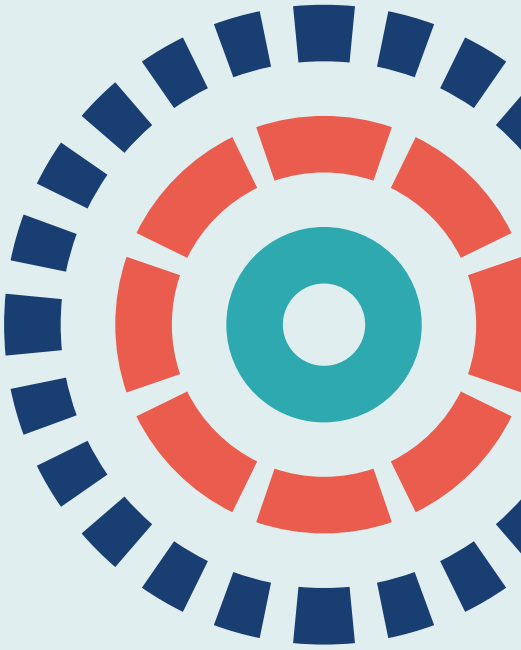

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Laparoscopic supracervical hysterectomy compared with second-generation endometrial ablation for heavy menstrual bleeding: the HEALTH RCT

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Abstract

Laparoscopic supracervical hysterectomy compared with second-generation endometrial ablation for heavy menstrual bleeding: the HEALTH RCT

Kevin Cooper,[1]* Suzanne Breeman,[2] Neil W Scott,[3] Graham Scotland,[2,4] Rodolfo Hernández,[4] T Justin Clark,[5] Jed Hawe,[6] Robert Hawthorn,[7] Kevin Phillips,[8] Samantha Wileman,[2] Kirsty McCormack,[2] John Norrie[9] and Siladitya Bhattacharya[1,10] on behalf of the HEALTH Study Group

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Background: Heavy menstrual bleeding (HMB) is a common problem that affects many British women. When initial medical treatment is unsuccessful, the National Institute for Health and Care Excellence recommends surgical options such as endometrial ablation (EA) or hysterectomy. Although clinically and economically more effective than EA, total hysterectomy necessitates a longer hospital stay and is associated with slower recovery and a higher risk of complications. Improvements in endoscopic equipment and training have made laparoscopic supracervical hysterectomy (LASH) accessible to most gynaecologists. This operation could preserve the advantages of total hysterectomy and reduce the risk of complications.

Objectives: To compare the clinical effectiveness and cost-effectiveness of LASH with second-generation EA in women with HMB.

Design: A parallel-group, multicentre, randomised controlled trial. Allocation was by remote web-based randomisation (1 : 1 ratio). Surgeons and participants were not blinded to the allocated procedure.

Setting: Thirty-one UK secondary and tertiary hospitals.

Participants: Women aged < 50 years with HMB. Exclusion criteria included plans to conceive; endometrial atypia; abnormal cytology; uterine cavity size > 11 cm; any fibroids > 3 cm; contraindications to laparoscopic surgery; previous EA; and inability to give informed consent or complete trial paperwork.

Interventions: LASH compared with second-generation EA.

Main outcome measures: Co-primary clinical outcome measures were (1) patient satisfaction and (2) Menorrhagia Multi-Attribute Quality-of-Life Scale (MMAS) score at 15 months post randomisation. The primary economic outcome was incremental cost (NHS perspective) per quality-adjusted life-year (QALY) gained.

Results: A total of 330 participants were randomised to each group (total $n = 660$). Women randomised to LASH were more likely to be satisfied with their treatment than those randomised to EA (97.1% vs. 87.1%) [adjusted difference in proportions 0.10, 95% confidence interval (CI) 0.05 to 0.15; adjusted odds ratio (OR) from ordinal logistic regression (OLR) 2.53, 95% CI 1.83 to 3.48; $p < 0.001$]. Women randomised to LASH were also more likely to have the best possible MMAS score of 100 (68.7% vs. 54.5%) (adjusted difference in proportions 0.13, 95% CI 0.04 to 0.23; adjusted OR from OLR 1.87, 95% CI 1.31 to 2.67; $p = 0.001$). Serious adverse event rates were low and similar in both groups (4.5% vs. 3.6%). There was a significant difference in adjusted mean costs between LASH (£2886) and EA (£1282) at 15 months, but no significant difference in QALYs. Based on an extrapolation of expected differences in cost and QALYs out to 10 years, LASH cost an additional £1362 for an average QALY gain of 0.11, equating to an incremental cost-effectiveness ratio of £12,314 per QALY. Probabilities of cost-effectiveness were 53%, 71% and 80% at cost-effectiveness thresholds of £13,000, £20,000 and £30,000 per QALY gained, respectively.

Limitations: Follow-up data beyond 15 months post randomisation are not available to inform cost-effectiveness.

Conclusion: LASH is superior to EA in terms of clinical effectiveness. EA is less costly in the short term, but expected higher retreatment rates mean that LASH could be considered cost-effective by 10 years post procedure.

Future work: Retreatment rates, satisfaction and quality-of-life scores at 10-year follow-up will help to inform long-term cost-effectiveness.

Trial registration: Current Controlled Trials ISRCTN49013893.

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List of abbreviations

AE	adverse event
BSO	bilateral salpingo-oophorectomy
CHaRT	Centre for Healthcare and Randomised Trials
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
DMC	Data Monitoring Committee
EA	endometrial ablation
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
GLM	generalised linear model
GP	general practitioner
HEALTH	Hysterectomy or Endometrial AbLation Trial for Heavy menstrual bleeding
HMB	heavy menstrual bleeding
HR	hazard ratio
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
KM	Kaplan–Meier
LASH	laparoscopic supracervical hysterectomy
LMS	leiomyosarcoma
MCS	mental component score
MMAS	Menorrhagia Multi-Attribute Quality-of-Life Scale
NICE	National Institute for Health and Care Excellence
OLR	ordinal logistic regression
OR	odds ratio
PCS	physical component score
PI	principal investigator
PMG	Project Management Group
QALY	quality-adjusted life-year
QoL	quality of life
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	randomised controlled trial
SAE	serious adverse event
SD	standard deviation
SF-12	Short Form questionnaire-12 items
TSC	Trial Steering Committee
VAS	visual analogue scale
WTP	willingness to pay

Plain English summary

Almost 1.5 million women in England and Wales suffer from heavy periods. Initial treatment involves tablets or a medicated coil inserted within the womb. Sometimes these treatments do not work and many women need an operation, either endometrial ablation (EA) (removing the lining of the womb) or a full hysterectomy (complete removal of the womb). Previous studies have shown that a full hysterectomy is better at relieving symptoms, but the risk of complications during surgery is higher and patients take longer to recover fully.

A newer operation, laparoscopic (keyhole) supracervical hysterectomy, or 'LASH', removes only the part of the womb that causes periods and preserves the cervix or neck of the womb. Women who have LASH can expect fewer complications, earlier discharge from hospital and quicker recovery time.

In this study, we compared EA with LASH by asking women who had either procedure how they felt about it 1 year after their operation.

Regardless of which operation they had, most women were very satisfied and felt that their symptoms were better. However, the results were much better for those who had the LASH operation, although these women stayed in hospital for longer and took more time to recover. There was no difference in complications from either surgery, although nearly 1 in 20 women who had an EA returned within 1 year to have their wombs removed in a second operation.

Although LASH led to a greater improvement in symptoms and levels of satisfaction, it was more expensive in terms of costs incurred by both the health service and society. Given that some women who had an EA are likely to need a second operation in the future, LASH surgery may provide better value for money in the long term.

Scientific summary

Background

Heavy menstrual bleeding (HMB) is a common problem that has a major impact on women's physical, emotional, social and material quality of life. The condition is initially treated in primary care by either oral medication or insertion of the levonorgestrel-releasing intrauterine system (Mirena®, Bayer, Whippany, NJ, USA). If medical therapy fails or is deemed unsuitable, surgical treatment can be offered: either endometrial ablation (EA), which destroys the lining of the uterine cavity (endometrium), or hysterectomy (removal of the uterus). Neither medical treatment nor EA can guarantee complete resolution of symptoms and up to 59% of women on oral drugs and 13.5% of those using the levonorgestrel-releasing intrauterine system (Mirena) need surgery within 2 years. Following initial treatment with EA, 19% of women require hysterectomy for relief of their symptoms.

Although clinically and economically more effective than EA, a conventional total hysterectomy is more invasive, poses a higher risk of injury to surrounding organs, involves a longer hospital stay and requires a longer postoperative recovery period. The advantages of total hysterectomy could be maintained, and the risk of complications reduced, by undertaking a laparoscopic supracervical hysterectomy (LASH), in which only the body of the uterus is removed and the cervix is preserved.

Objectives

To compare the clinical effectiveness and cost-effectiveness of LASH with second-generation EA in women with HMB.

Methods

The Hysterectomy or Endometrial AbLation Trial for Heavy menstrual bleeding (HEALTH) was a parallel-group, multicentre, randomised controlled trial involving 31 UK secondary and tertiary hospitals. Women aged < 50 years with HMB who wanted surgical treatment, and had no plans to conceive, were invited to participate. Women were excluded if they met any of the following exclusion criteria: endometrial atypia; abnormal cytology; uterine cavity size > 11 cm; any fibroids > 3 cm; contraindications to laparoscopic surgery; previous EA; and inability to give informed consent or complete trial paperwork.

Interventions and randomisation

Eligible and consenting women were randomised to one of the following two treatment arms in a 1 : 1 allocation ratio using a remote web-based randomisation service:

1. LASH (removal of the body of the uterus by means of keyhole surgery)
2. second-generation EA (destroying the endometrium by means of a silicone balloon containing hot fluid or radiofrequency energy).

The minimisation algorithm was based on centre and age group (< 40 years vs. ≥ 40 years).

Outcome measures

The co-primary clinical outcome measures were (1) patient satisfaction at 15 months post randomisation and (2) the Menorrhagia Multi-Attribute Quality-of-Life Scale (MMAS) score at 15 months post randomisation. The primary economic outcome was incremental cost per quality-adjusted life-year (QALY) gained.

Secondary outcome measures included pain score at days 1–14 and 6 weeks post surgery; acceptability of treatment at 6 weeks post surgery; satisfaction with treatment and MMAS score at 6 months post surgery; menstrual outcomes at 6 months post surgery and 15 months post randomisation; generic health-related quality of life [Short Form questionnaire-12 items (SF-12) and EuroQol-5 Dimensions, three-level version (EQ-5D-3L)] at 6 weeks and 6 months post surgery and 15 months post randomisation; perioperative complications, including recovery details and need for additional gynaecological surgery; cost; and cost-effectiveness.

Blinding

Surgeons and participants could not be blinded to the allocated procedure.

Delivery of the intervention

Randomised participants were placed on the waiting list for the allocated treatment with the anticipation that treatment would occur within 12–18 weeks of randomisation, as per the Scottish and UK government guidelines. Operative techniques were not modified for the purposes of the trial.

Data collection during follow-up

Participant-reported outcomes were assessed by self-completed questionnaires at baseline (before surgery), 6 weeks and 6 months post surgery, and 15 months post randomisation. A self-completed 14-day diary was also collected.

Sample size

It was originally anticipated that 292 participants per group would provide 90% power to detect a difference in satisfaction rates of 8%, and 95% power to detect a 10-point difference in MMAS score [assuming a standard deviation (SD) of 33 units]. Based on an expected 10% drop-out rate, the recruitment target was 648 participants in total (324 participants per group).

Statistical analysis

Stata® version 15 (StataCorp LP, College Station, TX, USA) was used to conduct analyses in accordance with the intention-to-treat principle. Analyses used a two-sided 5% significance level with corresponding 95% confidence intervals (CIs) generated as appropriate. Analysis of the two co-primary outcomes (patient satisfaction and MMAS score at 15 months post randomisation) was conducted in a hierarchy such that MMAS score was considered only if the difference in patient satisfaction was shown to be statistically significant. Secondary outcomes were compared by randomised groups. These analyses were regarded as hypothesis-generating and no adjustment was made for multiple statistical testing.

Economic evaluation

The economic analysis consisted of a trial-based analysis of individual patient-level cost and effect (QALY) data and a Markov modelling component to inform cost-effectiveness in the longer term. Given the limitations of the follow-up period for economic evaluation, the model-based approach forms the primary economic analysis. Costs and outcomes were assessed via the trial case report forms, patient diary of pain symptoms post surgery and postal questionnaires. The EQ-5D-3L scores were used to estimate QALYs.
To estimate longer-term economic differences, a simple Markov decision-analytic model was developed to extrapolate the estimated 15-month difference in utility and simulate the incidence of further gynaecological surgery over time. The key objective of the analysis was to inform the long-term cost-effectiveness of LASH compared with EA.

Management of the study

The study was supervised by the Project Management Group, which consisted of representatives from the study office and grant holders. The study was further overseen by a Trial Steering Committee, which comprised four independent members, and an independent Data Monitoring Committee.

Results

Recruitment

Between May 2014 and March 2017, 2552 potentially eligible patients were screened; 1351 (52.9%) were confirmed as eligible, of whom 664 (49.1%) gave their consent and were randomised. Following randomisation, four women were considered ineligible and treated as post-randomisation exclusions. Therefore, 660 women (330 in each group) were included in the main trial.

Clinical results

Women randomised to LASH or to EA were comparable at baseline in terms of mean age [42.2 (SD 4.89) years vs. 42.1 (SD 4.96) years], body mass index [29.1 kg/m^2 (SD 5.55 kg/m^2) vs. 29.0 kg/m^2 (SD 5.34 kg/m^2)], preoperative haemoglobin levels [131.0 g/l (SD 13.1 g/l) vs. 130.1 g/l (SD 12.6 g/l)] and duration of symptoms [227 (69.4%) participants in the LASH group vs. 216 (66.1%) participants in the EA group for symptoms in excess of 3 years].

There were also no differences between the LASH and EA groups at baseline in the mean values for the MMAS total score [30.5 (SD 19.0) vs. 32.3 (SD 20.0)], EQ-5D-3L utility score [0.71 (SD 0.30) vs. 0.70 (SD 0.31)] and SF-12 physical component score [45.0 (SD 9.0) vs. 44.9 (SD 9.7)] or mental component score [37.2 (SD 11.0) vs. 38.7 (SD 11.6)]. There were no clear differences between the randomised groups with respect to any of the baseline outcomes, including mean bleeding score and mean pain score.

A total of 44 participants who were randomised to either LASH (21/330, 6.4%) or EA (23/330, 7.0%) did not undergo an operation but were sent the final questionnaire at 15 months post randomisation.

The median number of days between randomisation and treatment was higher for those randomised to LASH [84 days, interquartile range (IQR) 57–127 days] than for those randomised to EA (63 days, IQR 41–97 days).

Of those undergoing treatment, 291 out of 309 (94.2%) women randomised to LASH and 297 out of 307 (96.7%) women randomised to EA received the allocated procedure. Women undergoing LASH were more likely to be operated on by a consultant [239 (77.3%) vs. 176 (57.3%)] and required more postoperative opiate injections [94/309 (30.4%) vs. 46/307 (15.0%)]. More women in the LASH arm stayed in hospital for over 24 hours post procedure [99/306 (32.4%) vs. 16/303 (5.3%)].

Primary outcomes at 15 months post randomisation

Based on responses from 278 out of 330 (84.2%) women randomised to the LASH group and 280 out of 330 (84.8%) women randomised to the EA group, women randomised to LASH were more likely to be satisfied with their treatment than those randomised to EA (97.1% vs. 87.1%) [adjusted difference in proportions 0.10, 95% CI 0.05 to 0.15; adjusted odds ratio (OR) from ordinal logistic regression (OLR) 2.53, 95% CI 1.83 to 3.48; $p < 0.001$].

Total MMAS scores, based on responses from 262 out of 330 (79.4%) women in the LASH group and 268 out of 330 (81.2%) women in the EA group, indicate that women randomised to receive LASH were more likely to have the best possible MMAS score of 100 (68.7% vs. 54.5%) (adjusted difference in proportions 0.13, 95% CI 0.04 to 0.23; adjusted OR from OLR 1.87, 95% CI 1.31 to 2.67; $p = 0.001$). They had almost twice the odds of being in a more favourable MMAS category than those allocated to EA (adjusted OR 1.87, 95% CI 1.31 to 2.67; $p = 0.001$).

Twenty-five women experienced a total of 26 serious adverse events (SAEs) (LASH, $n = 15$; EA, $n = 11$). There were no statistically or clinically significant differences between the randomised groups in the proportions having a SAE (adjusted OR 1.30, 95% CI 0.56 to 3.02; $p = 0.54$).

A total of 32 women experienced a complication following surgery. These included voiding dysfunction (LASH, $n = 14$; EA, $n = 2$), consultation for pain (LASH, $n = 1$; EA, $n = 1$), haematoma (LASH, $n = 1$; EA $n = 1$), blood loss > 500 ml (LASH, $n = 1$; EA, $n = 1$), inactive/blunt uterine perforation (LASH, $n = 1$; EA, $n = 3$), pyrexia requiring antibiotics (LASH, $n = 3$; EA, $n = 2$) and blood transfusion (LASH, $n = 0$; EA, $n = 1$).

Eighteen women randomised to EA and two women randomised to LASH received further treatment for HMB during the follow-up period. The most common reason was that the index EA procedure produced an unsatisfactory reduction in HMB ($n = 12$). A further seven women required unplanned further surgery because the index EA procedure could not be completed on first admission; this included one woman who was randomised to LASH but for whom an EA procedure was attempted. On five occasions, a hysterectomy was performed on the second admission.

Postoperative recovery

In the first 14 days following surgery, those in the LASH group had pain scores that were almost 1 point higher than those reported by the EA group (mean difference 0.92, 95% CI 0.59 to 1.24; $p < 0.001$).

By 6 weeks post surgery, over half of the women in both groups reported no pain on a 10-point scale. Those in the LASH group had higher odds of pain at 6 weeks than those in the EA group (adjusted OR 1.43, 95% CI 1.05 to 1.96; $p = 0.03$).

Women in the EA group returned to paid work sooner than those randomised to LASH (median time 10 days vs. 42 days; adjusted hazard ratio 0.23, 95% CI 0.18 to 0.30; $p < 0.001$).

Menstrual outcomes

Fewer women continued to have periods after receiving LASH than after receiving EA [6 months: LASH, 39/253 (15.4%); EA, 111/246 (45.7%) (adjusted OR 0.22, 95% CI 0.15 to 0.32; $p < 0.001$); 15 months: LASH, 52/277 (18.8%); EA, 117/278 (42.1%) (adjusted OR 0.32, 95% CI 0.21 to 0.48; $p < 0.001$)].

A higher proportion of all women (including those with no periods) experienced cyclical pain following EA [6 months: LASH, 68/236 (28.8%); EA, 108/199 (54.3%); 15 months: LASH, 71/224 (31.7%); EA, 118/196 (60.2%)].

Quality of life

At 6 weeks post surgery, those in the EA group had higher EQ-5D-3L utility scores than those in the LASH group (adjusted OR 0.66, 95% CI 0.48 to 0.90; $p = 0.009$). However, at 6 months post surgery and 15 months post randomisation, the point estimates favoured LASH, although the results were not statistically significant (6 months: adjusted OR 1.15, 95% CI 0.84 to 1.57, $p = 0.38$; 15 months: adjusted OR 1.21, 95% CI 0.89 to 1.64, $p = 0.23$).

The results for the visual analogue scale of the EQ-5D-3L tended to favour the LASH group, and this finding was statistically significant at 6 months post surgery and at 15 months post randomisation (6 weeks: adjusted OR 1.12, 95% CI 0.80 to 1.58, $p = 0.51$; 6 months: adjusted OR 1.53, 95% CI 1.08 to 2.17, $p = 0.02$; 15 months: adjusted OR 1.50, 95% CI 1.12 to 1.99, $p = 0.006$).

Health economic results

The mean initial episode costs for LASH and EA were £2757 and £1071, respectively. LASH was more costly than EA because surgical costs were higher, time spent in the anaesthetic room, theatre and in recovery was longer (178 minutes vs. 90 minutes) and discharge from hospital occurred later (23 hours vs. 6 hours). Taking all relevant NHS resource use into account over 15 months, unadjusted mean health service costs were £3004 for LASH compared with £1281 for EA.

Societal costs were also increased following LASH because women who received LASH took longer to return to paid and unpaid productive activities than than who received EA (£2586 vs. £990). Mean out-of-pocket expenses (£9 vs. £7) and the cost of time lost to attend outpatient appointments (£26 and £22) were slightly higher in the LASH group.

The mean EQ-5D-3L scores in the LASH group at baseline, 6 weeks and 6 months post surgery and 15 months post randomisation were 0.7065 (SD 0.30), 0.8279 (SD 0.22), 0.8315 (SD 0.27) and 0.8357 (SD 0.24), respectively. The corresponding mean scores in the EA group were 0.6983 (SD 0.31), 0.8282 (SD 0.28), 0.8269 (SD 0.25) and 0.8005 (SD 0.28), respectively. By 15 months, the EQ-5D-3L score was higher in the LASH group than in the EA group (unadjusted difference = 0.035), although the difference was not statistically significant. At 15 months post randomisation (12 months post surgery), the mean adjusted QALY gain was 0.978 and 0.974, whereas the mean adjusted costs were £2886 and £1282 for LASH and EA, respectively, producing adjusted differences of 0.004 QALYs and £1604. The incremental cost-effectiveness ratio (ICER) for LASH compared with EA was £458,334 per QALY gained at 15 months post randomisation.

Over a modelled 10-year time horizon, in comparison with EA, the intention to treat with LASH resulted in an increased cost to the health service of £1362 per woman, for an expected QALY gain of 0.111 per woman. The corresponding ICER was £12,314 per QALY gained for LASH compared with EA. The chance of LASH being cost-effective ranged from 53% to 80% at cost-effectiveness thresholds of £13,000 and £30,000, respectively. Extending the time horizon of the model from 1 to 10 years reduced the incremental cost of LASH by £242 (from £1604 to £1362), owing to incorporation of the expected costs of further gynaecological surgery.

Conclusion

Laparoscopic supracervical hysterectomy is superior to EA in terms of clinical effectiveness. As EA is quicker, cheaper and associated with an earlier discharge, it is less costly in the short term, but its expected higher failure rate means that LASH could be considered cost-effective by 10 years post procedure. Long-term follow-up is required to verify retreatment rates and their impact on cost-effectiveness.

Trial registration

This trial is registered as ISRCTN49013893.

Funding

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Chapter 1 Introduction

In 2014, the UK Government's National Institute for Health Research Health Technology Assessment (HTA) programme funded the Hysterectomy or Endometrial AbLation Trial for Heavy menstrual bleeding (HEALTH). This report describes the research. HEALTH was a multicentre UK randomised controlled trial (RCT) investigating the clinical effectiveness (including safety) and cost-effectiveness of laparoscopic supracervical hysterectomy (LASH) compared with second-generation endometrial ablation (EA).

Background

Heavy menstrual bleeding (HMB) is a common problem, affecting approximately 1.5 million women in England and Wales. It accounts for one-fifth of all gynaecology outpatient referrals and has a major impact on women's physical, emotional, social and material quality of life (QoL).[2] The condition is initially treated in primary care by either oral medication or insertion of the levonorgestrel-releasing intrauterine system (Mirena®; Bayer AG, Whippany, NJ, USA). If medical therapy fails or is deemed unsuitable, surgical treatment can be offered, either EA, which destroys the lining of the cavity of the uterus (endometrium), or hysterectomy (removal of the uterus). Neither medical treatment nor EA can guarantee complete resolution of symptoms and up to 59% of women on oral drugs[3] and 13.5% of those using the levonorgestrel-releasing intrauterine system (Mirena®)[4] ultimately undergo surgical treatment within 2 years. Over one-third (38%) of women referred to an English NHS hospital between April 2009 and March 2012 with HMB underwent a surgical procedure, with about three-quarters of these being EAs.[2] Of those treated with EA, 19% have required a subsequent hysterectomy for relief of their symptoms.[5]

Scale of the problem in the UK and use of NHS resources

Hospital Episode Statistics data indicate that a total of 136,921 hysterectomies and 128,434 EAs were performed in England and Wales for HMB between April 1997 and December 2009.[6] Current types of EA that are recommended by the National Institute for Health and Care Excellence (NICE) are second-generation (non-hysteroscopic) procedures, including bipolar radiofrequency ablation (Novasure®; Hologic Inc., Marlborough, MA, USA) and thermal balloon EA.[7]

Evidence explaining why this research is needed

The NICE guideline on HMB recommends both EA as well as hysterectomy as options for women with HMB resistant to medical treatment,[7] but a significant minority of women treated with EA are likely to need repeat EA or hysterectomy. A recent individual patient data meta-analysis[8] of results from randomised trials has shown that, despite the the greater invasiveness of conventional hysterectomy (removal of the uterus and the cervix) and associated longer hospital stay and prolonged recovery, fewer women are dissatisfied with it than with EA. Additionally, a health economic model based on these data showed that hysterectomy is more cost-effective.[9] The accompanying HTA monograph[10] showed that a quarter of all women who undergo EA will require subsequent gynaecological surgery, with just under one-fifth requiring hysterectomy.

These findings, which are consistent with those of a relevant Cochrane review,[11] suggest that the optimal surgical treatment for HMB that is unresponsive to medical treatment may well be hysterectomy, but its effectiveness needs to be balanced against its invasive nature and increased short- and long-term morbidity.[5]

Removal of the cervix as part of a conventional total hysterectomy can be technically challenging and result in injury to surrounding blood vessels, ureters and the bladder. In contrast, LASH is the use of keyhole surgery to remove the body or major part of the uterus, which is the part responsible for menstrual bleeding, but conserves the cervix. This approach reduces operating time as well as surgical morbidity, while conserving the uterosacral ligament support to the cervix and upper vagina. Routine cervical screening is required for women undergoing LASH. The procedure is quick, minimally invasive, relatively easy to learn and associated with a low risk of complications, short hospital stay (< 24 hours) and rapid recovery.[12,13]

Before this technique is incorporated into routine clinical practice, it is important that it is subjected to robust evaluation. The authors of two small RCTs comparing LASH with a first-generation EA (endometrial resection[13] or second-generation EA) thermal balloon[12] suggest that LASH could lead to a better QoL, but emphasised the need for larger evaluative studies to confirm this.

The last decade has seen widespread use of laparoscopic techniques in gynaecology due to increased familiarity with the procedures, more sophisticated instruments, better training and greater laparoscopic surgical skill. As a result of this, LASH could be delivered by most general gynaecologists, with minimal morbidity to women who are currently being treated with EA. Advances in perioperative care mean that, unlike conventional hysterectomy, women treated by this procedure may not need to stay in hospital any longer than those receiving EA.

HEALTH is a multicentre RCT comparing the clinical effectiveness and cost-effectiveness of LASH with second-generation EA (the current first-line surgical treatment for HMB) in women with HMB seeking surgery. The trial is relevant and timely, as rigorous evaluation of this new surgical option will provide much needed high-quality evidence to underpin any decision to use it in routine NHS practice.

Description of the surgical procedures

Laparoscopic supracervical hysterectomy

Laparoscopic supracervical hysterectomy involves keyhole surgery to remove the upper part of the uterus (the body). The uterine body contains the endometrial cavity lined with tissue that undergoes cyclic growth and shedding each month, thus causing menstrual bleeding. Increased access to specialised laparoscopic equipment and training means that LASH is quick and relatively easy to learn. It is associated with low morbidity, short hospital stay (< 24 hours) and rapid recovery. Unlike conventional total hysterectomy, the cervix is not removed, thus removing the need for extended surgery around the cervix, which can lead to serious complications, such as injury to the bladder, ureters and blood vessels.[14,15] As the cervix is retained, cervical smears are still required and, although most women will cease to have periods after the procedure, light menstrual loss or cyclical spotting can occur in 5–20% of cases.[16,17]

The body of the uterus is usually removed though a small 10- to 12-mm incision, often within the umbilicus or suprapubically by means of a ‘power’ morcellator, which breaks up the uterine tissue into small strips. Alternative options include removal of the uterine body through an internal incision at the top of the vagina (culdotomy) or, alternatively, morcellation within an intraperitoneal bag to prevent spread of fragmented tissue within the peritoneal cavity.

Second-generation endometrial ablation

Endometrial ablation aims to treat HMB by destroying the endometrium (lining of the womb), which is responsible for heavy periods. Historically, a number of methods have been used to achieve this. First-generation EA techniques use an operating hysteroscope under direct vision. Energy is deployed

through an electric loop, laser fibre or rollerball to remove or destroy the endometrium. First-generation techniques are more complicated, require a long learning curve, are slower to perform and have a higher risk profile than second-generation techniques. They are, however, highly versatile and are the recommended approach for distorted uterine cavities or repeat ablations, and are a sensible option when the patient has had more than one caesarean section.

This century, 'second-generation' techniques have become the most commonly used endometrial ablative procedures, as they are quicker to learn and undertake, and have lower associated risks. These are blind global energy sources which again aim to destroy the endometrium and superficial myometrium to a depth of 5 mm (to destroy the endometrial glands). Current second-generation procedures used in the UK include two forms of thermal balloon EA and a device known as Novasure. Thermal balloon EA is undertaken by means of a silicone balloon, which is introduced through the cervix into the uterine cavity. The balloon fills and expands to conform to the inside of the uterine cavity, compressing the endometrium. Hot fluid circulating within the balloon ensures endometrial destruction and the temperature and duration of treatment are carefully controlled electronically by means of a computer attached to the device. Novasure uses bipolar radiofrequency energy delivered through an intrauterine mesh electrode that expands on insertion through the cervix to fit the shape of the uterine cavity. The energy required is calculated by the device and treatment times are < 90 seconds. All three treatments significantly reduce menstrual loss and result in complete cessation of bleeding in 40–50% of women.[7] Second-generation EA can be performed as a day-case procedure, under either general or local anaesthetic, at a NHS cost of £995 per treatment.[18] It has also been widely used in the outpatient setting.[19,20]

Questions addressed by HEALTH

The aim of this study is to compare the clinical effectiveness and cost-effectiveness of LASH and second-generation EA in women with HMB.

The primary objective is to compare (1) patient-reported satisfaction, measured on a six-point Likert scale (from 'totally satisfied' to 'totally dissatisfied') and (2) condition-specific QoL, measured using the Menorrhagia Multi-Attribute Quality-of-Life Scale (MMAS), at 15 months post randomisation. The corresponding economic objective is to estimate the incremental cost per quality-adjusted life-year (QALY) gained for LASH compared with EA at 15 months post randomisation.

The hypothesis being tested is that LASH is superior to second-generation EA for the treatment of HMB in terms of patient satisfaction, QoL and costs.

Chapter 2 Methods and practical arrangements

Study design

HEALTH was a parallel-group, multicentre RCT designed to compare the clinical effectiveness and cost-effectiveness of LASH with second-generation EA in women with HMB. Further details of the study design have been described previously[1] and are represented in *Figure 1*. All trial case report forms (CRFs) and participant-completed questionnaires are available at URL: www.journalslibrary.nihr.ac.uk/programmes/hta/123523/#/ (accessed 22 May 2019).

Study population

Women aged < 50 years with HMB who were eligible for EA and willing to be randomised between LASH and EA.

Women were excluded from trial entry if any of the following criteria were met: they had plans to conceive; endometrial atypia; abnormal cytology; uterine cavity size > 11 cm; any fibroids > 3 cm; contraindications to laparoscopic surgery; previous EA; and inability to give informed consent or complete trial paperwork.

Recruitment

Investigations prior to consent

Pelvic ultrasound scanning was undertaken to identify uterine or endometrial abnormality, fibroid size and number. An endometrial biopsy was taken to measure cavity length and exclude endometrial atypia.

Consent to participate

Women with HMB who fulfilled the inclusion criteria were identified at gynaecology outpatient and pre-assessment clinics. They were supplied with the patient information leaflet and given the opportunity to discuss the study with the local clinical team, family and friends, and their general practitioner (GP), as appropriate. Women could make the decision to participate during their initial consultation, during a subsequent hospital visit or after a follow-up telephone consultation at home. Written informed consent was obtained from all participants prior to trial entry.

Health technologies being compared

Women were randomised to one of two surgical treatments for HMB:

1. LASH [removal of the uterine corpus (body) by means of keyhole surgery]
2. second-generation EA [destroying the endometrium (lining of the womb) by means of a silicone balloon containing hot fluid or radiofrequency energy delivered through an intrauterine mesh electrode].

Treatment allocation

Eligible and consenting women were randomised to one of the two treatment arms in a 1 : 1 allocation ratio, using the randomisation application at the trial office at the Centre for Healthcare and Randomised Trials (CHaRT). The randomisation application was available as both an interactive voice-response telephone system and as an internet-based application, and used a minimisation algorithm based on centre and age group (< 40 vs. ≥ 40 years).[21]

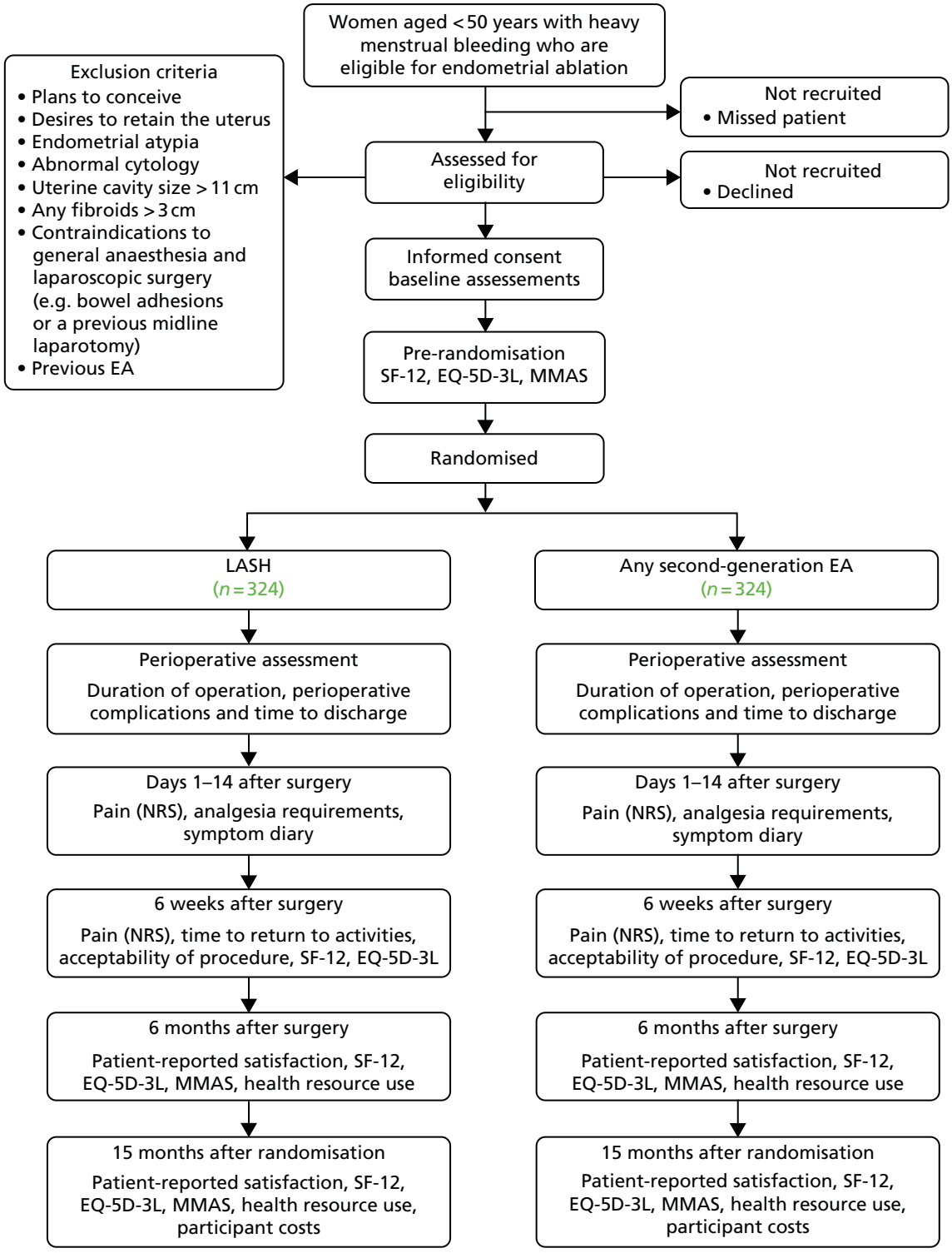

FIGURE 1 HEALTH flow diagram. EQ-5D-3L, EuroQol-5 Dimensions, three-level version; NRS, Numerical Rating Scale; SF-12, Short Form questionnaire-12 items. Reproduced from Cooper *et al.*[1] This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

Blinding

Baseline data were reported by women before randomisation using self-completed questionnaires. Surgeons and participants could not be blinded to the allocated procedure.

Delivery of the intervention

Following randomisation, participants were placed on the waiting list for the appropriate treatment. As per Scottish and UK government guidelines, it was anticipated that treatment would occur within 12–18 weeks of randomisation.[22–24] Surgeons used their standard practice so that the technique they normally used was not modified for the purposes of the trial. All other aspects of care were left to the discretion of the responsible surgeon.

Data collection during follow-up

Participant-reported outcomes were assessed by self-completed questionnaires at baseline (before surgery), 6 weeks and 6 months after surgery, and 15 months following randomisation (*Table 1*). A self-completed 14-day diary was also collected. Up to two reminders were sent to participants by post, e-mail, telephone or text message, taking into account any preferences they had for mode of communication.

TABLE 1 Measurement of outcomes (components and timing)

Outcome	Pre randomisation (baseline)	Surgery	Post surgery			Post randomisation (15 months)
			Days 1–14	6 weeks	6 months	
CRF	✗					
Surgical details		✗				
Pain NRS symptom diary			✗			
Pain NRS				✗		
Time to return to normal activities				✗		
Acceptability				✗		
Satisfaction					✗	✗
MMAS score	✗				✗	✗
Menstrual outcomes	✗				✗	✗
EQ-5D-3L and SF-12 scores	✗			✗	✗	✗
Health-care utilisation					✗	✗
Participant costs						✗

EQ-5D-3L, EuroQol-5 Dimensions, three-level version; NRS, Numerical Rating Scale; SF-12, Short Form questionnaire-12 items.

Intraoperative and postoperative data were collected by the local research team at the time of the randomised procedure. A short CRF was also completed for any related hospital readmissions during the follow-up period.

Study outcome measures

The co-primary clinical outcome measures were:

- patient satisfaction, measured on a six-point scale (from 'totally satisfied' to 'totally dissatisfied'), at 15 months after randomisation
- MMAS score, a condition-specific QoL outcome,[25] ranging from 0 (worst possible health state) to 100 (best possible health state), based on six items, measured at 15 months after randomisation.

The primary study objective was to compare the LASH and EA groups with respect to the two co-primary outcomes. These outcomes were addressed in a hierarchy. First, the patient satisfaction outcome was considered and, if this showed a statistically significant difference at a p-value of < 0.05, then the MMAS score outcome was also considered. By specifying this hierarchy, it was not necessary to apply any adjustment for multiple statistical testing, as the overall false-positive rate is controlled at 5%.

The 15-month follow-up post-randomisation time point was chosen to accommodate the 12- to 18-week waiting time for treatment. The intention was that the primary outcome questionnaire (triggered at 15 months post randomisation) would be completed at approximately 12 months post surgery, in order to facilitate comparison with the most similar RCTs in the literature.

The primary economic outcome was the incremental cost (to the health service) per QALY gained (LASH vs. EA).

Secondary outcome measures

Other outcome measures included pain score at days 1–14 and at 6 weeks post surgery; acceptability of treatment at 6 weeks post surgery; satisfaction with treatment at 6 months post surgery; MMAS score at 6 months post surgery; menstrual outcomes at 6 months post surgery and at 15 months post randomisation; generic health-related quality of life (HRQoL) [Short Form questionnaire-12 items (SF-12) and EuroQol-5 Dimensions, three-level version (EQ-5D-3L), scores at 6 weeks and 6 months post surgery and at 15 months post randomisation]; perioperative complications, including recovery details and need for additional gynaecological surgery; cost; and cost-effectiveness.

Pathology results for all endometrial biopsies and uterine specimens were also checked.

Statistical analyses were used to compare secondary outcomes by randomised groups. These analyses, however, were regarded as hypothesis-generating and no adjustment was made for multiple statistical testing.

Safety reporting

Adverse events (AEs) were either notified to the study office by the local research team or reported by the women in their follow-up questionnaires. If an AE was suspected, it was verified by the local research team, if possible. Unrelated AEs were not recorded.

In HEALTH, 'relatedness' was defined as an event that occurred as a result of a procedure required by the protocol, whether or not it was either (a) the specific intervention under investigation or (b) administered outside the study as part of normal care.

The following events were also potentially expected: admission to a high-dependency unit/intensive care; emergency hysterectomy; laparotomy; port site hernia; blood transfusion; wound infection; lower urinary tract infection; endometritis; blood stained vaginal discharge; anaesthetic complications; low-grade pyrexia; blood loss; haematoma; constipation; pelvic discomfort/pain; internal bleeding or injury; deep-vein thrombosis; pulmonary embolism; injury to the wall of the uterus; bladder/bowel/ureteric injury; and voiding dysfunction.

Any serious adverse events (SAEs) related to the participants' HMB treatment that were not further interventions (e.g. being admitted to hospital for an infection) were recorded on the SAE form. Hospital visits that were associated with further interventions due to HMB (e.g. further surgery) were recorded as an outcome measure. All deaths from any cause (related or otherwise) were recorded on the SAE form.

It was a requirement to report to the sponsor any SAEs that were deemed related and unexpected within 24 hours of receiving the signed SAE notification. Such SAEs would also be reported to the main Research Ethics Committee within 15 days of the chief investigator becoming aware of the event. All related SAEs were summarised and reported to the appropriate authorities within their regular progress reports.

Sample size

An individual participant data meta-analysis of abdominal hysterectomy compared with first-generation EA[8] suggested a target difference of an odds ratio (OR) of 2.84 (95% vs. 87%) for patient satisfaction. Such an OR also equates to a medium-sized standardised effect (Cohen's *d*). It was calculated that 292 participants per group would provide 90% power to detect a difference in total satisfaction rates of 8% (87% vs. 95%), using a two-sided continuity-corrected chi-squared test. This would also allow > 90% power to detect a 10-point difference in MMAS scores [assuming a standard deviation (SD) of 33 units]. Based on an expected 10% drop-out rate, the recruitment target was 648 participants in total (324 participants per group).

Owing to changes to the analysis plan during the trial, the implications for these calculations were later revisited (see *Statistical analysis*).

Data Monitoring Committee

The independent Data Monitoring Committee (DMC), which consisted of a methodologist, a clinician and a statistician, met on four occasions during the trial and considered interim reports of trial data by randomised groups (denoted as group 1 and group 2). On each occasion they agreed that the trial should continue as planned. At the final meeting, which took place in September 2017, after recruitment had ended, the DMC was shown the distributions of the primary outcomes using interim data.

Statistical analysis

Analyses were conducted using Stata® version 15 (StataCorp LP, College Station, TX, USA). Categorical variables were described with the number and percentage in each category. Continuous variables were described using mean and SD or median and interquartile range (IQR), depending on the distribution of data.

Analyses were based on the intention-to-treat principle, analysing women in the groups to which they were randomised. Analyses used a two-sided 5% significance level, with corresponding 95% confidence intervals (CIs) generated as appropriate [see URL: www.journalslibrary.nihr.ac.uk/programmes/hta/123523/#/ (accessed 22 May 2019)].

Analyses of the two co-primary outcomes (patient satisfaction and MMAS at 15 months after randomisation) were conducted independently.

Patient satisfaction was collected on a six-point scale: 'totally satisfied', 'generally satisfied', 'fairly satisfied', 'fairly dissatisfied', 'generally dissatisfied' or 'totally dissatisfied'. The original analysis plan specified that patient satisfaction be treated as a binary variable, but after considering the distribution of interim data (September 2017), and to make better use of the data collected, the DMC requested that this outcome be treated as ordinal with four categories ('totally satisfied', 'generally satisfied', 'fairly satisfied', with the remaining three categories combined into a single 'dissatisfied' category), and analysed using an ordinal logistic regression (OLR) model with adjustment for minimisation factors: age (< 40 vs. ≥ 40 years) and centre (treated as a random effect).

We originally intended the MMAS score to be treated as a continuous outcome and analysed using a linear regression model, adjusted for baseline MMAS scores (treated as a continuous variable) and the two minimisation factors (age and centre). However, interim data presented to the DMC were highly skewed, with over half of all trial participants reporting a maximum MMAS score of 100 at 15 months post randomisation. After discussion, the DMC recommended that the analysis of this outcome be changed to an OLR model with four categories (0–50, 51–75, 76–99, 100).

The Project Management Group (PMG) accepted the recommended changes to the analysis of the primary outcomes after viewing the distribution of these outcomes with both groups combined. The decision to change the analysis method for both co-primary outcomes to an ordered categorical analysis had implications for the power of the study. It seemed appropriate to continue to use a common OR of 2.84 in the revised power calculations. Based on the formulae in a report by Whitehead,[26] assuming a common OR of 2.84 and using the expected proportions in each category from interim trial data with treatment groups combined, a total of 292 participants per group would have $> 90\%$ power to detect statistically significant differences between the randomised groups for patient satisfaction. There were no accurate data on which to base our decisions regarding the MMAS outcome, so a pragmatic decision was made to use the same OR for this outcome. Both outcomes had similar distributions after classification into four categories and were addressed in a hierarchy (MMAS score was considered only if patient satisfaction showed a statistically significant difference). Therefore, it was considered unnecessary to recruit additional participants to the trial.

The MMAS total score was calculated only if the six constituent items were completed. There does not appear to be a precedent in the literature for imputing scores for MMAS items from other items as the response category weighting varies by item. In addition, to account for the nature of the treatments being offered (i.e. the vast majority of the women in the LASH arm and 40–50% of the women in the EA arm would be expected to be amenorrhoeic following treatment), the instructions for completion of the MMAS were altered slightly before the start of the study [see URL: www.journalslibrary.nihr.ac.uk/programmes/hta/123523/#/ (accessed 22 May 2019)].

It was expected that a small number of women might have to wait longer than 12–18 weeks for their operation and therefore would receive their 6 months post-surgery and 15 months post-randomisation questionnaires simultaneously. It was therefore agreed that scores for the co-primary outcomes and the main outcome used in the economic analysis (EQ-5D-3L utility score) could be used from the 6-month post-surgery questionnaire in lieu of the 15-month data, provided these were provided within 3 months of the due date of the latter.

A sensitivity analysis using a multiple imputation approach was used to explore the impact of missing data on the robustness of the results of the analyses of co-primary outcomes. Missing values for the outcome and for one covariate (MMAS score at baseline) were imputed using multiple imputation by chained equations using the *mi* package in Stata.[27] Twenty imputed data sets were created. There were no missing data for the other covariates (age group and centre), as these were required for the minimisation algorithm.

A further sensitivity analysis using the results of the original analysis method for MMAS score (i.e. a linear regression model treating MMAS score as a continuous outcome) was also presented.

Exploratory subgroup analyses were performed for the following groups: uterine cavity length (≤ 8 cm vs. > 8 cm), menstrual pain (dysmenorrhoea) at baseline (severe/crippling pain vs. other categories, determined using a five-point Likert scale), patient age (< 40 years vs. ≥ 40 years) and presence or absence of fibroids. These prespecified subgroup analyses were conducted by including a treatment by subgroup interaction term in the corresponding OLR model for the co-primary outcomes (patient satisfaction and MMAS score at 15 months post randomisation). The effect sizes from these subgroup analyses were displayed graphically in a forest plot, along with results for each recruiting centre and whether or not the operator was a consultant. Centres with fewer than 50 randomised participants were included in an 'other centre' category.

Secondary outcomes were analysed using generalised linear models (GLMs), adjusted for the minimisation factors and, when appropriate, a baseline measure. Continuous outcomes were analysed using linear regression, binary outcomes using logistic regression and ordered categorical outcomes using OLR. As many continuous outcomes had an extreme skewed distribution, an ordered categorical analysis had to be used instead. The category thresholds were decided by the PMG after viewing the distribution of the outcome of both groups combined.

Time-to-event outcomes such as time until return to normal activities (e.g. paid work for those in employment) were analysed using Cox proportional hazards regression models.

Pain data from the participant diaries (collected in the first 14 days after the operation) were analysed using a repeated-measures model.

All AEs were described using the number and percentage within each randomised group. All expected SAEs and other SAEs were recorded in detail and the number and percentage in each randomised group reported.

Economic evaluation

The economic analysis consisted of a trial-based analysis of individual patient-level cost and effect (QALY), and a decision modelling component to inform cost-effectiveness in the longer term. See *Chapters 5* and *6* for a detailed description of the methods used.

Management of the study

The trial management team, based within CHaRT, University of Aberdeen, provided day-to-day support for the recruiting centres led by a local principal investigator (PI). The PIs, supported by dedicated research nurses, were responsible for all aspects of local organisation, including recruitment of participants, delivery of the interventions and notification of any problems or unexpected developments during the study period.

The study was supervised by the PMG, which consisted of representatives from the study office and grant holders. The study was further overseen by a Trial Steering Committee (TSC), which comprised four independent members and an independent DMC (see *Data Monitoring Committee*).

Patient and public involvement

Pre-funding application and design of the research

Prior to the initial funding application, we sought support from the Royal College of Obstetricians and Gynaecologists (RCOG) Women's Network (URL: www.rcog.org.uk/our-profession/community/committees/rcog-womens-network, accessed 11 January 2013), a group of professional laywomen who work to advise and support the RCOG on women's perspectives on obstetrics and gynaecology. The proposal was discussed at the Women's Network meeting prior to the original application and the group fed back their comments to the rest of the research team. In addition, the vice chairperson of the RCOG Women's Network was a co-applicant on the grant and gave input into the application and continued to advise the study PMG until October 2016.

Oversight of the study

One of the independent members of the TSC was a patient representative. The TSC met throughout the study and reviewed all study documentation, including patient-facing documents, newsletters and questionnaires that were sent to potential and recruited participants in HEALTH. In addition to being an integral part of the study oversight, she provided the following feedback on what she felt were the key impacts and value of her recent contributions:

> *In my role as a patient representative I am a member of the HEALTH TSC and attend annual meetings as scheduled. I maintain an interest in all of the various aspects of the HEALTH trial but with a particular interest in patient-related issues and the drafting of patient information, etc. In 2017 a major problem arose when the success of the trial was threatened by the low return rate of the 12-month questionnaire. Three actions were then agreed. First, I was involved with drafting a new covering letter to be sent out with the questionnaire, the main aim of which was to emphasise the importance of returning the necessary information otherwise the trial would fail, and the main constraint of which was to avoid pressurising the women. Second, approval would be sought to offer the women a monetary incentive to return the questionnaire. Third, I drafted a supporting submission from the patient perspective to the Ethics Committee seeking approval for the above two actions.*

Report writing, academic paper preparation and dissemination

The patient and public involvement partner on the TSC has been actively involved in discussions of the trial results with the TSC, and has been supportive of the study in report preparation and has contributed towards the preparation of the *Plain English summary*. The partner will continue to be involved in dissemination activities and preparation of results dissemination to participants and academic papers.

Challenges in patient and public involvement

At the end of the study the patient and public involvement partner reflected on their input and made suggestions for possible improvements for future trials in this area:

> *One potential limitation might certainly be when there is only one PPI [patient and public involvement] partner on a trial. Perhaps the more important issues are the PP [patient and public] representative(s)'s (PPR's) background, understanding and commitment, but having more than one view or interpretation should offer a wider perspective of perceived patient need and possibly areas in which greater clarity is needed to ensure patient understanding, as far as possible.*

My involvement in trials has been as a member of the Project Management Group or of the Trials Steering Committee. As a member of the latter I have felt somewhat distanced from the projects because of the time lapse between meetings, normally around 12 months, and the lack of information during that interim period. I think I would have found it helpful to have had some continuity such as sight of, for instance, a copy of the PMG minutes, proposed changes to the Protocol, new developments etc. As patient representatives do not have a presence in the workplace, they obviously miss out on the various pieces of information that are discussed and circulated.

A patient representative can be used as a 'bridge' between the trials team and the Ethics Committee, when appropriate. For instance, my experience in some of the trials with which I have been involved has included producing a statement or proposal to assist in gaining approval from the Ethics Committee, an example of which is noted in the paragraph on 'Oversight of the study' above. I think this sort of direct contact can be very useful in conveying the patients' perspective to the Ethics Committee so as to further inform the latter as to the appropriateness of certain actions required of patients to assist in, say, the successful outcome of a trial which is the major aim.

Chapter 3 Baseline results

This chapter describes how the women were identified from 31 UK hospitals (see *Appendix 1, Table 26*) and reports the baseline characteristics up to the point of study entry. The subsequent findings are described in *Chapters 4* and *5*.

The flow of women through the study is shown in the Consolidated Standards of Reporting Trials (CONSORT) flow diagram (*Figure 2*) in line with the CONSORT recommendations.[28]

Between May 2014 and March 2017, 2552 potentially eligible patients were screened; 1351 (52.9%) were confirmed as eligible, of whom 664 (49.1%) gave their consent and were randomised, 331 to LASH and 333 to EA (see *Figure 2*).

After randomisation, four women were considered to be ineligible, regarded as post-randomisation exclusions and not included in any trial analyses. Therefore, 660 women (330 in each group) were included in the main trial analyses (see *Figure 2*).

Study recruitment

Study design and recruitment methodology have been described previously[1] (see also *Chapter 2*). Women with HMB who attended gynaecology outpatients and pre-assessment clinics, and who were eligible for EA, were invited to participate in HEALTH. Women were asked if they would be willing to be randomised to either LASH or second-generation EA. The centres that randomised women into HEALTH, including numbers recruited by centre, are described in *Appendix 1, Table 26*. The recruitment rate is illustrated in *Figure 3*.

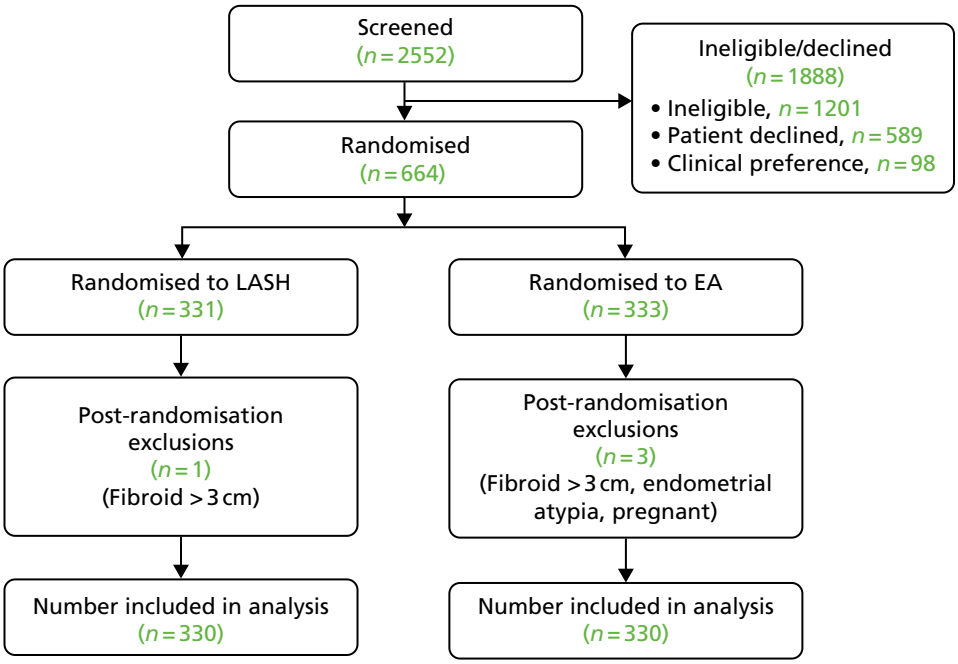

FIGURE 2 Flow of participants to the point of randomisation.

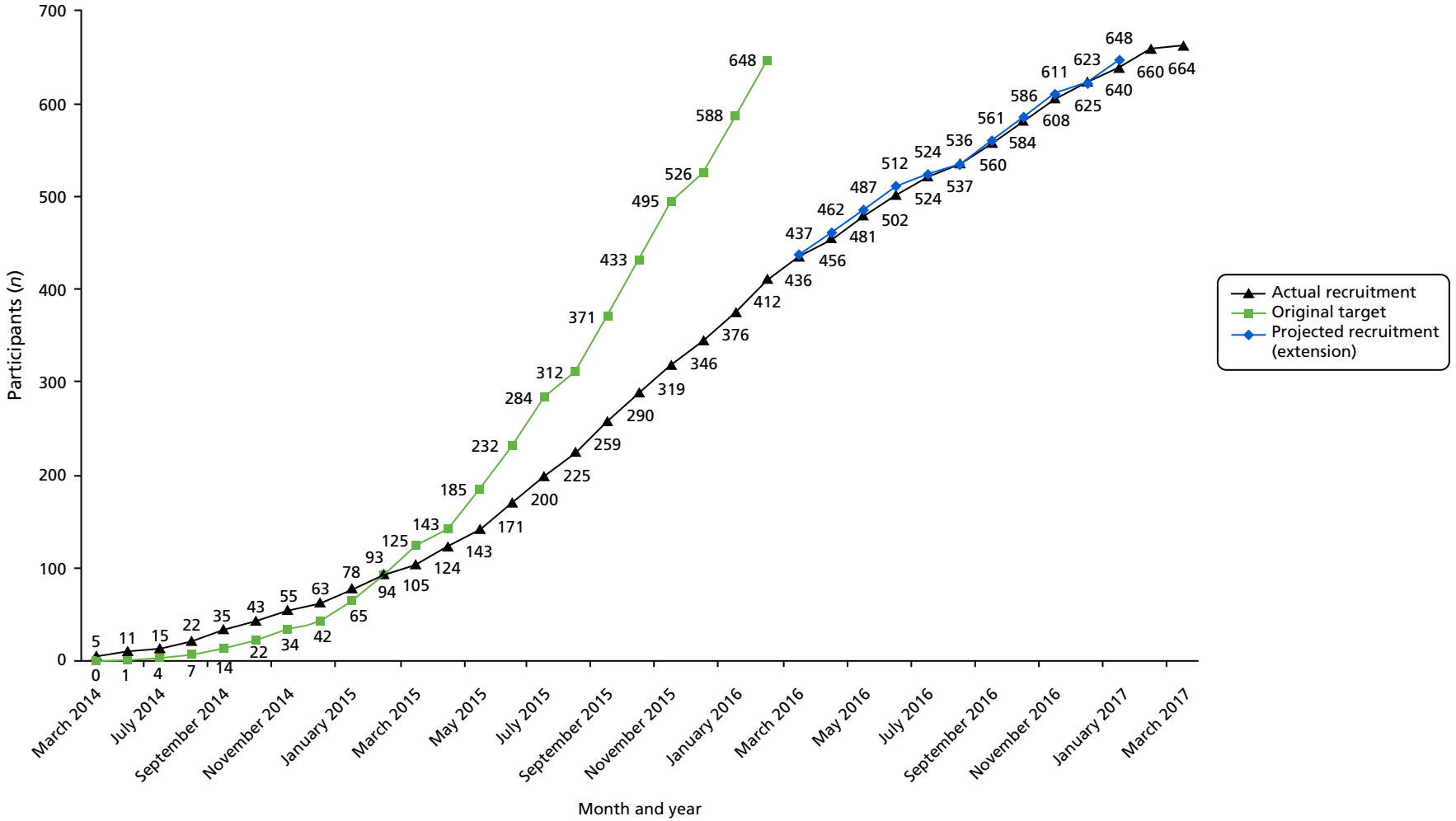

FIGURE 3 Recruitment to the trial over time.

Non-recruited women

Of the 2552 women approached, 1888 (74.0%) did not participate in the trial because they were ineligible (*n* = 1201, 47.1%) or declined participation (*n* = 589, 23.1%) or because their consultant later indicated a preference for a particular treatment (*n* = 98, 3.8%) (see *Figure 2* and *Appendix 1, Table 27*). The most common reasons for women declining to take part in the study were a preference for a particular treatment [preference for EA, *n* = 151 (25.6%); preference for hysterectomy, *n* = 126 (21.4%); preference for medical management, *n* = 89 (15.1%)] and an unwillingness to accept randomisation (*n* = 54, 9.2%). Ninety-eight women (16.6%) did not give a reason for declining to take part (see *Appendix 1, Table 28*).

Reasons for ineligibility included 'fibroids > 3cm' (*n* = 361, 30.1%), a preference to continue with medical management (*n* = 244, 20.3%) and age > 50 years (*n* = 239, 19.9%). In addition, 98 women who were deemed eligible for HEALTH were not included for other clinical reasons. In the majority of cases, this was because a treatment pathway had already been decided prior to study entry [hysterectomy, *n* = 25 (25.5%); EA, *n* = 18 (18.4%); and 'other' treatment, *n* = 16 (16.3%)] (see *Appendix 1, Table 28*).

Randomised participants: baseline characteristics

The baseline characteristics of the 660 women who agreed to participate in HEALTH and who were truly eligible to take part are described in *Tables 2–4* and *Appendix 1, Table 29*.

Participant characteristics

The two randomised groups were comparable at baseline. On average, women were around 42 years of age when considering surgical treatment for their HMB symptoms. There was no difference between the randomised groups in terms of age, body mass index or preoperative haemoglobin levels (see *Table 2*).

Heavy menstrual bleeding symptoms at baseline

Of the women who participated in HEALTH, 67.7% (443/654) had experienced trouble with their periods for > 3 years and the majority of the women (79.5%) described their periods as very heavy with clots and flooding (see *Table 3*). Just under half of the women (46.6%) described heavy bleeding for ≥ 7 days and 50.6% had experienced severe/crippling pain during their periods. Almost 80% of the women hoped the operation would stop their periods completely.

The randomised groups were comparable with respect to other characteristics, including mean bleeding score and mean pain score (see *Table 3*).

Generic quality of life at baseline

There were no differences between the randomised groups in either the MMAS total score, EQ-5D-3L utility score, EQ-5D-3L visual analogue scale (VAS), SF-12 physical component score (PCS) or SF-12 mental component score (MCS) at baseline (see *Table 4*).

TABLE 2 Baseline characteristics

Baseline characteristic	LASH (*N* = 330)	EA (*N* = 330)
Age (years), mean (SD) [*n*]	42.2 (4.89) [330]	42.1 (4.96) [330]
BMI (kg/m^2), mean (SD) [*n*]	29.1 (5.55) [309]	29.0 (5.34) [304]
Preoperative haemoglobin level (g/l), mean (SD) [*n*]	131.0 (13.1) [306]	130.1 (12.6) [282]
Number of vaginal deliveries, median (IQR) [*n*]	2 (1–3) [326]	2 (1–3) [330]
Number of caesareans, median (IQR) [*n*]	0 (0–1) [326]	0 (0–1) [327]

BMI, body mass index.

TABLE 3 Menstrual outcomes at baseline

Menstrual outcome	LASH (*N* = 330)	EA (*N* = 330)
How long have you had trouble with your periods?, *n* (%)		
< 1 year	16 (4.9)	18 (5.5)
1–3 years	84 (25.7)	93 (28.4)
> 3 years	227 (69.4)	216 (66.1)
Description of period, *n* (%)		
Light	2 (0.6)	0
Moderate	6 (1.8)	7 (2.1)
Heavy with clots	58 (17.7)	61 (18.7)
Very heavy with clots and flooding	261 (79.8)	259 (79.2)
On average, for how many days is the bleeding heavy?, *n* (%)		
Not heavy	3 (0.9)	2 (0.6)
1–3 days	50 (15.3)	51 (15.6)
4–6 days	118 (36.1)	125 (38.2)
≥ 7 days	156 (47.7)	149 (45.6)
At any time in the last 3 months have you needed to use more than one form of sanitary protection at a time?, *n* (%)		
No	27 (8.3)	25 (7.7)
Tampon and pad	117 (35.9)	118 (36.3)
Two pads	88 (27.0)	84 (25.8)
Tampon and two pads	48 (14.7)	56 (17.2)
More than this (e.g. bath towel)	46 (14.1)	42 (12.9)
Are your periods usually painful?, *n* (%)		
No	19 (5.8)	18 (5.5)
Mild pain	33 (10.1)	38 (11.7)
Moderate pain	104 (31.9)	110 (33.7)
Severe/crippling pain	170 (52.1)	160 (49.1)
Bleeding (mean score of up to 10 days of period, 0 = no bleeding, 5 = worst bleeding), mean (SD) [*n*]	3.59 (0.88) [322]	3.55 (0.78) [322]
Pain (mean score of up to 10 days of period, 0 = no pain, 5 = worst pain), mean (SD) [*n*]	2.76 (1.27) [311]	2.70 (1.30) [313]
What do you want from the operation?, *n* (%)		
No periods	265 (82.6)	253 (78.6)
Light periods	29 (9.0)	38 (11.8)
Normal periods	27 (8.4)	31 (9.6)

TABLE 4 Quality-of-life scores at baseline

QoL score	LASH (*N* = 330)	EA (*N* = 330)
MMAS		
Total score		
Mean (SD)	30.5 (19.0)	32.3 (20.0)
Median (IQR)	28.6 (14.7–43.7)	29 (15.7–47.7)
n	323	321
EQ-5D-3L		
Utility score		
Mean (SD)	0.71 (0.30)	0.70 (0.31)
Median (IQR)	0.76 (0.66–1.00)	0.79 (0.69–1.00)
n	319	322
VAS		
Mean (SD)	65.2 (24.2)	67.2 (23.5)
Median (IQR)	70 (50–85)	70 (52–85)
n	317	321
SF-12		
PCS		
Mean (SD)	45.0 (9.0)	44.9 (9.7)
Median (IQR)	45.8 (39.0–52.1)	46.5 (39.0–51.9)
n	318	321
MCS		
Mean (SD)	37.2 (11.0)	38.7 (11.6)
Median (IQR)	36.6 (29.8–45.1)	29 (15.7–47.7)
n	318	321

MCS, mental component score; PCS, physical component score; VAS, visual analogue scale.

Notes

MMAS total score: 0 represents worst possible health and 100 represents best possible.
EQ-5D-3L utility score: –0.59 represents worst possible QoL and 1 represents best possible.
EQ-5D-3L VAS: 0 represents worst imaginable health state and 100 represents best possible.
SF-12 PCS and MCSs: 0 represents worst possible QoL and 100 represents best possible.

Chapter 4 Clinical results

This chapter describes the main clinical findings of HEALTH. Details of the trial operations are presented first. This is followed by the results for the two co-primary outcomes (patient satisfaction and MMAS score at 15 months post randomisation). Finally, the results of the secondary outcomes are provided in chronological order. All results are presented by allocated randomised group (i.e. according to intention to treat).

Flow of participants through the trial

The CONSORT flow diagram shows the number of participants providing data at each stage of the trial (*Figure 4*). Response rates are based on the number receiving an operation (14-day diary, 6-week and 6-month questionnaire) or the number randomised (15-month questionnaire), after accounting for withdrawals. Questionnaire completion rates ranged between 80% and 89% (exact return rates are reported in the CONSORT flow diagram; see *Figure 4*).

Operation details and operative outcomes

Forty-four participants [21/330 (6.4%) randomised to LASH and 23/330 (7.0%) randomised to EA] did not undergo an operation. These women were not asked to complete the patient diary or questionnaires at 6 weeks and 6 months post surgery, but were sent the final questionnaire at 15 months post randomisation.

Table 5 provides details for the 616 women who received an operation. The median number of days between randomisation and treatment was higher in the LASH group [84 (IQR 57–127) days] than in the EA group [63 (IQR 41–97) days] (see *Appendix 2, Figure 16*). Six women across both arms waited a year or more for their operation and therefore received the 6 months post-surgery and the 15 months post-randomisation questionnaires at around the same time.

Of those undergoing treatment, 291 out of 309 (94.2%) randomised to LASH and 297 out of 307 (96.7%) randomised to EA received the allocated procedure. Twelve of those randomised to LASH actually received an EA, five underwent a total hysterectomy and one had a hysteroscopy/polypectomy. One woman randomised to EA received LASH, five had a total hysterectomy and four had a hysteroscopy/polypectomy (see *Figure 4*). In total, nine of the EA operations could not be completed during the first admission (one in the LASH group and eight in the EA group), three women were subsequently readmitted for LASH, two women were readmitted for the total hysterectomy and two women were readmitted for EA.

Compared with the EA group, the LASH group included higher proportions of women who were operated on by a consultant (77.3% vs. 57.3%), received thromboprophylaxis (98.4% vs. 69.2%) and received parenteral postoperative opiates (30.4% vs. 15.0%). Fewer women in the LASH group than in the EA group were noted to have a uterus free from fibroids during surgery (75.7% vs. 91.1%) and more (32.4% vs. 5.3%) stayed in hospital for > 24 hours (see *Table 5*).

Results for the co-primary outcomes

Satisfaction at 15 months post randomisation

The single question regarding satisfaction was answered by 278 out of 330 (84.2%) women randomised to the LASH group and 280 out of 330 (84.8%) women randomised to the EA group at 15 months post randomisation. This included one woman whose 6-month data were imputed for the 15-month time point (*Table 6*).

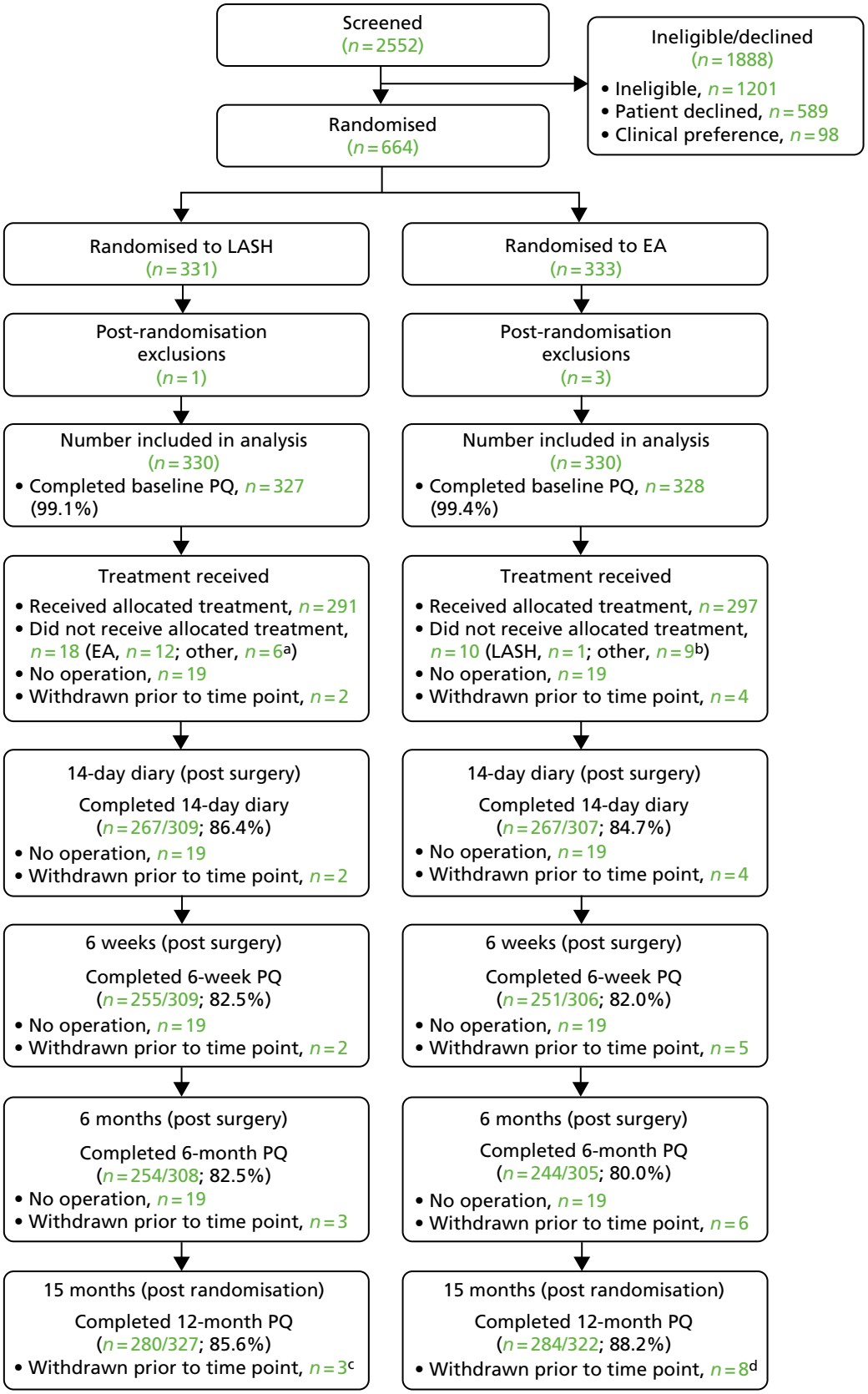

FIGURE 4 Consolidated Standards of Reporting Trials (CONSORT) flow diagram. a, Other operations (LASH group): total hysterectomy ($n = 5$), EA ($n = 1$), hysteroscopy/polypectomy ($n = 1$); b, other operations (EA group): total hysterectomy ($n = 5$), hysterectomy/polypectomy ($n = 4$); c, reasons included: unwillingness to have surgery ($n = 1$), private treatment ($n = 1$), no reason given ($n = 1$); and d, reasons included: unwillingness to have surgery ($n = 2$), requested a different operation ($n = 2$), family illness ($n = 1$), moved abroad ($n = 1$), did not want to complete questionnaires ($n = 2$). PQ, participant questionnaire. Reproduced from Cooper *et al.*[29]

TABLE 5 Surgical details for first admission

Detail from surgical procedure	LASH (maximum *N* = 309)	EA (maximum *N* = 307)
Grade of surgeon, *n* (%)		
Consultant	239 (77.3)	176 (57.3)
Specialty doctor	8 (2.6)	16 (5.2)
Nurse practitioner	0	10 (3.3)
Registrar/junior	62 (20.1)	105 (34.2)
Supervised by consultant (if surgeon not consultant), *n* (%)		
Yes	66 (96)	100 (78.1)
No	3 (4)	28 (21.9)
Not known	1	3
Type of procedure performed, *n* (%)		
LASH	291 (94.2)	1 (0.3)
EA	12 (3.9)	297 (96.7)
Total hysterectomy	5 (1.6)	5 (1.6)
Hysteroscopy/polypectomy	1 (0.3)	4 (1.3)
Was thromboprophylaxis used?, *n*/*N* (%)		
Any of below	303/308 (98.4)	209/302 (69.2)
Injectable heparinoid	236/309 (76.4)	23/307 (7.5)
TED stockings	254/309 (82.2)	194/307 (63.2)
Pneumatic anti-thrombosis boots	69/309 (22.3)	21/307 (6.8)
Type of anaesthesia, *n* (%)		
General	308 (100)	291 (94.8)
Local	0	12 (3.9)
Not known	1	4
Uterine cavity length (cm), mean (SD) [*n*]	8.38 (1.63) [259]	7.24 (1.97) [292]
Fibroids, *n* (%)[a]		
Normal	224 (75.7)	275 (91.1)
Type 0/1 fibroids ≤ 3 cm	11 (3.7)	11 (3.7)
Type 2 fibroids ≤ 3 cm	9 (3.0)	6 (2.0)
Intramural/subserosal fibroids ≤ 3 cm	50 (16.9)	10 (3.3)
Not known	15	5
Time from randomisation to operation (days), median (IQR) [range], *n*	84 (57–127) [0–579], 309	63 (41–97) [0–541], 307
Time from entry to anaesthetic room to exit from operating room (minutes), mean (SD) [*n*]	113.9 (38.1) [306]	44.3 (23.3) [295]
Time from operating room exit to exit from recovery room (minutes), mean (SD) [*n*]	75.8 (43.7) [305]	52.4 (33.1) [297]

continued

TABLE 5 Surgical details for first admission (*continued*)

Detail from surgical procedure	LASH (maximum $N = 309$)	EA (maximum $N = 307$)
Postoperative analgesia, *n*/*N* (%)		
Paracetamol/ibuprofen	269/309 (87.1)	226/307 (73.6)
Oral opiate	136/309 (44.0)	72/307 (23.4)
Opiate injection	94/309 (30.4)	46/307 (15.0)
Hours from operation to discharge, median (IQR) [*n*]	21.5 (17.0–26.1) [306]	3.2 (2.1–5.1) [303]
Total number of women who stayed > 24 hours, *n*/*N* (%)	99/306 (32.4)	16/303 (5.3)
Reason for stay (if stayed > 24 hours)		
Pain	30 (42)	3 (27)
Nausea/vomiting	2 (3)	1 (9)
Social/geographical	13 (18)	2 (18)
Voiding problems	14 (19)	1 (9)
Other	13 (18)	4 (36)
Not known	27	5

TED, thromboembolic-deterrent.
a Fibroids detected at baseline scan and at hysteroscopy/LASH procedure.

TABLE 6 Results for satisfaction and MMAS at 15 months post randomisation

Outcome	LASH ($N = 330$), *n* (%)	EA ($N = 330$), *n* (%)	Adjusted OR (95% CI), *p*-value
Satisfaction			
Total number of women	278	280	2.53 (1.83 to 3.48), $p < 0.001$
Totally satisfied	211 (75.9)	158 (56.4)	
Generally satisfied	40 (14.4)	57 (20.4)	
Fairly satisfied	19 (6.8)	29 (10.4)	
Fairly/generally/totally dissatisfied	8 (2.9)	36 (12.9)	
Total MMAS score			
Total number of women	262	268	1.87 (1.31 to 2.67), $p = 0.001$
0–50	15 (5.7)	29 (10.8)	
51–75	17 (6.5)	34 (12.7)	
76–99	50 (19.1)	59 (22.0)	
100	180 (68.7)	146 (54.5)	

Notes
Analyses used OLR adjusting for age group, centre and baseline score (if applicable). ORs > 1 favour the LASH group.
The results suggest that the odds of being in a more favourable satisfaction or MMAS category were, respectively, 2.53 and 1.87 times higher in the LASH group than in the EA group.
Interpretation of a proportional OR: given four categories, A (totally satisfied), B (generally satisfied), C (fairly satisfied) and D (dissatisfied, fairly/generally/totally), the assumption of the proportional odds model is that the effect of randomised treatment (the proportional OR) is the same when comparing A vs. BCD, AB vs. CD, and ABC vs. D.

The proportion of women who described themselves as satisfied with their treatment was higher in the LASH group [LASH = 97.1% (270/278); EA = 87.1% (244/280); OR 4.89 (95% CI 1.91 to 12.45)]. Women in the LASH group were also more likely to choose the 'totally satisfied' category [LASH = 75.9% (211/278); EA = 56.4% (158/280)].

This result was statistically significant in favour of LASH. In the primary analysis, OLR adjusted for age group and centres, the odds of being in a more favourable satisfaction category were two and a half times greater for women randomised to LASH than for women randomised to EA (OR 2.53, 95% CI 1.83 to 3.48; $p < 0.001$). The corresponding unadjusted result was similar (OR 2.55, 95% CI 1.79 to 3.63; $p < 0.001$) (see *Appendix 2, Table 30*).

The OLR method assumes that the same underlying OR would be obtained for all three splits of the 2 × 4 table (the proportional odds assumption). We investigated this by examining the ORs obtained using binary logistic regression (adjusted for age and centre) for these three splits of the data (see *Appendix 2, Table 30*). The result for two of these splits was very similar to the OLR result. The results for the satisfied versus dissatisfied split used in the individual patient data meta-analysis[8] had a wider CI because of the smaller cell counts involved, but the CIs were broadly consistent with the main result (OR 4.89, 95% CI 1.91 to 12.45). The Brant test was also not statistically significant ($p = 0.32$); therefore, there was no indication that the ordinal model was inappropriate.

There was also no difference in interpretation when considering per-protocol results (i.e. comparing those who actually received LASH with those who actually received EA), or when considering only those operated on by a consultant (see *Appendix 2, Table 30*).

It can be noted that the proportions who were satisfied (97% vs. 87%) were similar to those anticipated in the individual patient data meta-analysis[8] (95% vs. 87%). This corresponded to an adjusted difference in proportions of 0.10 (95% CI 0.05 to 0.15) (see *Appendix 2, Table 30*). Although the OR from the primary analysis (2.53) was less than the 2.84 specified as an important effect size in the original calculation, it nonetheless represents a difference in satisfaction that can be regarded as clinically important.

MMAS scores at 15 months post randomisation

Total MMAS scores were available for 262 out of 330 (79.4%) women in the LASH group and 268 out of 330 (81.2%) women in the EA group at 15 months post randomisation. This included MMAS scores for two women whose 6-month data were imputed for the 15-month time point. A further 29 women completed at least one of the six items, but were excluded from the primary analysis because a total score could not be derived.

The total MMAS score ranges from 0 (worst possible health) to 100 (best possible health). Both groups reported a considerable improvement in MMAS scores after surgery. At baseline, median scores were 28.6 (IQR 14.7–43.7) in the LASH group and 29 (IQR 15.7–47.7) in the EA group, but by 15 months post randomisation the majority of women in each group had the best possible score (MMAS score = 100) (*Figure 5* and *Appendix 2, Table 31*).

The results for the primary analysis, OLR adjusting for age, centre and baseline MMAS, are presented in *Table 6*. An OR of 1.87 (95% CI 1.31 to 2.67) was obtained, suggesting that women randomised to receive a LASH had almost twice the odds of being in a more favourable MMAS category than women randomised to EA ($p = 0.001$). The corresponding unadjusted OR was 1.90 (95% CI 1.35 to 2.68; $p < 0.001$) (see *Appendix 2, Table 32*).

The proportional odds assumption was investigated by examining binary logistic regression models using three splits of the data. All approaches yielded similar ORs that were consistent with the main result and the Brant test was not statistically significant ($p = 0.07$). There was also no change in interpretation using a

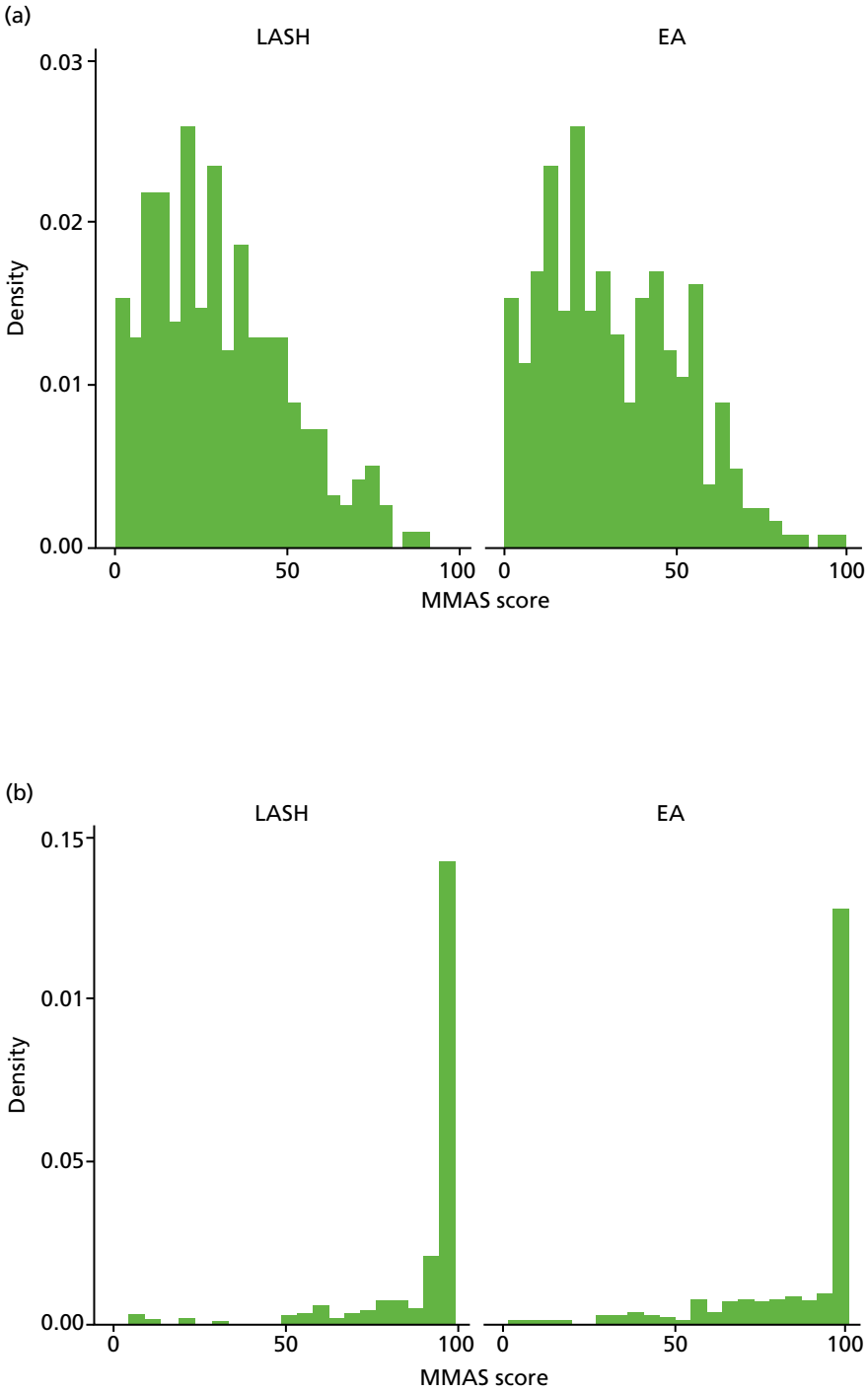

FIGURE 5 Total MMAS scores at (a) baseline; (b) 6 months post surgery; and (c) 15 months post randomisation. (*continued*)

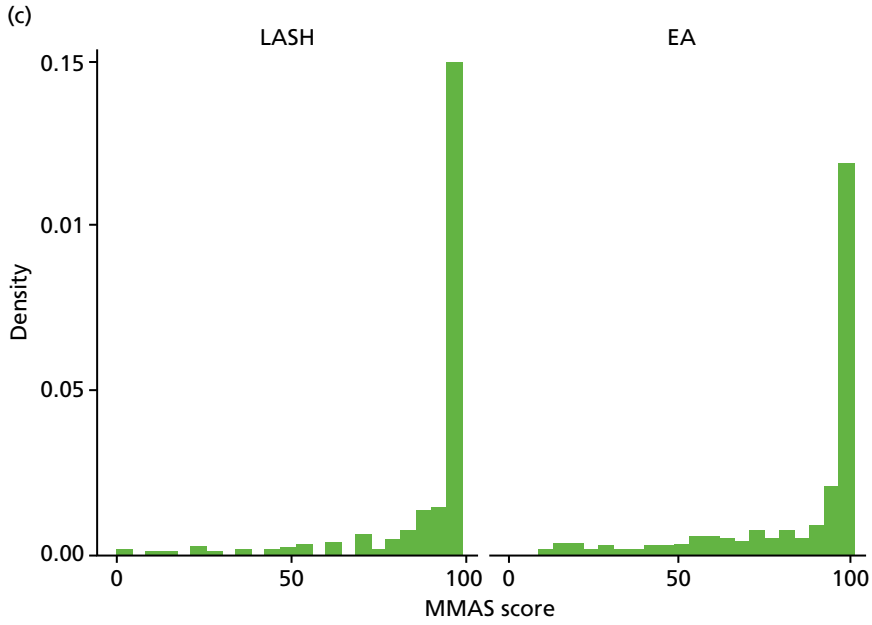

FIGURE 5 Total MMAS scores at (a) baseline; (b) 6 months post surgery; and (c) 15 months post randomisation.

per-protocol analysis, when restricting analyses to those operated on by a consultant or when treating the MMAS score as a continuous outcome (see *Appendix 2, Table 32*).

The mean between-group difference in MMAS scores of 6.3 points was lower than the difference of 10 points specified in the original sample size calculation. However, as the distribution of scores was highly skewed, the median is a more appropriate summary to use, and this was 100 in each group. The 95% CI for the effect size for the primary analysis did not include the OR of 2.84 specified in the revised sample size calculation, but an OR of 1.87 could still be considered to have a clinically important impact on patients.

Subgroup analyses

Exploratory subgroup analyses were conducted to determine if there was evidence of differential treatment effects for the co-primary outcomes by four binary factors: cavity length (< 8 cm vs. ≥ 8 cm), menstrual pain at baseline (severe/crippling period pain vs. other categories), age (< 40 years vs. ≥ 40 years) and presence or absence of fibroids.

One statistically significant interaction effect was identified. This suggested that women with fibroids who were randomised to the LASH operation had greater than expected levels of satisfaction (OR for interaction 7.27, 95% CI 2.32 to 41.8; $p = 0.002$). There was no evidence of any other interaction effects (see *Appendix 2, Table 33*). For the two primary outcomes, separate OLR results for the eight subgroups are also displayed graphically, along with results by recruiting centre and by whether or not the operator was a consultant (see *Appendix 2, Figure 17*). Except for the results for fibroids, each subgroup had broadly consistent results.

Sensitivity analyses

The primary analyses were limited to those with complete 15-month follow-up data. Multiple imputation techniques using chained equations were used to investigate the robustness of these findings.

For satisfaction at 15 months post randomisation, an OR of 2.15 (95% CI 1.53 to 3.02; $p < 0.001$) was obtained using an adjusted OLR model after combining the 20 imputed data sets (see *Appendix 2, Table 30*).

For MMAS score at 15 months post randomisation, an OR of 1.68 (95% CI 1.16 to 2.45; $p = 0.007$) was obtained (see *Appendix 2, Table 32*). There was therefore no change in interpretation for either outcome compared with the primary analysis approach.

Results for the secondary outcomes

Serious adverse events and complications

Twenty-five women experienced a SAE. One woman randomised to LASH experienced two such events, so there were a total of 26 SAEs (15 in the LASH group and 11 in the EA group) (*Table 7*). There was no statistically or clinically significant difference between the randomised groups in the proportions experiencing a SAE (adjusted OR 1.30, 95% CI 0.56 to 3.02; $p = 0.54$).

In the LASH group, five women had an infection, three women were catheterised for > 72 hours, three women experienced considerable pain, one woman had a conversion to open hysterectomy, one woman was readmitted for investigation of shortness of breath and one woman had a bladder injury. A single participant, whose bowel serosa was grazed at surgery, underwent prolonged admission for observation, but did not require any treatment. One of the women in the EA group had her operation converted to hysterectomy, five women had an infection, one woman was catheterised for > 72 hours and four women experienced considerable pain.

TABLE 7 Serious adverse events and complications

SAE/complication	LASH ($N = 309$), *n* (%)	EA ($N = 307$), *n* (%)
SAEs		
Any SAE[a]	14 (4.5)	11 (3.6)
Infection	5 (1.6)	5 (1.6)
Pain	3 (1.0)	4 (1.3)
Catheterisation for > 72 hours	3 (1.0)	1 (0.3)
Conversion to hysterectomy	1 (0.3)	1 (0.3)
Readmitted for investigation of shortness of breath	1 (0.3)	0
Prolonged admission for observation only	1 (0.3)	0
Bladder injury	1 (0.3)	0
Other complications		
Voiding dysfunction	14 (4.5)	2 (0.7)
Consultation for pain	1 (0.3)	1 (0.3)
Haematoma	1 (0.3)	1 (0.3)
Blood loss > 500 ml	1 (0.3)	1 (0.3)
Uterine perforation, inactive/blunt	1 (0.3)	3 (1.0)
Pyrexia requiring antibiotics	3 (1.0)	2 (0.7)
Blood transfusion	0	1 (0.3)

a Numbers refer to participants, not events. One woman in the LASH group had two AEs (infection and catheterisation); adjusted OR for any SAE 1.30 (95% CI 0.56 to 3.02); $p = 0.54$.

Notes

Complication data come from two sources (operation form and hospital readmission form).
Denominators for percentages are based on all those receiving an operation.

A list of other complications from either the index operation or on subsequent hospital readmissions associated with further treatment for HMB are provided in *Table 7*. A total of 32 women experienced a complication following surgery. These included voiding dysfunction (LASH, $n = 14$; EA, $n = 2$); consultation for pain (LASH, $n = 1$; EA, $n = 1$); haematoma (LASH, $n = 1$; EA, $n = 1$); blood loss > 500 ml (LASH, $n = 1$; EA, $n = 1$); inactive/blunt uterine perforation (LASH, $n = 1$; EA, $n = 3$); pyrexia requiring antibiotics (LASH, $n = 3$; EA, $n = 2$); and blood transfusion (LASH, $n = 0$; EA, $n = 1$).

Further treatment for heavy menstrual bleeding

Eighteen women randomised to EA and two women randomised to LASH received further treatment for HMB during the follow-up period (*Table 8*). The most common reason was that the index EA procedure produced an unsatisfactory reduction in HMB ($n = 12$). A further seven women required unplanned further surgery because the index EA procedure could not be completed on first admission; this included one woman who was randomised to LASH but in whom an EA procedure was attempted. On five occasions, a hysterectomy was performed on the second admission.

Patient diary (1–14 days)

Table 34 in *Appendix 2* reports data for the patient diary, which was completed in the first 14 days following surgery. In both groups there was a reduction in self-reported levels of pain (0 = no pain, 10 = worst imaginable pain) (*Figure 6*) and in the proportion of women taking paracetamol or other painkillers over these 2 weeks. In addition, fewer women were using pads for vaginal bleeding or discharge. By day 14, 177 out of 256 (69.1%) women in the EA group and 34 out of 267 (12.7%) women in the LASH group were using pads.

Overall, those in the LASH group had pain scores that were almost 1 point higher than those in the EA group (mean difference 0.92, 95% CI 0.59 to 1.24; $p < 0.001$; see *Appendix 2, Table 34*).

Pain and return to usual activities (6 weeks post surgery)

By 6 weeks after surgery, over half of the women in both groups reported no pain on a 10-point scale from 0, no pain, to 10, the worst pain imaginable (*Table 9*). After adjusting for the minimisation factors (age group and centre), an OR of 1.43 (95% CI 1.05 to 1.96; $p = 0.03$) was obtained, suggesting that those in the EA group had lower levels of pain at 6 weeks than those in the LASH group.

TABLE 8 Further treatment for HMB

Further treatment	LASH ($N = 309$), *n*	EA ($N = 307$), *n*
Total hysterectomy for failed (unsatisfactory outcome) EA	0	10
Subtotal hysterectomy for failed (unsatisfactory outcome) EA	0	2
Removal of cervical stump for cyclical pain/bleeding	1	0
Readmitted to perform total hysterectomy as EA could not be performed on first admission	0	2
Readmitted to perform subtotal hysterectomy as EA could not be performed on first admission	1	2
Readmitted to perform allocated procedure which could not be performed on first admission	0	2
Total HMB treatments[a]	2	18

a Adjusted OR for further treatment for HMB 0.11, 95% CI 0.04 to 0.28 ($p < 0.001$).

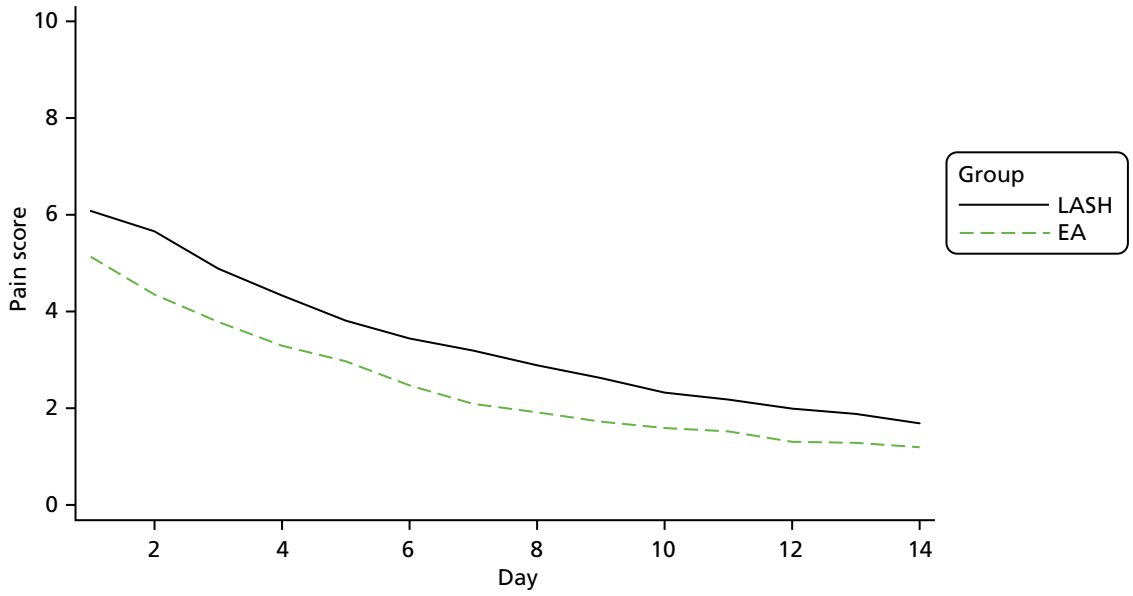

FIGURE 6 Mean pain during the first 14 days post surgery (0 = no pain, 10 = worst imaginable pain).

TABLE 9 Patient outcomes and return to normal activities 6 weeks post surgery

Outcome	LASH (*N* = 309)	EA (*N* = 307)	Adjusted OR[a] (95% CI), *p*-value
Level of pain today (0 = no pain, 10 = worst imaginable), median (IQR) [range], *n*	0 (0–1) [0–10], 241	0 (0–1) [0–10], 234	1.43 (1.05 to 1.96),[b] $p = 0.03$
Current employment, *n* (%)			
Full time	104 (43.7)	99 (42.1)	
Part time	82 (34.5)	82 (34.9)	
Not working	52 (21.8)	54 (23.0)	
			Adjusted HR[c] (95% CI), *p*-value
Days until return to paid work, median (95% CI)[d] [*n*]	42 (37 to 42) [186]	10 (7 to 14) [181]	0.23 (0.18 to 0.30),[b] $p < 0.001$
Days until return to unpaid work, median (95% CI)[d] [*n*]	21 (17 to 25) [255]	7 (5 to 7) [251]	0.64 (0.57 to 0.73),[b] $p < 0.001$
Days until return to sporting or social activities, median (95% CI)[d] [*n*]	42 (34 to 42) [255]	14 (14 to 18) [250]	0.48 (0.42 to 0.56),[b] $p < 0.001$

HR, hazard ratio.
a OLR using categories 0, 1–5, 6–10.
b Favours EA ($p < 0.05$).
c Cox regression.
d Estimated median (95% CI) from Cox regression.

Figure 7 shows the time to return to work by randomised group for the women in full- or part-time paid employment. Those in the LASH group returned to work after a median of 42 days, whereas those in the EA group returned after a median of 10 days (see *Table 9*). A Cox proportional hazards regression model adjusted for age group and centre suggested a statistically significant difference in favour of EA [adjusted hazard ratio (HR) 0.23, 95% CI 0.18 to 0.30; $p < 0.001$].

Those in the EA group returned more rapidly to both unpaid work (adjusted HR 0.64, 95% CI 0.57 to 0.73; $p < 0.001$) and sporting or social activities (adjusted HR 0.48, 95% CI 0.42 to 0.56; $p < 0.001$) (see *Table 9*).

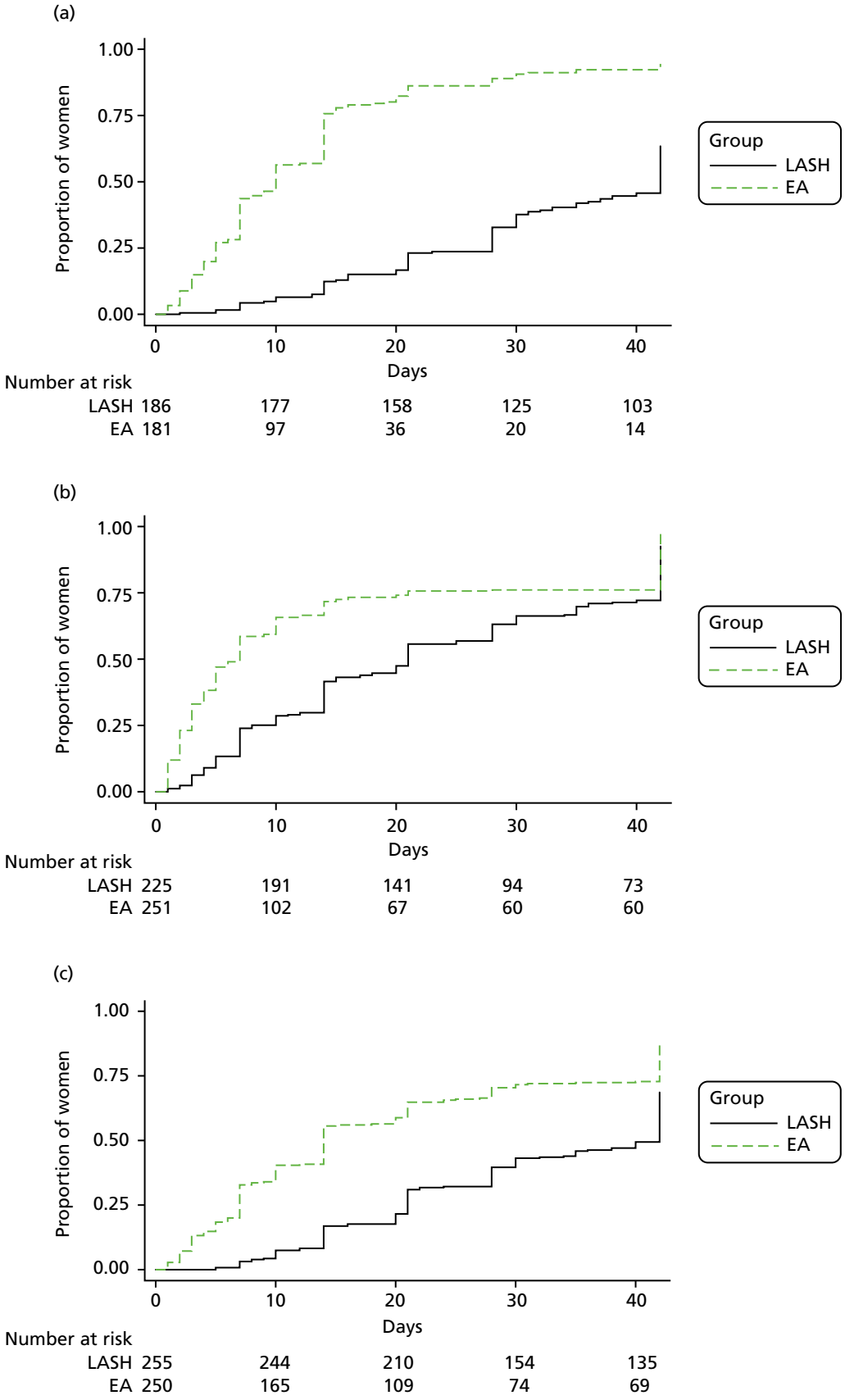

FIGURE 7 Time to return to (a) paid work; (b) unpaid work; and (c) sporting or social activities.

Menstrual outcomes (6 months post surgery and 15 months post randomisation)

The proportion of women who continued to have periods was lower in the LASH group than in the EA group [6 months: LASH, 39/253 (15.4%), EA, 111/246 (45.7%), adjusted OR 0.22, 95% CI 0.15 to 0.32, $p < 0.001$; 15 months: LASH, 52/277 (18.8%), EA, 117/278 (42.1%), adjusted OR 0.32, 95% CI 0.21 to 0.48, $p < 0.001$] (*Table 10*).

Those in the LASH group had lighter and less painful periods, fewer days with heavy bleeding and lower median bleeding scores and were less likely to require sanitary protection (see *Table 10* and *Appendix 2, Table 35*).

TABLE 10 Patient outcomes at baseline, 6 weeks and 6 months post surgery and 15 months post randomisation

Participant outcome	LASH ($N = 330$)[a]	EA ($N = 330$)[b]	Adjusted effect size (95% CI)	*p*-value
Are you still having periods? (6 months),*[c] n *(%)				
Yes	39 (15.4)	111 (45.7)	0.22 (0.15 to 0.32)[d]	< 0.001
No	214 (84.6)	132 (54.3)		
Are you still having periods? (15 months),*[c] n *(%)				
Yes	52 (18.8)	117 (42.1)	0.32 (0.21 to 0.48)[d]	< 0.001
No	225 (81.2)	161 (57.9)		
***MMAS total score*[e]**				
Baseline				
Mean (SD)	30.5 (19.0)	32.3 (20.0)		
Median (IQR)	28.6 (14.7–43.7)	29.0 (15.7–47.7)		
n	323	321		
6 months				
Mean (SD)	91.3 (18.1)	86.3 (21.9)	1.48 (1.02 to 2.14)[d]	0.04
Median (IQR)	100 (91–100)	100 (78.2–100)		
n	230	224		
15 months				
Mean (SD)	91.2 (19.0)	84.9 (23.5)	1.87 (1.31 to 2.67)[d]	0.001
Median (IQR)	100 (93.3–100)	100 (77.9–100)		
n	262	268		
***EQ-5D-3L utility score*[e]**				
Baseline				
Mean (SD)	0.71 (0.30)	0.70 (0.31)		
Median (IQR)	0.76 (0.66–1.00)	0.79 (0.69–1.00)		
n	319	322		
6 weeks				
Mean (SD)	0.83 (0.22)	0.83 (0.28)	0.66 (0.48 to 0.90)[f]	0.009
Median (IQR)	0.88 (0.74–1.00)	1.00 (0.76–1.00)		
n	251	246		
6 months				
Mean (SD)	0.83 (0.27)	0.83 (0.25)	1.15 (0.84 to 1.57)	0.38
Median (IQR)	1.00 (0.80–1.00)	0.85 (0.76–1.00)		
n	251	237		

TABLE 10 Patient outcomes at baseline, 6 weeks and 6 months post surgery and 15 months post randomisation (*continued*)

Participant outcome	LASH ($N = 330$)[a]	EA ($N = 330$)[b]	Adjusted effect size (95% CI)	*p*-value
15 months				
Mean (SD)	0.84 (0.24)	0.80 (0.28)	1.21 (0.89 to 1.64)	0.23
Median (IQR)	1.00 (0.73–1.00)	0.85 (0.72–1.00)		
n	281	281		
EQ-5D-3L VAS[e]				
Baseline				
Mean (SD)	65.2 (24.2)	67.2 (23.5)		
Median (IQR)	70 (50–85)	70 (52–85)		
n	317	321		
6 weeks				
Mean (SD)	78.4 (18.6)	76.6 (20.7)	1.12 (0.80 to 1.58)	0.51
Median (IQR)	80 (70–90)	80 (70–90)		
n	248	245		
6 months				
Mean (SD)	79.9 (19.2)	75.9 (20.5)	1.53 (1.08 to 2.17)[d]	0.02
Median (IQR)	85.5 (75–90)	80 (69–90)		
n	246	235		
15 months				
Mean (SD)	80.1 (17.6)	76.9 (19.5)	1.50 (1.12 to 1.99)[d]	0.006
Median (IQR)	85 (70–90)	80 (65–90)		
n	279	282		
SF-12 PCS[g]				
Baseline				
Mean (SD)	45.0 (9.0)	44.9 (9.7)		
Median (IQR)	45.8 (39.0–52.1)	46.5 (39.0–51.9)		
n	318	321		
6 weeks				
Mean (SD)	44.9 (10.1)	49.5 (9.6)	–4.97 (–6.31 to –3.63)[f]	< 0.001
Median (IQR)	46.4 (38.3–52.9)	52.2 (45.2–56.1)		
n	249	234		
6 months				
Mean (SD)	53.2 (8.7)	52.4 (9.6)	0.83 (–0.70 to 2.35)	0.28
Median (IQR)	56.1 (52.1–57.8)	55.1 (50.4–58.3)		
n	223	226		
15 months				
Mean (SD)	53.5 (8.9)	52.4 (9.0)	1.08 (–0.65 to 2.81)	0.21
Median (IQR)	56.1 (52.7–57.8)	55.1 (48.8–57.8)		
n	219	216		

continued

TABLE 10 Patient outcomes at baseline, 6 weeks and 6 months post surgery and 15 months post randomisation (*continued*)

Participant outcome	LASH ($N = 330$)[a]	EA ($N = 330$)[b]	Adjusted effect size (95% CI)	*p*-value
SF-12 MCS[g]				
Baseline				
Mean (SD)	37.2 (11.0)	38.7 (11.6)		
Median (IQR)	36.6 (29.8–45.1)	29.0 (15.7–47.7)		
n	318	321		
6 weeks				
Mean (SD)	48.0 (11.2)	46.9 (11.8)	1.33 (–0.78 to 3.44)	0.21
Median (IQR)	50.7 (41.2–57.2)	49.6 (40.7–56.0)		
n	249	234		
6 months				
Mean (SD)	48.2 (12.0)	45.4 (12.0)	3.36 (1.69 to 5.03)[d]	< 0.001
Median (IQR)	51.5 (40.2–57.2)	48.4 (37.8–56.0)		
n	223	226		
15 months				
Mean (SD)	48.5 (11.2)	46.6 (11.1)	2.47 (1.07 to 3.87)[d]	0.001
Median (IQR)	50.7 (43.3–57.1)	48.8 (38.9–55.3)		
n	219	216		

a Maximum $n = 330$ for baseline, 15 months; maximum $n = 309$ for 6 weeks, 6 months.
b Maximum $n = 330$ for baseline, 15 months; maximum $n = 307$ for 6 weeks, 6 months.
c Analysis method (effect size) = OR (Log Reg).
d Favours LASH ($p < 0.05$).
e Analysis method (effect size) = OR (OLR).
f Favours EA ($p < 0.05$).
g Analysis method (effect size) = MD (Lin Reg).

Notes
MMAS total score: 0 represents worst possible health and 100 represents best possible health.
EQ-5D-3L utility score: –0.59 represents worst possible QoL and 1 represents best possible QoL.
EQ-5D-3L VAS: 0 represents worst imaginable health state and 100 represents best possible health state.
SF-12 PCS and MCS: 0 represents worst possible QoL and 100 represents best possible QoL.
Analyses used OLR adjusting for age group, centre and baseline score (if applicable).

Following EA, a higher proportion of all women (including those with no periods) experienced cyclical pain [6 months: LASH, 68/236 (28.8%), EA, 108/199 (54.3%); 15 months: LASH, 71/224 (31.7%), EA 118/196 (60.2%)] (see *Appendix 2, Table 35*). Women in the LASH group generally had less pain during intercourse. Similar proportions of women in each group had bladder problems (see *Appendix 2, Table 35*).

Table 36 in *Appendix 2* shows results for menstrual outcomes by actual treatment received (per-protocol analysis). The results were generally similar to those of the intention-to-treat analysis.

Quality of life (6 weeks and 6 months post surgery, 15 months post randomisation)

The quality-of-life results are presented in *Table 10*. An alternative presentation using categories used in the OLR models is provided in *Appendix 2, Table 37*.

The results for the MMAS total score at 15 months have been described previously (see *MMAS scores at 15 months post randomisation*). The results for MMAS scores at 6 months showed more favourable scores for those in the LASH group (adjusted OR 1.48, 95% CI 1.02 to 2.14; $p = 0.04$).

At 6 weeks post surgery, those in the EA group had higher EQ-5D-3L utility scores than those in the LASH group (adjusted OR 0.66, 95% CI 0.48 to 0.90; $p = 0.009$). However, at 6 months post surgery and 15 months post randomisation, the point estimates favoured LASH, although the results were not statistically significant (6 months: adjusted OR 1.15, 95% CI 0.84 to 1.57, $p = 0.38$; 15 months: adjusted OR 1.21, 95% CI 0.89 to 1.64, $p = 0.23$).

The results for the VAS score of the EQ-5D-3L tended to favour the LASH group, and this finding was statistically significant at 6 months post surgery and 15 months post randomisation (6 weeks: adjusted OR 1.12, 95% CI 0.80 to 1.58, $p = 0.51$; 6 months: adjusted OR 1.53, 95% CI 1.08 to 2.17, $p = 0.02$; 15 months: adjusted OR 1.50, 95% CI 1.12 to 1.99, $p = 0.006$).

In the case of the SF-12 PCS, the EA group was favoured at 6 weeks post surgery (adjusted mean difference –4.97, 95% CI –6.31 to –3.63; $p < 0.001$), but there was no evidence of group differences at 6 months post surgery (adjusted mean difference 0.83, 95% CI –0.70 to 2.35; $p = 0.28$) or at 15 months post randomisation (adjusted mean difference 1.08, 95% CI –0.65 to 2.81; $p = 0.21$). There was evidence of improved SF-12 MCS in the LASH group at the final two time points only (6 weeks: adjusted mean difference 1.33, 95% CI –0.78 to 3.44, $p = 0.21$; 6 months: adjusted mean difference 3.36, 95% CI 1.69 to 5.03, $p < 0.001$; 15 months: adjusted mean difference 2.47, 95% CI 1.07 to 3.87, $p = 0.001$).

Satisfaction and acceptability (6 weeks and 6 months post surgery, 15 months post randomisation)

Women receiving treatment were asked questions about the acceptability of treatment (6 weeks post surgery) and satisfaction with treatment (6 months post surgery) (*Table 11*). Both these results favoured LASH (acceptability of treatment at 6 weeks: adjusted OR 4.73, 95% CI 2.86 to 7.81, $p < 0.001$; satisfaction with treatment at 6 months: adjusted OR 2.91, 95% CI 2.04 to 4.16, $p < 0.001$).

Women were also asked at 6 months post surgery and 15 months post randomisation whether or not they agreed that they would recommend their treatment to a friend. Over 85% of women in each group agreed that they would, but at both time points there was strong evidence in favour of the LASH group (6 months: adjusted OR 4.49, 95% CI 2.44 to 8.27, $p < 0.001$; 15 months: adjusted OR 4.52, 95% CI 2.14 to 9.53, $p < 0.001$) (see *Table 11*).

Summary of the clinical effectiveness results

Table 38 in *Appendix 2* provides a summary of the primary and secondary analyses, including both adjusted and unadjusted effect sizes for all outcomes as follows: mean differences for continuous outcomes; both ORs and risk differences for binary outcomes (i.e. both relative and absolute effect sizes); ORs for ordered categorical outcomes and HRs for time-to-event outcomes. Adjusted analyses include the minimisation factors, age group and centre (random effect), in the model, as well as a baseline score, if this is available.

The results of the unadjusted analyses tended to be similar to those of the adjusted analyses.

Using a threshold of a p-value of < 0.05, there was evidence that those randomised to EA had lower levels of pain in the first 6 weeks following treatment. In addition, those randomised to EA also had improved EQ-5D-3L utility scores and SF-12 PCSs at 6 weeks, but there was no evidence of a difference between groups at later time points. Women in the EA group also returned to work and usual activities sooner than those in the LASH group.

Most self-reported outcomes at the 6 months post surgery and 15 months post-randomisation time points tended to favour LASH. There was evidence that women in the LASH group had better QoL outcomes and were more satisfied with their treatment than those in the EA group.

TABLE 11 Patient outcomes at 6 months post surgery and 15 months post randomisation

Participant outcome	Analysis method (effect size)	LASH ($N = 330$), n (%)[a]	EA ($N = 330$), n (%)[b]	Adjusted effect size (95% CI)	p-value
Acceptability of treatment					
Totally acceptable	OR (OLR)	205 (84.4)	130 (54.9)	4.73 (2.86 to 7.81)[c]	< 0.001
Generally acceptable		30 (12.3)	53 (22.4)		
Fairly acceptable		6 (2.5)	37 (15.6)		
Fairly unacceptable		2 (0.1)	7 (3.0)		
Generally unacceptable		0	4 (1.7)		
Totally unacceptable		0	6 (2.5)		
Satisfaction with treatment (6 months)					
Totally satisfied	OR (OLR)	181 (73.9)	123 (51.3)	2.91 (2.04 to 4.16)[c]	< 0.001
Generally satisfied		46 (18.8)	52 (21.7)		
Fairly satisfied		9 (3.7)	33 (13.8)		
Fairly unsatisfied		3 (1.2)	9 (3.8)		
Generally unsatisfied		1 (0.4)	10 (4.2)		
Totally unsatisfied		5 (2.0)	13 (5.4)		
Satisfaction with treatment (15 months)					
Totally satisfied	OR (OLR)	211 (75.9)	158 (56.4)	**2.53 (1.83 to 3.48)**[c]	**< 0.001**
Generally satisfied		40 (14.4)	57 (20.4)		
Fairly satisfied		19 (6.8)	29 (10.4)		
Fairly unsatisfied		2 (0.7)	9 (3.2)		
Generally unsatisfied		1 (0.4)	15 (5.4)		
Totally unsatisfied		5 (1.8)	12 (4.3)		
Recommend treatment to friend? (6 months)					
Yes	OR (Log Reg)	245 (96.5)	208 (85.6)	4.49 (2.44 to 8.27)[c]	< 0.001
No		9 (3.5)	35 (14.4)		
Recommend treatment to friend? (15 months)					
Yes	OR (Log Reg)	263 (97.0)	246 (87.9)	4.52 (2.14 to 9.53)[c]	< 0.001
No		8 (3.0)	34 (12.1)		

Log Reg, logistic regression.
a Maximum $n = 330$ for baseline, 15 months; maximum $n = 309$ for 6 months.
b Maximum $n = 330$ for baseline, 15 months; maximum $n = 307$ for 6 months.
c Favours LASH ($p < 0.05$).
Note
Analyses used OLR, adjusting for age group, centre and baseline score (if applicable).
Co-primary outcome is highlighted in bold.

The results of both co-primary outcomes (satisfaction and MMAS score at 15 months post randomisation), both strongly favoured those in the LASH group. The results of the secondary outcomes should be treated as exploratory because no adjustment was made for multiple statistical testing. There is, however, a pattern suggesting greater short-term benefits for EA but longer-term improvements in patient-reported outcomes for the LASH group. In particular, LASH was strongly favoured for all the questions concerning acceptability, satisfaction and recommendation to a friend.

Chapter 5 Economic evaluation: within-trial analysis

Introduction

This chapter reports on the within-trial economic evaluation of LASH compared with second-generation EA.[1] The rationale for the economic evaluation in health care is to help inform the adoption of technologies that provide good value for money in the context of constrained health service resources. The within-trial economic analysis reported in this chapter considers the 15-month post-randomisation follow-up period only. As the full impact of the alternative interventions on resource use and individuals' HRQoL is likely to accrue over a much longer time horizon, a Markov model was also developed to extrapolate the trial-based findings. This model-based economic analysis is reported in *Chapter 6* and constitutes the primary economic analysis for HEALTH.

Objectives of the economic evaluation

The primary economic objective of the within-trial cost-effectiveness analysis was to estimate the incremental cost per QALY gained for LASH compared with EA at 15 months post randomisation. Two of the three secondary economic objectives are addressed in the current chapter: (1) to compare the costs and consequences of LASH and EA at 15 months; and (2) to assess the wider societal costs associated with changes in productivity. The third secondary economic objective of modelling the longer-term cost-effectiveness of LASH compared with EA is addressed in *Chapter 6*.

Methods

Study design and participants

Details of the trial design are provided in the study protocol[1] and in *Chapter 2*. The economic analysis was based on all women randomised, with the exception of four post-randomisation exclusions, and follows the same intention-to-treat principles as the statistical analysis.

Cost and outcome assessment

Costs and outcomes were assessed via the trial CRFs, patient diary of pain symptoms at days 1–14 post surgery, and postal questionnaires at 6 weeks and 6 months post surgery and 15 months post randomisation [see URL: www.journalslibrary.nihr.ac.uk/programmes/hta/123523/#/ (accessed 22 May 2019)]. Health-care utilisation questions at 6 months post surgery and 15 months post randomisation were included for the purpose of costing follow-up health-care resource use. The patient questionnaires also informed time taken to return to normal activities and time off work due to ongoing/recurrent symptoms over the follow-up period. The EQ-5D-3L and SF-12 were measured at baseline, 6 weeks and 6 months post surgery, and at 15 months post randomisation. These measures of HRQoL were used in the economic analysis for estimating QALYs out to 15 months post randomisation.

Assessment of health service costs

As the economic evaluation seeks to inform the efficient allocation of the NHS budget, the base-case analysis adopted a health service perspective. Nevertheless, the effect of incorporating patient productivity costs was also considered as a secondary analysis.

Cost of the primary interventions

The unit costs used for the valuation of health service resource use are reported in *Table 12*. The costs of the initial HEALTH interventions were estimated from resource use data recorded in the HEALTH operation form for each participant. In addition to the date and time of admission and operation, this CRF captured the type of procedure carried out, time in theatre, grade of surgeon, time in recovery, postoperative analgesic requirements, perioperative complications and time to discharge at the individual patient level [see URL: www.journalslibrary.nihr.ac.uk/programmes/hta/123523/#/ (accessed 22 May 2019)].

TABLE 12 Unit costs (NHS perspective)

Resource	How measured	Source of measurement	Unit cost (£)	Source of valuation
Time in anaesthetic room	Time in hours	HEALTH operation form	151 per hour	Band 6 nurse (£45) + consultant anaesthetist (£106); *Unit Costs of Health and Social Care 2017*[30]
Time in theatre	Time in hours	HEALTH operation form		
Surgeon time				*Unit Costs of Health and Social Care 2017*[30]
Consultant			107 per hour	
Associate specialist			101 per hour	
Registrar			43 per hour	
Foundation FY2			30 per hour	
Foundation FY3			26 per hour	
Nurse consultant			62 per hour	
Anaesthetist time, consultant			106 per hour	*Unit Costs of Health and Social Care 2017*[30]
Theatre costs (excluding medical and nursing staff)			596 per hour	Table R140; Information Services Division[31]
Procedure consumables				
LASH (morcellator and loop package)	See *Cost of the primary interventions*	Clinical advice	Commercial-in-confidence information	Kebomed UK, 14 May 2018, personal communication
LASH haemostatic dissecting device (e.g. Enseal™, Ethicon, Johnson & Johnson, Bridgewater, NJ, USA; Ligasure™, Medtronic plc, Dublin, Ireland)	See *Cost of the primary interventions*		Commercial-in-confidence information	Nicki Baxter, NHS Grampian, 28 March 2018, personal communication
EA (disposable ablation kit)	See *Cost of the primary interventions*	Clinical advice	Commercial-in-confidence information	Alan Blair, Hologic, 28 March 2018, personal communication
Perioperative complication costs	See *Costs of perioperative complications and readmissions*	HEALTH operation form	Various	Based on recorded reasons and procedures; *NHS Reference Costs 2016–2017*[32]
Readmissions	See *Costs of perioperative complications and readmissions*	Additional hospital admission CRFs; patient questionnaire	Various	Based on recorded reasons and procedures; *NHS Reference Costs 2016–2017*[32]

TABLE 12 Unit costs (NHS perspective) (*continued*)

Resource	How measured	Source of measurement	Unit cost (£)	Source of valuation
Outpatient appointments	See *Costs of subsequent health-care utilisation*	Patient questionnaires		
Non-admitted face-to-face attendance, first appointment			155 per attendance	*NHS Reference Costs 2016–2017*[32]
Non-admitted face-to-face attendance, follow-up			130 per attendance	*NHS Reference Costs 2016–2017*[32]
Primary care contacts	See *Costs of subsequent health-care utilisation*	Patient questionnaires		
GP visits			37 per visit	*Unit Costs of Health and Social Care 2017*[30]
GP home visits			45.98 per visit	*Unit Costs of Health and Social Care 2017*[30]
GP phone consultation			37 per visit	*Unit Costs of Health and Social Care 2017*[30]
Medications	See *Costs of subsequent health-care utilisation*	Patient questionnaires	Various	*British National Formulary*[33]

The primary costing approach assigned costs to these individual components of resource use to capture patient-level variation in costs. Time in the anaesthetic room was costed using the cost per hour (incorporating overheads) for a consultant anaesthetist and an anaesthetist nurse.[30] For time in theatre, the unit costs of the recorded grade of surgeon and a consultant anaesthetist were applied.[30] Nursing staff were costed at the requirement for gynaecology day surgery: one anaesthetic nurse, a scrub nurse and two further theatre nurses. In addition, a published unit cost was applied for time in theatre to reflect the average cost of other staff, supplies and consumables, and allocated capital charges and overheads.[31] This detailed unit cost of theatre time is available only for Scottish hospitals. However, the average cost per theatre hour in general hospitals in Scotland (£1144 including medical and nursing staff) is comparable to a previously published estimate for England (£1200 per hour).[34] Therefore, the average Scottish estimate (£596 per hour, excluding medical and nursing staff) was applied in the base-case analysis. In addition to this, we applied the unit costs of major consumable items specific to the alternative procedures. For LASH, this includes a disposable morcellator (LiNA Xcise™; LiNA Medical, Norcross, GA, USA), a disposable loop (LiNA Loop™; LiNA Medical, Norcross, GA, USA) and a disposable haemostatic dissecting device. A survey of participating centres suggested that the above consumables, or similar disposable items, were used for the majority of LASH procedures in HEALTH. However, a small number of centres reported using a reusable morcellator and/or reusable dissecting/sealing devices, so we also conducted a sensitivity analysis to assess the impact of removing the relevant consumable costs from operations carried out at these centres. For EA, the cost of a disposable NovaSure™ (Hologic Inc., Santa Clara, CA, USA) radiofrequency ablation device was used for all procedures, as the alternative Thermachoice thermal balloon (Ethicon, Inc., Johnson & Johnson, New Brunswick, NJ, USA) has been removed from the market. The cost of the NovaSure™ controller has not been included as this is loaned free of charge.

With respect to preoperative care, we assumed that the procedures would have similar workup costs. However, we did include the cost of preoperative overnight stays, which were more frequent in the LASH arm. As histopathology is a requirement before EA and following LASH (not necessarily before LASH) in routine practice, we assumed that these costs would balance out. We also assessed the impact on cost-effectiveness of including an extra cost for pathology testing in the LASH arm of the model

presented in *Chapter 6*, to reflect the possibility that pathology costs following LASH may be higher than they are prior to EA.

Time in recovery following surgery was costed using the unit cost of a grade 6 nurse (inclusive of overheads), assuming one-to-one care. Time on the ward following recovery was costed using an estimate of the cost per excess bed-day (transformed to an hourly rate) following EA or LASH.[32]

As an alternative approach to costing the initial HEALTH procedure episode, each patient record was mapped to the appropriate Healthcare Resource Group (HRG) and costed using the relevant NHS reference cost.[32] The core HRG code for second-generation EA procedures is MA12 (Resection or Ablation Procedures for Intra-Uterine Lesions). The core HRG code for LASH is MA08 (Major, Laparoscopic or Endoscopic, Upper Genital Tract Procedures). The procedures were costed by applying either the day-case reference cost (patient discharged same day) or the elective inpatient cost (stay $\geq$ 1 day), adjusted for length of stay using the excess bed-day cost.

Costs of perioperative complications and readmissions

For perioperative complications leading to prolonged hospital stay, the clinical management costs were based on the NHS reference cost for any additional procedures and adjustment for prolonged length of stay. The information on the type of complications experienced and any procedures undertaken were obtained from the HEALTH operation form and associated SAE forms.

Data on hospital readmissions were obtained from the 'additional hospital admission form' and associated SAE forms [see URL: www.journalslibrary.nihr.ac.uk/programmes/hta/123523/#/ (accessed 22 May 2019)]. Descriptions of the reason for admission and clinical procedures conducted were used to assign a HRG-based reference cost to each readmission.[32] A hospital readmission form was triggered by patients reporting readmissions in the questionnaire, but sites could also report these based on their own internal records.

Costs of subsequent health-care utilisation

Related primary and secondary outpatient care, incurred over the 15-month follow-up period, were obtained from the patient questionnaires at 6 months post surgery and 15 months post randomisation. Medications prescribed for any ongoing problems with pelvic pain, vaginal bleeding or discharge, pain at intercourse, or any new urinary problems were also recorded in these questionnaires. All the primary care contacts were costed using the *Unit Costs of Health and Social Care 2017*,[30] and outpatient visits were costed using the NHS reference cost for a gynaecology outpatient visit (see *Table 12*).[32] For each participant, the number of visits reported was multiplied by the appropriate unit cost. Relevant medications and quantities prescribed at 6 months post surgery and 15 months post randomisation were costed using prices recorded in the *British National Formulary*.[33]

Indirect costs

Indirect costs, which account for time lost from productive activities, were estimated based on time taken to return to normal activities (from the 6 weeks post-surgery questionnaire) combined with questions on work productivity delivered at 6 months post surgery and 15 months post randomisation. The time taken away from normal productive activities was estimated in hours and appropriate unit costs were used to estimate the opportunity cost of time. Gross age- and sex-specific wage rates published by the Department of Work and Pensions were used to cost time lost from paid employment.[35] Time lost from unpaid work, such as housework, was estimated using appropriate shadow prices reflecting the nature of the role. Forgone leisure time, associated with travel to and from health-care appointments, was valued at the current value of travel time savings available from the Department of Transport.[36] The productivity questions at 6 months post surgery and 15 months post randomisation related to the preceding 4 weeks.

In addition, the cost of any private health care falling on participants was estimated based on details provided by participants in the 6 months post-surgery questionnaire and the 15 months post-randomisation questionnaire.

Outcome measures

Effectiveness for the economic evaluation was measured in terms of QALYs, estimated using the EQ-5D-3L questionnaire, completed by participants at baseline and at 6 weeks and 6 months post surgery and 15 months post randomisation. Participant responses were assigned a utility score based on the UK time trade-off tariff.[37] For the base-case analysis, QALYs were estimated using the area under the curve approach, assuming a baseline utility score up to the time of the index intervention and a linear change in utility between the observed follow-up time points thereafter. The SF-12 provided an alternative source of health state utility data via the Short Form questionnaire-6 Dimensions scoring algorithm.[38] These values were used to calculate QALYs in a sensitivity analysis.

Statistical analysis of trial economic data

Aggregating costs and effects

All cost and QoL elements were summed over the follow-up period (to 15 months post randomisation), to estimate total costs and QALYs per participant. As the 6-month questionnaire was anchored on the date of surgery, and the 15-month final questionnaire on randomisation date, there was a degree of overlap or a gap between the 6-month recall periods of the questionnaires. We therefore adjusted the patient-reported use of primary care and outpatient care to avoid double counting or undercounting, by applying a multiplicative factor to the patient-reported resource use data at 15 months. The factor was equal to the duration in months between the 15-month follow-up date and the 6 months post-surgery follow-up date, divided by six. For example, if 8 months elapsed between the 15-month follow-up date and the 6 months post-surgery follow-up date, the factor was equal to 1.333 (i.e. equal to 8/6), to account for the 2-month gap between the recall periods. When < 6 months elapsed between the follow-up questionnaires, the recall periods overlapped and the multiplicative factor was < 1. Cost were expressed in 2016–17 prices.

Missing data

Economic evaluations based on participant-level trial data are likely to encounter challenges with missing data. The total estimated cost is the sum of numerous components over the observed follow-up period of the trial. Furthermore, QALYs can be computed only when participants have responded to the relevant QoL questionnaires at every follow-up point. Collected data allowed the estimation of total cost and total QALYs for 57% (53% for EA, 60% for LASH) and 63% (65% for EA, 69% for LASH) of the study sample, respectively (see *Appendix 3*). Reliance on complete-case data for cost-effectiveness analysis can introduce bias, unless the data are missing completely at random. It was considered more likely that data were missing at random (i.e. missing values can be predicted based on the observed data). Therefore, multiple imputation was implemented as part of the within-trial analysis, using chained equations with predicted mean matching (*k*th-nearest neighbour = 5) to generate 20 complete data sets with plausible fitted values assigned for missing cost and utility elements. The imputation model for each variable included all the variables incorporated in the analysis model, all the other cost and utility variables being imputed and one of the co-primary clinical outcome measures (patient satisfaction) as a further auxiliary variable (see *Appendix 3*). Rubin's rules were used to pool estimates across the multiple imputation data sets.[39] Missing cost data were imputed at the level of the main cost categories at the different follow-up time points and EQ-5D data were imputed at the level of the index score. Hospital readmission costs were assumed to be zero when no readmission form was completed. This was done because these forms could be triggered by patient-reported readmission or by centres reporting readmissions independently. Given the associated uncertainty with respect to rates of readmission for further surgery in the year following surgery, the modelling reported in *Chapter 6* explored the impact of applying higher rates in year 1, derived from external sources.

Incremental cost-effectiveness analysis

The trial-based economic analysis estimated the joint difference in mean costs and QALYs between LASH and EA (to 15 months post randomisation). GLMs with adjustment for minimisation factors (centre, age) and baseline EQ-5D-3L score were used. A modified Park test was implemented to select an appropriate family function. Moreover, Pearson's correlation, Pregibon link and modified Hosmer–Lemeshow tests were used to select the link function.[40] Details of these test results are reported in *Appendix 3*. Based on the

above, a Gaussian family with identity link function and a Poisson family with identity link were selected for the cost data and QALY data, respectively. Recycled predictions were used to recover adjusted mean values by treatment allocation group and the incremental differences between groups.[40] The incremental cost-effectiveness ratio (ICER) for LASH compared with EA was calculated as the difference in mean cost divided by difference in mean QALYs. The variance surrounding the joint incremental costs and effects was characterised using non-parametric bootstrapping (1000 iterations), with multiple imputation ($m = 5$) nested within the bootstrap loops.[41]

Sensitivity analysis

Sensitivity analysis focused on the costing methodology for the initial interventions and the use of the SF-12 as an alternative method for deriving QALYs. In addition, predefined subgroup analyses were conducted according to uterine cavity length (≤ 8 cm vs. > 8 cm), severity of dysmenorrhoea at baseline (severe vs. non-severe), age category at baseline (< 40 years vs. ≥ 40 years) and the presence of fibroids. An indicator variable for the selected subgroup, and the interaction term between the selected subgroup indicator and the treatment group indicator, were added to the base-case analysis regression model to conduct these analyses.

Results

Resource use and costs

Table 13 summarises health service resource use and costs by intention to treat from an NHS perspective. LASH required a substantially longer time in the anaesthetic room, theatre and recovery than EA. The average time from entry into the anaesthetic room to arrival on the ward following recovery was almost 3 hours (178 minutes) for LASH, whereas the corresponding time for EA was approximately half of that (90 minutes). Hospital stay on the ward following recovery was also longer for LASH (23 hours on average, compared with 6 hours for EA). The consumed hospital resources translated into mean initial episode costs of £2757 and £1071 for LASH and EA, respectively. The corresponding costs based on alternative HRG costing methodology were £2774 and £1197 for LASH and EA, respectively.

In addition to the information on the initial procedure, follow-up data are reported in *Table 13*. Fourteen participants had further hospital admissions in the LASH group within 15 months post randomisation, compared with 24 participants in the EA group. Reasons for subsequent hospital admission included abdominal pain, urinary tract infections, cervical stump removal following LASH ($n = 1$) and hysterectomy following EA ($n = 13$). The duration of hospital readmissions was also slightly lower for LASH (1.07 days for LASH vs. 1.13 days for EA). Average readmission costs were therefore lower for LASH than for EA (£53 vs. £140). No major differences were observed on the average number of outpatient hospital visits or GP contacts. The number of participants reporting prescribed medications related to the condition over the follow-up period were low in both groups, but slightly lower in the LASH group than in the EA group (5 women vs. 18 women).

The combined initial treatment and follow-up resource use translated into total average NHS costs of £3004 for LASH compared with £1281 for EA, resulting in an unadjusted difference of £1722.

Utility scores and quality-adjusted life-years

Table 14 summarises the mean utility scores based on EQ-5D-3L and SF-12 responses at baseline, at 6 weeks and 6 months post surgery and at 15 months post randomisation. There was a small non-significant difference in the EQ-5D-3L score at baseline in favour of LASH. The mean EQ-5D-3L data for LASH showed an upwards trend from baseline until 15 months post randomisation, suggesting continued improvement in QoL. For EA, the increase in the EQ-5D-3L from baseline was initially greater at 6 weeks compared with LASH, but then stabilised before dropping by 15 months post randomisation. Notably, by 15 months, the EQ-5D-3L score was higher in the LASH group than in the EA group (unadjusted difference = 0.035), although not statistically significant.

TABLE 13 Health service resource use and costs by treatment allocation

Variable	Number of observations	LASH ($N = 330$)	EA ($N = 330$)
Resource use *Initial procedure, mean (SD)*			
Time in anaesthetic room (minutes)	643	16.4 (10.3)	10.8 (8.8)
Time in theatre (minutes)	651	90.5 (41.2)	30 (22.1)
Time in recovery (minutes)	646	70.9 (46.2)	48.6 (34.6)
Length of hospital stay on ward (hours)	647	22.9 (16.5)	6 (10)
Further follow-up			
Hospital readmission, *n* (%)	660	14 (4.2)	24 (6.4)
Readmission length of stay (days), mean (SD)	38	1.07 (1.1)	1.13 (1.2)
Number of outpatient visits, mean (SD)	395	0.32 (1)	0.29 (0.9)
Number of GP contacts			
Face-to-face visits, mean (SD)	391	0.89 (2.2)	0.87 (1.7)
Telephone consultations, mean (SD)	391	0.01 (0.1)	0.01 (0.1)
Home visits, mean (SD)	391	0.17 (0.6)	0.22 (0.7)
Medication prescribed, *n* (%)	391	5 (2.4)	18 (9.7)
Costs: initial surgical episode cost, mean (SD)			
Primary analysis (microcosting)	639	2757 (1030)	1071 (617)
HRG-based estimates	660	2774 (906)	1197 (539)
Readmission costs for further treatment (£)	660	53 (309)	140 (662)
Outpatient costs (£)	393	33 (85)	30 (79)
Primary care costs (£)	391	40 (96)	40 (77)
Medication costs (£)	391	0.04 (0.3)	1.38 (7)
Total NHS cost (£)	374	3004 (725)	1281 (668)

TABLE 14 Health state utility scores by treatment allocation

Variable	Number of observations	LASH ($N = 330$)	EA ($N = 330$)
EQ-5D-3L, mean (SD)			
Baseline	641	0.7065 (0.30)	0.6983 (0.31)
6 weeks post surgery	497	0.8279 (0.22)	0.8282 (0.28)
6 months post surgery	488	0.8315 (0.27)	0.8269 (0.25)
15 months post randomisation	562	0.8357 (0.24)	0.8005 (0.28)
SF-12, mean (SD)			
Baseline	568	0.6174 (0.12)	0.6249 (0.14)
6 weeks post surgery	345	0.6762 (0.14)	0.7506 (0.16)
6 months post surgery	412	0.8036 (0.14)	0.7757 (0.15)
15 months post randomisation	405	0.8094 (0.14)	0.7818 (0.14)

Baseline utility scores obtained from the SF-12 were slightly higher for EA than for LASH. Data from both study groups show a persistent improvement in utility scores from baseline until the end of follow-up. However, the substantially lower response rate on this secondary economic outcome measure is notable.

Cost–utility analysis results

The incremental analysis was conducted using the multiple imputation data set and is presented in *Table 15*. The adjusted mean costs per participant were £2886 and £1282 for LASH and EA, respectively, producing an adjusted difference of £1604. The average cost difference resulting from the imputed data was slightly narrower than the unadjusted difference based on complete data (see *Table 13*). The mean adjusted QALYs per participant were 0.978 and 0.974 for LASH and EA, respectively, giving an adjusted QALY difference of 0.004 in favour of LASH.

Therefore, intention to treat with LASH resulted in significantly higher mean costs and a slight non-significant QALY gain compared with EA at 15 months post randomisation. The ICER for LASH compared with EA came to £458,334 per QALY gained over this relatively short time horizon. Although the EQ-5D-3L health state utility was higher in the LASH group by 15 months post randomisation, the mean QALYs accruing over 15 months remained very similar between groups owing to the earlier improvement in HRQoL with EA than with LASH.

Figure 8 shows the scatterplot of the difference in mean costs and difference in mean QALYs based on the 1000 bootstrapped iterations of the regression analysis with nested multiple imputation. LASH was clearly

TABLE 15 Trial-based incremental cost-effectiveness analysis (base case; NHS perspective; 15 months post randomisation)

Intervention	Total cost (£)	Incremental cost (£)[a]	Total QALYs	Incremental QALYs[a]	ICER (£/QALY gained)
EA	1282		0.974		
LASH	2886	1604	0.978	0.004	458,334

a Differences adjusted by study minimisation variables.

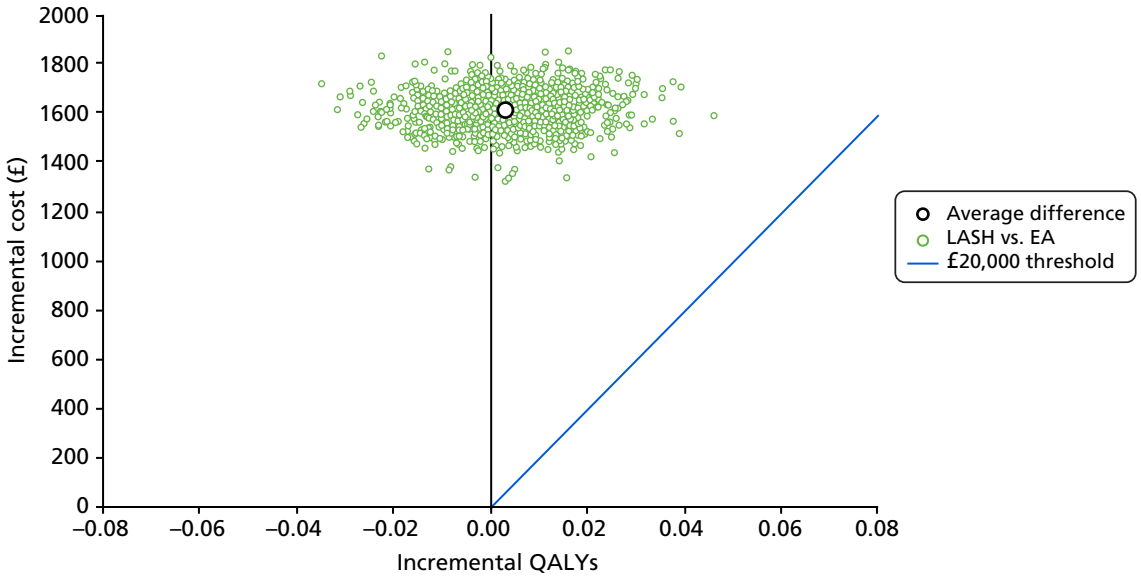

FIGURE 8 Trial-based incremental cost-effectiveness scatterplot for LASH vs. EA (base case; imputed data; 1000 bootstrap iterations).

more costly, on average, than EA, as all the iterations resulted in mean cost differences that were greater than zero. However, the mean difference in QALYs was centred on 0.004 (favouring LASH), with a substantial proportion of the bootstrapped iterations favouring EA. Although *Figure 8* shows that ≈60% of the bootstrapped iterations generated a QALY gain favouring LASH over EA, all these points lie above accepted cost-effectiveness thresholds,[42] suggesting that LASH had little chance of being considered cost-effective based on its incremental cost-per-QALY ratio over a 15-month time horizon. This was to be expected, given the relatively short duration of follow-up combined with the higher initial treatment costs for LASH and the more delayed pattern of improvement in HRQoL described above.

Sensitivity, subgroup and secondary analyses

Further to the base-case analysis, several sensitivity analyses were conducted using alternative costing methodology and QoL instruments to estimate QALYs (*Table 16*). In addition, the results of the prespecified subgroup analyses are presented in *Table 17* and indirect costs are reported in *Table 18*. Finally, the differences in cost are summarised in relation to the main clinical findings (cost–consequences analysis).

Alternative costing and utility instrument

Table 16 summarises the results of the key sensitivity analyses. The analysis using HRG-based reference costs for the index procedure generates a very similar incremental cost for LASH compared with EA, and led to the same finding as the base case, with the ICER for LASH at 15 months post randomisation being above accepted cost-effectiveness thresholds. The sensitivity analysis results, using the SF-12 instrument to estimate QALYs, are also reported in *Table 16*. The adjusted difference in QALYs was similarly very small and in favour of LASH.

TABLE 16 Trial-based sensitivity analysis

Intervention	Total cost (£)	Incremental cost (£)	Total QALYs	Incremental QALYs	ICER[a] (£)	Probability cost-effective		
						£13,000	£20,000	£30,000
Base-case analysis								
EA	1282		0.974			1.000	1.000	1.000
LASH	2886	1604	0.978	0.004	458,334	0.000	0.000	0.000
HRG-based reference costs to cost initial surgical episode								
EA	1417		0.974			1.000	1.000	1.000
LASH	2905	1488	0.978	0.004	425,229	0.000	0.000	0.000
Removal of relevant LASH consumable costs from procedures carried out using reusable equipment								
EA	1280		0.974			1.000	1.000	1.000
LASH	2815	1535	0.978	0.004	438,709	0.000	0.000	0.000
QALYs based on Short Form questionnaire-6 Dimensions								
EA	1282		0.921			1.000	1.000	1.000
LASH	2886	1604	0.927	0.007	239,428	0.000	0.000	0.000

a £/QALY gained.

Note

Differences adjusted by study minimisation variables.

TABLE 17 Trial-based incremental cost-effectiveness analysis by predefined subgroups

Intervention	Total cost (£)	Incremental cost (£)	Total QALYs	Incremental QALYs	ICER[a] (£)	Probability cost-effective		
						£13,000	£20,000	£30,000
Base-case analysis (full cohort)								
EA	1282		0.974			1.000	1.000	1.000
LASH	2886	1604	0.978	0.004	458,334	0.000	0.000	0.000
Uterine cavity length < 8 cm								
EA	1333		0.969			1.000	0.993	0.937
LASH	2876	1543	0.984	0.015	102,877	0.000	0.007	0.063
Uterine cavity length ≥ 8 cm								
EA	1465		1.005			1.000	1.000	1.000
LASH	3189	1724	0.998	–0.007	Dominated[b]	0.000	0.000	0.000
Severe dysmenorrhoea at baseline								
EA	1295		0.954			1.000	0.997	0.969
LASH	2848	1553	0.976	0.022	72,225	0.000	0.003	0.031
Non-severe dysmenorrhoea at baseline								
EA	1289		0.995			1.000	1.000	1.000
LASH	2934	1645	0.982	–0.013	Dominated[b]	0.000	0.000	0.000
Fibroids present								
EA	1600		1.020			0.991	0.964	0.917
LASH	3208	1608	0.989	–0.031	Dominated[b]	0.009	0.036	0.083
Fibroids absent								
EA	1341		0.975			1.000	1.000	0.997
LASH	3056	1714	0.992	0.017	110,249	0.000	0.000	0.003
Age < 40 years								
EA	1310		0.963			1.000	0.996	0.937
LASH	2919	1609	0.982	0.020	81,277	0.000	0.004	0.063
Age ≥ 40 years								
EA	1270		0.979			1.000	1.000	0.996
LASH	2873	1603	0.978	–0.001	Dominated[b]	0.000	0.000	0.004

a £/QALY gained.
b Dominated means that, on average, LASH is more costly and produces fewer expected QALYs than EA.
Note
Differences adjusted by study minimisation variables.

Subgroup analyses

The results of the prespecified subgroup analyses are reported in *Table 17*. The ICER for LASH compared with EA remained unfavourable against accepted cost-effectiveness thresholds applied in the UK NHS. In several subgroups, the estimated QALY gain favoured EA, but this may be due to the small numbers and should be treated with caution. Moreover, all the *p*-values for the interaction terms between the corresponding subgroup and treatment effect variables were > 0.05 (i.e. none of the subgroup indicators were found to have a statistically significant effect on incremental health service costs or incremental QALYs) (see *Appendix 3, Table 45*).

TABLE 18 Time to return to paid or unpaid work and productivity costs (6 weeks post surgery)

Variable	Number of observations	LASH ($N = 330$)	EA ($N = 330$)
Time to return to usual activities (number of days)			
Time to return to paid work, mean (SD)	368	33.2 (11.6)	13 (11)
Time to return to unpaid work, mean (SD)	408	18.9 (12.8)	7.3 (8.7)
Time to return to leisure/social activities, mean (SD)	438	30.2 (12.3)	16.5 (13.4)
Productivity costs (£)			
Cost of time lost from paid work	367	1886 (919)	719 (677)
Cost of time lost from unpaid work	408	700 (475)	271 (321)

Indirect costs

Table 18 shows the time to return to paid work, unpaid work and leisure or social activities, reported at 6 weeks post surgery. Women in the LASH group took longer to return to all of these activities. The productivity costs associated with time away from paid and unpaid work in the LASH group came to £2586, compared with £990 following EA. Women in the LASH and EA groups reported similar amounts of time away from paid and unpaid employment and leisure activities at 6 months post surgery and 15 months post randomisation (see *Appendix 3, Table 45*).

Data were also collected on out-of-pocket expenses and time costs associated with travel to and from health-care appointments. There were no notable between-group differences in mean out-of-pocket expenses (£9 and £7 for the LASH and EA, respectively) or in the value of time lost to attend outpatient appointments (£26 and £22 for the LASH and EA, respectively).

Summary of costs and consequences

The results of the cost-effectiveness analysis focused on the ICER using generic QALYs as the unit of effectiveness, as prespecified in the HEALTH protocol. Although the trial-based cost-effectiveness analysis did not show any significant difference in QALYs by 15 months post randomisation, LASH was superior on both primary outcome measures for clinical effectiveness, as well as a range of secondary outcomes. To summarise, although LASH conferred significantly higher direct costs on the health service (+£1604) and indirect costs on society (+£1596) over 15 months of follow-up (post randomisation), it also provided significantly greater benefits at 15 months in terms of satisfaction with treatment, MMAS score, EQ-5D-3L VAS score, SF-12 MCS, acceptability of treatment and willingness to recommend treatment (see *Tables 10* and *11* for effect sizes). These benefits were consistent with an emerging difference in the EQ-5D-3L score favouring LASH at 15 months. Although the difference in the EQ-5D-3L score did not reach statistical significance by 15 months, it pointed to the need to extrapolate over a longer time horizon to adequately inform the cost-effectiveness of LASH compared with EA.

Discussion

The within-trial cost–utility analysis reported in this chapter indicated that, over a 15-month post-randomisation follow-up period, intention to treat with LASH resulted in increased costs to the health service (mean difference £1604). This was mainly driven by the cost of the initial procedure, with LASH taking twice as long to perform and resulting in a longer hospital stay than EA. Costs to society were also increased following LASH (£1596), because women treated with LASH took longer to return to paid and unpaid productive activities than those treated with EA. There was very little difference in QALYs between the treatment allocation groups, assessed over 15 months from randomisation, resulting in the ICER for LASH being unfavourable at this time point. The 15-month ICER also remained unfavourable to LASH in all the sensitivity analyses and subgroup analyses performed.

Strengths of the trial-based economic analysis include the availability of randomised data on resource use and HRQoL profiles collected prospectively as part of HEALTH. This enables accurate and unbiased estimation of mean differences in costs and QALYs over the trial follow-up period. The pragmatic design and intention-to-treat principles also enhance the generalisability of the findings to routine practice in the UK NHS.

The key limitation of the trial-based economic analysis relates to the relatively short duration of follow-up. Although there was no notable difference in QALYs between the groups by 15 months post randomisation, this time horizon was insufficient for drawing any conclusions on cost-effectiveness. The follow-up data indicate that there were more readmissions to hospital among those randomised to EA ($n = 27$) than there were among those randomised to LASH ($n = 15$), including 13 hysterectomies following EA compared with only one surgical episode related to menstrual bleeding post LASH. This trend for an increased incidence of further gynaecological surgery following EA is likely to become more pronounced in the future,[10] reducing the incremental cost of LASH and resulting in QALY gains favouring it. Furthermore, the lack of difference in QALYs by 15 months post randomisation belied the fact that the EQ-5D-3L health state utility curves crossed during follow-up. Those randomised to EA experienced a shorter waiting time and quicker rise in health state utility following surgery, but then a subsequent decline in their EQ-5D-3L score by 15 months. The LASH group, on the other hand, experienced continued improvement in their EQ-5D-3L score out to 15 months post randomisation, by which time the mean score was higher than the EA group. As QALYs were computed as the area under the health state utility curve, terminating follow-up at 15 months has truncated the incremental QALY gains that would be expected to accrue to LASH if the 15-month difference in health state utility was maintained or increased over time. It is therefore necessary to extrapolate the trial results over a longer time horizon to inform cost-effectiveness. This is the focus of *Chapter 6*.

Chapter 6 Economic modelling

Introduction

The purpose of this chapter is to report on the details of further modelling conducted to extrapolate the trial-based cost-effectiveness findings beyond 15 months post randomisation. Although the within-trial analysis is useful for informing differences in costs and outcomes over a relatively short time horizon, it does not capture expected differences over the medium (2–5 years) to long term (5–10 years). Eventually 20–25% of women assigned to EA are expected to require further surgical treatment,[5,9,10] resulting in downstream QALY losses and higher readmission costs than with LASH. These anticipated costs and consequences should be accounted for in a full economic evaluation.[43] Furthermore, although there was no significant between-group difference in QALYs observed by 15 months post randomisation in HEALTH, the mean health state utility scores appeared to be diverging by this time point (see *Chapter 5*, *Table 14*). Although the difference was not statistically significant, the direction of the effect in favour of LASH is consistent with the reported superiority of LASH on the primary clinical outcomes and with the expectation of higher repeat surgery rates in the EA group.

To estimate longer-term economic differences, a simple Markov model was developed to extrapolate the estimated 15-month difference in utility and simulate the incidence of further gynaecological surgery over time. The key objective of the analysis was to inform the long-term cost-effectiveness of LASH compared with EA.[1] This analysis forms the primary economic analysis of HEALTH.

Methods

Model structure

The Markov model was constructed in TreeAge Pro software (TreeAge Software, Inc., Williamstown, MA, USA) and was informed by reviewing decision models identified in a recent systematic review that was undertaken to inform the NICE clinical guidelines on the assessment and management of HMB.[43] A structure similar to that of other models was developed to assess the cost-effectiveness of treatments for HMB in the UK NHS was chosen.[9,10,43] The state occupancy and estimated pay-offs are updated on a constant monthly Markov cycle.

A cohort of women with HMB enter the model in the 'HMB' health state and are assigned to treatment with either EA or LASH. Women are modelled to receive treatment as observed in HEALTH by intention to treat. However, for simplicity, index procedures are modelled to occur in the first cycle of the model, with the waiting time factored out.

Following the index treatment in the EA arm (*Figure 9*), women move to either the 'post EA' or 'complication post EA' health state. The complication health state is designed to capture the cost and utility impact of postoperative complications resulting in readmission to hospital. These events are assumed to be transitory and so the health state utility impact is modelled to last for one cycle (1 month). Following this, women transit to the 'post EA' health state for the subsequent model cycle unless they progress to further surgery. The transition to further surgery from the 'post EA' health state is modelled on a monthly basis. Although the model has the capability to include first-generation EA (rollerball) as a second-line surgical treatment, the base case assumes that hysterectomy is the treatment of choice for women who require further surgery following failed second-generation EA. Repeat EA is not explicitly recommended as a treatment option in the recently updated NICE clinical guidelines for HMB.[43] For women who transition to 'hysterectomy post EA', the surgical intervention occurs in the first model cycle following the transition. Following this, women either enter a temporary health state representing severe postoperative complications, or they move to

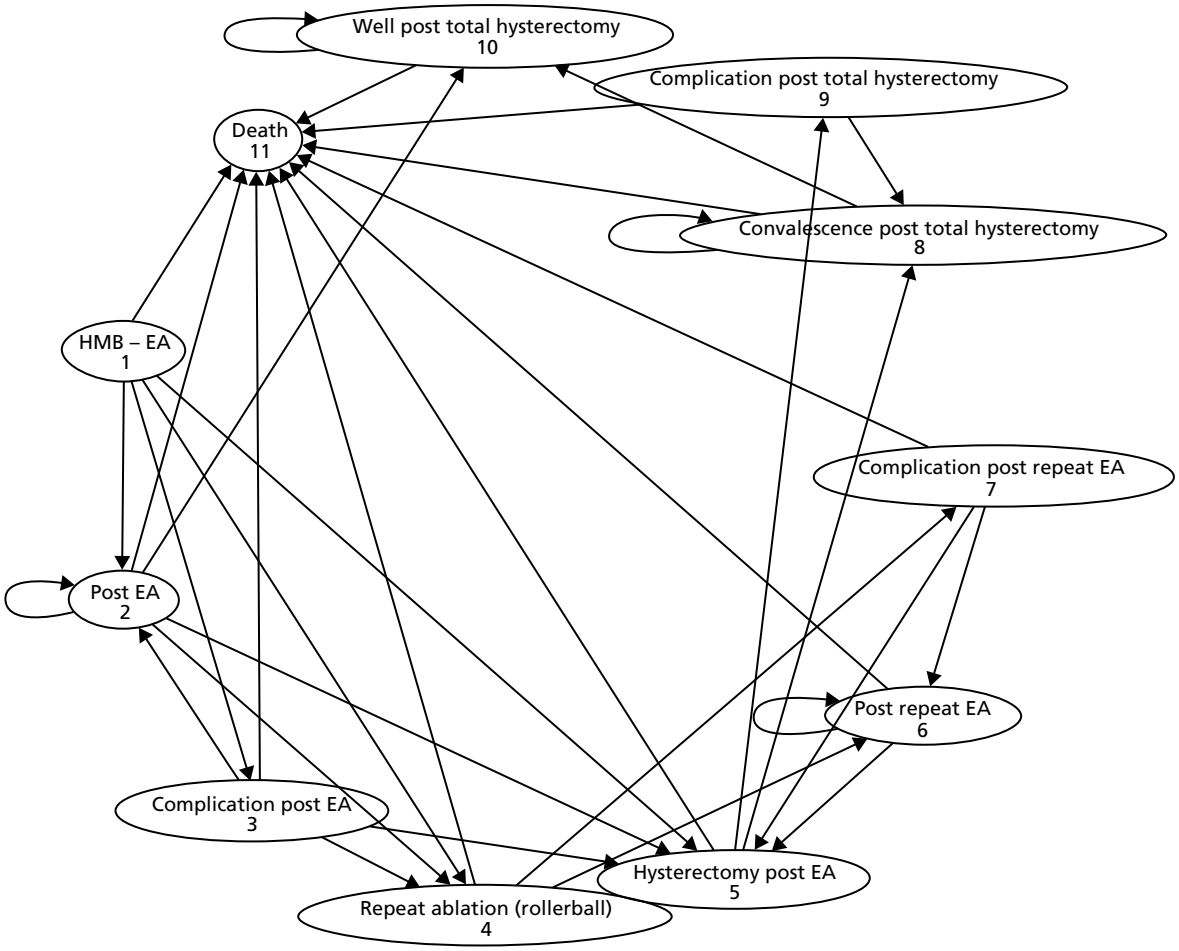

FIGURE 9 Simplified schematic for the EA arm of the Markov model. The transition from 'Post EA' to 'Well post total hysterectomy' is included as a one off transition at month 12 to account for the small proportion of patients who had a total hysterectomy instead of EA for their index treatment.

'convalescence post total hysterectomy'. The convalescence period is modelled to last for 3 months, after which all women transition to the 'well post total hysterectomy' health state. Finally, 'death' is included as an absorbing state in the model, which can be entered from any other state based on age-specific mortality rates reported for females in UK life tables.[44]

The structure of the model in the LASH arm is similar to that in the EA arm (*Figure 10*). However, following index treatment women either enter a temporary health state to capture postoperative complications or they transition to 'convalescence post LASH'. The complication state serves the same purpose as it does in the EA arm. The convalesce state is included to capture the longer time to full recovery observed for LASH than for EA in HEALTH. From the post-LASH health states, a monthly probability of requiring further related gynaecological surgery is also applied. This includes further surgery related to ongoing bleeding or pain following LASH, specifically removal of the cervical stump, laparoscopy to investigate/treat pain and laparoscopic bilateral salpingo-oophorectomy (BSO). Following further surgery post LASH, women enter a post-surgical state dependent on the type of surgery received. For women who undergo cervical stump removal, a probability of severe post-surgical complications is applied and a convalescence period of 3 months is also assumed. Following convalescence, women are assumed to be well for the remainder of the modelled time horizon. For women who require laparoscopy for pain or laparoscopic BSO, no further postoperative complications or convalescence period are modelled, but women attract lower health state utility in the cycle leading up to surgery. After surgery they are also assumed to be well for the remaining time horizon.

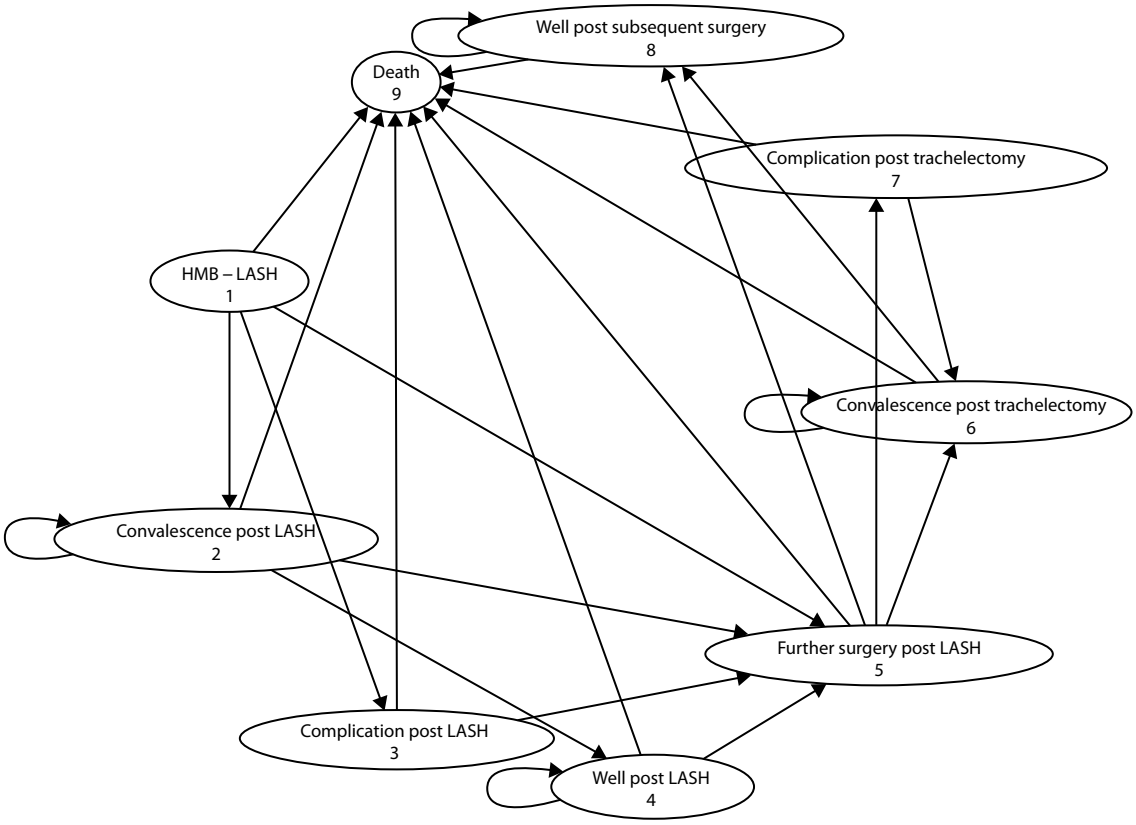

FIGURE 10 Simplified schematic for the LASH arm of the Markov model.

Population

The model analysis was conducted for a cohort of women with characteristics matching those of the HEALTH cohort (mean age equals 42 years at baseline). The estimation of input parameters for the economic model was based on the same intention-to-treat principles applied in the HEALTH analysis. Thus, the model reflects the fact that a number of women do not receive their intended treatment. A scenario analysis was also conducted to assess cost-effectiveness based on the restricted cohort that received their allocated treatment (per-protocol analysis).

Time horizon and discounting

In line with a previous UK HTA conducted by Bhattacharya *et al.*,[10] a long-term, 10-year time horizon was applied in the model base case. This is consistent with the average age at onset of menopause in the UK, and observational data which shows that the incidence of subsequent hysterectomy following EA continues to rise out to 10 years post surgery.[5] The impact of adopting a medium-term time horizon of 5 years was assessed in a sensitivity analysis. Costs and QALYs accruing beyond year 1 in the model are discounted using an annual discount rate of 3.5%.[42,45]

Clinical input parameters

The key clinical input parameters in the model are tabulated in *Table 19*. The rates of post-surgical complications following EA and LASH were based on HEALTH data, as were the rates of subsequent gynaecological surgery for HMB out to 1 year following index surgery. *Figure 11* shows the Kaplan–Meier (KM) plots for further gynaecological surgery by treatment arm in HEALTH (conditioned on receipt of index surgery); the estimated 12-month probabilities were 3% in the EA arm and 0.7% in the LASH arm. These probabilities were transformed into monthly probabilities for application over the first 12 cycles in the model.

TABLE 19 Clinical input parameters applied in the model

Variable	Point estimate	Standard error	Distributional form	Source
Probability of readmission for complications post EA	0.033	0.01	Beta	HEALTH
OR for postoperative complications (LASH vs. EA)	1.107	0.420	Lognormal	HEALTH
Probability of hysterectomy post EA (by 12 months)[a]	0.03	0.0098	Beta	HEALTH
Probability of further surgery for bleeding post LASH (by 12 months)[a]	0.0069	0.0049	Beta	HEALTH
Probability of hysterectomy post EA (beyond 12 months up to 10 years)			Applied and tested deterministically	
Weibull rate parameter (λ)	0.119			Cooper *et al.*[5]
Weibull shape parameter (γ)	0.397			Cooper *et al.*[5]
Log HR for hysterectomy (second- vs. first-generation techniques)[b]	–0.274	0.0532	Lognormal	Bansi-Matharu *et al.*[46]
Inferred log HR for further surgery post LASH vs. EA[c]	–0.4886	0.122	Lognormal	Calibrated to Lieng *et al.*, 2008[17]; see *Extrapolation of subsequent surgery following laparoscopic supracervical hysterectomy*
Probability of severe complications post hysterectomy	0.0102	0.001	Beta	Maresh *et al.*[47]; Bhattacharya *et al.*[10]
Probability of severe complications post trachelectomy	0.0102	0.001	Beta	Assumption

a Observed further surgery included hysterectomy following EA and trachelectomy following LASH.
b Applied in sensitivity analysis to adjust down the incidence of hysterectomy following EA.
c Further surgery beyond 12 months post LASH includes laparoscopic surgery to remove the cervical stump, laparoscopy to investigate/treat pain and laparoscopic BSO.

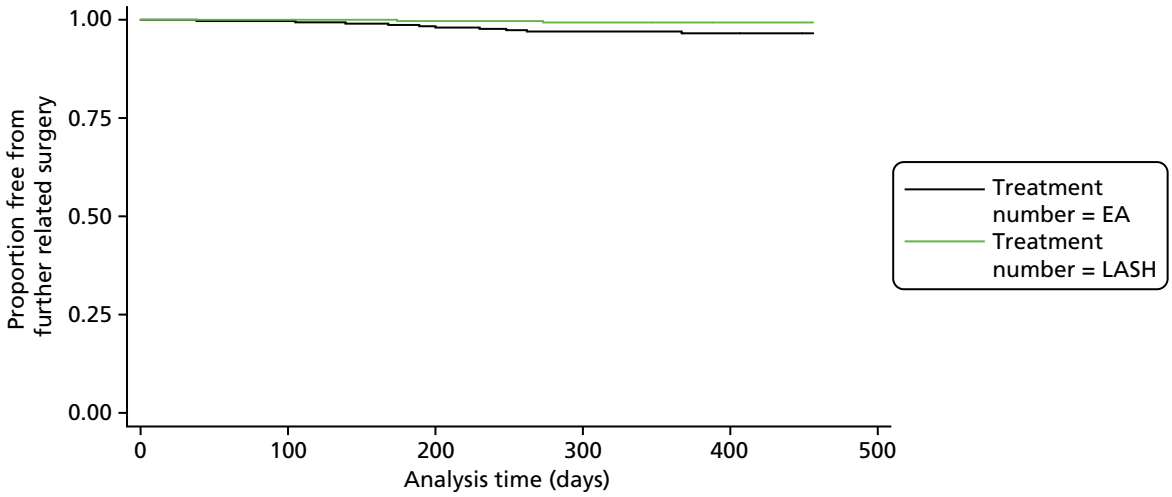

FIGURE 11 Kaplan–Meier plot of time from index operation to further related surgery by treatment allocation.

Extrapolation of subsequent hysterectomy following endometrial ablation

Given what is known about the probability of hysterectomy following EA, it is anticipated that the KM curves for time to further surgery will continue to diverge over time. In addition, as the follow-up of HEALTH is currently truncated at 15 months post randomisation and waiting times for the index surgery were 3–4 months on average, only 69% of women in the EA group and 56% in the LASH group were observed to 12 months post surgery at the time of writing. Coupled with the current waiting times for subsequent surgery among those who need it, HEALTH data do not currently give an accurate picture of further surgery rates by treatment allocation group.

Given these limitations, external data were used to inform rates of subsequent surgery beyond 12 months in the model. A focused search of MEDLINE was conducted to identify randomised trials comparing EA and LASH using the Ovid interface (see *Appendix 4*). This identified one small RCT which included long-term follow-up of patients. Zupi *et al.*[48] reported that, after a mean follow-up of 14.4 years, 20 out of 71 patients (28.1%) required a reoperation for menstrual bleeding in the EA arm of the trial, compared with none in the LASH arm (out of 82 available for analysis). They did report that 6 out of 82 women (7.3%) required further surgery in the LASH arm for indications other than menstrual bleeding (five requiring a laparoscopy to investigate pain). Although this RCT provides evidence in favour of a lower rate of subsequent related surgery following LASH, it is a small, single-centre study. Given this limitation, a further focused literature search was undertaken to identify cohort studies reporting rates of hysterectomy following EA or rates of cervical stump removal, laparoscopy and BSO following LASH (see *Appendix 4*). Priority was placed on identifying large population-based cohort studies reporting long-term rates. This yielded three[5,46,49] population-based cohort studies reporting rates of hysterectomy following EA and eight[17,50–56] smaller observational studies reporting rates of further surgery following LASH (see *Appendix 4* for details).

For the probability of hysterectomy following EA, we used data from a large observational study carried out using routine Scottish health service data. Based on linked health episode data, Cooper *et al.*[5] reported on 14,078 women identified as having received primary EA for HMB between 1989 and 2006 in Scotland. Over a median duration of 6.8 years follow-up, 2779 (19.7%) women were observed to receive a subsequent hysterectomy. Data were extracted from the published KM curve using digitising software (WebPlotDigitizer, V4.1, 2018; URL: https://automeris.io/WebPlotDigitizer/) and regression methods were then used to fit a Weibull distribution to the observed time-to-event data (see *Appendix 5* for details).

A limitation of the study by Cooper *et al.*[5] was an inability to discriminate between EAs carried out using second- and first-generation techniques, and a number of studies have suggested that some second-generation techniques may incur a lower risk of post-ablation hysterectomy.[46,57] However, a very similar rate of post-ablation hysterectomy has been reported following second-generation procedures carried out between 1997 and 2007 in a Finnish registry study (1086/5484, 19.8%).[49] The Weibull distribution fitted to the Scottish data was therefore used in the model to derive time-dependent probabilities of transition to hysterectomy in the EA arm (see *Appendix 5* for details regarding the derivation of transition probabilities). Sensitivity analysis was used to explore the impact of adjusting the hazard rate downwards using a HR for radiofrequency ablation (HR 0.76, 95% CI 0.69 to 0.85), reported by Bansi-Matharu *et al.*[46] and based on a large English population-based cohort study. Further sensitivity analysis was also conducted to explore the impact of using time-dependent transition probabilities for hysterectomy following EA, derived directly from the KM curve reported by Cooper *et al.*[5] The model projections of post-ablation hysterectomy were compared against the 5-year rates reported by Bansi-Matharu *et al.*[46] as means of external validation (see *Model validation*).

Extrapolation of subsequent surgery following laparoscopic supracervical hysterectomy

Several studies of variable size and quality were identified to inform the risk of further surgery following LASH (see *Appendix 4*). The reported incidence of post-LASH cervical stump removal ranged from 0.9% to 23%.[17,50–53,58] Based on length of follow-up, consistency with the observed 12-month rate in HEALTH, and a similar rate of post-LASH menstrual bleeding (24% vs. 19%), a Norwegian cohort reported by Lieng *et al.*[17] was considered the most useful for informing longer-term rates in the model (see *Appendix 4* for

details). Lieng *et al.*[17] reported that, of 308 women undergoing LASH at a university hospital in Oslo during 2004 and 2005, six (1.9%) subsequently underwent laparoscopic adhesiolysis, seven (2.3%) underwent laparoscopic cervical stump removal, one (0.3%) underwent BSO and eight underwent other procedures in the 12–36 months of follow-up after LASH. The other reported procedures included laparoscopic drainage of postoperative abscess ($n = 1$), laparoscopy with bowel resection for postoperative peritonitis ($n = 1$), scar correction ($n = 3$), umbilical hernia repair ($n = 1$) and tension-free vaginal tape procedures ($n = 2$). These procedures were not included in the model as they were considered to be either short-term postoperative complications (included in the model based on HEALTH data) or of uncertain association with the LASH procedure. The model was therefore calibrated to yield the combined cumulative incidence of laparoscopic adhesiolysis, laparoscopic cervical stump removal and BSO (4.5%), reported by Lieng *et al.*[17] by month 36. This was done by applying a HR to the rate parameter of the Weibull distribution used to model time to hysterectomy following EA. Thus, it is assumed that the hazard for further surgery post LASH is proportional to the hazard of hysterectomy post EA. This approach yields a cumulative incidence of further surgery of ≈11% by 10 years post LASH in the model.

Postoperative complications following hysterectomy and removal of the cervical stump

For those women modelled to go on to receive a hysterectomy following EA, or cervical stump removal following LASH, an associated postoperative complication rate is applied. This probability is taken from the previous HTA study conducted by Bhattacharya *et al.*,[10] originally sourced from Maresh *et al.*[47] As no data were available to inform the risk of severe postoperative complications following cervical stump removal, the same probability of complications was applied to this procedure.

Health state utilities

The health state utilities applied in the model were derived primarily from the EQ-5D-3L data from HEALTH (*Table 20*). For the first 12 months in the model, adjusted utility estimates are applied by treatment arm. Beyond 12 months, extrapolation assumptions are applied.

Post-endometrial ablation and post-laparoscopic supracervical hysterectomy health state utility (to 12 months)

The baseline utility estimate for women entering the model was taken as the mean baseline EQ-5D-3L index score observed across treatment groups. Following treatment in the first cycle of the model, the cohort is distributed between the relevant post-treatment states. In cycle 2, the cohort is dichotomised by whether or not early postoperative complications occur. Health state utility values were therefore estimated

TABLE 20 EuroQol-5 Dimensions, three-level version-based health state utilities applied to the post-EA and post-LASH health states

Variable	EA (mean)	LASH (mean)	Mean difference (95% CI)	Distributional form	Source
Baseline	0.702	0.702	–	Beta	HEALTH
6 weeks post surgery (no complications)	0.829	0.820	–0.009 (–0.05 to 0.032)	Beta + normal for (increment)	HEALTH
6 weeks post surgery (postoperative complications)	0.786	0.739	–0.047 (–0.275 to 0.182)	Beta + normal for (increment)	HEALTH
6 months post surgery (from cycle 3)[a]	0.815	0.817	0.0019 (–0.041 to 0.044)	Beta + normal for (increment)	HEALTH
12 months post surgery (from cycle 9)[a]	0.787	0.825	0.038 (–0.013 to 0.090)	Beta + normal for (increment)	HEALTH

a Note, utility values are reported for those remaining in the post-EA and post-LASH states, free from subsequent surgery. All values are adjusted for baseline utility and minimisation factors using lineal regression, with adjustment for clustering within centres.

by treatment allocation group and the occurrence of postoperative complications resulting in readmission to hospital. This was done by regressing the 6-week utility data on indicators for treatment allocation, readmission for complications (yes/no) and the interaction between treatment allocation and readmission. The regression also adjusted for baseline utility and age (< 40 years vs. ≥ 40 years) as a minimisation factor used in the randomisation process. Ordinary least squares regression was used for the analysis of the utility data, given the moderately large sample size, but with cluster robust standard errors.[59] The method of recycled predictions was used to recover the adjusted mean value in the base group, and the estimated incremental effects and robust standard errors from the regression models were used to define the distributions on effect differences in the Markov model. The analyses to inform the model utility inputs were based on available complete data for the relevant variables.

Beyond cycle 2 in the model, those remaining in the post-EA or post-LASH health states were assigned the corresponding treatment arm-specific 6-month utility values derived from HEALTH data. Those remaining in the post-EA or post-LASH treatment states were then modelled to receive the relevant treatment arm-specific 15-month utility value from cycle 9 (month 9) post surgery. This assumes that, on average, the 15-month post-randomisation utility estimate from HEALTH corresponds to 12-month postoperative utility, and that the change in health state utility between 6 months and 12 months post surgery is linear. For those modelled to incur a hysterectomy following EA, or subsequent surgery post LASH, further health state utility assumptions were applied as described below under *Extrapolations of post-endometrial ablation and post-laparoscopic supracervical hysterectomy health state utility*.

Extrapolations of post-endometrial ablation and post-laparoscopic supracervical hysterectomy health state utility

Table 20 shows that health state utility was slightly increased following EA, relative to LASH, in the short term (6 weeks), but, by 15 months post randomisation (≈12 months post surgery), there was an emerging difference that favoured LASH. Although this difference was not significant ($p = 0.14$), the direction of effect is consistent with superior satisfaction and MMAS scores observed in the LASH group at 15 months (see *Tables 10* and *11*). A lower utility value among those remaining in the post-EA health state at 12 months is also consistent with the expected higher incidence of further surgery (hysterectomy) beyond 12 months. It may reflect an increased number of women experiencing treatment failure or recurrence by 12 months post EA, who are yet to return for further surgery.

Therefore, the model extrapolated the estimated 12-month (post-surgery) between-group difference in health state utility over an extended time horizon (*Figure 12*). However, it is anticipated that it will be those women who have a poorer outcome at 12 months following EA who return in the future for a hysterectomy. Thus, the average utility score among those remaining in the post-EA state would be expected to rise over time. Conversely, it is possible that the recurrence of symptoms following EA has yet to peak and that the utility curves will continue to diverge further beyond 12 months before beginning to converge. It is also uncertain to what extent the post-EA and post-LASH utility curves may converge, and how quickly. In our base-case analysis, we adopted a conservative approach (in favour of EA) and assumed that the mean difference in utility between the post-EA and post-LASH health states would diminish over time in proportion to the total expected number of post-EA hysterectomies completed. For example, from a baseline of 12 months post surgery, 50% of the further post-EA hysterectomies will have been completed after a further 3 years, by which time the extrapolated utility difference is approximately half of that observed at 12 months. By 10 years in the model, the utility difference is assumed to have diminished to zero. We explored the impact of applying alternative extrapolation assumptions in sensitivity analysis, including retention of the full 12 months post-surgery utility difference over the entire duration of the model and allowing it to diminish over a shorter time.

Health state utilities associated with further surgery

Regarding the heath state utility of those transitioning to hysterectomy following EA, similar assumptions to those used in the HTA by Bhattacharya *et al.*[10] were applied. Women were assigned the baseline utility value of 0.702 in the cycle preceding hysterectomy. Following that, a utility value appropriate to the

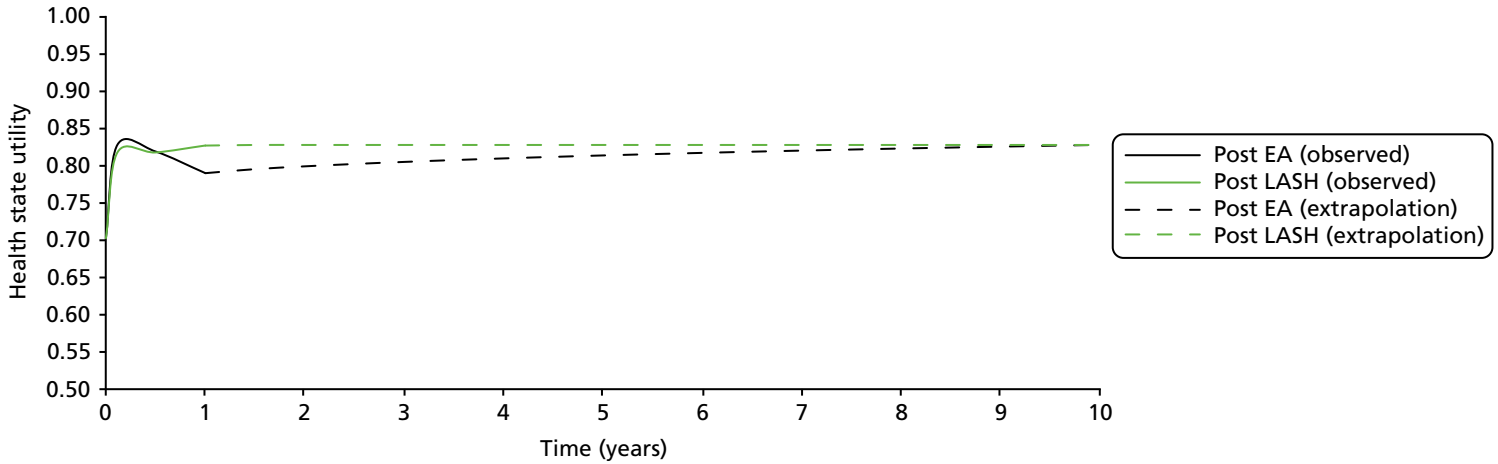

FIGURE 12 Observed and extrapolated health state utility post LASH and post EA.

post-hysterectomy state was applied. For severe postoperative complications following hysterectomy, a utility value of 0.49 was sourced from Bhattacharya *et al.*,[10] originally from Clegg *et al.*,[60] and applied for a single cycle. For the convalescence period following hysterectomy (3 months), a utility value of 0.74 was applied.[10,61] Finally, it was assumed that health state utility in the 'well post hysterectomy' health state is equivalent to that in the 'well post LASH' health state. *Table 21* provides a summary of health state utility inputs applied for the further surgery states.

For women requiring cervical stump removal following LASH, the same utility assumptions pertaining to total hysterectomy were applied. For post-LASH laparoscopy or BSO, we applied baseline utility in the cycle preceding treatment and the cycle of treatment, but then assumed a return to the 'well post LASH' state. Thus, overall, the model base case assumes that, after 10 years, women ultimately end up at the same level of health state utility, although the pathway to that outcome varies.

Health service resource use and costs

Health service costs applied in the model were informed by the analysis of HEALTH data to 12 months post surgery. As with the analysis of health state utility data, the individual cost inputs in the economic model were informed, where possible, by ordinary least squares regression of the relevant complete trial cost variables in the first 12 cycles. Costs were regressed on indicators for treatment allocation and age group, with adjustment for clustering by centre. The method of recycled predictions was used to recover the mean adjusted costs in the base treatment group, and the estimated incremental effects and cluster robust standard errors from the regressions were used to define distributions for the cost differences applied in the model. The mean initial treatment cost was estimated by intention to treat and applied in the first cycle of the model. A two-part regression model was used to estimate the probability of further admission for postoperative complications by treatment arm and the cost of treating these complications, conditional on readmission. The first part utilised logistic regression and the second part OLS, to estimate adjusted mean readmission costs by treatment allocation, conditional on readmission. These postoperative complication costs were applied in the second cycle of the model following the initial treatment episode. Subsequent hysterectomies following EA, and cervical stump removal and further laparoscopic surgery following LASH, were costed using the appropriate HRG-based reference costs (*Table 22*).[32]

Finally, HEALTH follow-up data were used to estimate other costs (outpatient appointments, medications and primary care use) to the health service post LASH and post EA. These were transformed into monthly costs for application as health state costs in the model. The post EA costs were applied to the post-EA states, and the post-LASH costs were applied to the post-LASH and post-hysterectomy health states. These costs were stripped of outpatient costs during the extrapolation phase of the model and a separate outpatient referral cost was applied on transition to further surgery for those requiring it.

Values based on the analysis of HEALTH data are adjusted for baseline utility and minimisation factors using lineal regression, with adjustment for clustering within centres.

TABLE 21 Health state utility values applied for further surgery states

Variable	Mean	SEM	Distributional form	Source
Symptomatic requiring further surgery	0.702	0.012	Beta	HEALTH
Severe postoperative complication following hysterectomy or removal of cervical stump	0.49	0.049	Beta	Clegg *et al.*[60]
Convalescence post hysterectomy or removal of cervical stump	0.74	0.05	Beta	Sculpher[61]
Well post hysterectomy	0.827		Beta	Assumption (see *Health state utilities associated with further surgery*)

SEM, standard error of the mean.

TABLE 22 Health service costs applied in the model

Variable	Mean (£)	SE	Distributional form	Source
Initial hospital episode cost (EA)	1071	34.79	Gamma	HEALTH
Incremental cost of initial episode (LASH)	1686	75.32	Normal	HEALTH
Postoperative complication cost (EA)	854	176.81	Gamma	HEALTH
Incremental cost of postoperative complications (LASH)	194	149.47	Normal	HEALTH
Hysterectomy post EA	3408	725	Gamma	*NHS Reference Costs 2016–2017*[32] (HRG MA08, elective inpatient)
Removal of cervical stump post LASH	2776	704	Gamma	*NHS Reference Costs 2016–2017*[32] (HRG MA03, elective inpatient)
Laparoscopic investigation for pain (post LASH)	2482	628	Gamma	*NHS Reference Costs 2016–2017*[32] (HRG MA29, average)
Laparoscopic BSO	3408	725	Gamma	*NHS Reference Costs 2016–2017*[32] (HRG MA08, elective inpatient)
Post-EA monthly health state cost (first year)	5.96	0.84	Gamma	HEALTH
Post-LASH monthly health state cost (first year)	6.04	0.92	Gamma	HEALTH
Post-EA monthly health state cost (> 1 year)	3.49	0.48	Gamma	HEALTH
Post-LASH monthly health state cost (> 1 year)	3.30	0.56	Gamma	HEALTH

SE, standard error.

Model validation

To assess the internal validity of the model we compared the 12-month model-based cost and QALY estimates with the 15-month trial-based estimates. These data are provided in *Table 23*. Although the expected QALYs were lower in both arms in the model, the estimated incremental difference was similarly very small. The lower average QALY estimates are accounted for by the simplifying assumption of omitting the pre-treatment waiting period and running the model for 12 months rather than 15 months. The mean treatment arm costs were also very similar between the model and trial-based analyses, as was the incremental cost. The small differences are attributable to the fact that the model was populated using the available complete data for each input parameter, rather than the multiple imputation data set used in the trial-based analysis.

To assess the validity of projected rates of further surgery beyond 12 months, the modelled cumulative incidence following EA and LASH was plotted over the 10-year time horizon (*Figure 13*). The model

TABLE 23 Trial- and model-based estimates of mean costs and effects, at 15 months post randomisation and 12 months post surgery, respectively

Variable	EA	LASH	Difference
Trial-based estimates			
Mean cost (£)	1282	2886	1604
Mean QALY	0.974	0.978	0.004
Model-based 12-month estimates			
Mean cost (£)	1277	2890	1612
Mean QALY	0.8119	0.8140	0.0021

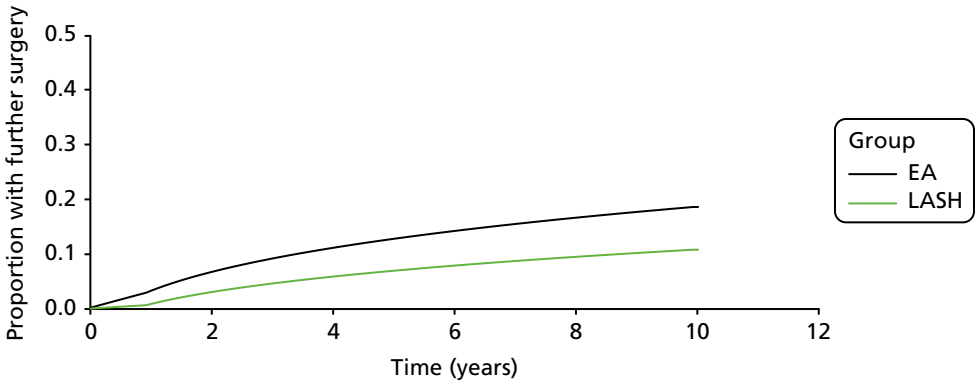

FIGURE 13 Modelled incidence of further surgery following EA and LASH.

projected that cumulative incidence of hysterectomy following EA was 3.3%, 6.8% and 12.8% after 1, 2 and 5 years, respectively. This compares to estimates from a large population-based English study of 5.6%, 9.6% and 13.5%, respectively, at these corresponding time points.[46] The incidence was lower in the model because the lower 12-month rate from HEALTH was applied in year 1. There were few data against which to validate the projections for further surgery following LASH. As previously discussed under *Extrapolation of subsequent surgery following laparoscopic supracervical hysterectomy*, the projected estimates are in line with the incidence observed at 12–36 months in a Norwegian cohort,[17] and reach ≈11% by 10 years post surgery when combined with the extrapolation assumptions.

Model analysis

The model-based analysis utilised second-order Monte Carlo simulation to characterise the joint uncertainty surrounding the estimated incremental costs and effects of LASH compared with EA.[62] A probability distribution was assigned to each model input parameter, reflecting the degree of uncertainty surrounding it owing to sampling variation. The functional form and variance of each input distribution are provided in *Tables 20–23*. In general, gamma distributions were used to represent uncertainty surrounding cost inputs, beta distributions were applied for probabilities and utility parameters and lognormal distributions were used for HRs. The probabilistic analysis was run using 10,000 random draws from the assigned input distributions, generating 10,000 estimates of incremental costs and effects. The point estimate of the ICER was expressed as the mean incremental cost divided by the mean incremental effect across the 10,000 iterations. Tabulated results express the probability of each treatment option being preferred on grounds of cost-effectiveness at willingness-to-pay (WTP) thresholds of £13,000, £20,000 and £30,000 per QALY gained.[42,63] Cost-effectiveness scatterplots and acceptability curves are provided to further summarise the uncertainty surrounding the results. Further deterministic analysis was also conducted to assess the sensitivity of the model results to changes in key input parameters and structural assumptions.

Key assumptions

The following points summarise some of the key assumptions applied in the base-case analysis:

- Index surgery costs associated with randomisation to EA or LASH were modelled to occur in the first cycle of the model and are estimated by intention to treat.
- Data inputs were derived entirely from HEALTH over the first 12 cycles (months) of the model. The 15 months post-randomisation utility estimates were applied as 12 months post-surgery estimates.
- The difference in health state utility between the post-EA and post-LASH health states is at its maximum by 12 months post surgery.
- The difference in utility between the post-EA and post-LASH health state diminished over time in the model, in proportion with the number of post-EA hysterectomies expected to have been completed. Thus, post-EA and post-LASH health state utility converges completely by 10 years in the model.
- Health state utility in the 'well post total hysterectomy' state was set equal to health state utility in the 'well post LASH' state of the model (i.e. this assumes that those requiring a hysterectomy following EA ultimately achieve the same level of HRQoL as those who remain well following LASH).

- Beyond 12 months, the incidence of post-EA hysterectomy was based on Scottish data reported by Cooper *et al.*,[5] with the modelled cumulative incidence reaching 18.6% by 10 years.
- Beyond 12 months, the incidence of further related surgery following LASH (removal of the stump and/or ovaries or laparoscopy investigation for pain) was calibrated to Norwegian data reported by Lieng *et al.*[17] The combined cumulative modelled incidence reaches 4.5% by 3 years and 11% by 10 years. It was assumed that all related surgery will have been completed by this time.

Results

Base-case analysis

Table 24 presents the results of the base-case analysis. Over the modelled 10-year time horizon, intention to treat with LASH resulted in an increased cost to the health service of £1362 per woman, for an expected QALY gain of 0.111 per woman, compared with EA. The corresponding ICER was £12,314 per QALY gained for LASH compared with EA. The chance of LASH being cost-effective ranged from 53% to 80% at WTP per QALY thresholds of £13,000 and £30,000, respectively. It can be noted that extending the time horizon of the evaluation from 1 year to 10 years reduced the incremental cost of LASH by £250 (£1362 at 10 years vs. £1612 at 1 year). This is due to the incorporation of expected costs of further surgery. The QALY gain associated with LASH resulted primarily from extrapolation of the estimated difference in 12-month post-EA and post-LASH health state utility. Further temporary reductions in utility associated with further surgery accounted for only a very small proportion of the incremental QALY.

Figures 14 and *15* further illustrate the uncertainty surrounding the estimated incremental costs and effects of LASH compared with EA. LASH remained the significantly more costly strategy based on extrapolation to 10 years, with all the estimated points being above zero on the *y*-axis of *Figure 14*. Most points (≈93%) also lie to the right of zero on the *x*-axis, indicating a 93% chance that LASH will generate more QALYs based on the simulation. The cost-effectiveness acceptability curve for LASH (see *Figure 15*) therefore asymptotes to 93%, as the threshold of WTP per QALY increases towards infinity. This is analogous to finding a *p*-value (one-sided) of 0.07 for an estimated difference in QALYs favouring LASH.

TABLE 24 Base-case model results

						Probability cost-effective		
Strategy	Cost (£)	Δ cost (£)	QALYs	Δ QALYs	ICER (£)	£13,000	£20,000	£30,000
EA	2089		6.938			0.468	0.291	0.201
LASH	3452	1362	7.049	0.111	12,314	0.532	0.709	0.799

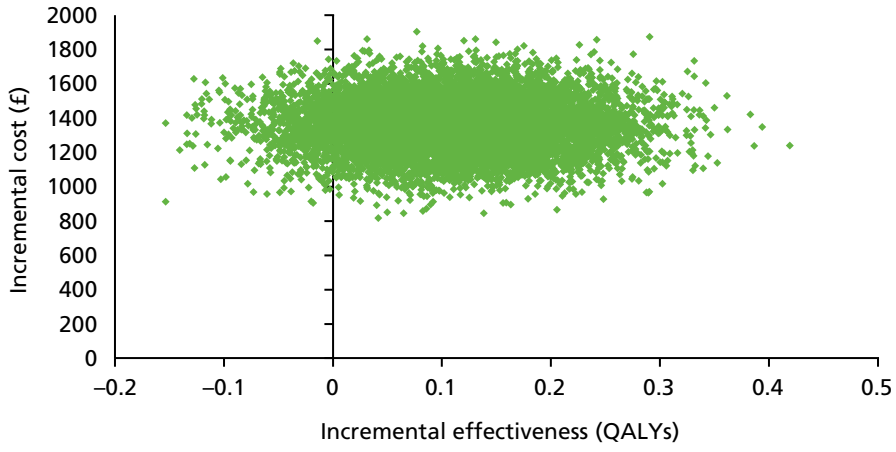

FIGURE 14 Incremental cost-effectiveness scatterplot (LASH vs. EA).

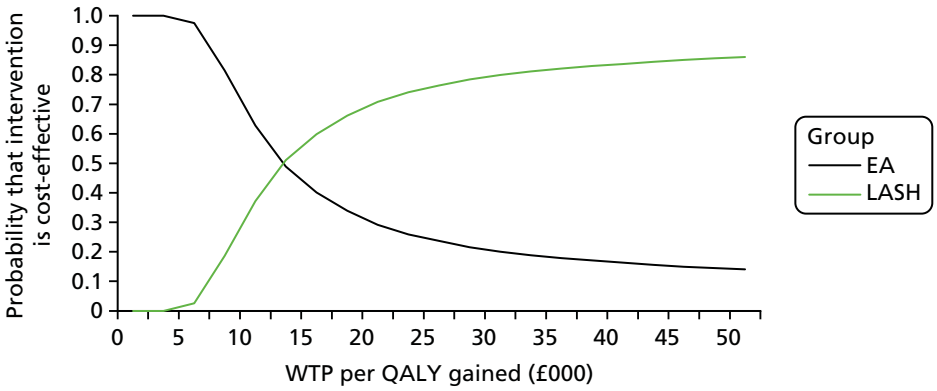

FIGURE 15 Cost-effectiveness acceptability curve (LASH vs. EA).

Scenario analyses

Further scenario analyses were conducted to assess the sensitivity of the model results to changes in key input parameters and assumptions. These included the following:

1. Running the model over a 5-year time horizon instead of a 10-year time horizon.
2. Lowering the rate of hysterectomy following EA, by applying a HR or 0.76 reported by Bansi-Matharu *et al.*[46] for radiofrequency ablation compared with first-generation techniques. The cumulative incidence of hysterectomy following EA drops to 15% by 10 years in this scenario.
3. Applying a lower rate of further surgery following LASH, by assuming that all further surgery will be complete by 5 years at a cumulative incidence of 7%.
4. Applying the estimated 12-month difference in post-EA and post-LASH utility over the entire time horizon of the model with no convergence.
5. Capping convergence of the post-EA and post-LASH health state utility at 50% of the 12-month difference.
6. Applying total convergence of the post-EA and post-LASH health state utility by 5 years post surgery, but retaining a 10-year time horizon.
7. Setting long-term health state utility following total hysterectomy (or removal of the cervical stump) 0.05 units higher than post-LASH health state utility.
8. Basing model input parameters on a per-protocol analysis of HEALTH data.
9. Inclusion of repeat ablation (first-generation rollerball) in the treatment pathway following failed second-generation ablation. Under this scenario, 2.5% of the EA cohort receive repeat ablation over the first 3 years of the model.[5]
10. Inclusion of a separate pathology examination cost of £31.08 to reflect possible increased pathology costs with LASH compared with EA.[31]
11. Utilisation of time-dependent transition probabilities derived directly from the KM curve reported by Cooper *et al.*,[5] to model the incidence of hysterectomy following EA beyond month 12 in the model. In this scenario the HR for further surgery following LASH relative to EA is recalibrated to yield the 4.5% incidence at 36 months. This results in a cumulative incidence of 8% for further surgery by 10 years following LASH.
12. Utilisation of time-dependent transition probabilities derived directly from the KM curve reported by Cooper *et al.*[5] to model the incidence of hysterectomy over the entire time horizon of the model (i.e. from month 1). In this scenario the HR for further surgery following LASH relative to EA is recalibrated to yield the 4.5% incidence at 36 months. This results in a cumulative incidence of 8% for further surgery by 10 years following LASH.

The results of these scenario analyses are presented in *Table 25*. They illustrate that the ICER was most sensitive to changes in the extrapolation assumptions applied to the 12-month difference in post-EA and post-LASH health state utility (scenarios 5 to 6). When no convergence was applied in the model, the QALY gain associated with LASH increased substantially and the ICER dropped to around £5000 per

TABLE 25 Selected scenario analyses

Strategy	Cost	Incremental cost (£)	QALY	Incremental QALYs	ICER (£)	Probability cost-effective		
						£13,000	£20,000	£30,000
Base case								
EA	2089	–	6.938	–	–	0.468	0.291	0.201
LASH	3452	1362	7.049	0.111	12,314	0.532	0.709	0.799
Scenario 1: 5-year time horizon								
EA	1759	–	3.747	–	–	0.656	0.414	0.268
LASH	3205	1446	3.834	0.087	16,628	0.344	0.586	0.732
Scenario 2: lower rate of hysterectomy following EA (see *Scenario analyses*)								
EA	1979	–	6.936	–	–	0.476	0.296	0.205
LASH	3393	1414	7.050	0.114	12,429	0.524	0.704	0.795
Scenario 3: lower rate of further related surgery following LASH (see *Scenario analyses*)								
EA	2088	–	6.936	–	–	0.427	0.269	0.184
LASH	3362	1274	7.048	0.112	11,385	0.573	0.731	0.816
Scenario 4: no convergence of 12-month post-EA and post-LASH health state utility								
EA	2089	–	6.794	–	–	0.191	0.138	0.110
LASH	3451	1362	7.048	0.253	5377	0.809	0.862	0.890
Scenario 5: convergence of post-EA and post-LASH health state utility capped at 50% of the 12-month difference								
EA	2088	–	6.894	–	–	0.319	0.203	0.149
LASH	3450	1362	7.047	0.153	8907	0.681	0.797	0.851
Scenario 6: total convergence of 12-month post-EA and post-LASH health state utility by 5 years post surgery								
EA	2089	–	6.989	–	–	0.819	0.552	0.359
LASH	3452	1363	7.051	0.062	21,992	0.181	0.448	0.641
Scenario 7: long-term health state utility following total hysterectomy (or removal of the cervical stump) is 0.05 higher than it is post LASH								
EA	2088	–	6.986	–	–	0.597	0.410	0.300
LASH	3452	1364	7.072	0.086	15,864	0.403	0.590	0.700
Scenario 8: model parameters based on per-protocol analysis of HEALTH data								
EA	2093	–	6.985	–	–	0.636	0.381	0.241
LASH	3677	1584	7.084	0.099	15,927	0.364	0.619	0.759
Scenario 9: include repeat ablation (first-generation rollerball) in the treatment pathway following failed second-generation ablation								
EA	2137	–	6.934	–	–	0.433	0.273	0.187
LASH	3451	1315	7.048	0.114	11,544	0.567	0.727	0.813
Scenario 10: include the cost of additional pathology testing for LASH								
EA	2088	–	6.938	–	–	0.488	0.300	0.202
LASH	3480	1392	7.049	0.111	12,589	0.512	0.700	0.798

TABLE 25 Selected scenario analyses (*continued*)

Strategy	Cost	Incremental cost (£)	QALY	Incremental QALYs	ICER (£)	Probability cost-effective		
						£13,000	£20,000	£30,000
Scenario 11: use extracted KM data from Cooper *et al.*[5] (1–10 years) to estimate transition probabilities for hysterectomy post EA (beyond year 1)[a]								
EA	2159	–	6.961	–	–	0.533	0.327	0.217
LASH	3386	1227	7.050	0.089	13,774	0.467	0.673	0.783
Scenario 12: use extracted KM data from Cooper *et al.*[5] (0–10 years) to estimate transition probabilities for hysterectomy post EA (entire time horizon)[a]								
EA	£2364	–	6.963	–	–	0.454	0.278	0.191
LASH	3386	1022	7.048	0.085	11,991	0.546	0.722	0.809

a Model recalibrated to retain cumulative incidence of further surgery post LASH of 4.5% by 36 months.

additional QALY gained over EA (scenario 4). When complete convergence of the health state utility values was modelled to occur by 5 years, the QALY gain associated with LASH was approximately halved and the ICER increased substantially (scenario 6). The ICER also increased substantially when the model inputs were informed by a per-protocol analysis of HEALTH (scenario 8). This was primarily due to the cost increment being greater in this restricted population who received their allocated treatment as their index operation.

Discussion

The modelling exercise reported in this chapter indicates that intention to treat with LASH has the higher probability of being cost-effective in the longer term across a range of plausible values of WTP per QALY gained. The key sources of uncertainty in the model relate to the extrapolation of the observed difference in health state utility between the post-EA and post-LASH health states, and the impact that the incidence of further surgery will have on this parameter. The ICER for LASH ranged from as low as £5377, when the observed 15 months post-randomisation (12 months post surgery) utility difference was maintained over the entire time horizon of the model, to £21,992 when it was assumed to diminish to zero by 5 years post surgery. The further collection of patient-reported outcome data and the need for subsequent surgery at 3–5 years would help to reduce this uncertainty.

A strength of the modelling is its basis on randomised data from a large multicentre and pragmatic RCT. HEALTH utilised a detailed approach to costing the initial surgical episode and captured subsequent complications out to 15 months post randomisation (≈12 months post surgery). However, the censoring of patients for longer-term post-surgery health state utility is a limitation based on the trial design. Had a larger percentage of the cohort reached a minimum of 12 months post surgery by 15 months post randomisation, we may have observed a more marked difference in health state utility between the randomisation groups.

A further limitation relating to the duration of HEALTH was the need to rely on external non-randomised data to inform the expected longer-term incidence of further surgery by treatment allocation group. Although good data were available on the incidence of hysterectomy following EA, limited published data were available to inform the incidence of subsequent surgery post LASH. Therefore, conservative assumptions (favouring EA) were applied in the base-case analysis, with further surgery following LASH modelled to reach ≈11% by 10 years. This is substantially higher than the long-term incidence of further gynaecological surgery following total hysterectomy, reported to be 4% at a median duration of 11 years, based on Scottish population data.[5]

As indicated above, the 15-month post-randomisation follow-up also necessitated the application of assumptions to extrapolate observed differences in health state utility over time. Again, conservative assumptions were applied, in that the observed 15-month (post-randomisation) difference in health state utility between the post-EA and post-LASH health states was modelled to diminish to zero by 10 years. This may underestimate the QALY gain for LASH compared with EA if the observed difference in utility at 15 months were to diverge further before converging, and/or converge less quickly over time. Nevertheless, the QALY gain for LASH compared with EA remains uncertain as it accrued primarily during the extrapolation phase of the model. A further uncertainty relates to the fact that the difference in health state utility observed at 15 months post randomisation (≈12 months post surgery) was not statistically significant. This uncertainty was propagated through the model and was reflected in the probabilistic model output. Furthermore, the direction of the effect observed for the EQ-5D-3L score at 12 months was consistent with the observed significant differences in the primary clinical outcomes.

Currently, no published studies have assessed the cost-effectiveness of LASH compared with EA, but several studies have assessed the cost-effectiveness of total hysterectomy compared with EA from a UK NHS perspective. These have generally found that hysterectomy is likely to be cost-effective.[9,10,43] These previous studies utilised a similar model structure to the one described in this chapter, but made less conservative assumptions regarding the extrapolation of the estimated difference in post-EA and post-hysterectomy utility. Thus, the above-mentioned studies reported a larger QALY gain for total hysterectomy compared with EA than we report here for LASH compared with EA. Nevertheless, when applying a cost-effectiveness threshold ratio of £20,000 per QALY gained, our results indicate a relatively high probability that LASH offers a cost-effective alternative to EA for women with HMB. It may also prove a more acceptable alternative to total hysterectomy in terms of risks of AEs. If applying the more recently suggested cost-effectiveness threshold of £13,000 per QALY,[63] there is greater uncertainty surrounding the cost-effectiveness of LASH. It will therefore be important to assess the longer-term risks of subsequent surgery following LASH and to formalise comparisons with total hysterectomy through indirect treatment comparisons and decision modelling. The first of these issues will be addressed through extended follow-up of the HEALTH cohort.

In conclusion, the cost-effectiveness analysis based on HEALTH participant data indicates that LASH cannot be considered cost-effective by 15 months post randomisation (≈12 months post surgery). However, based on extrapolation over a more relevant time horizon, there is a relatively high probability that LASH offers a cost-effective alternative to EA at thresholds of WTP per QALY gained typically applied in the UK NHS (£20,000–30,000). Longer-term follow-up of HEALTH participants will be beneficial for reducing the current decision uncertainty.

Chapter 7 Discussion

Aim and overview

Heavy menstrual bleeding is a common condition that affects many women of reproductive age and significantly impairs their QoL. For those for whom medical treatment is ineffective, NICE recommends either EA or hysterectomy.[43] In comparison with EA, total hysterectomy is a more definitive procedure but is associated with higher surgical morbidity and slower postoperative recovery.[8] Two small randomised trials have suggested that a less invasive form of hysterectomy, LASH, is superior to EA but with similar morbidity and recovery.[12,13] Our large, pragmatic, randomised trial was designed to determine whether or not LASH was more effective than EA without incurring additional risks or recovery time.

Our primary clinical outcomes were satisfaction and condition-specific QoL (MMAS). Additional secondary clinical outcomes were collected along with economic end points.

Summary of findings

Primary outcomes

This large multicentre RCT showed that LASH is superior to EA in terms of the primary clinical outcomes of satisfaction and MMAS score. The levels of improvement achieved from both LASH and EA demonstrate a clear clinical benefit of both techniques, although the clinical outcomes following LASH are significantly better and are comparable with outcomes obtained following total hysterectomy.[8] The results of the health economic analyses indicate that LASH cannot be considered cost-effective compared with EA at 15 months post randomisation, but it has a 70–80% chance of being considered cost-effective at accepted cost-effectiveness thresholds (£/QALY) based on extrapolation over a 10-year time horizon.

Secondary outcomes

Both operations were associated with high rates of acceptability, but more women favoured LASH. There was a similar reduction in cyclical pain with both procedures, favouring EA at 6 weeks post surgery but LASH at 6 months post surgery and 15 months post randomisation. There was no change or difference in urinary symptoms following either procedure. Most generic QoL scores favoured the EA group at 6 weeks post surgery and LASH at 15 months post randomisation. Women who had EA were discharged more quickly and returned to work and social activities much sooner than those who had LASH. This resulted in EA imposing lower production costs on society in the short term (£990 vs. £2586).

Although the shorter recovery times following EA are to be expected, it was anticipated that the resumption of social activities and return to work following LASH would occur earlier than our data suggest. Despite making women allocated to LASH aware that there were no restrictions postoperatively, their expectations of recovery may have been coloured by more traditional views on hysterectomy and its required convalescence, as expressed by relatives, nurses and GPs. Patients are advised and know that they are entitled to up to 12 weeks off work following a hysterectomy and this information needs to be revised and based on the underlying condition, the route of procedure and other mitigating factors. It would be worth exploring this by asking patients about the factors influencing their recovery and return to activities.

Theatre time associated with EA was almost half of that for LASH. Although surgical morbidity and postoperative complications were comparable in both groups, women who had undergone EA needed less pain relief after surgery and were discharged much sooner than those treated with LASH. Improvements in immediate postoperative recovery and discharge times could probably be attained with the introduction of

an enhanced recovery programme. Fourteen women in the EA group were readmitted for hysterectomy (12 for total hysterectomy and two for LASH) within 15 months of randomisation.

The results of our predetermined subgroup analyses showed that the presence of fibroids was associated with poorer outcomes following EA than following LASH. The opportunity to make a definitive diagnosis of fibroids was greater in the LASH arm, in which visual inspection of the pelvis and uterus by laparoscopy in addition to an initial screening ultrasound allowed small fibroids not identified at baseline scan to be detected. It is likely, however, that the actual numbers with fibroids up to 3 cm were similar in both arms owing to randomisation.

Strengths and limitations of the trial

To our knowledge, this was the first large randomised trial comparing LASH with EA and the first study to undertake a cost-effectiveness analysis. The pragmatic nature of the trial and inclusion of centres across the UK has generated results that are robust, reliable and generalisable.

The main weakness of our trial was a higher loss to follow-up than anticipated. As soon as we became aware of this problem, we implemented a number of strategies, including cash incentives (an unconditional £25 gift voucher issued with the first reminder) and telephone follow-up from the trial office, which enabled us to increase our response rates from 74% to 85% for the primary outcome questionnaire.

As a surgical trial recruiting within NHS hospitals with variable waiting lists, we were unable to enforce a standard time between randomisation and surgery. In view of the NHS waiting list target of 12 weeks for routine operations, we chose to collect primary outcome data at 15 months post randomisation, believing that this would give us a 12-month duration of follow-up. Although this was appropriate for most women, a minority (10%) faced delays in receiving treatment. This occurred as a result of patient unavailability through either illness or preference, theatre staff shortages in some centres and seasonal pressures on elective hospital admission. However, these were balanced across the groups, although those allocated to LASH did have to wait slightly longer for their procedures than those allocated to EA.

A strength of the economic modelling based on randomised data from a large trial was that it enabled a detailed approach to costing of the initial surgical episode and the capture of subsequent events, including complications. However, the censoring of patients for subsequent surgery and longer-term post-surgery health state utility is a limitation, as is the need to rely on external non-randomised data to inform the longer-term risk of further surgery. Although data on the incidence of hysterectomy following EA are relatively robust, this is not currently the case for the chance of subsequent surgery post LASH.

The 15-month time horizon post randomisation also required us to make assumptions about differences in health state utility over time. Again, conservative estimates were applied, in that the observed 15-month (post-randomisation) difference in health state utility between the post-EA and post-LASH health states was modelled to diminish to zero by 10 years, which may underestimate the QALY gain for LASH compared with EA if the observed difference in utility at 15 months were to diverge further before converging, and/or converge less quickly. Future longer-term follow-up of the HEALTH cohort would help to reduce the current uncertainties in the economic model. As is most commonly practised in the UK NHS, EA procedures in HEALTH were carried out in theatre as admitted patient care, the majority (95%) under general anaesthetic. Scope may exist for cost-effectiveness to move in favour of EA if it were to prove widely acceptable to deliver in an ambulatory outpatient setting in the NHS.

To our knowledge, no published studies assess the cost-effectiveness of LASH compared with EA, but several studies[9,10,43] have assessed the cost-effectiveness of total hysterectomy compared with EA. These have generally found that hysterectomy is likely to be cost-effective from a UK NHS perspective.[9,10,43]

Interpretation in the context of available literature

At 15 months post randomisation (approximately 12 months post surgery), our results show high levels of satisfaction in both groups, which are similar to those reported in an individual participant data meta-analysis of total hysterectomy compared with EA.[8] The key difference between the two is that total hysterectomy, but not LASH, guarantees amenorrhoea. In our trial, both types of surgery resulted in high rates of patient satisfaction, but women had 2.5 times higher odds of being in a more favourable satisfaction category following LASH without any appreciable increase in surgical or postoperative risk.

Both LASH and EA resulted in significant improvements in MMAS scores from baseline that are higher than those reported in a previous trial evaluating medical treatment for HMB.[64] Women randomised to LASH had almost twice the odds of being in a more favourable MMAS score category, and a higher proportion of women (69% vs. 54%) reported the maximum score of 100.

The amenorrhoea rate of 60% achieved in the EA arm of our trial is higher than reported in previous randomised trials, in which rates of around 40% are commonly described.[65] However, those women allocated to LASH reported an amenorrhoea rate of 80%, which is lower than the 90–95% rates quoted by a Cochrane review[16] but consistent with results reported by Lieng *et al.*[17]

Women who underwent EA spent half as much time in theatre as those who underwent LASH, required significantly less postoperative analgesia and were discharged after a median of 3 hours post procedure (compared with 22 hours following LASH). Surgical morbidity and postoperative complications were comparable in both groups.

Fourteen women in the EA arm were readmitted for hysterectomy within 15 months after randomisation. Long-term hysterectomy rates of almost 20% following EA are described in population studies.[5,49] Rates for further surgery after LASH in the longer run are less well known as follow-up of only 3 years has been reported and rates are quoted as 7% at this point.[17] An English population-based study showed that 10% of women aged > 45 years have further surgery 5 years following EA, compared with about one-third of women aged < 35 years.[46] We found no such association with age in this trial. There were poorer outcomes following EA in women with fibroids, although more fibroids were diagnosed in the LASH arm because of laparoscopy. There was no association with cavity length, which is at odds with a meta-analysis of trials on second-generation EA, which found that a uterine cavity length of > 8 cm had an adverse impact on patient satisfaction.[8]

A Cochrane review of total versus subtotal hysterectomy suggests a cyclical bleeding rate of 5–10% following LASH,[16] whereas a higher rate of 23% was reported by Lieng *et al.*[17] Despite a standardised procedure of cervical canal cautery after removal of the body of the uterus, the observed rate of cyclical bleeding in the LASH group was 19%. This is in some way explained by the fact that, of 330 women allocated to the LASH group, 21 women had no treatment and 11 women had EA. Even so, it seems that our rates of post-LASH cyclical bleeding lie between those quoted by the Cochrane database[16] and the longer-term rates quoted by Lieng *et al.*[17]

The potential risk of malignancy is always an important consideration in planning conservative surgical treatments for HMB. In EA, in which the uterus, tubes and ovaries are conserved, an endometrial biopsy is undertaken before surgery to exclude endometrial atypia. As the cervix is retained in both techniques, ongoing cervical screening is required in all women. The risk of cervical stump carcinoma in women with a previously normal Pap smear is no more than 0.3%[66] and is not considered to be a justification for total over subtotal hysterectomy in countries with cervical screening programmes,[16] especially where immunisation against human papillomavirus (HPV) virus is the norm.

At the time when this trial was launched, concerns were raised by the US Food and Drug Administration about the potential risk of disseminating cells from undiagnosed uterine malignancy associated with the use

of morcellators during laparoscopic hysterectomy in women with fibroids.[67] This prompted us to modify our eligibility criteria to exclude women with fibroids measuring > 3 cm, as the risk of malignancy is associated with fibroid size. The results from our trial are reassuring, as specimens from the 308 women who underwent hysterectomy have not shown any evidence of histological atypia or malignancy. The initial estimate of risk of 1 in 350 for unexpected/unknown malignancy within a presumed fibroid by the Food and Drug Administration has been revised, and a recent review puts this risk figure closer to 1 in 2000.[68] Updated estimates of leiomyosarcoma (LMS) rates at hysterectomy have been published, and show that women aged > 50 years with larger presumed fibroids are at particular risk. These are exclusion criteria for participation in HEALTH.[69] Although we have been reassured by the absence of any histological abnormalities in this trial, continued vigilance is required, and morcellation avoided and total hysterectomy performed if there are concerns of possible sarcomatous change within a fibroid based on morphological appearance or rapid growth. Dissemination of morcellated material can be avoided by using containment bags, although these have not been formally assessed. An alternative is to remove unmorcellated specimens in a bag through a culdotomy, but this may be associated with different morbidities and also needs to be assessed. It must be remembered that if a woman with unknown LMS has conservative treatment of her HMB, such as EA, she continues with an unknown and untreated LMS. It is worth noting that the routine removal of fallopian tubes during LASH could halve the subsequent risk of epithelial ovarian cancer,[70] without any increase in surgical risk.

Conclusions

Laparoscopic supracervical hysterectomy is superior to EA in terms of clinical effectiveness. EA is quicker, cheaper and associated with an earlier discharge and shorter recovery than LASH. It is less costly in the short term, but its higher failure rate means that LASH is more likely to be considered more cost-effective than EA by 10 years post procedure.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Additional information for baseline results

TABLE 26 Participating centres

Centre recruiting	LASH (*N* = 330), *n*	EA (*N* = 330), *n*	Total (*N*)
Aberdeen	77	75	152
Birmingham	39	37	76
Glasgow	23	22	45
South Tees	22	20	42
Chester	16	17	33
Forth Valley	15	16	31
Hull	14	15	29
Poole	14	14	28
North Tees	12	12	24
Cornwall	11	10	21
Northampton	9	9	18
Kilmarnock	8	9	17
Basildon	8	8	16
Winchester	7	7	14
Newcastle	6	6	12
Basingstoke	6	5	11
Sunderland	5	6	11
Edinburgh	4	5	9
Southampton	4	5	9
Preston	4	4	8
Whipps Cross	4	4	8
Surrey	3	4	7
Durham	3	4	7
Fife	4	3	7
Wirral	3	4	7
Kent	2	3	5
Plymouth	2	2	4
Worcester	2	2	4
Stockport	1	2	3
Sheffield	1	0	1
Worthing	1	0	1

TABLE 27 Approached participants

Participant status	*n* (%)
Screened	2552 (100.0)
• Randomised	664 (26.0)
• Not included	1888 (74.0)
Ineligible	1201 (47.1)
Patient declined	589 (23.1)
Clinical preference	98 (3.8)

TABLE 28 Reasons for non-inclusion

Reason	*n* (%)
Ineligible	1201 (100.0)
Fibroids > 3cm	361 (30.1)
Preference to continue with medical management	244 (20.3)
Aged ≥ 50 years	239 (19.9)
Previous EA	145 (12.1)
Plans to conceive	128 (10.7)
Contraindications for laparoscopic surgery	44 (3.7)
Uterine cavity > 11cm	12 (1.0)
Unable to understand or complete study documentation	12 (1.0)
Abnormal cytology	10 (0.8)
Endometrial atypia	6 (0.5)
Eligible but patient declined randomisation/participation	589 (100.0)
Preference: EA	151 (25.6)
Preference: hysterectomy	126 (21.4)
No reason given	98 (16.6)
Preference: medical management	89 (15.1)
Patient did not want to be randomised	54 (9.2)
Unable to make contact with patient	25 (4.2)
Preference: unknown	18 (3.1)
Patient did not want to participate in research	10 (1.7)
Preference: no treatment	8 (1.4)
Personal reason	8 (1.4)
Other	2 (0.3)
Eligible but not recruited due to clinical preference/decision	98 (100)
Clinical decision	39 (39.8)
Planned hysterectomy	25 (25.5)
Planned EA	18 (18.4)
Other treatment planned	16 (16.3)

TABLE 29 Additional participant-reported outcomes at baseline

Outcome	LASH (*N* = 330), *n* (%)	EA (*N* = 330), *n* (%)
Pain at intercourse?		
No	106 (35.5)	120 (39.2)
Rarely	90 (30.1)	69 (22.5)
Often	81 (27.1)	87 (28.4)
Always	22 (7.4)	30 (9.8)
Not applicable	26	20
Severity of pain at intercourse		
Mild	78 (41.5)	81 (42.0)
Moderate	76 (40.4)	85 (44.0)
Severe	34 (18.1)	27 (14.0)
Do you have problems with your bladder?		
No	135 (41.8)	147 (45.2)
Yes, I need to dash to the toilet (urgency), but don't leak	43 (13.3)	58 (17.8)
Yes, I need to dash to the toilet (urgency), but often don't make it and leak	26 (8.0)	24 (7.4)
Yes, I regularly leak when I cough, sneeze or exercise	69 (21.4)	64 (19.7)
Yes, both. I have urgency and I also leak when I cough, sneeze or exercise	50 (15.5)	32 (9.8)

Appendix 2 Additional information for clinical results

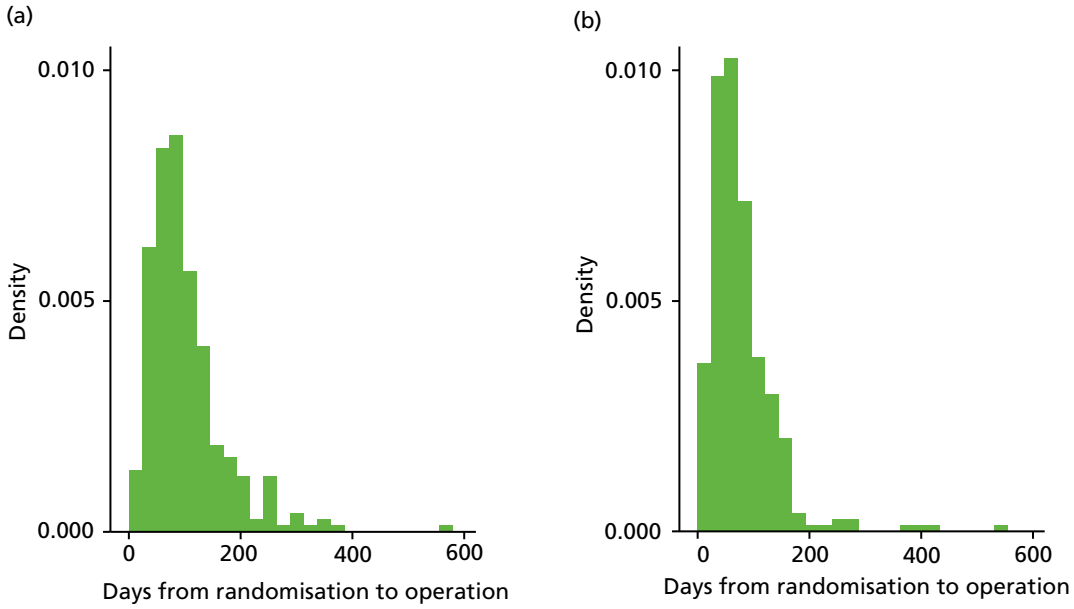

FIGURE 16 Days from randomisation to operation by randomised group: (a) LASH; and (b) EA.

TABLE 30 Results for satisfaction at 15 months post randomisation (LASH vs. EA) by analysis approach

Analysis approach		Effect size (95% CI)	*p*-value
OLR (primary analysis, adjusted)	**OR**	**2.53 (1.83 to 3.28)**	**< 0.001**
OLR (unadjusted)	OR	2.55 (1.79 to 3.63)	< 0.001
Binary logistic regression (totally satisfied vs. other, adjusted)	OR	2.40 (1.77 to 3.26)	< 0.001
	RD	0.19 (0.13 to 0.25)	
Binary logistic regression (totally/generally satisfied vs. other, adjusted)	OR	2.78 (1.50 to 5.13)	0.001
	RD	0.13 (0.07 to 0.20)	
Binary logistic regression (satisfied vs. dissatisfied, adjusted)	OR	4.89 (1.91 to 12.45)	0.001
	RD	0.10 (0.05 to 0.15)	
OLR (multiple imputation, adjusted)	OR	2.15 (1.53 to 3.02)	< 0.001
OLR (by actual treatment received, adjusted)	OR	2.60 (1.91 to 3.55)	< 0.001
OLR (including only those operated on by consultant, adjusted)	OR	2.52 (1.74 to 3.66)	< 0.001

RD, risk difference.
Notes
Adjusted: adjusted for age category and centre (random effect).
ORs > 1 favour LASH.
The primary analysis approach is highlighted in bold.

TABLE 31 Menorrhagia Multi-Attribute Quality-of-Life Scale items by randomised group at baseline, 6 months post surgery and 15 months post randomisation

Outcome	Item response	Baseline		6 months post surgery		15 months post randomisation	
		LASH ($n = 330$), *n* (%)	EA ($n = 330$), *n* (%)	LASH ($n = 309$), *n* (%)	EA ($n = 307$), *n* (%)	LASH ($n = 330$), *n* (%)	EA ($n = 330$), *n* (%)
Practical difficulties	1	4 (1.2)	5 (1.5)	222 (93.7)	194 (84.0)	247 (91.1)	226 (81.9)
	2	70 (21.5)	65 (19.9)	5 (2.1)	14 (6.1)	11 (4.1)	30 (10.9)
	3	109 (33.5)	97 (29.7)	3 (1.3)	14 (6.1)	6 (2.2)	9 (3.3)
	4	142 (43.7)	160 (48.9)	7 (3.0)	9 (3.9)	7 (2.6)	11 (4.0)
	NK	2	1	16	13	9	9
Social life	1	12 (3.7)	12 (3.7)	215 (90.3)	186 (80.2)	249 (92.2)	215 (77.1)
	2	93 (28.6)	95 (29.1)	13 (5.5)	30 (12.9)	13 (4.8)	37 (13.3)
	3	141 (43.4)	144 (44.0)	7 (2.9)	8 (3.4)	5 (1.9)	22 (7.9)
	4	79 (24.3)	76 (23.2)	3 (1.3)	8 (3.4)	3 (1.1)	5 (1.8)
	NK	2	1	16	12	10	6
Psychological health	1	13 (4.0)	24 (7.3)	187 (78.9)	166 (71.6)	207 (76.4)	192 (69.6)
	2	128 (39.4)	124 (37.9)	37 (15.6)	48 (20.7)	48 (17.7)	50 (18.1)
	3	120 (36.9)	123 (37.6)	9 (3.8)	12 (5.2)	10 (3.7)	26 (9.4)
	4	64 (19.7)	56 (17.1)	4 (1.7)	6 (2.6)	6 (2.2)	8 (2.9)
	NK	2	1	17	12	9	9
Physical health and well-being	1	6 (1.8)	9 (2.8)	176 (73.9)	155 (66.8)	210 (77.8)	176 (64.0)
	2	36 (11.1)	51 (15.6)	34 (14.3)	39 (16.8)	36 (13.3)	44 (16.0)
	3	190 (58.5)	175 (53.7)	23 (9.7)	32 (13.8)	19 (7.0)	49 (17.8)
	4	93 (28.6)	91 (27.9)	5 (2.1)	6 (2.6)	5 (1.9)	6 (2.2)
	NK	2	2	16	12	10	10
Work/daily routine	1	17 (5.2)	13 (4.0)	207 (87.7)	175 (76.1)	233 (86.0)	210 (75.8)
	2	83 (25.5)	91 (28.2)	21 (8.9)	36 (15.7)	27 (10.0)	42 (15.2)
	3	146 (44.9)	134 (41.5)	4 (1.7)	12 (5.2)	7 (2.6)	20 (7.2)
	4	79 (24.3)	85 (26.3)	4 (1.7)	7 (3.0)	4 (1.5)	5 (1.8)
	NK	2	5	18	14	9	8
Family life/ relationships	1	17 (5.2)	30 (9.2)	190 (80.2)	158 (67.8)	221 (81.5)	200 (72.2)
	2	106 (32.4)	111 (34.0)	40 (16.9)	55 (23.6)	38 (14.0)	54 (19.5)
	3	131 (40.1)	121 (37.1)	7 (3.0)	16 (6.9)	7 (2.6)	20 (7.2)
	4	73 (22.3)	64 (19.6)	0	4 (1.7)	5 (1.8)	3 (1.1)
	NK	0	2	17	11	9	8

NK, not known.

Note

For each item, 1 represents the best outcome and 4 the worst; response category labels vary by item.

TABLE 32 Results for MMAS total score at 15 months post randomisation (LASH vs. EA)

Analysis approach (MMAS split)		Effect size (95% CI)	*p*-value
OLR (primary analysis, adjusted)	**OR**	**1.87 (1.31 to 2.67)**	**0.001**
OLR (unadjusted)	OR	1.90 (1.35 to 2.68)	< 0.001
Binary logistic regression (0–49.9 vs. 50–100, adjusted)	OR	1.84 (1.04 to 3.25)	0.04
	RD	0.04 (0.00 to 0.08)	
Binary logistic regression (0–74.9 satisfied vs. 75–100, adjusted)	OR	2.10 (1.35 to 3.27)	0.001
	RD	0.10 (0.04 to 0.16)	
Binary logistic regression (0–99.9 vs. 100, adjusted)	OR	1.79 (1.18 to 2.70)	0.006
	RD	0.13 (0.04 to 0.29)	
OLR (multiple imputation, adjusted)	OR	1.68 (1.16 to 2.45)	0.007
OLR (by actual treatment received, adjusted)	OR	1.96 (1.40 to 2.77)	0.001
OLR (including only those operated on by consultant, adjusted)	OR	2.19 (1.33 to 3.62)	0.002
Linear regression analysis treating MMAS as continuous (adjusted)	MD	5.59 (1.93 to 9.25)	0.004

MD, mean difference; RD, risk difference.

Notes

Adjusted: adjusted for age category, centre (random effect) and baseline MMAS (continuous).

ORs > 1, RDs < 1 and MDs > 0 favour LASH.

The primary analysis approach is highlighted in bold.

TABLE 33 Subgroup analyses

		Satisfaction at 15 months post randomisation		MMAS at 15 months post randomisation	
Category	Studied category	Adjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Cavity length	≥ 8 cm	0.55 (0.25 to 1.22)	0.14	0.85 (0.52 to 3.28)	0.57
Menstrual pain at baseline	Severe/crippling pain	1.44 (0.72 to 2.89)	0.31	1.15 (0.61 to 2.20)	0.66
Age (years)	≥ 40	1.59 (0.77 to 3.29)	0.21	1.35 (0.68 to 2.68)	0.39
Fibroids	Present	7.27 (2.32 to 41.8)	0.002	1.26 (0.39 to 4.10)	0.70

Notes

The table shows interaction terms (ORs and their 95% CIs) from two OLR models including interactions between the treatment group and four binary variables. ORs represent the additional effect of being in both the LASH group and in the studied category. Models are also adjusted for centre and baseline scores (if applicable).

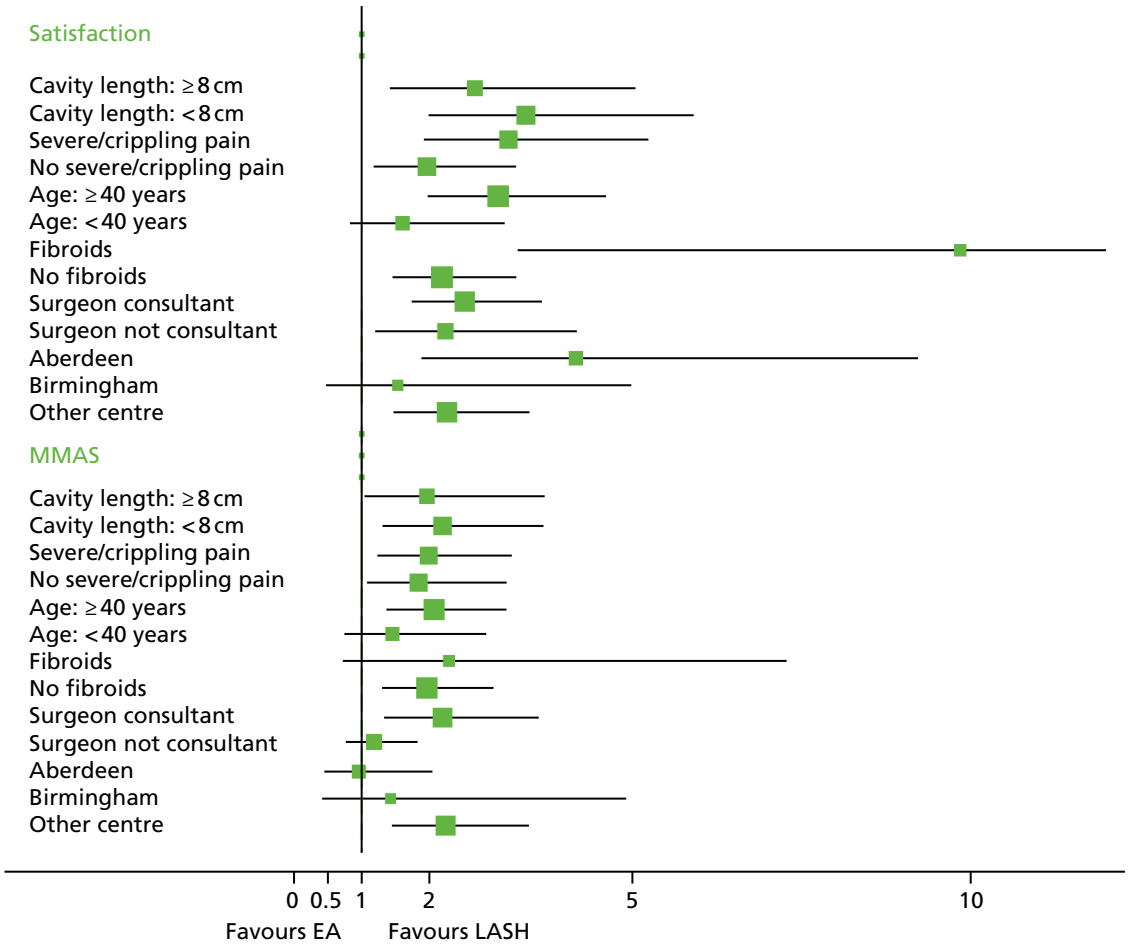

FIGURE 17 Odds ratios (95% CI) from OLR models by subgroup. For the two co-primary outcomes (satisfaction and MMAS at 15 months post randomisation) the horizontal lines show ORs and 95% CIs from eight OLR models, including particular subgroups of participants and adjusting for age and baseline score (if appropriate). The size of the square is proportional to the number of women in each subgroup. The result for fibroids for the satisfaction outcome (OR 9.85, 95% CI 3.30 to 29.34) has been truncated because of space considerations.

TABLE 34 Patient diary (1–14 days post surgery)

Outcome	LASH (*N* = 309)	EA (*N* = 307)
Level of pain today (0 = no pain, 10 = worst imaginable), mean (SD) [*n*]		
Day 1	6.08 (2.35) [265]	5.13 (2.60) [257]
Day 2	5.66 (2.32) [265]	4.35 (2.61) [254]
Day 3	4.89 (2.34) [264]	3.78 (2.67) [251]
Day 4	4.33 (2.36) [263]	3.29 (2.62) [250]
Day 5	3.81 (2.34) [264]	2.97 (2.55) [251]
Day 6	3.44 (2.30) [265]	2.47 (2.41) [250]
Day 7	3.19 (2.37) [262]	2.09 (2.34) [248]
Day 8	2.89 (2.23) [259]	1.92 (2.39) [249]
Day 9	2.63 (2.22) [256]	1.72 (2.31) [245]
Day 10	2.32 (2.20) [254]	1.59 (2.26) [244]
Day 11	2.18 (2.08) [257]	1.52 (2.22) [240]

TABLE 34 Patient diary (1–14 days post surgery) (*continued*)

Outcome	LASH (*N* = 309)	EA (*N* = 307)
Day 12	1.99 (1.98) [257]	1.31 (2.07) [245]
Day 13	1.88 (1.94) [255]	1.28 (2.12) [243]
Day 14	1.69 (1.94) [256]	1.19 (2.05) [243]
Used pads for vaginal bleeding or discharge?, *n* (%)		
Day 1	182 (68.2)	238 (91.9)
Day 2	134 (50.2)	227 (87.6)
Day 3	80 (30.0)	206 (79.8)
Day 4	54 (20.2)	197 (77.0)
Day 5	43 (16.2)	200 (78.1)
Day 6	29 (10.9)	205 (79.5)
Day 7	36 (13.5)	200 (77.8)
Day 8	33 (12.5)	193 (75.1)
Day 9	34 (12.8)	190 (73.9)
Day 10	34 (12.9)	184 (71.9)
Day 11	33 (12.5)	181 (71.0)
Day 12	29 (10.9)	178 (69.0)
Day 13	34 (12.8)	177 (68.9)
Day 14	34 (12.7)	177 (69.1)
Took paracetamol?, *n* (%)		
Day 1	223 (94.5)	166 (86.5)
Day 2	213 (94.7)	147 (84.0)
Day 3	195 (91.6)	128 (81.5)
Day 4	180 (89.1)	107 (74.8)
Day 5	164 (89.6)	104 (73.8)
Day 6	145 (84.8)	77 (70.6)
Day 7	138 (83.6)	69 (65.7)
Day 8	127 (80.4)	54 (57.4)
Day 9	112 (78.3)	48 (54.5)
Day 10	103 (74.6)	42 (53.8)
Day 11	92 (72.4)	40 (51.3)
Day 12	86 (68.8)	30 (44.8)
Day 13	77 (67.0)	38 (49.4)
Day 14	67 (62.0)	40 (50.6)
Took other painkillers?, *n* (%)		
Day 1	256 (95.9)	234 (90.7)
Day 2	253 (95.1)	208 (81.3)
Day 3	235 (88.7)	174 (69.3)

continued

TABLE 34 Patient diary (1–14 days post surgery) (*continued*)

Outcome	LASH (*N* = 309)	EA (*N* = 307)
Day 4	220 (84.0)	147 (59.3)
Day 5	195 (75.3)	138 (56.3)
Day 6	180 (67.9)	109 (44.1)
Day 7	164 (64.3)	97 (39.6)
Day 8	159 (61.2)	84 (34.1)
Day 9	139 (54.1)	82 (34.0)
Day 10	127 (49.2)	68 (27.9)
Day 11	119 (46.5)	63 (26.4)
Day 12	111 (43.0)	51 (20.7)
Day 13	102 (39.2)	56 (23.3)
Day 14	88 (34.0)	61 (25.2)

TABLE 35 Menstrual outcomes at baseline, 6 months post surgery and 15 months post randomisation

	Baseline		6 months after surgery		15 months after randomisation	
Outcome	LASH (*N* = 330)	EA (*N* = 330)	LASH (*N* = 309)	EA (*N* = 307)	LASH (*N* = 330)	EA (*N* = 330)
Are you still having periods?, *n* (%)						
Yes	nc	nc	39 (15.4)	111 (45.7)	52 (18.8)	117 (42.1)
No	nc	nc	214 (84.6)	132 (54.3)	225 (81.2)	161 (57.9)
Description of period, *n* (%)						
Light	2 (0.6)	0	27 (73.0)	56 (49.6)	35 (76.1)	56 (54.4)
Moderate	6 (1.8)	7 (2.1)	7 (18.9)	29 (25.7)	5 (10.9)	27 (26.2)
Heavy with clots	58 (17.7)	61 (18.7)	3 (8.1)	19 (16.8)	3 (6.5)	17 (16.5)
Very heavy with clots and flooding	261 (79.8)	259 (79.2)	0	9 (8.0)	3 (6.5)	3 (2.9)
On average for how many days is the bleeding heavy?, *n* (%)						
Not heavy	3 (0.9)	2 (0.6)	25 (67.6)	54 (47.8)	26 (57.8)	56 (54.9)
1–3 days	50 (15.3)	51 (15.6)	9 (24.3)	32 (28.3)	9 (20.0)	28 (27.5)
4–6 days	118 (36.1)	125 (38.2)	2 (5.4)	23 (20.4)	8 (17.8)	13 (12.7)
≥ 7 days	156 (47.7)	149 (45.6)	1 (2.7)	4 (3.5)	2 (4.4)	5 (4.9)
At any time in the last 3 months have you needed to use more than one form of sanitary protection at a time?, *n* (%)						
No	27 (8.3)	25 (7.7)	15 (39.5)	30 (27.0)	19 (40.4)	25 (23.8)
Tampon and pad	117 (35.9)	118 (36.3)	15 (39.5)	29 (26.1)	14 (29.8)	32 (30.5)
Two pads	88 (27.0)	84 (25.8)	6 (15.8)	35 (31.5)	9 (19.1)	25 (23.8)
Tampon and two pads	48 (14.7)	56 (17.2)	2 (5.3)	17 (15.3)	5 (10.6)	23 (21.9)
More than this (e.g. bath towel)	46 (14.1)	42 (12.9)	0	0	0	0

TABLE 35 Menstrual outcomes at baseline, 6 months post surgery and 15 months post randomisation (*continued*)

Outcome	Baseline		6 months after surgery		15 months after randomisation	
	LASH (*N* = 330)	EA (*N* = 330)	LASH (*N* = 309)	EA (*N* = 307)	LASH (*N* = 330)	EA (*N* = 330)
Are your periods usually painful?, *n* (%)						
No	19 (5.8)	18 (5.5)	42 (97.7)	89 (70.2)	41 (85.4)	88 (82.2)
Mild pain	33 (10.1)	38 (11.7)	1 (2.3)	20 (17.5)	2 (4.2)	11 (10.3)
Moderate pain	104 (31.9)	110 (33.7)	0	11 (9.6)	5 (10.4)	6 (5.6)
Severe/crippling pain	170 (52.1)	160 (49.1)	0	3 (2.6)	0	2 (1.9)
Bleeding score [0 = none (baseline only), 1 = mild, 5 = worst imaginable], median (IQR) [*n*]	3.67 (3.1–4.2) [322]	3.5 (3.1–4.1) [322]	1 (1–1.7) [34]	1.75 (1–2.6) [107]	1.25 (1–2.25) [37]	1.67 (1–2.35) [92]
Are you having cyclical (period like) pain?, *n* (%)						
Yes	nc	nc	68 (28.8)	108 (54.3)	71 (31.7)	118 (60.2)
No	nc	nc	168 (71.2)	91 (45.7)	153 (68.3)	78 (39.8)
Cyclical pain score (1 = mild, 5 = worst imaginable), median (IQR) [*n*]	nc	nc	1.5 (1–2.3) [58]	2 (1.4–2.8) [107]	1.33 (1–2.3) [62]	2 (1.33–3) [113]
Pain at intercourse?, *n* (%)						
No	106 (35.5)	120 (39.2)	153 (71.5)	141 (65.6)	151 (70.9)	124 (60.8)
Rarely	90 (30.1)	69 (22.5)	40 (18.7)	38 (17.7)	42 (19.7)	44 (21.6)
Often	81 (27.1)	87 (28.4)	17 (7.9)	29 (13.5)	18 (8.5)	27 (13.2)
Always	22 (7.4)	30 (9.8)	4 (1.9)	7 (3.3)	2 (0.9)	9 (4.4)
Not applicable	26	20	29	20	21	20
Severity of pain at intercourse, *n* (%)						
Mild	78 (41.5)	81 (42.0)	44 (63.8)	42 (51.9)	39 (65.0)	46 (59.7)
Moderate	76 (40.4)	85 (44.0)	22 (31.9)	33 (40.7)	18 (30.0)	26 (33.8)
Severe	34 (18.1)	27 (14.0)	3 (4.3)	6 (7.4)	3 (5.0)	5 (6.5)
Do you have problems with your bladder?, *n* (%)						
No	135 (41.8)	147 (45.2)	125 (50.4)	123 (51.3)	116 (50.0)	110 (49.3)
Yes, I need to dash to the toilet (urgency), but don't leak	43 (13.3)	58 (17.8)	29 (11.7)	30 (12.5)	21 (9.1)	21 (9.4)
Yes, I need to dash to the toilet (urgency), but often don't make it and leak	26 (8.0)	24 (7.4)	24 (9.7)	24 (10.0)	18 (7.8)	22 (9.9)
Yes, I regularly leak when I cough, sneeze or exercise	69 (21.4)	64 (19.7)	46 (18.6)	50 (20.8)	45 (19.4)	48 (21.5)
Yes, both. I have urgency and I also leak when I cough, sneeze or exercise	50 (15.5)	32 (9.8)	24 (9.7)	13 (5.4)	32 (13.8)	22 (9.9)

nc, not collected.

TABLE 36 Menstrual outcomes at 15 months post randomisation by actual treatment received (per-protocol analysis)

Outcome	LASH (*N* = 297), *n* (%)	EA (*N* = 303), *n* (%)
Are you still having periods?		
Yes	41 (16.1)	106 (40.3)
No	213 (83.9)	157 (59.7)
Description of period		
Light	33 (80.5)	58 (58.6)
Moderate	4 (9.8)	24 (24.2)
Heavy with clots	2 (4.9)	14 (14.1)
Very heavy with clots and flooding	2 (4.9)	3 (3.0)
On average for how many days is the bleeding heavy?		
Not heavy	25 (64.1)	55 (56.1)
1–3 days	8 (20.5)	26 (26.5)
4–6 days	4 (10.3)	12 (12.2)
≥ 7 days	2 (5.1)	5 (5.1)
At any time in the last 3 months have you needed to use more than one form of sanitary protection at a time?		
No	17 (41.5)	26 (26.0)
Tampon and pad	14 (34.1)	31 (31.0)
Two pads	6 (14.6)	23 (23.0)
Tampon and two pads	4 (9.8)	20 (20.0)
More than this (e.g. bath towel)	0	0
Are your periods usually painful?		
No	38 (90.5)	85 (82.5)
Mild pain	2 (4.8)	11 (10.7)
Moderate pain	2 (4.8)	5 (4.9)
Severe/crippling pain	0	2 (1.9)

TABLE 37 Quality-of-life outcomes reported using categories used in the OLR models

Outcome	LASH (*N* = 330), *n* (%)[a]	EA (*N* = 330), *n* (%)[b]	OR (95% CI)	*p*-value
MMAS total score (baseline)				
0–50	274 (84.8)	256 (79.8)		
51–75	42 (13.0)	59 (18.4)		
76–99	7 (2.2)	6 (1.9)		
100	0	0		
MMAS total score (6 months)			1.48 (1.02 to 2.14)[c]	0.04
0–50	9 (3.9)	19 (8.5)		
51–75	20 (8.7)	32 (14.3)		
76–99	46 (20.0)	38 (17.0)		
100	155 (67.4)	135 (60.3)		
MMAS total score (15 months)			**1.87 (1.31 to 2.67)[c]**	**0.001**
0–50	15 (5.7)	29 (10.8)		
51–75	17 (6.5)	34 (12.7)		

TABLE 37 Quality-of-life outcomes reported using categories used in the OLR models (*continued*)

Outcome	LASH ($N = 330$), n (%)[a]	EA ($N = 330$), n (%)[b]	OR (95% CI)	p-value
76–99	50 (19.1)	59 (22.0)		
100	180 (68.7)	146 (54.5)		
EQ-5D-3L utility score (baseline)				
–0.59 to 0.49	56 (17.6)	63 (19.6)		
0.5–0.99	176 (55.2)	170 (52.8)		
1	87 (27.3)	89 (27.6)		
EQ-5D-3L utility score (6 weeks)			0.66 (0.48 to 0.90)[d]	0.009
–0.59 to 0.49	14 (5.6)	23 (9.3)		
0.5–0.99	129 (51.4)	88 (35.8)		
1	108 (43.0)	135 (54.9)		
EQ-5D-3L utility score (6 months)			1.15 (0.84 to 1.57)	0.38
–0.59 to 0.49	27 (10.8)	20 (8.4)		
0.5–0.99	87 (34.7)	102 (43.0)		
1	137 (54.6)	115 (48.5)		
EQ-5D-3L utility score (15 months)			1.21 (0.89 to 1.64)	0.23
–0.59 to 0.49	23 (8.2)	33 (11.7)		
0.5–0.99	115 (40.9)	115 (40.9)		
1	143 (50.9)	133 (47.3)		
EQ-5D-3L VAS (baseline)				
0–50	101 (31.9)	79 (24.6)		
51–75	96 (30.3)	105 (32.7)		
76–100	120 (37.9)	137 (42.7)		
EQ-5D-3L VAS (6 weeks)			1.12 (0.80 to 1.58)	0.51
0–50	26 (10.5)	35 (14.3)		
51–75	54 (21.8)	51 (20.8)		
76–100	168 (67.7)	159 (64.9)		
EQ-5D-3L VAS (6 months)			1.53 (1.08 to 2.17)[c]	0.02
0–50	26 (10.6)	29 (12.3)		
51–75	47 (19.1)	66 (28.1)		
76–100	173 (70.3)	140 (59.6)		
EQ-5D-3L VAS (15 months)			1.50 (1.12 to 1.99)[c]	0.006
0–50	29 (10.4)	46 (16.3)		
51–75	51 (18.3)	57 (20.2)		
76–100	199 (71.3)	179 (63.5)		

a Maximum $n = 330$ for baseline, 15 months; maximum $n = 309$ for 6 weeks, 6 months.
b Maximum $n = 330$ for baseline, 15 months; maximum $n = 307$ for 6 weeks, 6 months.
c Favours LASH ($p < 0.05$).
d Favours EA ($p < 0.05$).

Notes
MMAS total score: 0 represents worst possible health and 100 represents best possible health.
EQ-5D-3L utility score: –0.59 represents worst possible QoL and 1 represents best possible QoL.
EQ-5D-3L VAS: 0 represents worst imaginable health state and 100 represents best possible health state.
SF-12 PCS and MCS: 0 represents worst possible QoL and 100 represents best possible QoL.
Analyses used OLR, adjusting for age group, centre and baseline score (if applicable).
Co-primary outcomes are highlighted in bold.

TABLE 38 Summary of adjusted and unadjusted effect sizes (LASH vs. EA)

Outcome	Analysis method (effect size)	Adjusted effect size (95% CI)	*p*-value	Unadjusted effect size (95% CI)	*p*-value
AE					
Any SAE	Log Reg (OR, RD)	1.30 (0.56 to 3.02), 0.01 (–0.02 to 0.04)	0.54	1.28 (0.57 to 2.87), 0.01 (–0.02 to 0.04)	0.54
Further treatment for HMB	Log Reg (OR, RD)	0.11 (0.04 to 0.28),[a] –0.05 (–0.07 to –0.02)	< 0.001	0.11 (0.02 to 0.46), –0.05 (–0.07 to –0.02)	0.003
Pain					
Pain (0–10) (patient diary, 1–14 days)	RM (MD)	0.92 (0.59 to 1.24)[b]	< 0.001	0.91 (0.58 to 1.23)[b]	< 0.001
Level of pain (0–10) (6 weeks)	OLR (OR)	1.43 (1.05 to 1.96)[b]	0.03	1.40 (0.96 to 2.05)	0.08
Time-to-event outcome					
Time to return to paid work (6 weeks)	Cox Reg (HR)	0.23 (0.18 to 0.30)[b]	< 0.001	0.24 (0.18 to 0.30)[b]	< 0.001
Time to return to unpaid work (6 weeks)	Cox Reg (HR)	0.64 (0.57 to 0.73)[b]	< 0.001	0.65 (0.54 to 0.78)[b]	< 0.001
Time to return to sporting or social activities (6 weeks)	Cox Reg (HR)	0.48 (0.42 to 0.56)[b]	< 0.001	0.49 (0.40 to 0.59)[b]	< 0.001
Menstrual outcome					
Are you still having periods? (6 months)	Log Reg (OR, RD)	0.22 (0.15 to 0.32),[a] –0.30 (–0.37 to –0.22)	< 0.001	0.22 (0.14 to 0.33),[a] –0.30 (–0.38 to –0.23)	< 0.001
Are you still having periods? (15 months PR)	Log Reg (OR, RD)	0.32 (0.21 to 0.48),[a] –0.23 (–0.31 to –0.15)	< 0.001	0.32 (0.22 to 0.47),[a] –0.23 (–0.31 to –0.16)	< 0.001
QoL outcome					
MMAS (6 months)	OLR (OR)	1.48 (1.02 to 2.14)[a]	0.04	1.49 (1.03 to 2.17)[a]	0.04
MMAS (15 months post randomisation)	**OLR (OR)**	**1.87 (1.31 to 2.67)[a]**	**0.001**	**1.90 (1.35 to 2.68)[a]**	**< 0.001**
EQ-5D-3L utility score (6 weeks)	OLR (OR)	0.66 (0.48 to 0.90)[b]	0.009	0.71 (0.50 to 1.00)	0.05
EQ-5D-3L utility score (6 months)	OLR (OR)	1.15 (0.84 to 1.57)	0.38	1.18 (0.83 to 1.66)	0.35
EQ-5D-3L utility score (15 months post randomisation)	OLR (OR)	1.21 (0.89 to 1.64)	0.23	1.20 (0.88 to 1.65)	0.25
EQ-5D-3L VAS (6 weeks)	OLR (OR)	1.12 (0.80 to 1.58)	0.51	1.18 (0.82 to 1.70)	0.39
EQ-5D-3L VAS (6 months)	OLR (OR)	1.53 (1.08 to 2.17)[a]	0.02	1.54 (1.06 to 2.23)[a]	0.02
EQ-5D-3L VAS (15 months post randomisation)	OLR (OR)	1.50 (1.12 to 1.99)[a]	0.006	1.47 (1.04 to 2.08)[a]	0.03
SF-12 PCS (6 weeks)	Lin Reg (MD)	–4.97 (–6.31 to –3.63)[b]	< 0.001	–4.58 (–6.34 to –2.81)[b]	< 0.001
SF-12 PCS (6 months)	Lin Reg (MD)	0.83 (–0.70 to 2.35)	0.28	0.83 (–0.87 to 2.53)	0.34
SF-12 PCS (15 months post randomisation)	Lin Reg (MD)	1.08 (–0.65 to 2.81)	0.21	1.16 (–0.53 to 2.85)	0.18
SF-12 MCS (6 weeks)	Lin Reg (MD)	1.33 (–0.78 to 3.44)	0.21	1.10 (–0.94 to 3.15)	0.29
SF-12 MCS (6 months)	Lin Reg (MD)	3.36 (1.69 to 5.03)[a]	< 0.001	2.75 (0.52 to 4.98)[a]	0.02
SF-12 MCS (15 months post randomisation)	Lin Reg (MD)	2.47 (1.07 to 3.87)[a]	0.001	1.83 (–0.27 to 3.93)	0.09

TABLE 38 Summary of adjusted and unadjusted effect sizes (LASH vs. EA) (*continued*)

Outcome	Analysis method (effect size)	Adjusted effect size (95% CI)	*p*-value	Unadjusted effect size (95% CI)	*p*-value
Satisfaction with treatment					
Acceptability of treatment (6 weeks)	OLR (OR)	4.73 (2.86 to 7.81)[a]	< 0.001	4.74 (3.10 to 7.27)[a]	< 0.001
Satisfaction with treatment (6 months)	OLR (OR)	2.91 (2.04 to 4.16)[a]	< 0.001	2.96 (2.04 to 4.30)[a]	< 0.001
Satisfaction with treatment (15 months post randomisation)	**OLR (OR)**	**2.53 (1.83 to 3.48)[a]**	**< 0.001**	**2.55 (1.79 to 3.63)[a]**	**< 0.001**
Recommend treatment to friend (6 months)	Log Reg (OR, RD)	4.49 (2.44 to 8.27),[a] 0.11 (0.07 to 0.14)	< 0.001	4.58 (2.15 to 9.75),[a] 0.11 (0.06 to 0.16)	< 0.001
Recommend treatment to friend (15 months post randomisation)	Log Reg (OR, RD)	4.52 (2.14 to 9.53),[a] 0.09 (0.04 to 0.14)	< 0.001	4.54 (2.06 to 10.01),[a] 0.09 (0.05 to 0.14)	< 0.001

Cox Reg, Cox proportional hazards regression; Lin Reg, linear regression; Log Reg, logistic regression; MD, mean difference; RD, risk difference; RM, repeated measures.
a Favours LASH ($p < 0.05$).
b Favours EA ($p < 0.05$).
Note
Co-primary outcomes are indicated in bold font.

Appendix 3 Additional information for the economic evaluation (within-trial analysis)

Within-trial economic evaluation: further details on the statistical analysis

Model selection

A number of regression model specifications were explored on the study raw data for total cost and total QALYs. For total cost, a GLM with a gamma family and identity link was defined initially. A modified Park test[71] was conducted (*Table 39*), showing a Gaussian family as a better model specification. This family can be linked using identity, logarithmic or power functions and therefore alternative models were fitted using these links. Based on the *p*-values for the Pearson's correlation test, the Pregibon link test and the modified Hosmer–Lemeshow test[71] makes it impossible to unambiguously select one link function. Therefore, a final model specifying a Gaussian family and identity link was chosen for the base-case analysis for total costs. Alternative models fitting Gaussian family and log or power links were run showing trivial differences in the estimation of cost differences (i.e. < £1 difference in the treatment dummy coefficient between identity, log and power 2 link functions).

A similar approach was followed for selecting the model for total QALYs. However, it was not possible to identify a family distribution for the raw QALY data and a simple transformation was conducted (i.e. maximum possible total QALYs at 15 months follow-up (1.25) minus observed QALYs). *Table 40* reports the results for the modified Park test on the transformed QALY data, supporting a Poisson family model specification. A number of link functions were fitted (*see Table 40* for selected test results), and a model defining a Poisson family and identity link was finally selected for the QALY analysis.

TABLE 39 Model selection test results: total costs

Fitted model: link = identity; family = gamma			
Coefficient	0.172825		
Family, chi-squared and* p-*value in descending order of likelihood			
Family	*Chi-squared*	p-*value*	
Gaussian	0.3319	0.5645	
Poisson	7.6031	0.0058	
Gamma	37.0985	0.0000	
Inverse Gaussian or Wald	88.8181	0.0000	
Results of tests for link;* p-*values			
GLM, Gaussian family	*Identity link*	*Log-link*	*Power 2 link*
Pearson's correlation test	1.0000	0.9989	0.9952
Pregibon link test	0.6039	0.9376	0.5032
Modified Hosmer–Lemeshow	0.5487	0.5804	0.4929

TABLE 40 Model selection test results: total QALYs

Fitted model: link = identity; family = Gaussian			
Coefficient	0.86363		
Family, chi-squared and* p-*value in descending order of likelihood			
Family	*Chi-squared*	p-*value*	
Poisson	0.7180	0.3968	
Gaussian	28.80	0.0000	
Gamma	49.86	0.0000	
Inverse Gaussian or Wald	176.21	0.0000	
Results of tests for link;* p-*values			
GLM, Poisson family	*Identity link*	*Log-link*	*Power 0.5 link*
Pearson's correlation test	0.6656	0.1427	0.0723
Pregibon link test	0.4768	0.0000	0.0003
Modified Hosmer–Lemeshow	0.0000	0.0000	0.0239

Missing data

Table 41 reports the proportion of missing data on costs. Relying on complete data allowed us to calculate total costs for 57% of the study sample. However, total cost results and total cost differences between study groups were driven by the cost of the index interventions. It was possible to estimate index intervention costs for 97% ($n = 639$) of individuals. Complete data analysis would result in many of these observations being discarded (see *Table 41*); this issue was crucial to decide relying on multiple imputed data for the base-case analysis. In addition, the proportion of missing data differs slightly between treatment groups, dismissing the notion that data could be missing completely at random and supporting the view that data are missing at random. This missing mechanism could be explained by, for example, the treatment allocation.

Table 42 reports the proportion of missing data for QoL. Between 2% (baseline) and 27% (6 months post intervention) of observations were missing for EQ-5D-3L score data. Therefore, total QALY calculations were possible for 64% of the study sample. Again, the proportion of missing data differs between study groups, supporting the notion that data are missing at random.

Imputation model

Multiple imputation was implemented as part of the within-trial analysis, using chained equations and predictive mean matching for continuous variables with imputed values drawn from the five closest observations (*k*th nearest neighbour = 5). The method was implemented in Stata and starts with the variable with fewer missing observations. Predictive mean matching imputes an observed value from another individual whose predicted value is close to the predicted value of the individual with the missing observation. All other variables being imputed and those included in the imputation model are used in the prediction models. This process generated 20 complete data sets, with plausible fitted values assigned for missing cost [i.e. cost of anaesthetic room, operation room, recovery room, subsequent hospital stay, operation, 6- and 15-month outpatient visits, GP visits (practice, home and telephone calls) and medications] and utility elements (i.e. EQ-5D-3L and SF-12 scores at baseline, 6 weeks and 6 months post surgery and 15 months post randomisation). The imputation model included all variables incorporated in the analysis model (centre number, age, treatment dummy), plus randomisation date and one of the co-primary clinical outcome measures (i.e. patient satisfaction as a binary variable: totally satisfied/not totally satisfied) included as auxiliary variables. Rubin's rules were used to pool estimates across the multiple imputation data sets.

TABLE 41 Missing data proportions by treatment allocation: costs

Variable	LASH		EA	
	Number of missing observations	Proportion (%) of missing data (over 330 possible observations)	Number of missing observations	Proportion (%) of missing data (over 330 possible observations)
Index operation	6	1.82	15	4.55
Readmissions	0	0.00	0	0.00
6-month data				
Outpatient visits	94	28.48	99	30.00
GP visits	96	29.09	102	30.91
GP home visits	96	29.09	102	30.91
GP telephone consultations	96	29.09	102	30.91
Medications	96	29.09	102	30.91
15-month data				
Outpatient visits	101	30.61	112	33.94
GP visits	99	30.00	115	34.85
GP home visits	99	30.00	115	34.85
GP telephone consultations	99	30.00	115	34.85
Medications	99	30.00	115	34.85
Total costs	131	30.00	155	46.97

TABLE 42 Missing data proportions by treatment allocation: EQ-5D-3L and QALYs

Variable	LASH		EA	
	Number of missing observations	Proportion (%) of missing data (over 330 possible observations)	Number of missing observations	Proportion (%) of missing data (over 330 possible observations)
Baseline EQ-5D-3L score	11	3.33	8	2.42
6-week post-surgery EQ-5D-3L score	78	25.08[a]	82	26.37[a]
6-month post-surgery EQ-5D-3L score	75	24.12[a]	90	28.94[a]
15-month post-randomisation EQ-5D-3L score	49	14.85	49	14.85
QALYs	103	31.21	117	35.45

a Percentages calculated over 311 possible observations, as 19 participants in each arm did not have surgery.

Regression model results: base case

Tables 43 and *44* report regression results for total costs and total QALYs for the base-case analysis based on the imputed data. The methods of recycled predictions[71] was used to obtain the within-trial economic evaluation results reported in *Chapter 5*.

TABLE 43 Regression results: total cost base case (multiple imputed data)

GLMs; Gaussian family, identity link		
Variable	**Coefficient**	**Standard error[a]**
Treatment dummy (1 = LASH)	1604***	63.7
Baseline EQ-5D-3L score	–9	142.6
Age dummy (1 = ≥ 40 years)	–32	98.8
Constant	1312***	118.7
Observations	660	

***$p < 0.01$.
a Robust standard errors.

TABLE 44 Regression results: total QALYs (transformed[a]) base case (multiple imputed data)

GLM, Poisson family, identity link		
Variable	**Coefficient**	**Standard error[b]**
Treatment dummy (1 = LASH)	–0.004	0.015
Baseline EQ-5D-3L score	–0.669***	0.042
Age dummy (1 = ≥ 40 years)	–0.007	0.015
Constant	0.752***	0.039
Observations	660	

***$p < 0.01$.
a QALY transformed = 1.25 – observed QALYs (1.25 being maximum possible QALYs at 15 months).
b Robust standard errors.

Subgroup analyses

Subgroup analyses are shown in *Table 45*.

Productivity costs

Productivity costs are shown in *Table 46*.

TABLE 45 Subgroup analyses: *p*-values for interaction term with treatment effect variable – multiple imputed data

Variable	Cost (£)	QALY
Uterine cavity length ≥ 8 cm	0.19	0.25
Severe dysmenorrhoea at baseline	0.56	0.29
Fibroids present	0.57	0.21
Age ≥ 40 years	0.92	0.68

TABLE 46 Time to return to paid or unpaid work and productivity costs: 6 months post surgery and 15 months post randomisation

Variable	Number of observations	LASH	EA
6 months post surgery *Time lost from usual activities (days within last 4 weeks)*			
From paid work: *n* (%); mean [SD]	33	15 (6.3); 6.1 [8.1]	18 (7.7); 7.2 [7.9]
From unpaid work: *n* (%); mean [SD]	64	25 (11.5); 10.1 [8.4]	39 (18.3); 5.7 [4.4]
From leisure/social activities: *n* (%); mean [SD]	70	29 (14.5); 7.9 [8.5]	41 (21.5); 6.4 [5.8]
Productivity costs (£)			
Cost of time from paid work, mean (SD)	470	26 (171)	40 (210)
Cost of time from unpaid work, mean (SD)	423	96 (544)	113 (512)
15 months post randomisation *Time lost from usual activities (days within last 4 weeks)*			
From paid work: *n* (%); mean [SD]	43	16 (6.9); 8.1 [11]	27 (12.2); 4.4 [4.2]
From unpaid work: *n* (%); mean [SD]	67	25 (11.8); 8.9 [8.6]	42 (20.7); 6.9 [7.3]
From leisure/social activities: *n* (%); mean [SD]	72	27 (13.4); 7.7 [7.5]	45 (23.8); 5.4 [5.3]
Productivity costs (£)			
Cost of time from paid work, mean (SD)	452	39 (260)	54 (234)
Cost of time from unpaid work, mean (SD)	401	81 (460)	144 (539)

Appendix 4 Literature searches for trials, cohort studies or case series reporting the incidence of further related surgery following endometrial ablation or laparoscopic supracervical hysterectomy

As HEALTH reported at 15 months post randomisation, too early to observe all further associated gynaecological surgery following treatment with EA or LASH, focused literature searches of MEDLINE were conducted to identify relevant studies to inform the model.

First, a search was conducted during the model development phase for RCTs of LASH. The search was broad in that it did not specify the indication or comparators of interest (*Box 1*).

This search identified nine reviews and 84 primary studies of potential relevance. The abstracts were reviewed to identify any trials comparing LASH with EA for HMB. Only two trials were identified meeting these criteria. Zupi *et al.*[13] compared hysteroscopic endometrial resection with LASH for abnormal uterine bleeding, and the primary results were published in 2003. A further long-term follow-up paper, including reoperations, was published in 2010.[48] The latter paper was considered potentially useful for informing the economic model and is discussed in the main body of the report in *Extrapolation of subsequent hysterectomy following endometrial ablation*. Sesti *et al.*[12] compared thermal balloon ablation with LASH for the surgical treatment of HMB, but reported only on short-term (30-day) complications resulting in readmission to hospital. Therefore, this study was not considered useful for informing the model.

BOX 1 Search strategy for trials comparing EA and LASH

1. exp clinical trial/ (850,485)
2. randomized controlled trial.pt. (414,266)
3. controlled clinical trial.pt. (91,931)
4. randomi?ed.ab. (404,360)
5. placebo.ab. (169,219)
6. drug therapy.fs. (1,848,006)
7. randomly.ab. (242,942)
8. trial.ab. (351,099)
9. groups.ab. (1,513,597)
10. 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 (3,886,527)
11. exp animals/not humans/ (4,132,479)
12. 51 not 52 (3,369,623)
13. (laparoscop* and supracervical).tw. (240)
14. (laparoscop* and supra-cervical).tw. (5)
15. (hysterectomy and laparoscop* and subtotal).tw. (110)
16. (hysterectomy and laparoscop* and sub-total).tw. (2)
17. 54 or 55 or 56 or 57 (334)
18. 53 and 58 (93)
19. limit 59 to 'review articles' (9)
20. 59 not 60 (84)

Date searched: October 2015.
No limits applied to date range searched.

In addition to the trials of ablation compared with LASH, the above search identified a retrospective study[53] that reported on comparative reoperation rates following total laparoscopic hysterectomy ($n = 567$) and laparoscopically assisted supracervical hysterectomy ($n = 300$). A further study[72] was also identified that reported on long-term outcomes following laparoscopic ($n = 315$) and abdominal ($n = 134$) supracervical hysterectomies performed at a university hospital in Oslo, Norway. These studies were considered further to inform the economic model.

Given the limited comparative evidence on the incidence of further related surgery following LASH and EA, a broader search was developed to identify cohort studies or case series reporting on the longer-term follow-up of these procedures. The search strategy is provided in *Table 47*. The results were restricted to published articles in the English language from 2010 onwards, to capture follow-up of reasonably contemporary cohorts.

The 379 identified abstracts were reviewed to identify studies reporting long-term rates of related gynaecological surgery following EA or LASH. When selecting studies for use in informing the rate of hysterectomy following EA, the focus was on identifying large population-based cohort studies relevant to the UK NHS. With respect to further surgery following LASH, the focus was on informing the rate of surgery considered to be directly related to the initial procedure or continued menstrual bleeding, subsequent removal of the cervical stump, laparoscopy to investigate subsequent pain and salpingo-oophorectomy. Given the paucity of published data on further relevant surgery following LASH, a less restrictive approach was applied, focusing on larger cohort studies ($n > 150$) reporting longer-term follow-up (> 1 year). This process yielded three large population-based cohort studies[5,46,49] reporting the incidence of further surgery following EA and three smaller cohort studies reporting on rates of subsequent surgery following LASH.[54–56] The two non-randomised comparative studies identified above[53,72] were added to this pool, as were three additional studies identified through the reference lists of other included studies,[50–52] providing a total of eight observational studies of potential use for informing rates of post-LASH surgery in the model.

The reported incidence of trachelectomy (removal of the cervical stump) following supracervical hysterectomy has ranged from 0.9% to 23%.[50,51] The highest reported incidence of 23% comes from an older UK series performed by a single surgeon (Okaro *et al*[50]). In this series, 16 out of 70 patients who received LASH between 1992 and 1995 were reported to require subsequent trachelectomy, with mean time to treatment of 14 months. It has been noted that 82.3% of women who required removal of the cervical stump in the Okara study had been previously treated for endometriosis (Jenkins *et al.*[58]), and endometriosis has subsequently been identified as a significant risk factor for trachelectomy following hysterectomy (Tsafrir *et al.*[51]). This high rate does not appear applicable to the population enrolled in HEALTH, as it suggests that the incidence of trachelectomy should already be > 10% by 12 months post LASH. Only one person is known to have required a trachelectomy following LASH by 15 months post randomisation in HEALTH.

The most recent study by Tsafrir *et al.*[51] reported that only 17 (0.9%) out of 1892 women who underwent supracervical hysterectomy between 2002 and 2014 at a single US medical centre subsequently underwent removal of the cervical stump. However, the duration of follow-up to which this incidence relates was not clearly reported.

From 192 laparoscopic subtotal hysterectomies carried out at three teaching hospitals in the Netherlands between 1998 and 2007 for benign and malignant indications, van Evert *et al.*[52] reported that four patients (2%) required further surgery to remove the cervix. The corresponding duration of follow-up was not clearly reported but the minimum was 6 months.

The study by Boosz *et al.*[53] turned out to include only short-term follow-up data and reported that 3.7% of 300 women receiving LASH at a university hospital in Germany (between January 2002 and December 2009) had a subsequent operation within 6 months of the initial surgery. It was reported that 2.7% required

TABLE 47 Ovid MEDLINE®: literature search results on cohorts or case series reporting follow-up of laparoscopic supracervical or subtotal hysterectomy, or EA

#	Search	Result	Type
1	Menorrhagia/	4050	Advanced
2	Menorrhagia.tw.	2730	Advanced
3	(heavy and menstrua*).tw.	1091	Advanced
4	abnormal uterine bleeding.tw.	1568	Advanced
5	1 or 2 or 3 or 4	7008	Advanced
6	(laparoscop* and supracervical).tw.	276	Advanced
7	(laparoscop* and supra-cervical).tw.	5	Advanced
8	(hysterectomy and laparoscop* and subtotal).tw.	126	Advanced
9	(hysterectomy and laparoscop* and sub-total).tw.	5	Advanced
10	Endometrial Ablation Techniques/	337	Advanced
11	endometrial ablation.tw.	1037	Advanced
12	thermal balloon.tw.	182	Advanced
13	radio frequency.tw.	5267	Advanced
14	Novasure.tw.	49	Advanced
15	thermachoice.tw.	43	Advanced
16	cavaterm.tw.	17	Advanced
17	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	6822	Advanced
18	Hysterectomy/	27,214	Advanced
19	Hysterectomy.tw.	28,028	Advanced
20	6 or 7 or 8 or 9	390	Advanced
21	(18 or 19) and 20	387	Advanced
22	17 or 21	6822	Advanced
23	exp Cohort Studies/	1,774,326	
24	exp case-control studies/	937,492	Advanced
25	case series.ti,ab,kw.	49,673	Advanced
26	treatment outcome/or treatment failure/	885,911	Advanced
27	23 or 24 or 25 or 26	2,514,214	
28	22 and 27	1305	Advanced
29	(surgery or surgical).ti,ab. or su.fs.	2,469,340	
30	28 and 29	1029	Advanced
31	limit 30 to (english language and humans and yr = '2010 -Current')	379	Advanced

Date searched: September 2018.
Date range searched: 1946 to August Week 4 2018.

removal of the cervical stump.[53] This 6-month rate is significantly higher than the observed rate in HEALTH at 15 months post randomisation and is not useful for informing longer-term extrapolation.

Graziano *et al.*[54] reported on mainly perioperative and early postoperative complications occurring in 365 women undergoing LASH, but also reported one later vaginal trachelectomy and operative laparoscopies ($n = 4$) performed beyond 6 months.[54] However, the precise follow-up time for these further procedures was not reported.

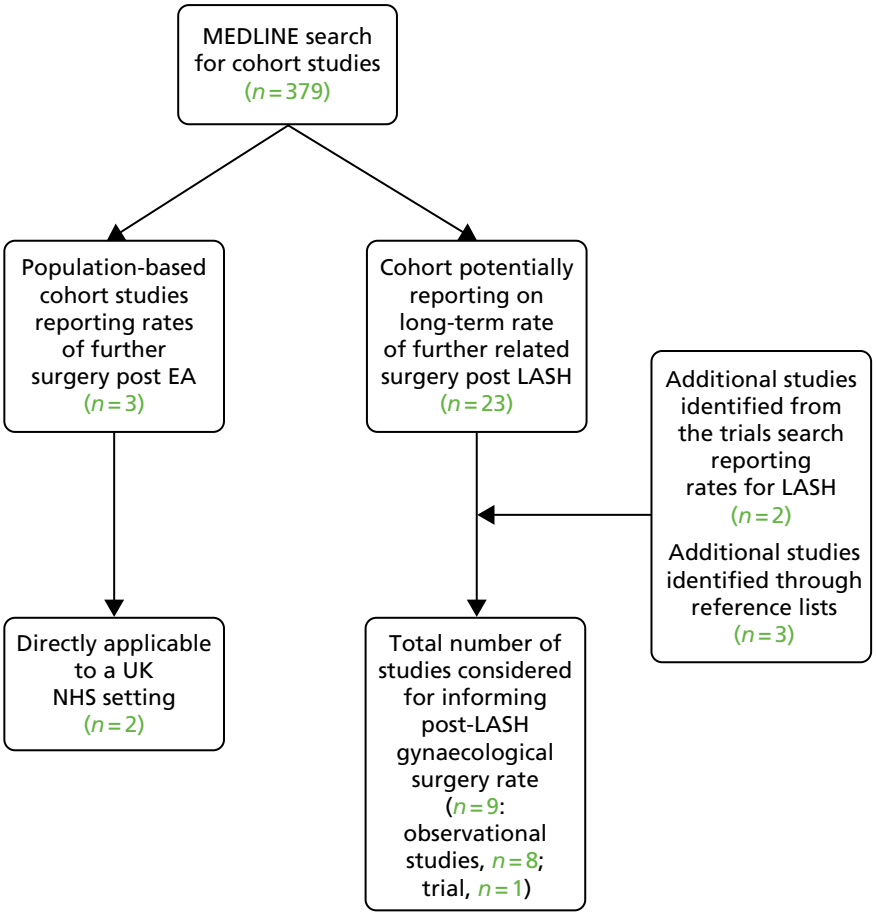

FIGURE 18 Identification of studies.

Schuster *et al.*[55] reported that 5 out of 277 (1.8%) women undergoing LASH in a single Canadian centre had a repeat operative procedure for pain or bleeding. However, again, the duration of follow-up was unclear.

Wallwiener *et al.*[56] provided an analysis of a prospective cohort of women who underwent LASH ($n = 1658$) or total laparoscopic hysterectomy ($n = 294$) at a single centre in Germany and reported that 20 (1.2%) patients had a postoperative complication requiring surgical intervention [with adhesions being the most common reason ($n = 9$)].[56] This was over mean follow-up of 2.5 years.

Finally, Lieng *et al.*[17] reported that 7% (22/315) of women in a Norwegian cohort had further gynaecological surgery up to 36 months following LASH. The main surgical interventions were laparoscopic adhesiolysis (1.9%) and laparoscopic extirpation of the cervical stump (2.3%). It was also noted that one woman (0.3%) underwent subsequent BSO. The other reported procedures included scar correction (1%), umbilical hernia repair (0.3%), tension-free vaginal tape procedures (0.6%), laparotomy for postoperative peritonitis (0.3%) and laparoscopic drainage of postoperative abscess (0.3%). These other surgical procedures were not included in the long-term rate of further surgery post LASH in the economic model. Some reflect short-term postoperative complications that are already informed in the model using HEALTH data, and the others are of very low incidence and of uncertain association with LASH.

Appendix 5 Extrapolation of hysterectomy post endometrial ablation

As the primary analysis of HEALTH took place at 15 months post randomisation, further modelling was conducted to extrapolate cost-effectiveness over a longer time horizon. Ten years was selected based on existing modelling studies and the availability of long-term follow-up data for a population-based cohort of similarly aged women who received primary EA on the UK NHS.

The cohort study by Cooper *et al.*[5] provided a published KM curve of time to subsequent hysterectomy based on 14,078 women identified as having received primary EA for HMB between 1989 and 2006 in Scotland. The data indicated that > 50% of hysterectomies were performed in the first year post ablation, but the percentage went on increasing steadily out to and beyond 10 years post ablation. The historical Scottish data also indicated that ≈10% of patients had a hysterectomy by 12 months following ablation, a substantially greater proportion than the estimated 3% by 12 months in HEALTH. Therefore, for consistency with the trial-based evaluation at 15 months post randomisation, we used the HEALTH data to inform the hysterectomy rate in the first 12 cycles (12 months) of the economic model. We then used the data reported by Cooper *et al.*[5] (beyond year 1) to guide extrapolation of the expected rate of further hysterectomies in the longer term. This was achieved by fitting a mathematical function to the observed KM data reported by Cooper *et al.*[5] and then referencing it for the estimation of cycle-specific transition probabilities from month 13 onwards in the economic model.

In order to achieve this, a sample of data points were extracted from the published KM curve using WebPlotDizitizer software [URL: https://automeris.io/WebPlotDigitizer/ (accessed 22 May 2019)]. An attempt was made to reconstruct the individual patient data behind the published KM curve using the spreadsheet developed by Hoyle and Henley.[73] This was challenging due to the large sample informing the KM plot, resolution of the published figure and lack of details on numbers at risk over time. Nevertheless, a reconstructed data set was approximated based on 15 extracted points. Alternative parametric survival functions were then fitted to the reconstructed KM data, including an exponential, Weibull, logistic, log-normal and log-logistic function. Of these alternative distributions, the Weibull provided the best statistical fit based on the Akaike information criterion and Bayesian information criterion (*Table 48*). However, this Weibull function did not provide a good visual fit to the extracted data points, resulting in underprediction of the event (hysterectomy) in the short term and overprediction in the longer term [*Figure 19*, *S*(*t*)_Weibull A]. Therefore, we utilised an alternative regression-based method to fit a Weibull function to KM data, ignoring extracted points in the first year. This involved regressing log(–log(*S*)) on log(*t*), where *S* represents the extracted survivor proportions and *t* represents the corresponding survival times. The constant term from this model gives the log of the rate parameter (lambda) for a fitted Weibull distribution, and the parameter

TABLE 48 Akaike information criterion for alternative functional forms of time to hysterectomy following EA

Model	Intercept	Log(scale parameter)	AIC	BIC
Exponential	3.353	0.0190	25,850.18	25,857.59
Weibull	4.378	0.564	24,560.75	24,575.56
Logistic	16.256	1.820	30,952.16	30,966.97
Log-normal	3.459	0.847	24,648.1	24,662.91
Log-logistic	3.382	0.244	24,948.85	24,963.65

AIC, Akaike information criterion; BIC, Bayesian information criterion.

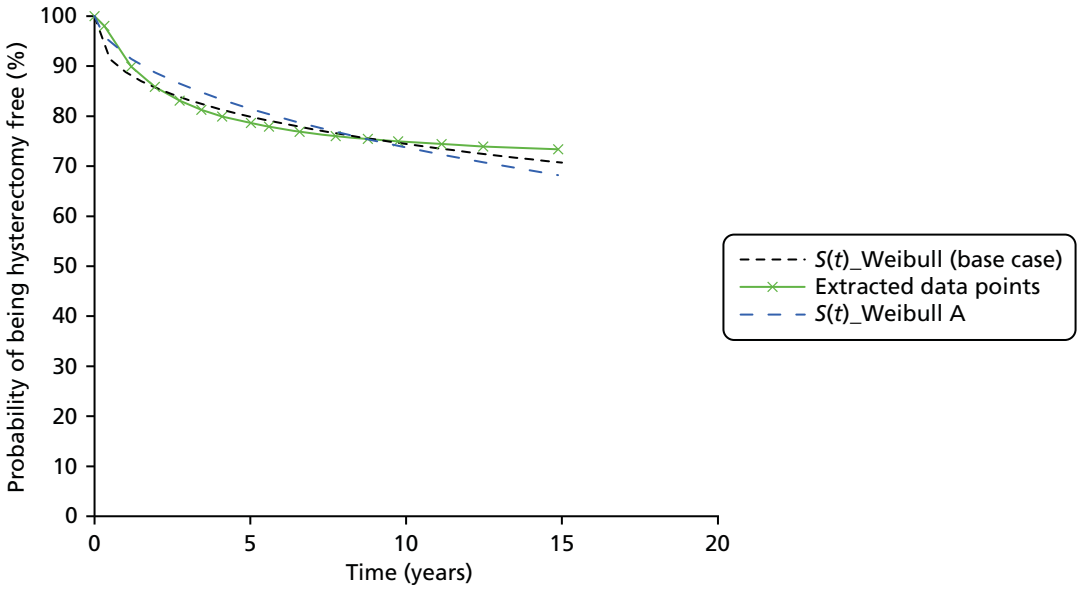

FIGURE 19 Extracted data points and fitted Weibull curves for hysterectomy following EA. Survivor function ($S(t)$).

estimate for log(t) provides the shape parameter (gamma). This fitted curve provided a better visual fit against the extracted KM data beyond year 1, the time period requiring extrapolation in the economic model (see *Figure 19*). Although the fitted curve is initially slightly shallower than the observed KM curve, this may not be inappropriate for extrapolation of HEALTH, in which the 1-year KM data illustrates a slower rate of progression to hysterectomy than expected based on the historical cohort (see *Figure 19*). The slight over prediction of hysterectomy beyond 10 years is of limited concern because the time horizon of the model is curtailed at 10 years. Therefore, this fitted Weibull curve was used to derive time-dependent monthly probabilities of hysterectomy beyond year 1 in the base case. The time-dependent monthly transition probabilities were calculated using the following equation:

$$1 - \exp(\lambda(t_0^{\gamma} - t_1^{\gamma})), \quad (1)$$

in which λ (lambda) is the rate parameter of the Weibull distribution, γ (gamma) is the shape parameter (indicating a diminishing hazard over time when < 1), t_0 is the time at the beginning of the interval of interest and t_1 is the time at the end of the interval of interest. The parameter estimates for lambda and gamma are provided in *Table 19*.

Given the uncertainty surrounding time to hysterectomy following EA, and its importance in the model with respect to extrapolation of QALYs, further sensitivity analysis was undertaken using cycle-specific transition probabilities derived directly from the published KM curve reported by Cooper *et al.*[5] For this analysis, further data points were extracted from the published KM curve at approximately 6-month intervals (*Figure 20*). A transition probability for each extracted 6-month interval was then estimated as $1 - (S(t_1)/S(t_0))$. These were further transformed into constant monthly transition probabilities corresponding to each extracted 6-month interval for application in the model, using the following equations:

$$r = -\ln(1 - p)\,/\,t, \quad (2)$$

$$p = 1 - \exp(-rt), \quad (3)$$

where r is a constant rate (expressed per unit of time at risk), t is the time period to which the initial probability relates (6 months) and p is the transition probability. which is rescaled to the time period of

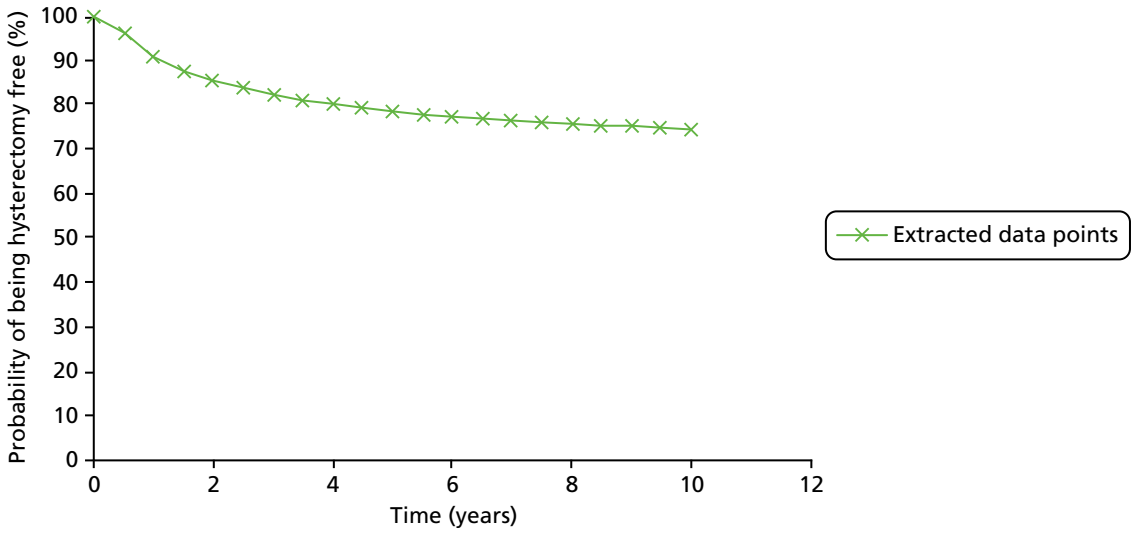

FIGURE 20 Extracted 6-monthly data points for hysterectomy following EA. Survivor function ($S(t)$).

interest (1 month). In the first sensitivity analysis, the HEALTH KM data were used up to 12 months in the model, with the transition probabilities derived from year 1 onwards (see *Figure 20*) applied thereafter. In an alternative specification, transition probabilities derived from *Figure 20* were applied over the full duration of the model. This latter scenario assessed the impact of assuming a higher probability of hysterectomy in year 1 and a long-term probability of 25% by 10 years, as indicated in the population based KM curve reported by Cooper *et al.*[5]

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