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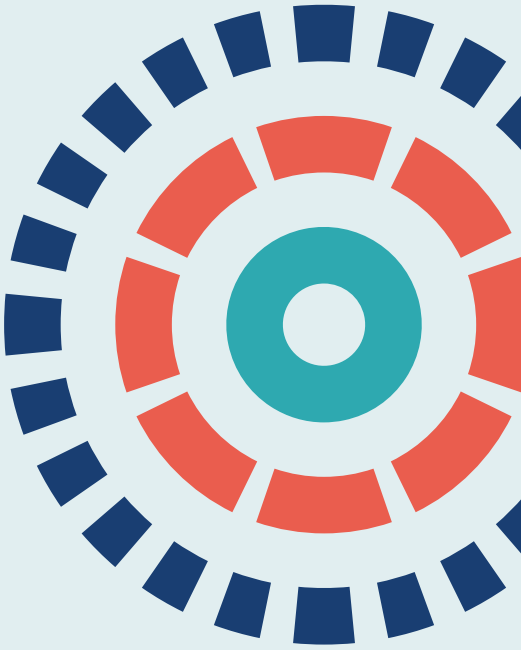

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Uterine artery embolisation versus myomectomy for premenopausal women with uterine fibroids wishing to avoid hysterectomy: the FEMME RCT

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This report

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Abstract

Uterine artery embolisation versus myomectomy for premenopausal women with uterine fibroids wishing to avoid hysterectomy: the FEMME RCT

Jane Daniels[1*] Lee J Middleton[2] Versha Cheed[2] William McKinnon[2] Dikshyanta Rana[3] Fusun Sirkeci[4] Isaac Manyonda[5] Anna-Maria Belli[6] Mary Ann Lumsden[7] Jonathan Moss[7] Olivia Wu[3] and Klim McPherson[8]

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Background: Uterine fibroids are the most common tumour in women of reproductive age and are associated with heavy menstrual bleeding, abdominal discomfort, subfertility and reduced quality of life. For women wishing to retain their uterus and who do not respond to medical treatment, myomectomy and uterine artery embolisation are therapeutic options.

Objectives: We examined the clinical effectiveness and cost-effectiveness of uterine artery embolisation compared with myomectomy in the treatment of symptomatic fibroids.

Design: A multicentre, open, randomised trial with a parallel economic evaluation.

Setting: Twenty-nine UK hospitals.

Participants: Premenopausal women who had symptomatic uterine fibroids amenable to myomectomy or uterine artery embolisation were recruited. Women were excluded if they had significant adenomyosis, any malignancy or pelvic inflammatory disease or if they had already had a previous open myomectomy or uterine artery embolisation.

Interventions: Participants were randomised to myomectomy or embolisation in a 1 : 1 ratio using a minimisation algorithm. Myomectomy could be open abdominal, laparoscopic or hysteroscopic. Embolisation of the uterine arteries was performed under fluoroscopic guidance.

Main outcome measures: The primary outcome was the Uterine Fibroid Symptom Quality of Life questionnaire (with scores ranging from 0 to 100 and a higher score indicating better quality of life) at 2 years, adjusted for baseline score. The economic evaluation estimated quality-adjusted life-years (derived from EuroQol-5 Dimensions, three-level version, and costs from the NHS perspective).

Results: A total of 254 women were randomised – 127 to myomectomy (105 underwent myomectomy) and 127 to uterine artery embolisation (98 underwent embolisation). Information on the primary outcome at 2 years was available for 81% ($n = 206$) of women. Primary outcome scores at 2 years were 84.6 (standard deviation 21.5) in the myomectomy group and 80.0 (standard deviation 22.0) in the uterine artery embolisation group (intention-to-treat complete-case analysis mean adjusted difference 8.0, 95% confidence interval 1.8 to 14.1, $p = 0.01$; mean adjusted difference using multiple imputation for missing responses 6.5, 95% confidence interval 1.1 to 11.9). The mean difference in the primary outcome at the 4-year follow-up time point was 5.0 (95% CI –1.4 to 11.5; $p = 0.13$) in favour of myomectomy. Perioperative and postoperative complications from all initial procedures occurred in similar percentages of women in both groups (29% in the myomectomy group vs. 24% in the UAE group). Twelve women in the uterine embolisation group and six women in the myomectomy group reported pregnancies over 4 years, resulting in seven and five live births, respectively (hazard ratio 0.48, 95% confidence interval 0.18 to 1.28). Over a 2-year time horizon, uterine artery embolisation was associated with higher costs than myomectomy (mean cost £7958, 95% confidence interval £6304 to £9612, vs. mean cost £7314, 95% confidence interval £5854 to £8773), but with fewer quality-adjusted life-years gained (0.74, 95% confidence interval 0.70 to 0.78, vs. 0.83, 95% confidence interval 0.79 to 0.87). The differences in costs (difference £645, 95% confidence interval –£1381 to £2580) and quality-adjusted life-years (difference –0.09, 95% confidence interval –0.11 to –0.04) were small. Similar results were observed over the 4-year time horizon. At a threshold of willingness to pay for a gain of 1 QALY of £20,000, the probability of myomectomy being cost-effective is 98% at 2 years and 96% at 4 years.

Limitations: There were a substantial number of women who were not recruited because of their preference for a particular treatment option.

Conclusions: Among women with symptomatic uterine fibroids, myomectomy resulted in greater improvement in quality of life than did uterine artery embolisation. The differences in costs and quality-adjusted life-years are very small. Future research should involve women who are desiring pregnancy.

Trial registration: This trial is registered as ISRCTN70772394.

Funding: This study was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme, and will be published in full in *Health Technology Assessment*; Vol. 26, No. 22. See the NIHR Journals Library website for further project information.

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List of abbreviations

AE	adverse event
AMH	anti-Müllerian hormone
BNF	*British National Formulary*
CEMRI	contrast-enhanced magnetic resonance imaging
CI	confidence interval
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
FSH	follicle-stimulating hormone
FUME	Fibroids of the Uterus: Myomectomy versus Embolization
GP	general practitioner
HMB	heavy menstrual bleeding
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
ITT	intention to treat
LH	luteinising hormone
LOS	length of stay
MRgHIFU	magnetic resonance-guided high-intensity transcutaneous-focused ultrasound
MRI	magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NMB	net monetary benefit
PBAC	pictorial bleeding assessment chart
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	risk ratio
SAE	serious adverse event
SD	standard deviation
TSC	Trial Steering Committee
TVUS	transvaginal ultrasound scan
UAE	uterine artery embolisation
UFS-QOL	Uterine Fibroid Symptom Quality of Life
UPA	ulipristal acetate
VAS	visual analogue scale
WTP	willingness to pay

Plain English summary

What is the problem?

Uterine fibroids are the most common non-cancerous tumour in women of childbearing age. Uterine fibroids are associated with heavy bleeding, lower chances of having children and reduced quality of life. Traditional surgical options were either to remove the fibroids (via myomectomy) or to completely remove the womb. A newer approach, known as uterine artery embolisation, involves blocking the blood supply to the fibroids in the womb.

What did we plan to do?

We compared myomectomy with uterine artery embolisation in women with fibroids who wanted to keep their womb. We wanted to see which treatment improved quality of life, was associated with the fewest complications and was the best value for money for the NHS. We also wanted to see if either treatment had an impact on women's ability to get pregnant and give birth.

We included 254 women in a clinical trial. Women were assigned to have myomectomy or uterine artery embolisation at random to ensure a fair comparison. Women completed questionnaires about their symptoms and quality of life at intervals up to 4 years after treatment.

What did we find?

We found that myomectomy improved women's quality of life more than uterine artery embolisation. Complications from the treatments occurred in a similar proportion of women. There appeared to be no difference on reproductive hormone levels between treatments. Too few women in the trial got pregnant for any difference in the numbers of women having children to be seen. The differences in costs and overall disease burden were small.

What does this mean?

Both treatments improve quality of life and cost about the same to the NHS but, on average, myomectomy will provide greater benefit to women. There is no evidence to suggest that either treatment is unsuitable for women wanting to get pregnant, but more research is needed in younger women.

Scientific summary

Background

Uterine fibroids are the most common tumour in women of reproductive age and are associated with heavy menstrual bleeding (HMB), abdominal discomfort, subfertility and reduced quality of life. For women seeking to retain their uterus and who do not respond to medical treatment, myomectomy and uterine artery embolisation (UAE) are therapeutic options.

Surgery, either myomectomy or hysterectomy, has traditionally been the main approach for management of symptomatic fibroids. Myomectomy involves the surgical removal of the fibroid, preserving the uterus, and, although significantly reducing heavy bleeding symptoms, can involve myometrial trauma. To the best of our knowledge, there are no reliable randomised trial data to confirm a benefit on reproductive outcomes. UAE involves temporary occlusion of the arteries supplying the uterus using biocompatible particles and is usually performed under local anaesthetic. Concern around the potential impact of UAE on ovarian and uterine function has resulted in recommendations against the procedure for women seeking pregnancy, but a recent meta-analysis suggested no appreciable impact on ovarian reserve (El Shamy T, Amer SAK, Mohamed AA, James C, Jayaprakasan K. The impact of uterine artery embolization on ovarian reserve: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand* 2020;**99**:16–23.).

Objectives

The primary aim of this randomised trial of treating Fibroids with either Embolisation or Myomectomy to Measure the Effect on quality of life among women wishing to avoid hysterectomy (the FEMME trial) was to examine the effect of these interventions on quality of life at 6 months and at 1, 2 and 4 years.

The secondary objectives were to compare the two interventions with respect to:

- relative cost-effectiveness at 2 and 4 years from the perspective of the NHS
- HMB symptoms
- pregnancy rates and outcomes
- adverse events and post-procedure complications
- reintervention rates.
- hormones associated with ovarian reserve at 6 weeks and 6 and 12 months post procedure.

Design

A multicentre, open, randomised trial with a parallel economic evaluation.

Setting

Twenty-nine UK hospitals.

Participants

Premenopausal women who had symptomatic uterine fibroids amenable to myomectomy or UAE were recruited. Women were excluded if they had significant adenomyosis, had any malignancy or pelvic inflammatory disease or had already had a previous open myomectomy or UAE.

Interventions

Online randomisation was performed centrally using minimisation to balance the study group allocations in a 1 : 1 ratio and according to the longest dimension of the largest fibroid (i.e. ≤ 7 cm or > 7 cm), number of fibroids (i.e. 1–3, 4–10 or > 10) and whether or not the woman wanted to get pregnant.

Myomectomy could be open abdominal, laparoscopic or hysteroscopic according to the location of the fibroid and the preference of the operating gynaecologist.

Bilateral UAE was performed under fluoroscopic guidance. The embolic agent was at the discretion of the interventional radiologist and the end point of the embolisation procedure was complete or near-complete stasis of blood flow in the uterine artery.

Main outcome measures

The primary outcome measure was the condition-specific quality-of-life domain score from the Uterine Fibroid Symptom Quality of Life (UFS-QOL) questionnaire at 2 years post randomisation [with scores ranging from 0 (worst) to 100 (best)].

The following prespecified secondary outcomes were collected at 6 months and at 1, 2 and 4 years (unless otherwise stated):

- health-related quality-of-life (HRQoL) domain from the UFS-QOL at 6 months and 1 and 4 years
- symptom severity domain from the UFS-QOL
- EuroQol-5 Dimensions, three-level version (EQ-5D-3L), score
- EuroQol-5 Dimensions (EQ-5D) visual analogue scale
- menstrual blood loss using the pictorial bleeding assessment chart
- pregnancy and associated outcomes, specifically the ability to conceive (i.e. overall and in the population of women who at the time of randomisation reported that they wanted to get pregnant) and the subsequent pregnancy outcome (i.e. live birth, miscarriage, stillbirth and termination)
- participant acceptability, as defined by responses to 'Would you have your operation again?'
- participant acceptability, as defined by responses to 'Would you recommend operation to a friend?'
- length of hospital stay
- further treatment for fibroids or recurrence of symptoms, including hysterectomies
- measure of ovarian reserve by assay of follicle-stimulating hormone, anti-Müllerian hormone and luteinising hormone at 6 weeks, 6 months and 12 months post procedure
- serious adverse events and procedural complications considered to be related to the study protocol or intervention.

The economic evaluation estimated quality-adjusted life-years (QALYs) derived from EQ-5D-3L and costs from the NHS perspective over the time horizons of 2 and 4 years. Cost-effectiveness was expressed as incremental cost per QALY gained. Cost-effectiveness acceptability curves were used to present uncertainty in the decision regarding cost-effectiveness over a range of thresholds of willingness to pay (WTP) for a gain of 1 QALY.

Sample size

A sample size of 250 participants had 90% power to detect a moderate difference between groups [i.e. 12 points, 0.55 of a standard deviation (SD)] in the UFS-QOL HRQoL domain, allowing for approximately 20% loss of primary outcome data. The analysis of the primary outcome was performed according to the intention-to-treat (ITT) principle and analyses were performed on (1) complete

observed data and (2) all randomised participants at all assessment times through imputation of missing responses.

Results

The randomisation of participants commenced on 6 February 2012 and the last woman was randomised on 21 May 2015. A total of 254 women were randomised: 127 to myomectomy (105 underwent myomectomy) and 127 to UAE (98 underwent embolisation). Information on the primary outcome at 2 years was available for 81% ($n = 206$) of women. Of the 123 women randomised to myomectomy for whom initial treatments details were known, 105 (85%) had a myomectomy as their initial operation. Similarly, 98 of the 122 (80%) women in the UAE group underwent UAE. Women were, on average, 41 years old and classed as overweight by their body mass index.

The average UFS-QOL HRQoL score at 2 years was 84.6 (SD 21.5) in the myomectomy group and 80.0 (SD 22.0) in the UAE group [ITT complete-case analysis mean-adjusted difference 8.0, 95% confidence interval (CI) 1.8 to 14.1, $p = 0.01$; mean-adjusted difference using multiple imputation for missing responses 6.5, 95% CI 1.1 to 11.9]. Sensitivity analysis returned comparable results. The mean difference in the primary outcome at the 4-year follow-up time point was 5.0 (95% CI −1.4 to 11.5) in favour of myomectomy.

The UFS-QOL symptom severity domain scores at 6 months and 1 year were higher in the UAE group than in the myomectomy group, indicating more residual symptoms in the former group. Small, but consistent, differences were seen for the two EQ-5D instrument domains that favoured myomectomy. Over the 2 years of follow-up, there were no apparent and sustained differences between the two groups in the bleeding scores, or in the proportions of women reporting amenorrhoea or heavy bleeding. Perioperative and postoperative complications from all initial procedures occurred in similar percentages of women in both groups (29% in the myomectomy group vs. 24% in the UAE group). The cumulative repeat procedure rate to 4 years was 24% in the UAE group and 13% in the myomectomy group (hazard ratio 0.53, 95% CI 0.27 to 1.05).

There were 15 pregnancies in the UAE group and seven in the myomectomy group, with a cumulative pregnancy rate to 4 years of 15% and 6%, respectively (hazard ratio 0.48, 95% CI 0.18 to 1.28). There was no evidence of any material difference between the levels of hormones associated with ovarian reserve in each group. There were no apparent differences in the participants' rating of their operation by 4 years, which remained high overall.

Over a 2-year time horizon, UAE was associated with higher costs than myomectomy (£7958, 95% CI £6304 to £9612, vs. £7314, 95% CI £5854 to £8773), but with fewer QALYs gained (0.74, 95% CI 0.70 to 0.78, vs. 0.83, 95% CI 0.79 to 0.87). The differences in costs (difference £645, 95% CI −£1381 to £2580) and QALYs (difference −0.09, 95% CI −0.11 to −0.04) were small. Similar results were observed over the 4-year time horizon. At a £20,000 WTP threshold, the probability of myomectomy being cost-effective is 98% at 2 years and 96% at 4 years.

Conclusions

Although both procedures improved participant-reported HRQoL scores, women assigned to myomectomy reported higher scores (i.e. a mean difference of 8 points on a 100-point scale) than those in the UAE group. Menstrual bleeding scores appeared similar in both groups. Overall, complication rates from all initial procedures occurred in a similar proportion of women in both groups. The hospital stay was shorter in the UAE group, but the need for reintervention was higher in the UAE group. There were no consistent differences between groups in biomarkers of ovarian reserve.

There were 15 pregnancies in the UAE group and seven in the myomectomy group, but these numbers were too small to draw a conclusion on the effect of the procedures on fertility. The economic evaluation showed that UAE was associated with higher costs and fewer QALYs than myomectomy. Future research should involve younger women who want to get pregnant.

Both UAE and myomectomy are effective treatments for improving the quality of life of women with symptomatic uterine fibroids. Women with fibroids, including those wanting to get pregnant in the future, should be provided with the evidence generated by the FEMME trial to enable a fully informed decision regarding their fibroid treatment.

The most important research now required is the investigation of the impact of UAE and myomectomy on fertility. The lack of compelling evidence for adverse effects of myomectomy and UAE from the FEMME trial and other sources should reduce the barriers to a new randomised trial in women seeking to get pregnant naturally or undergoing assisted reproduction treatment.

Trial registration

This trial is registered as ISRCTN70772394.

Funding

This study was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme, and will be published in full in *Health Technology Assessment*; Vol. 26, No. 22. See the NIHR Journals Library website for further project information.

Chapter 1 Introduction

Symptomology of uterine fibroids

Uterine fibroids are the most common tumour in women of reproductive age and increase in prevalence as women get older. Around 80% of women will have developed a fibroid by the time that they are 50 years old. Approximately half of women with fibroids experience significant symptoms, which can include heavy menstrual bleeding (HMB), pain on intercourse, abdominal pain and a feeling of pressure,[2] all of which can have a significant impact on a woman's quality of life.[3,4]

The symptoms experienced by women with fibroids may vary depending on the position, size and number of fibroids. Intramural fibroids are the most common form of fibroid, but are frequently asymptomatic. Subserosal fibroids, located on the outer surface of the uterus, can become very large and create feelings of bulkiness. Submucosal fibroids project into the uterine cavity and are associated with HMB. As submucosal fibroids may distort the uterus and change the local morphology of the uterine tissue, some clinicians believe that the presence of fibroids may have a negative impact on fertility,[5,6] although data are contradictory.[7]

Burden of disease

According to Hospital Episode Statistics, there were just under 31,000 finished consultant episodes of women with fibroids of the uterus in 2012 and 2013 in the UK. The majority of these women were aged between 40 and 54 years.[8]

Diagnosis of fibroids

Fibroids can occur anywhere in the uterus and vary in size from 1 cm to over 30 cm in diameter. Intramural fibroids, the most common type of fibroid, develop in the myometrium. Subserosal fibroids develop outside the wall of the uterus into the pelvis and can become very large. Submucosal fibroids develop in the myometrium but are visible in the uterine cavity. In some cases, subserosal or submucosal fibroids are attached via narrow stalk of tissue, in which case they are known as pedunculated fibroids.[9]

Initial investigations include taking a structured medical history, including menstrual patterns, and a physical examination. Pelvic ultrasound is the first-line diagnostic tool for identifying fibroids and distinguishing them from polyps. Further investigation would involve contrast-enhanced magnetic resonance imaging (CEMRI), which is also extremely helpful in determining suitability for surgical or minimally invasive treatments.[10]

Medical treatment for fibroids

Pharmaceutical treatment of HMB is recommended when fibroids are < 3 cm and are causing no distortion of the uterine cavity, with the levonorgestrel-releasing intrauterine system the first-line treatment. Gonadotropin-releasing hormone analogues could be considered if all other treatment options are contraindicated.[10]

Ulipristal acetate (UPA) (Esmya; Gedeon Richter plc, Budapest, Hungary) is licensed for preoperative treatment of fibroids and intermittent treatment of fibroid-associated bleeding for a maximum of four cycles of 3 months, with dramatic effects on HMB.[11,12] In March 2020, the European Medicines Agency

temporarily suspended UPA treatment for uterine fibroids while a safety review considered the risk of liver injury. A 2018 review concluded that there was a risk of rare but serious liver injury from UPA and introduced measures, including liver function tests, to minimise the risk.[13]

With the suspension of UPA, and the previous concerns around endometrial changes arising from use of asoprisnil,[14] new progesterone receptor modulators are being investigated. Clinical trials of vilaprisan have shown promise,[15] but subsequent studies were halted by the pharmaceutical company[16] and it remains to be seen whether or not any further drugs in this class will receive marketing authorisation.

Oral gonadotropin-releasing hormone receptor antagonists are also being investigated for the treatment of fibroid-associated HMB. The leading drug in this class, elagolix (ORILISSA®; AbbVie Inc., Lake Bluff, IL, USA), has a licensed indication for endometriosis-related pain and has been shown in placebo-controlled trials to be effective in reducing HMB when taken with add-back hormonal treatment.[17] Another drug in this class, relugolix (RELUMINA®; Takeda, Tokyo, Japan), has been found to improve fibroid-associated pain in the short term.[18] Finally, linzagolix (Yselty®; ObsEva, Plan-les-Ouates, Switzerland) has been found to rapidly reduce bleeding, but simultaneous add-back treatment was necessary to avoid hot flushes.[19]

Women with symptomatic fibroids often respond poorly to drug management or risk unacceptable side effects from hormonal preparations. Therefore, these treatments are often used to relieve symptoms over the short term while awaiting an invasive procedure.

Surgical treatment for fibroids

Surgery, either myomectomy or hysterectomy, has traditionally been the main approach for the management of symptomatic fibroids if medical management is ineffective or for fibroids > 3 cm in size. Myomectomy involves the surgical removal of the fibroid, preserving the uterus, and, although significantly reducing heavy bleeding symptoms, can involve myometrial trauma. Depending on the size and position of the fibroid, myomectomy can be undertaken laparoscopically, hysteroscopically, transvaginally or by a laparotomy.

Non-surgical treatment for uterine fibroids

Uterine artery embolisation (UAE) involves temporary occlusion of the arteries supplying the uterus using biocompatible particles and is usually performed under local anaesthetic. UAE causes ischaemic infarction, from which the uterus usually recovers but the fibroids do not.

The use of UAE in women who may want to conceive is controversial in some sections of the medical community. Some clinicians are concerned by the reduction in blood flow to the ovaries. This reduction in blood flow has been suggested to occur if there are significant communications between the ovarian and the uterine arteries, and this has been proposed to decrease ovarian function.[20] The extent of this decreased function, how long it is maintained for and if it occurs at all are disputed.[21,22]

There are other non-surgical minimally invasive interventions that aim to ablate fibroids. According to the National Institute for Health and Care Excellence (NICE), there is adequate evidence of the short-term efficacy of magnetic resonance-guided high-intensity transcutaneous-focused ultrasound (MRgHIFU), but further research, both on long-term outcomes and in women who want to get pregnant, is required.[23] A randomised trial of MRgHIFU compared with myomectomy is under way in Germany (NCT03948789), whereas another trial comparing MRgHIFU with UAE showed a lower reintervention rate and greater improvement in symptoms and quality of life from UAE.[24] NICE considers that the evidence on efficacy of ultrasound-guided high-intensity transcutaneous-focused ultrasound is limited and that the procedure should be used only with special arrangements for consent or within a research setting.[23] Transcervical radiofrequency ablation shows significant clinical improvement up to 2 years post procedure.[25] Microwave ablation is also being evaluated for safety and efficacy.[26]

Previous research comparing uterine artery embolisation with surgery

Procedural and symptom relief outcomes

There have been two reported randomised trials[27,28] comparing UAE with myomectomy. One single-centre trial from Czechia randomised 121 women with intramural fibroids to be treated by myomectomy or UAE.[27] These authors reported statistically significant reductions in the length of the procedures, hospital stay and recovery period in women who had undergone a UAE. There was a much higher reintervention rate in the UAE group than in the myomectomy group. After a mean follow-up period of about 2 years, 19 out of 58 (33%) women in the UAE group had a subsequent myomectomy, compared with 2 out of 62 (3%) women in the myomectomy group, although myomectomy was recommended if 6 months after the UAE there had been no reduction in the size of the fibroid or there was a fibroid measuring > 5 cm.[28] There was no evidence of a difference in reported symptomatic relief, with both groups demonstrating high rates in both the short and the medium term.

The FUME (Fibroids of the Uterus: Myomectomy versus Embolization) study[29] was conducted at St George's Hospital (London, UK). A total of 160 women with symptomatic uterine fibroids were randomised to UAE or myomectomy. The authors reported that by 1 year there was no difference between groups in the substantial improvement of the quality of life in women. However, the reintervention rate was higher in the UAE group than in those who had undergone a myomectomy (i.e. 9/61 women in the UAE group had a second procedure, compared with 3/73 women in the myomectomy group).[29] Unfortunately, there was substantial attrition in this trial, with no follow-up data on 26% of those randomised.

Five randomised controlled trials (RCTs)[30–34] compared UAE with either hysterectomy or a mix of hysterectomy and myomectomy. Of the latter, the REST (Randomised trial of Embolisation versus Surgical Treatment) trial[30] randomised a total of 157 women in a 2 : 1 ratio to UAE and either myomectomy or hysterectomy before assessing quality of life at 5 years with the Short Form questionnaire-36 items general health survey. Secondary measures included the frequency of complications and adverse events (AEs) and the need for further intervention. A trial of 127 women in China collected similar outcomes.[31] Meta-analysis of the two studies comparing UAE with hysterectomy or myomectomy showed no difference in the number of repeat interventions [pooled risk ratio (RR) 3.45, 95% confidence interval (CI) 0.18 to 64.35; $p = 0.45$, $I^2 = 75\%$] within 2 years and no evidence of a difference in the proportion of women who after 5 years would recommend their procedure (RR 1.11, 95% CI 0.94 to 1.32; $p = 0.16$, $I^2 = 50\%$).[35]

Pregnancy and pregnancy outcomes

Perhaps as a result of the uncertainty of the effect of UAE on fertility, some previous RCTs have not included women wishing to get pregnant,[29] and those including hysterectomy in the comparison group uninformative. In a study from Czechia,[27,28] there was a significant imbalance in the numbers of women attempting to conceive, with 17 pregnancies reported among 26 women in the UAE group and 32 pregnancies reported among 40 women in the myomectomy group. The authors[27,28] also reported that, on average, the women in the myomectomy group had become pregnant sooner postoperatively than the women in the UAE group. Notably, live birth rates were significantly lower among those in the UAE group than among those in the myomectomy group (RR 2.32, 95% CI 1.19 to 4.53; $p = 0.01$). A small Phase II non-randomised study[36] from France enrolled 15 women, of whom nine actively tried to get pregnant in the year following UAE and of whom five conceived and had a live birth.[36]

These results and uncertainty around the potential impact of UAE on ovarian and uterine function have resulted in recommendations against UAE for women seeking pregnancy. A recent meta-analysis[37] suggested that UAE had no appreciable impact on ovarian reserve, as measured by mean serum concentrations of anti-Müllerian hormone (AMH) and follicle-stimulating hormone (FSH).

Previous research on the cost and cost-effectiveness of treatments for uterine fibroids

The cost-effectiveness of different interventions for the management of uterine fibroids has been evaluated in nine studies.[30,38–45] These studies utilised data from different sources and one study was based solely on a RCT.[30] Economic studies reporting only cost data were not considered here. The interventions used in these studies consisted of MRgHIFU, hysterectomy, myomectomy, UAE and medical management. Cost-effectiveness was assessed from the perspectives of the payer and the society. Only three studies[30,39,40] were specific to the UK setting, the remainder being from Canada, the USA and Hong Kong.

The clinical studies underpinning the economic evaluations sometimes gave inconsistent and conflicting results on the clinical effectiveness and safety. Some of the variation can be explained by small sample size and, particularly in the case of the non-randomised studies, considerable differences in baseline characteristics. For example, those undergoing UAE tended to be older and of higher parity and to have poorer quality of life and larger fibroids. This has a direct impact on the results of the associated economic evaluations.

All studies included UAE as a comparator. Six[30,38,39,41–43] of the nine studies also included myomectomy as a comparator. Often, myomectomy was considered to be a second-/third-line treatment[43,44] or a treatment option when less-invasive methods failed to improve symptoms.[40] The RCT-based study[30] categorised UAE as 'surgical treatment', along with hysterectomy.

The results showed UAE to be cost-effective when compared with hysterectomy[41,44,45] and myomectomy.[41] However, it was not cost-effective when compared with MRgHIFU.[46] In the study conducted by Wu *et al.*,[40] UAE was cost-effective compared with hysterectomy over the first year after treatment, but this was no longer the case when adopting a longer time horizon. The RCT-based study supports this result,[30] as UAE was associated with a greater resource use and higher costs than the surgical treatments (i.e. hysterectomy and myomectomy) during the 1- to 5-year follow-up. However, within the first year, it was associated with lower costs than the surgical treatments. In another two studies,[41,43] myomectomy was found to incur higher costs and provide less health benefit than MRgHIFU and UAE (i.e. myomectomy was dominated by these two procedures).[41,43] By contrast, one study[42] found that myomectomy was cost-effective when compared with MRgHIFU if productivity costs were not included. However, even when productivity costs were included, the differences in cost and health benefits between myomectomy and MRgHIFU were small. Similarly, in the same study by Cain-Nielsen *et al.*,[42] UAE was found to be dominated by myomectomy, but, again, the differences in cost and health benefits were small. A study by You *et al.*,[38] which directly compared UAE with myomectomy from a Hong Kong society perspective over 5 years, reported similar findings (i.e. myomectomy compared with UAE was cost-effective, but with minimal difference).

National and international guidelines on treatment for fibroids

The Royal College of Obstetricians and Gynaecologists (London, UK) and the Royal College of Radiologists (London, UK) jointly issued clinical practice guidelines during recruitment to FEMME (randomised trial of treating Fibroids with either Embolisation or Myomectomy to Measure the Effect on quality of life).[47] These guidelines[47] stated that UAE should be considered alongside surgical treatments, endometrial ablation and medical management for women with symptomatic fibroids. These guidelines[47] also highlighted that evidence for fertility and pregnancy outcomes after UAE and myomectomy is limited and that there is no robust comparative evidence. Therefore, the guidelines[47] deferred making a recommendation for women with fibroids who might want to become pregnant.

In 2012, the American Association of Gynecologic Laparoscopists (Cypress, CA, USA) published a practice guideline[48] solely about submucosal fibroids, stating that UAE and MRgHIFU are not appropriate for women who want to get pregnant, while acknowledging that this recommendation was based on expert opinion alone. The American College of Radiology (Reston, VA, USA) presented a variety of clinical vignettes of women with fibroids and derived appropriateness criteria for each potential treatment strategies for each scenario.[49] The American College of Radiology considers UAE appropriate in all situations and myomectomy in most situations, except where there are multiple submucosal fibroids. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (Melbourne, VIC, Australia) recommendations advise caution and recommends that the routine use of UAE in young women wishing to conceive should be avoided as the effects are uncertain[50] again based on expert opinion. We are unaware of the production of any other subsequent guidelines on fibroid management from professional societies in English-speaking countries.

Rationale

Both myomectomy and UAE appear to improve the quality of life of women with symptomatic uterine fibroids, but data derived from high-quality RCTs that would support these very different options are sparse.[51] For symptom control, the choice is currently very uncertain, and indications and clinical preferences for either modality are varied. There is a perception that fertility and pregnancy outcomes are poorer following UAE, but there are few RCT data to support this.[52,53] Given that the options are so different, with very different impact on clinical, patient-reported and economic outcomes, a fair and comprehensive comparison is both overdue and necessary.

Specific objectives

Primary objective

The aim of the FEMME trial was to examine the clinical effectiveness of UAE in comparison with myomectomy in the treatment of symptomatic fibroids. This was achieved by conducting a large, multicentre, open RCT with quality of life as the primary outcome.

Secondary objectives

- Conduct an economic evaluation to determine the relative cost-effectiveness of these two interventions, at 2 and 4 years after randomisation, from the perspective of the NHS.
- Explore the relative effectiveness of the interventions on HMB symptoms.
- Explore differences in pregnancy rates and outcomes in women seeking pregnancy.
- Compare AEs and complications of the two interventions.
- Compare reintervention rates.
- Investigate whether or not presenting characteristics have an impact on the comparative clinical effectiveness of the interventions.
- Measure hormones associated with ovarian reserve following treatment and compare these between the women in each study group.

Chapter 2 Methods for the randomised controlled trial

Design

The FEMME trial was a randomised, open, parallel, multicentre trial of UAE and myomectomy in women with symptomatic uterine fibroids wishing to avoid a hysterectomy. The trial had a favourable ethics opinion from National Research Ethics Service Committee Coventry and Warwickshire (reference 11/WM/0149).

Trial oversight

Trial oversight and monitoring were provided by a Trial Steering Committee (TSC) and by an independent Data Monitoring Committee.

The TSC provided independent supervision for the trial, providing advice to the chief investigator, co-investigators and the sponsor on all aspects of the trial throughout the trial. The Data Monitoring Committee adopted the DAMOCLES charter[54] to define its terms of reference and operation in relation to oversight of the FEMME trial. Both the TSC and Data Monitoring Committee met on an approximately annual basis during the period of recruitment and follow-up.

Participants

The participants in the FEMME trial were recruited in gynaecology and interventional radiology clinics in a diverse range of NHS hospitals located across the UK. Hospitals could participate if their patient pathway allowed eligible women to undergo either myomectomy or UAE, whether at the same hospital, in another hospital within the same trust/board or under an arrangement with another NHS trust/board.

Screening of potential participants

A full gynaecological and general history was taken by the gynaecologist alongside a general and pelvic examination. The initial diagnosis of fibroids was informed by the woman's medical history and symptoms, and was confirmed by transabdominal or transvaginal ultrasound scan (TVUS) or hysteroscopy.

If fibroids were visible and considered to be the likely cause of symptoms, and the felt that the women could respond equally well to UAE or myomectomy, then the clinician made the initial approach to the woman to discuss treatment options and participation in the FEMME trial. Women who were referred to a recruiting gynaecologist with a diagnosis then received written information about the FEMME trial before their appointment. If a woman expressed an interest in taking part in the FEMME trial, an approved member of the local research team discussed the trial with them and provided written information. Women who consented to participate in the FEMME trial were provided with a baseline

questionnaire and a diary to estimate their menstrual blood loss and were asked to use this to record when they started their next menstrual period (prior to randomisation). Prior to treatment, most women underwent magnetic resonance imaging (MRI), CEMRI ideally, to enable the gynaecologist to accurately visualise the uterus and locate any fibroids.

Eligibility criteria

Women were eligible for randomisation if they met all inclusion criteria and no exclusion criteria.

Inclusion criteria

- Women with symptomatic fibroids who did not wish to have a hysterectomy, but who were prepared to accept one in an emergency.
- Women suitable for, and accepting of, either treatment (i.e. myomectomy or UAE).
- Women for whom the clinical team were uncertain as to which treatment was indicated.
- Women who provided written informed consent.

Exclusion criteria

- Women who refused a hysterectomy, even if an intraoperative complication made this an advisable procedure.
- Women with recent or ongoing pelvic inflammatory disease.
- Women with significant adenomyosis, as identified by TVUS or CEMRI. (Women with concurrent adenomyosis were eligible if fibroids were believed to be the predominant cause of their symptoms.)
- Women with a positive pregnancy test just before consent.
- Women who were postmenopausal, as defined as > 1 year since previous menstrual period.
- Women with suspected malignancy.
- Women aged < 18 years.
- Women who were unable to provide informed consent because of incapacity [as defined by the Mental Capacity Act 2005[55] or the Adults with Incapacity (Scotland) Act 2000[56]].
- Non-English-speaking women for whom translation or interpretation facilities were insufficient to guarantee informed consent.
- Women who had previously undergone myomectomy via a laparotomy or had previously undergone embolisation.

Recruitment

In the majority of cases, CEMRI was performed to confirm the presence of fibroids, to determine whether or not the fibroids were amenable to treatment by either myomectomy or UAE and to rule out any other pathologies. Consent was obtained in writing from confirmed eligible women who agreed to participate in the trial. The recruitment pathway is summarised in *Figure 1*.

Participating sites were asked to record the number of women who were initially eligible but later excluded or women who were eligible but who declined consent, alongside the reason for non-inclusion.

Randomisation

Allocation concealment

Participants were randomised via a secure, centralised, online randomisation system provided by the University of Birmingham Clinical Trials Unit. No allocation could be given until all participant entry criteria were confirmed by the local study team.

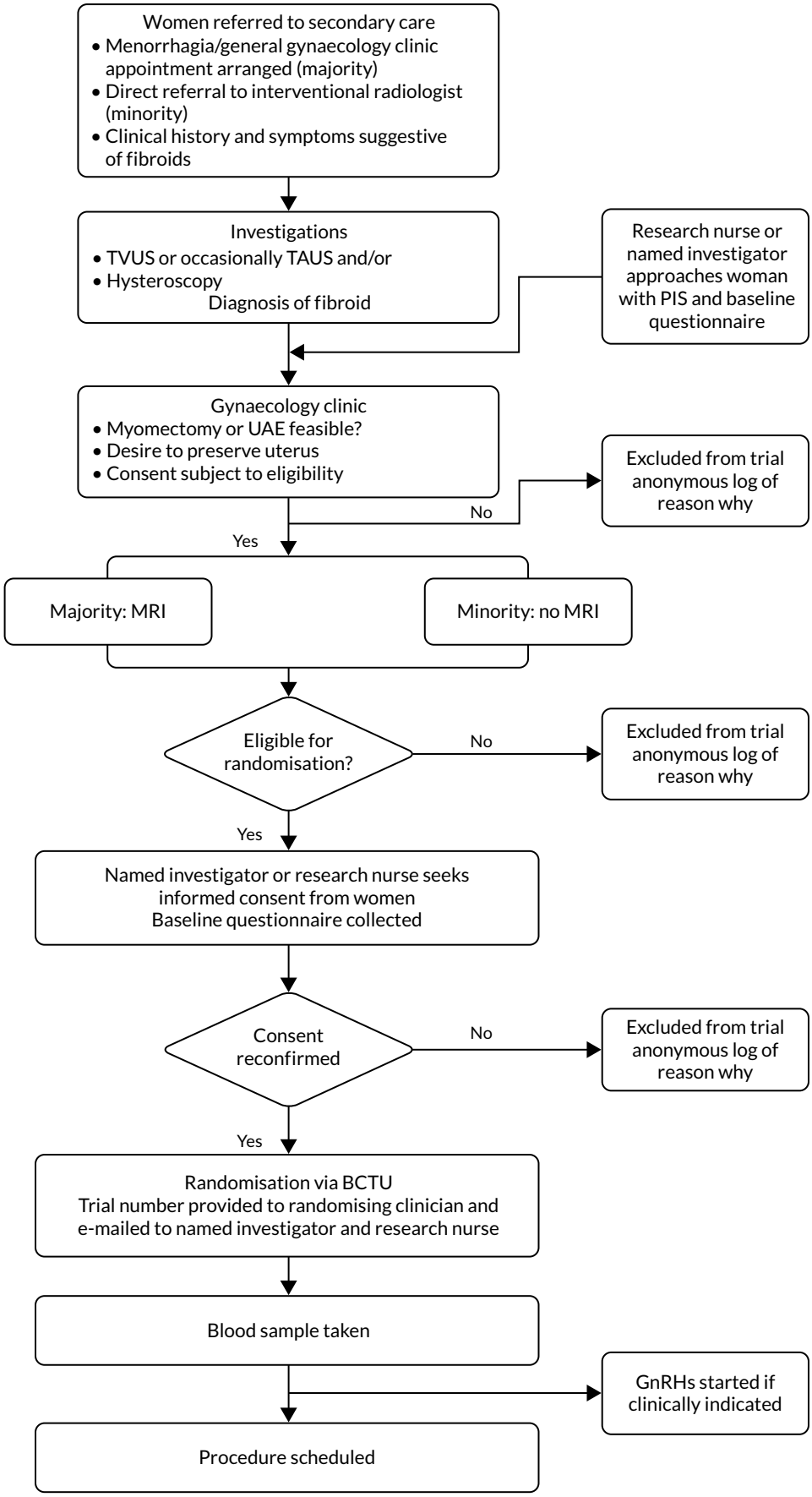

FIGURE 1 Eligibility pathway to recruitment and randomisation. BCTU, Birmingham Clinical Trials Unit; GnRH, gonadotropin-releasing hormone; PIS, participant information sheet; TAUS, transabdominal ultrasound.

Sequence generation and minimisation

Participants were randomised to undergo myomectomy or UAE in a 1 : 1 ratio. A minimisation procedure using a computer-based algorithm was used to avoid chance imbalances in important stratification variables. The stratification variables used for minimisation were:

- longest dimension of largest fibroid (≤ 7 cm or > 7 cm)
- number of fibroids present (1–3, 4–10 or > 10)
- women desires pregnancy (yes or no).

The choice of subgroups was informed by data from the UK Fibroid Registry, which indicated that 45% of women have fewer than four fibroids and in 50% of women the dominant fibroid is ≤ 7 cm at the time of intervention.

Baseline information

The following demographic and clinical criteria were requested on each randomised participant:

- age at randomisation
- ethnicity, if declared, using standard NHS categories
- height and weight
- number of fibroids present (estimated if necessary)
- location of largest fibroid and its dimensions
- presence of ovarian pathology
- uterine dimensions
- parity and gravidity
- current use of contraceptives, hormonal treatments or other treatments for HMB
- previous abdominal surgery.

Baseline blood sample

After randomisation, but before treatment, 5–10 ml of blood was collected into a serum separation Vacutainer tube (Beckton Dickinson UK Ltd, Oxford, UK). This blood sample was sent to the University of Birmingham's Biobank, where it was transformed into serum on receipt. The serum sample was aliquoted and then stored at –70 °C until assay.

Interventions

Following randomisation, the allocated treatment was scheduled for the woman in accordance with local hospital practice. A negative pregnancy test was required immediately prior to the intervention being performed. Pre-myomectomy treatment of fibroids using gonadotropin-releasing hormone analogues and, later, pre-treatment with UPA could be initiated at the discretion of the gynaecologist, but was not recommended. Immediate pre-procedure use of any medical treatment or hormonal contraceptive to reduce HMB was recorded.

Myomectomy

Myomectomy was performed using the technique preferred by the operating gynaecologist (i.e. open, hysteroscopic or laparoscopic). If thought appropriate, and in consultation with the woman, the gynaecologist could morcellate the fibroid in accordance with local guidelines. The use of morcellation was not recorded.

Uterine artery embolisation

Uterine artery embolisation was performed by an interventional radiologist experienced in the technique. Bilateral selective catheterisation and embolisation of the uterine arteries was performed

under fluoroscopic guidance, either in a single procedure or in two-staged unilateral procedures. The angiographic end point of the embolisation procedure was complete or near-complete stasis of blood flow in the uterine artery. The embolic agent used was at the discretion of the interventional radiologist, but was required to carry a Conformitè Europëenne (CE) mark.

Other treatments

The trial did not preclude gynaecologists performing other appropriate procedures (e.g. adhesionolysis) at the time of the allocated procedure. Basic details regarding these additional procedures were recorded.

Participants were free to choose the brand and type of sanitary protection that they used. Participants were free to use any prescribed or over-the-counter pharmacological agents that they required.

Where the woman withdrew her consent to proceed with the allocated treatment, or where immediate preoperative concerns precluded her from proceeding, this was recorded.

Withdrawal from the trial

Participants could voluntarily withdraw their consent to trial participation at any time. It was reiterated to the investigator and participant that non-compliance with the allocated procedure did not mean withdrawal from the trial, and that some procedural data and all participant-reported outcomes would be requested. If a participant did not return for a scheduled visit for follow-up scans or blood samples, numerous attempts by a variety of methods were made to contact her and (where possible) to review compliance and AEs. The reason(s) for self-withdrawal were documented where possible. If participants did not respond to postal questionnaires, attempts were made to contact them by telephone, their general practitioner (GP), their gynaecologist or an approved member of the local research team. Non-response was not considered withdrawal of consent. If a participant explicitly withdrew consent to any further data recording, then this decision was respected and recorded. All communications surrounding the withdrawal were noted in study records and no further data were collected for such participants.

Blinding

Owing to the very different natures of the interventions, it was not possible to blind participants, investigators, research nurses and other attending clinicians to the trial treatment allocation.

Outcomes and assessment

Primary outcome

The primary outcome was the participant-reported health-related quality-of-life (HRQoL) domain of the Uterine Fibroid Symptom Quality of Life (UFS-QOL) tool.[57] The HRQoL domain contains 29 questions over the following six subscales: (1) concern, (2) activities, (3) energy/mood, (4) control, (5) self-consciousness and (6) sexual function. Responses for the HRQoL questions ranged from ‘none of the time’ to ‘all of the time’. Response options for the eight-item severity subscale ranged from ‘not at all’ to ‘a very great deal’. Scores ranged from 0, indicating worst HRQoL, to 100, indicating the best HRQoL. Participants were asked to respond considering their experiences over the previous 3 months. The instrument demonstrates face, construct and discrimination validity and has been demonstrated to be responsive to change.[58,59] The HRQoL score at 2 years of follow-up was the primary outcome. Two years was considered an appropriate medium-term time point, sufficiently distant from the procedure to observe a stable effect, but also able to capture any recurrence of symptoms.

Secondary outcomes

Prespecified secondary outcomes were as follows (see *Data collection schedule* for assessment times):

- The HRQoL domain from the UFS-QOL at the other time points (that were not the primary outcome assessment time).
- The symptom severity domain from the UFS-QOL [scores ranged from 0 (no symptoms) to 100 (worst symptoms)].
- EuroQol-5 Dimensions, three-level version (EQ-5D-3L), score [on a scale of −0.59 (worst outcome) to 1.0 (best outcome)].[60]
- EuroQol-5 Dimensions (EQ-5D) visual analogue scale (VAS) [on a scale of 0 (worst outcome) to 100 (best outcome)].[60]
- Menstrual blood loss using the pictorial bleeding assessment chart (PBAC)[61] [on a scale of 0 (no bleeding) as a minimum, but with no fixed upper limit]. This is a validated and well-used assessment of menstrual blood loss in women with uterine fibroids. Further analysis on PBAC scores was carried out by categorising blood loss as amenorrhoea (a score of 0) or light (scores > 0 to ≤ 10), normal (scores > 10 to ≤ 100) or heavy (scores > 100) bleeding. The last cut-off point was chosen because it is known to have good predictive ability for heavy bleeding[61] and can also be used to generate rates of amenorrhoea and non-heavy bleeding (defined as a score of < 100).
- Pregnancy and associated outcomes, specifically the ability to conceive (i.e. overall and in the population who, at the time of randomisation, reported that they wanted to get pregnant) and the subsequent outcome (i.e. live birth, miscarriage, stillbirth and termination). Pregnancy could be reported to the study office either by the women or by a member of the local study team in the first instance.
- Participant acceptability, as defined by responses to 'Would you have your operation again?'.
- Participant acceptability, as defined by responses to 'Would you recommend operation to a friend?'.
- Length of hospital stay.
- Further treatment for fibroids (including hysterectomies) or recurrence of symptoms.
- Measure of ovarian reserve by assay of FSH, AMH and luteinising hormone (LH). See *Ovarian reserve tests* for details of the assay.
- Serious adverse events (SAEs) and procedural complications considered to be related to the study protocol or intervention were collected (see *Ovarian reserve tests*). SAEs are defined in *Serious adverse events*.

Ovarian reserve tests

Anti-Müllerian hormone and day 2–4 plasma levels of the gonadotropins FSH and LH were determined. At the time that blood samples were drawn, the woman was asked if she was on day 2, 3 or 4 of her menstrual cycle. Samples were processed as described in *Baseline blood sample*. The serum aliquots were sent separately in two batches on dry ice to the laboratories of the University of Glasgow (Glasgow, UK) for analysis.

Resource use outcomes

Resource use outcomes are detailed in *Chapter 5*.

Data collection schedule

The trial addressed outcomes over three time frames, with outcome measures described in *Primary outcome* and *Secondary outcomes*. The data collection schedule is summarised in *Table 1* and below:

- Short-term data – immediate impact of UAE and myomectomy on fertility potential up to 1 year, immediate postoperative AEs, resources used in diagnosis and intervention. Operative details and complications will be collected in two time frames: (1) up to discharge from hospital and (2) from discharge to 6 weeks post procedure.
- Medium-term data – up to 2 years for symptom-specific and generic quality-of-life outcomes and initial cost-effectiveness, fertility potential and pregnancy rates.
- Long-term data – up to 4 years for pregnancy and further treatment rates, together with quality-of-life outcomes.

TABLE 1 Outcome assessments and time points

Outcome measure	Time point						
	Prior to randomisation	Before discharge	6 weeks	6 months	1 year	2 years	4 years
UFS-QOL	✗			✗	✗	✗	✗
EQ-5D-3L and VAS	✗			✗	✗	✗	✗
PBAC	✗			✗	✗	✗	✗
Pregnancy and associated outcomes						✗	✗
Participant acceptability				✗	✗	✗	✗
Fertility potential (hormonal ovarian reserve)	✗		✗	✗	✗		
Resource use (clinical)	✗					✗	✗
SAEs		Throughout					
Further treatment						✗	✗

Sample size

The original sample size was 650 participants. This would have provided 90% power (at a two-sided alpha level of 0.05) to detect a small to moderate difference of 8 points [i.e. 0.29 of a standard deviation (SD)] in the primary outcome, allowing for approximately 20% loss of primary outcome data. There is no validated minimally important difference for the UFS-QOL scale[58] and, therefore, this target difference to detect was considered meaningful and plausible based on the results of a similar published study.[29]

Following slower than anticipated recruitment to the trial, and with access to individual participant UFS-QOL data from a previous study,[12,29] the sample size target was revised to 250 participants in October 2013, when 114 women had been randomised. A re-analysis of these data, using more appropriate regression methods accounting for baseline imbalances, suggested that a larger difference of 12 points was attainable and that the pooled-group SD of UFS-QOL scores was slightly lower than that originally estimated. The revised sample size had 90% power to detect a moderate-sized difference between groups (i.e. 0.55 of a SD). The Data Monitoring Committee and TSC, which remained blind to contemporaneous primary outcome data, approved the changes on the grounds that this revised effect difference was plausible.

Statistical methods

A comprehensive statistical analysis plan was drawn up prior to the 2-year analysis and was provided to the independent TSC for review. A summary of the analytical approaches is described here.

The analysis of the primary outcome was performed in accordance with the intention-to-treat (ITT) principle. Analyses were performed on (1) complete observed data and (2) all randomised participants at all assessment times through imputation of missing responses. Repeated-measures linear regression models, including data at all time points, were used to estimate least-square mean differences (with 95% two-sided CIs) in the primary outcome at 2 years.[57,62] Parameters allowing for participant, treatment group, baseline score, time, time-by-treatment interaction and the minimisation variables were included. For analysis 1, participants were included in the model provided that they had at least one response at any of the three assessment times. For analysis 2, multiple imputation using a Markov chain Monte Carlo

method, assuming a joint multivariate normal distribution, was used. The imputation model was consistent with the analysis model in terms of the variables used. All response times were included.[63]

For the primary outcome, a *p*-value was generated through the aforementioned linear regression model. Observed data from secondary continuous outcomes were analysed in a similar fashion to the primary outcome. Reproductive hormone levels were log-transformed and, therefore, for ease of interpretation, are presented as geometric mean ratios. Log-binomial regression was used to estimate relative rates and 95% CIs for binary outcomes, making similar adjustments to the other analyses. The widths of the CIs were not adjusted for multiplicity and, therefore, the intervals should not be used to infer definitive treatment effects.

Several sensitivity analyses for the primary outcome were also performed, including inclusion of time as a continuous linear predictor, assuming no interaction with treatment; addition of a parameter for treating hospital; and a per-protocol analysis, including only those who received the allocated treatment. Some questionnaires were incomplete and, therefore, an additional sensitivity analysis used available subscale scores to generate an overall score.

For 4-year data, continuous outcomes were analysed by adding responses at this time point to the aforementioned regression models. For time to first pregnancy and time to first further procedure for treatment of fibroids, a Cox proportional hazard model was carried out, adjusting for the minimisation variables. Kaplan–Meier plots were produced in which women were censored if they had withdrawn, were lost to follow-up or had undergone a hysterectomy.

We analysed the treatment effect on the primary outcome in prespecified subgroups that matched the minimisation variables. These analyses involved adding the subgroup-by-treatment group interaction parameters to the linear regression model. All analyses were performed using SAS (SAS Institute Inc., Cary, NC, USA) software, version 9.4.

The Data Monitoring Committee reviewed accruing safety data during the period of recruitment.

Serious adverse events

Serious adverse events were defined as AEs that are attributable to the study protocol or study interventions and caused or resulted in any of the following:

- death
- life-threatening complications
- inpatient hospitalisation or prolongation of existing hospitalisation
- persistent or significant disability or incapacity
- congenital anomaly/birth defect
- intervention to prevent disability or incapacity.

For each SAE, the following information was requested:

- full details in medical terms with a diagnosis, if possible
- the duration
- any action taken
- the outcome
- causality in the opinion of the investigator and in relation to the study protocol or intervention received and expectedness.

An assessment of causality and expectedness of the SAE in relation to the study protocol or intervention was made by a clinician at the randomising centre. The information was also assessed by one of the clinical lead investigators, although the clinical lead investigator could not contradict any assessment that a SAE had a reasonable causal relationship with the trial intervention.

Participants were asked to report hospitalisations when followed up by the study team. Reported events were followed up in conjunction with the randomising hospital to ascertain if the event constituted a SAE.

The outcome of pregnancies reported to the study was collected by a member of the local research team, although women could also report pregnancies and their outcomes in the participant questionnaires and directly to the FEMME trial office.

Chapter 3 Clinical effectiveness results: postoperative and 2-year follow-up data

This chapter reports the clinical results of the FEMME trial, including postoperative and follow-up data to 2 years post randomisation. The chapter starts with a description of the flow of participants through the trial and is followed by demographic information and results of the primary and secondary outcome measures, and postoperative complications.

Recruitment of participants

The randomisation of participants commenced on 6 February 2012 and the last woman was randomised on 21 May 2015. The monthly rate of recruitment of participants into the FEMME trial is shown in *Table 2*. Participants were recruited from 29 hospitals across England, Scotland and Wales, as shown in *Figure 2*.

TABLE 2 Recruitment to the FEMME trial by hospital

Recruiting centre	Number (%) of patients randomised
St George's Hospital	102 (40)
Glasgow Royal Infirmary	36 (14)
Royal Infirmary of Edinburgh	25 (10)
Queen's Hospital, Romford	14 (6)
John Radcliffe Hospital	10 (4)
St Thomas' Hospital	10 (4)
Birmingham Women's Hospital	6 (2)
Birmingham Heartlands Hospital	5 (2)
Mayday University Hospital	5 (2)
St Mary's Hospital	5 (2)
City General Hospital (University Hospital of North Staffordshire)	3 (1)
City Hospital Birmingham	3 (1)
East Surrey Hospital	3 (1)
Leicester General Hospital	3 (1)
The Royal Victoria Infirmary	3 (1)
Royal Blackburn Hospital	3 (1)
Luton and Dunstable Hospital	2 (1)
Neath Port Talbot Hospital	2 (1)
Queen's Medical Centre	2 (1)
St Helier Hospital	2 (1)
York Hospital	2 (1)

continued

TABLE 2 Recruitment to the FEMME trial by hospital (*continued*)

Recruiting centre	Number (%) of patients randomised
City Hospitals Sunderland	1 (< 1)
Crosshouse Hospital	1 (< 1)
Leeds General Infirmary	1 (< 1)
Ninewells Hospital	1 (< 1)
Norfolk and Norwich University Hospital	1 (< 1)
Royal Free Hospital	1 (< 1)
Royal Hallamshire Hospital	1 (< 1)
St Peter's Hospital	1 (< 1)
Total	254

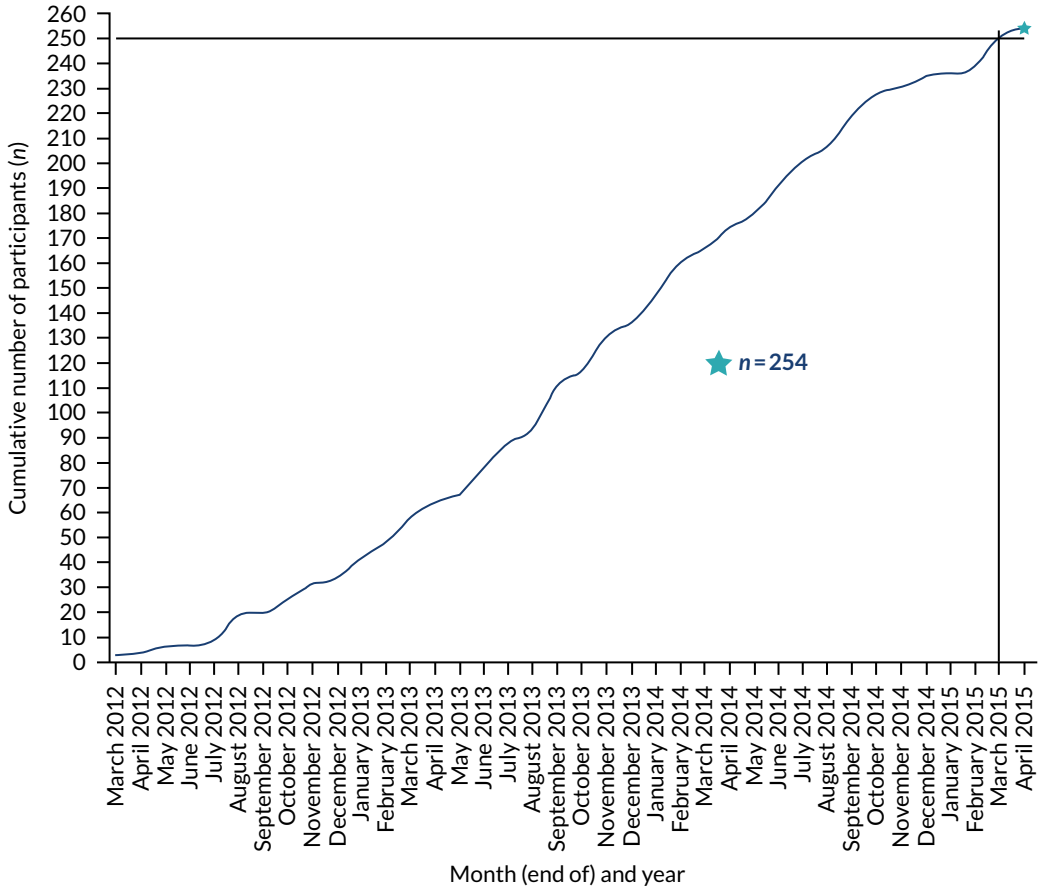

FIGURE 2 Recruitment of participants to the FEMME trial over time.

Information was sought for reasons why women declined their invitation to participate in the FEMME trial up to March 2014, at which point 170 women had been randomised. Not every participating hospital provided data on the number of women declining participation and, even among hospitals that did, many did not do so consistently and, therefore, the ratio of women randomised to women declining participation cannot be reliably calculated. Data on 335 women who were assumed to be eligible for randomisation and who declined participation are available. Of these 335 women, 84 (25.1%) requested

UAE, 79 (23.6%) requested a myomectomy and 56 (16.7%) requested a hysterectomy. The remaining 116 (34.6%) women gave either another reason or no reason. No accurate information is available on the number of women who were initially approached for participation but were ultimately found to be ineligible for randomisation.

Participant follow-up within 2 years

A total of 127 women were assigned to myomectomy and 127 women were assigned to UAE (*Figure 3*). The follow-up rate for the primary outcome was 206 out of 254 (81%) women at 2 years (see *Figure 3*). A total of 227 (89%) women provided scores at least at one assessment time.

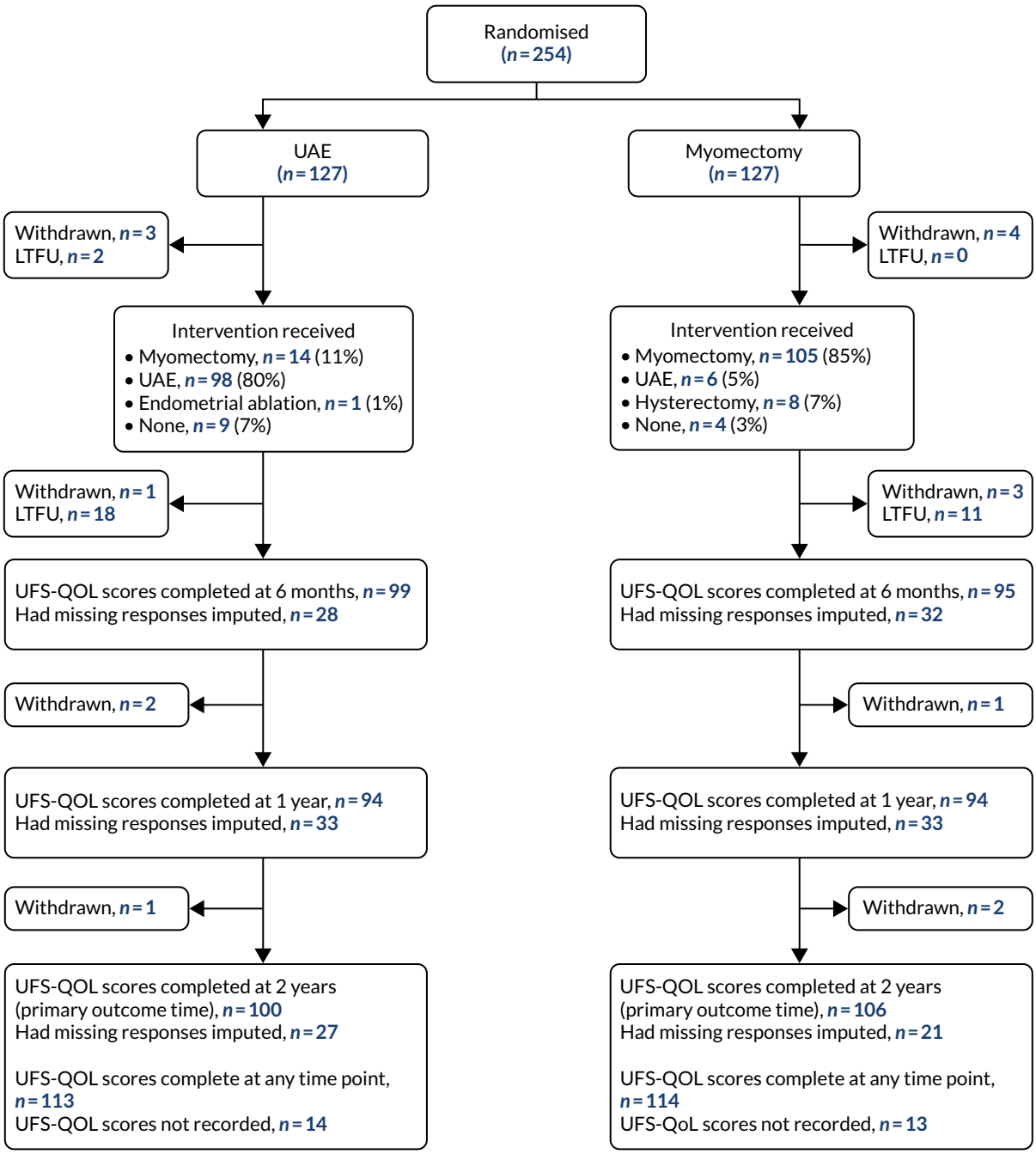

FIGURE 3 Flow of participants through the FEMME trial up to 2 years of follow-up. LTFU, lost to follow-up. Manyonda *et al.*[64] Copyright © 2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Compliance to treatment allocation

Of the 123 women who were randomised to myomectomy and who did not withdraw from the trial prior to the procedure, 105 (85%) had a myomectomy as their initial operation. Similarly, 98 of the 122 (80%) women in the UAE group underwent UAE. Four women in the myomectomy group and nine women in the UAE group chose not have either procedure initially. The initial procedures following randomisation for each allocation group are shown in *Figure 4*.

Of those participants who crossed over groups on the basis of a clinical recommendation after randomisation (as opposed to a participant-driven decision), one participant in the myomectomy group was found to have adenomyosis (alongside fibroids) and was offered UAE and two women in the UAE group had a myomectomy (one woman because of heavy bleeding and anaemia and one for an unknown reason).

Four women in the myomectomy group underwent hysterectomy: one because of suspected pelvic infection, one because MRI showed no fibroids but, instead, a large area of adenomyosis, one because she was admitted with acute abdominal pain and one because the surgeon was unable to perform myomectomy. There was one emergency conversion to hysterectomy during a laparoscopic myomectomy following a massive haemorrhage. In the UAE group, one woman underwent a transcervical resection of her fibroids instead.

Baseline characteristics of trial participants

The baseline characteristics of the trial participants are shown in *Table 3*. Women were, on average, 41 years old and classed as overweight by their body mass index. Although 48% of participants in both groups responded positively to the question 'at this time, are you seeking to get pregnant?', about 58% of women were taking treatments, including contraceptives and hormones, to control their HMB or shrink their fibroids.

Procedural details

The details of the initial procedures undertaken are shown in *Table 4*. Combinations of procedure specifics were possible, according to the clinical situation: one participant from the UAE group had a hysteroscopic myomectomy and then went on to have an open myomectomy; one participant from the myomectomy group had a laparoscopic myomectomy that was converted to an open myomectomy; and six participants from the myomectomy group had a hysteroscopic myomectomy and then went on to have an open myomectomy.

The vast majority of the UAE procedures were successfully completed in the opinion of the radiologist at the time of procedure. However, among those women who had MRI after 6 months, around one-quarter had fibroids that were considered to be < 90% infarcted.

Primary outcome results

The average HRQoL score at 2 years was substantially improved in both groups, approximately doubling in each group, but these improvements were greater at 2 years in those assigned to the myomectomy group (mean difference from observed data 8.0 points, 95% CI 1.8 to 14.1 points, $p = 0.01$; mean adjusted difference with missing responses imputed 6.5 points, 95% CI 1.1 to 11.9 points). Significant results were seen at earlier time points, as shown in *Table 5* and *Figure 5*.

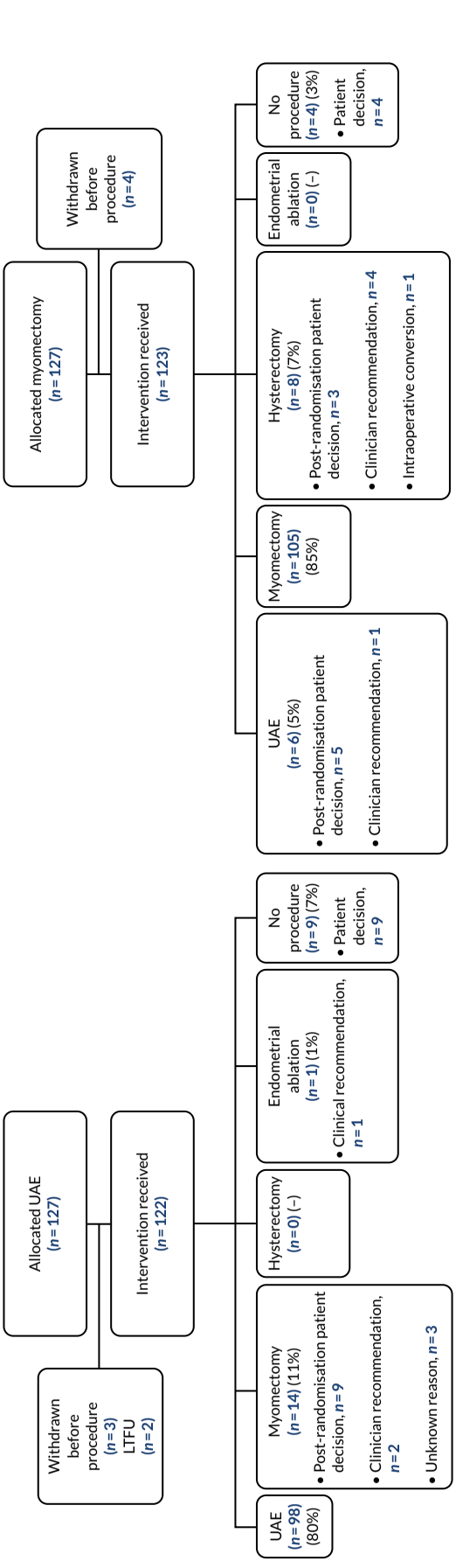

FIGURE 4 Compliance with treatment allocation, by group. LTFU, lost to follow-up. Manyonda *et al.*[64] Copyright © 2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

TABLE 3 Baseline demographic, medical, surgical and fibroid characteristics of trial participants

Baseline characteristic	UAE group (*N* = 127)	Myomectomy group (*N* = 127)
Demographics and obstetric history		
Age (years), mean (SD), *n*	40.2 (6.55), 127	42.7 (6.4), 127
Ethnic group, *n* (%)		
White (British/other)	59 (46)	57 (45)
Black (Caribbean/African/other)	48 (38)	54 (43)
South Asian (Indian/Pakistani/Bangladeshi)	10 (8)	5 (4)
Mixed (white/black/Asian/other)	6 (5)	8 (6)
Other	4 (3)	3 (2)
BMI (kg/m^2), mean (SD), *n*	28.2 (6.2), 119	28.1 (5.3), 123
Desiring pregnancy at time of randomisation, *n* (%)[a]	61 (48)	61 (48)
Parity, median (IQR), *n*	0 (0–1), 125	1 (0–2), 127
Gravidity, median (IQR), *n*	1 (0–2), 125	2 (0–3), 127
Fibroid assessment		
Imaging modality to diagnose fibroid, *n* (%)[b]		
MRI	89 (70)	99 (78)
Ultrasound	36 (28)	27 (21)
Not stated	2 (2)	1 (1)
Location of largest fibroid, *n* (%)		
Submucosal	6 (5)	14 (11)
Submucosal (pedunculated)	1 (1)	1 (1)
Subserosal	30 (24)	21 (17)
Subserosal (pedunculated)	6 (5)	5 (4)
Intramural	74 (58)	81 (64)
Other	4 (3)	0
Not stated	6 (5)	5 (4)
Longest dimension of largest fibroid (cm)[a]		
≤ 7, *n* (%)	64 (50)	64 (50)
> 7, *n* (%)	63 (50)	63 (50)
Mean (SD)	7.6 (3.2)	7.7 (4.2)
Number of fibroids[a]		
1–3, *n* (%)	84 (66)	84 (66)
4–10, *n* (%)	37 (29)	37 (29)
> 10, *n* (%)	6 (5)	6 (5)
Median (IQR)	2 (1–5)	2 (1–5)
Largest fibroid volume (cm^3), mean (SD), *n*	436 (594), 124	446 (548), 126
Uterine volume (cm^3), mean (SD), *n*	1170 (1280), 118	1240 (1120), 118
Medical and surgical history		
Previous abdominal surgery, *n* (%)[c]		
Caesarean section	12 (9)	19 (15)
Laparoscopy	19 (15)	15 (12)
Endometrial ablation	3 (2)	2 (2)

TABLE 3 Baseline demographic, medical, surgical and fibroid characteristics of trial participants (*continued*)

Baseline characteristic	UAE group (*N* = 127)	Myomectomy group (*N* = 127)
Appendectomy	8 (6)	7 (6)
Sterilisation	4 (3)	5 (4)
Other	10 (8)	15 (12)
Taking contraceptive/hormonal treatments to control symptoms at randomisation, *n* (%)	75 (59)	73 (57)

BMI, body mass index; IQR, interquartile range.
a Minimisation variable.
b More than one type of scan possible.
c More than one previous abdominal surgery possible.

Notes
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Owing to rounding, some percentages do not add up to 100% exactly.

TABLE 4 Procedure details

Procedure	UAE group (*N* = 113)	Myomectomy group (*N* = 119)
Time from randomisation to procedure (weeks), median (IQR), *n*	13 (9–20), 113	14 (9–20), 119
Length of time of intervention (leaving/entering theatre or suite) (minutes), median (IQR), *n*	90 (60–110), 94	120 (94–150), 105
Length of hospital stay (days to discharge), median (IQR), *n*	2 (2–3), 112	4 (3–5), 117
Procedure undertaken: UAE	**n = *98***	**n = *6***
In the opinion of radiologist, successful embolisation of both arteries? *n* (%)		
Yes	92 (94)	5 (83)
No	4 (4)	0
Missing	2 (2)	1 (17)
If no, what is the plan? *n* (%)		
Repeat UAE at a later date	1 (1)	0
Unknown	3 (3)	0
6-month post-procedure assessment scan: radiologist opinion of fibroid infarction, *n* (%)		
Complete (100%)	32 (40)	3 (75)
Near complete (≥ 90%)	26 (33)	0
Incomplete (< 90%)	22 (28)	1 (25)
Missing	18	2
Procedure undertaken: myomectomy	**n = *14***	**n = *105***
Type of myomectomy, *n* (%)		
Laparoscopic	4 (29)	10 (10)
Hysteroscopic	2 (14)	9 (9)
Open abdominal	9 (64)	93 (89)
Laparoscopic converted to open abdominal	0	1 (1)
Hysteroscopic converted to open abdominal	1 (7)	6 (6)

IQR, interquartile range.
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TABLE 5 Health-related quality-of-life domain scores from the UFS-QOL

Time point	Mean (SD) score, *n*		Estimated mean difference from observed data (95% CI)[a,b]
	UAE group	Myomectomy group	
Baseline	42.1 (26.4), 116	37.0 (23.9), 119	
6 months	73.9 (26.7), 99	80.5 (21.7), 95	7.4 (0.5 to 14.2)
1 year	75.7 (26.1), 94	84.7 (22.1), 94	10.8 (4.2 to 17.5)
2 years	80.0 (22.0), 100	84.6 (21.5), 106	8.0 (1.8 to 14.1)

a Least-square mean differences estimated from regression model described in *Chapter 2, Statistical methods*. Estimates were adjusted for baseline value and minimisation variables.
b Scores ranged from 0 (worst) to 100 (best). A difference of > 0 favours myomectomy.
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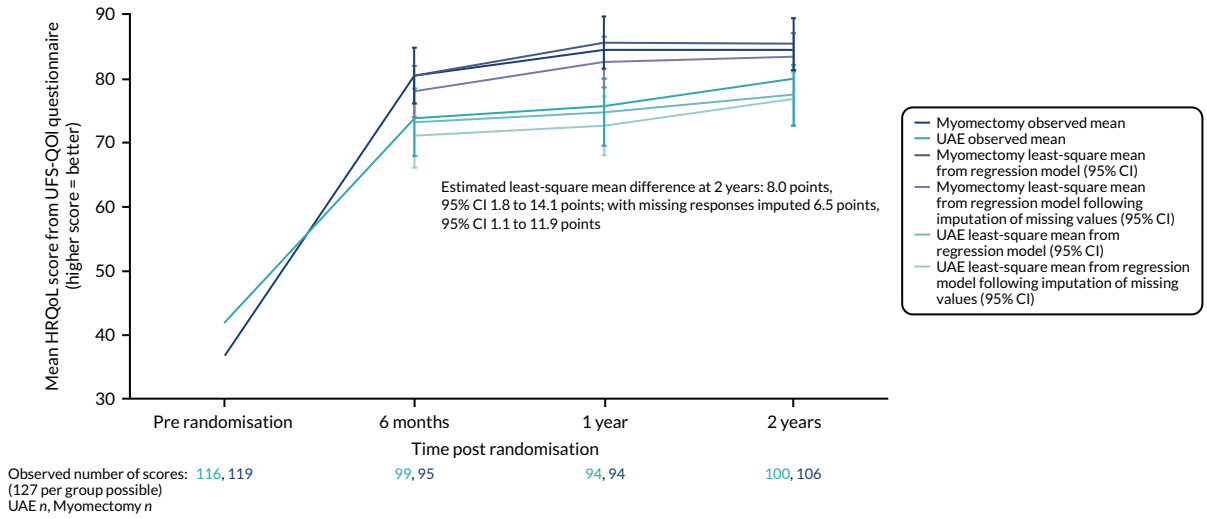

FIGURE 5 Evolution over mean responses over time of UFS-QOL HRQoL scores by group. Manyonda *et al.*[64] Copyright © 2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Sensitivity and subgroup analyses of the primary outcome

Sensitivity analyses

A number of sensitivity analyses were conducted for the primary outcome. These analyses returned estimates of mean differences that were between 6.5 and 8 points, with CIs ranging from 0 to 15 points. The results of all sensitivity analyses are shown in *Table 6*.

Subgroup analyses

Although the mean differences were higher in the subgroups of women whose largest fibroid measured > 7 cm, with four or more fibroids and not desiring pregnancy at the time of randomisation than in other subgroups, there was no compelling evidence of any differential effect in any of the subgroups in relation to the primary outcome, which is shown by the interaction *p*-values in *Table 7*.

TABLE 6 Primary outcome sensitivity analyses

Sensitivity analysis	Estimated mean difference (95% CI)[a]
Inclusion of time as a continuous linear predictor (over all time points)	8.6 (3.2 to 14.0)
Multiple imputation for missing responses with inclusion of time as a continuous linear predictor (no interaction with treatment; over all time points)	7.5 (2.8 to 12.2)
Multiple imputation for missing responses following use of available subscores to create overall score (where some responses are missing)	6.6 (1.0 to 12.1)
Multiple imputation for missing responses with inclusion of time as a continuous linear predictor (no interaction with treatment) and following use of available subscores to create overall score (where some responses are missing)	7.3 (2.5 to 12.0)
Per-protocol analysis	8.1 (1.5 to 14.8)
Tobit regression model	7.2 (–0.8 to 15.1)
Removing women who have had hysterectomy	7.4 (1.4 to 13.5)
Hospital as fixed	6.9 (0.7 to 13.2)

a Differences of > 0 favour myomectomy. Estimates adjusted for baseline value and minimisation variables.
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TABLE 7 Primary outcome subgroup analyses within 2 years

Subgroup	Mean (SD), *n*		Estimated mean difference (95% CI)[a]	Interaction *p*-value
	UAE group	Myomectomy group		
Longest dimension (cm) of largest uterine fibroid				
> 7	77.7 (23.3), 52	86.5 (18.7), 51	12.8 (4.6 to 21.0)	0.13
≤ 7	82.5 (20.5), 48	82.8 (23.8), 55	3.1 (–5.9 to 12.0)	
Number of fibroids				
1–3	80.9 (21.8), 64	84.0 (22.4), 68	6.4 (–1.45 to 14.3)	0.86
4–10+	78.4 (22.7), 36	85.7 (20.1), 38	10.4 (0.7 to 20.1)	
Currently desiring pregnancy (at time of randomisation)				
Yes	78.6 (24.5), 48	81.4 (25.2), 48	7.1 (–2.8 to 17.1)	0.41
No	81.3 (19.7), 52	87.2 (17.7), 58	8.6 (1.1 to 16.1)	

a Differences of > 0 favour myomectomy. Estimates adjusted for baseline value and other minimisation variables.
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Secondary outcomes within 2 years

Symptom severity and quality-of-life questionnaires

The UFS-QOL symptom severity domain scores were higher in the UAE group (*Table 8*). Small, but consistent, differences in scores on the two EQ-5D instrument domains were observed, in both cases in favour of myomectomy.

Menstrual bleeding outcomes within 2 years

There were no apparent differences between groups in terms of menstrual regularity, although no formal comparisons were made. *Table 9* shows the women's reported impression of their menstrual cycle regularity.

TABLE 8 Quality-of-life questionnaire results within 2 years

Quality-of-life questionnaire	Mean (SD) score, *n*		Estimated mean difference (95% CI)[a]
	UAE group	Myomectomy group	
UFS-QOL symptom severity domain[b]			
Baseline	58.5 (26.0), 122	59.4 (21.0), 125	
6 months	27.3 (21.2), 100	21.6 (17.1), 97	−6.1 (−11.4 to −0.9)
1 year	25.7 (21.5), 95	20.4 (19.0), 96	−5.4 (−11.0 to 0.2)
2 years	21.9 (20.8), 100	19.5 (20.0), 106	−3.8 (−9.4 to 1.8)
EQ-5D-3L[c]			
Baseline	0.62 (0.34), 125	0.63 (0.32), 127	
6 months	0.77 (0.30), 100	0.85 (0.17), 98	0.09 (0.03 to 0.14)
1 year	0.77 (0.30), 98	0.85 (0.23), 98	0.08 (0.01 to 0.15)
2 years	0.80 (0.29), 99	0.88 (0.20), 106	0.07 (0.01 to 0.13)
EQ-5D VAS[d]			
Baseline	62.9 (23.8), 125	62.7 (23.2), 127	
6 months	74.2 (20.9), 98	79.7 (15.7), 100	5.7 (1.1 to 10.3)
1 year	74.4 (21.1), 98	81.3 (15.4), 97	7.0 (2.1 to 11.9)
2 years	74.7 (19.4), 101	80.8 (14.7), 106	6.1 (1.7 to 10.6)

a Least-square mean differences estimated from the regression mode described in *Chapter 2, Statistical methods*. Estimates were adjusted for baseline value and minimisation variables.
b Scores ranged from 0 (no symptoms) to 100 (worst symptoms). Differences of < 0 favour myomectomy.
c Scores ranged from −0.59 (worst outcome) to 1.00 (best outcome). Differences of > 0 favour myomectomy.
d Scores ranged from 0 (worst outcome) to 100 (best outcome). Differences of > 0 favour myomectomy.
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TABLE 9 Menstrual cycle regularity within 2 years

Menstrual cycle regularity	Number of participants (%)	
	UAE group	Myomectomy group
6 months		
Currently having periods: yes	88	81
Cycle regularity		
Regular	29 (34)	15 (19)
Fairly regular	40 (47)	47 (59)
Irregular	16 (19)	16 (20)
Bleeding on and off	0	2 (3)
1 year		
Currently having periods: yes	85	78
Cycle regularity		
Regular	20 (25)	20 (26)
Fairly regular	41 (52)	42 (55)
Irregular	18 (22)	12 (16)
Bleeding on and off	2 (2)	2 (3)

TABLE 9 Menstrual cycle regularity within 2 years (*continued*)

Menstrual cycle regularity	Number of participants (%)	
	UAE group	Myomectomy group
2 years		
Currently having periods: yes	77	73
Cycle regularity		
Regular	28 (37)	27 (37)
Fairly regular	27 (36)	30 (41)
Irregular	16 (21)	14 (19)
Bleeding on and off	5 (7)	2 (3)

There were no apparent and sustained differences between the two groups in the bleeding scores or in the proportions of women reporting amenorrhoea or heavy bleeding over the 2 years of follow-up, as illustrated in *Table 10*.

Pregnancy and associated outcomes within 2 years

Fourteen women reported a pregnancy within 2 years of randomisation (nine women in the UAE group and five women in the myomectomy group, accounting for, respectively, 17% and 10% of women who at the time of randomisation expressed a desire to get pregnant). The outcome of preganancy was a live birth for six women in the UAE group and four women in the myomectomy group. There were two miscarriages among women in the UAE group (*Table 11*).

TABLE 10 Pictorial blood assessment chart bleeding scores and categories within 2 years

Pictorial blood assessment chart bleeding score	UAE group	Myomectomy group	Estimated mean difference or relative risk (95% CI)[a]
Baseline			
Sample size, (*n*)	102	100	
Total score, median (IQR)[b]	133 (63–275)	180 (100–383)	
Total score, log-transformed mean (SD)[c]	5.0 (1.1)	5.2 (1.1)	
Amenorrhoea, *n* (%)[d]	0	1 (1)	
Light bleeding, *n* (%)	0	1 (1)	
Normal bleeding, *n* (%)	40 (39)	23 (23)	
Heav bleeding y, *n* (%)[e]	62 (62)	75 (75)	
6 months			
Sample size, (*n*)	90	93	
Total score, median (IQR)[b]	58 (17–126)	46 (9–83)	
Total score, log-transformed mean (SD)[c]	3.6 (1.9)	3.2 (1.8)	−0.5 (−1.05 to −0.06)
Amenorrhoea, *n* (%)[d]	14 (16)	16 (17)	1.1 (0.6 to 2.1)
Light bleeding, *n* (%)	5 (6)	8 (9)	
Normal bleeding, *n* (%)	45 (50)	51 (55)	
Heavy bleeding, *n* (%)[e]	26 (29)	18 (19)	0.7 (0.4 to 1.1)[f]

continued

TABLE 10 Pictorial blood assessment chart bleeding scores and categories within 2 years (*continued*)

Pictorial blood assessment chart bleeding score	UAE group	Myomectomy group	Estimated mean difference or relative risk (95% CI)[a]
1 year			
Sample size, (*n*)	81	90	
Total score, median (IQR)[b]	48 (13–94)	39 (12–83)	
Total score, log-transformed mean (SD)[c]	3.4 (1.7)	3.2 (1.7)	−0.2 (−0.6 to 0.2)
Amenorrhoea, *n* (%)[d]	11 (14)	15 (17)	0.9 (0.1 to 6.1)
Light bleeding, *n* (%)	5 (6)	7 (8)	
Normal bleeding, *n* (%)	46 (57)	53 (59)	
Heavy bleeding, *n* (%)[e]	19 (23)	15 (17)	0.7 (0.4 to 1.3)[f]
2 years			
Sample size, (*n*)	75	77	
Total score, median (IQR)[b]	32 (0–88)	41 (11–84)	
Total score, log-transformed mean (SD)[c]	2.9 (1.9)	3.3 (1.9)	−0.07 (−0.5 to 0.3)
Amenorrhoea, *n* (%)[d]	19 (25)	14 (18)	0.7 (0.4 to 1.3)[f]
Light bleeding, *n* (%)	5 (7)	5 (6)	
Normal bleeding, *n* (%)	36 (48)	41 (53)	
Heavy bleeding, *n* (%)[e]	15 (20)	17 (22)	1.0 (0.5 to 1.8)[f]

IQR, interquartile range.
a Estimates adjusted for baseline value and minimisation variables.
b Scores ranged from 0 (no bleeding) to ∞ (worst bleeding). Differences of < 0 favour myomectomy.
c For PBAC scores of 0 to be included in the log-transformed scores, all responses were transformed by adding 1 and then taking the log.
d Relative risk for amenorrhoea shown. Estimates of > 1 favour myomectomy.
e Relative risk for heavy bleeding shown. Estimates of < 1 favour myomectomy.
f Unadjusted model due to non-convergence in adjusted model.
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TABLE 11 Pregnancy outcomes within 2 years

Pregnancy outcome	Proportion, *n/N* (%)		Estimated relative risk (95% CI)[a]
	UAE group	Myomectomy group	
Women reporting pregnancy	9/112 (8)[b]	5/112 (4)	0.6 (0.2 to 1.7)
Pregnancy (in women desiring pregnancy at time of randomisation)	9/52 (17)	5/48 (10)	
Pregnancy outcome/woman			
Live birth	6/106 (6)	4/107 (4)	
Miscarriage[b]	2/106 (2)	0/107	
Termination of pregnancy	1/106 (1)	1/107 (1)	

a Estimates of > 1 favour myomectomy.
b One woman had two pregnancies that both ended in miscarriage and these have been reported once.
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Reproductive hormone levels as markers of ovarian reserve

Hormone assay data are reported as geometrical means, unadjusted and adjusted for baseline scores and age, in *Table 12*. The adjusted analysis was a deviation from the statistical analysis plan, as there was a 2.5-year age difference between the two groups and hormonal levels are strongly associated with age.

Neither analysis provides any evidence of any material difference between the levels of hormones associated with uterine reserve in each group.

Participant satisfaction

Participants were asked if they would have their procedure again and if they would recommend the procedure to a friend. In both groups, positive responses were high to the questions of having their procedure again and very high in terms of recommending the operation to a friend in similar circumstances. The latter responses were approximately 10% higher in the myomectomy group than in the UAE at every time point (relative risk 1.1, 95% CI 1.0 to 1.2), as shown in *Table 13*.

Hospital stay and further procedures for fibroids

Among the 112 participants in the UAE group for whom length of hospital stay data were available, the median stay was 2 [interquartile range (IQR) 2–3] days, whereas among the 117 women in the myomectomy group for whom data were available, the median stay was 4 (IQR 3–5) days.

More women in the UAE group than in the myomectomy group underwent further fibroid treatment within 2 years (*Table 14*), with hysterectomy the most common subsequent procedure in both groups.

TABLE 12 Reproductive hormone levels

Reproductive hormone	Geometric mean (95% CI), *n*		Estimated geometric mean ratio, adjusted for baseline[a] (95% CI)	Estimated geometric mean ratio, adjusted for baseline and age[a] (95% CI)
	UAE group	Myomectomy group		
AMH (pmol/l)				
Baseline	0.70 (0.52 to 0.94), 122	0.40 (0.29 to 0.56), 123		
6 weeks	0.45 (0.31 to 0.63), 90	0.26 (0.18 to 0.37), 103	0.74 (0.54 to 1.01)	0.82 (0.61 to 1.10)
6 months	0.49 (0.34 to 0.71), 92	0.26 (0.17 to 0.39), 94	0.96 (0.72 to 1.29)	1.08 (0.81 to 1.43)
1 year	0.43 (0.27 to 0.66), 84	0.20 (0.13 to 0.30), 92	0.66 (0.49 to 0.89)	0.75 (0.57 to 0.98)
FSH (IU/ml)				
Baseline	5.48 (3.90 to 7.71), 41	5.65 (4.04 to 7.90), 38		
6 weeks	6.45 (5.31 to 7.82), 35	8.27 (6.31 to 10.83), 37	1.20 (0.86 to 1.67)	1.11 (0.79 to 1.54)
6 months	6.41 (4.85 to 8.46), 34	7.37 (4.84 to 11.21), 35	1.14 (0.70 to 1.84)	1.03 (0.64 to 1.65)
1 year	7.90 (5.66 to 11.04), 36	10.80 (6.74 to 17.29), 34	1.38 (0.80 to 2.39)	1.26 (0.74 to 2.13)
LH (IU/ml)				
Baseline	5.26 (3.70 to 7.46), 41	5.09 (3.64 to 7.13), 38		
6 weeks	7.05 (5.38 to 9.23), 35	5.91 (3.83 to 9.14), 37	0.82 (0.51 to 1.34)	0.80 (0.49 to 1.29)
6 months	5.79 (4.45 to 7.53), 34	6.90 (4.56 to 10.45), 35	1.22 (0.76 to 1.96)	1.16 (0.73 to 1.86)
1 year	7.69 (5.43 to 10.90), 36	7.42 (4.67 to 11.78), 34	0.95 (0.53 to 1.67)	0.91 (0.52 to 1.59)

IU, international unit.
a Estimates of > 0 favour myomectomy.
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TABLE 13 Participant rating of operation within 2 years

Participant rating of operation	Proportion, *n/N* (%)		Estimated relative risk[a] (95% CI)
	UAE group	Myomectomy group	
Would you have your operation again?			
6 months	70/94 (74)	67/94 (71)	1.0 (0.8 to 1.1)
1 year	68/90 (76)	68/90 (76)	1.0 (0.8 to 1.2)
2 years	70/95 (74)	73/94 (78)	1.1 (0.9 to 1.2)
Would you recommend operation to a friend?			
6 months	78/94 (83)	88/95 (93)	1.1 (1.0 to 1.2)
1 year	77/90 (86)	87/92 (95)	1.1 (1.0 to 1.2)
2 years	79/94 (84)	87/94 (93)	1.1 (1.0 to 1.2)

a Estimates of > 1 favour myomectomy. Estimates adjusted for minimisation variables where possible.
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TABLE 14 Further procedures for fibroids within 2 years

Further surgical procedure	UAE group	Myomectomy group	Estimated relative risk[a] (95%CI)
Total number of procedures, *n/N* (%)	18/110 (16)	8/111 (7)	0.4 (0.2 to 1.0)
Myomectomy, *n* (%)	5 (5)	1 (1)	
Hysterectomy, *n* (%)	8 (7)	4 (4)	
Transcervical resection, *n* (%)	5 (5)	3 (3)	

a Estimates of < 1 favour myomectomy.
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Procedural complications and adverse events

Perioperative and postoperative complications

Perioperative and postoperative complications occurred in 27 out of 113 (24%) women in the UAE group and 34 out of 118 (29%) women in the myomectomy group, with a relative risk of 1.2 (95% CI 0.8 to 1.9; $p = 0.4$) (*Table 15*). *Table 16* presents the same complications according to the actual initial procedure undertaken.

Serious adverse events

There was systematic variation in the way that participating sites reported SAEs, which arised from different interpretations of the definition. This resulted in perioperative and postoperative complications also being reported as SAEs, for example if a wound infection resulted in an overnight re-admission. Repeat procedures were occasionally reported as SAEs. *Table 17* shows the numbers of reported SAEs and the number of women experiencing SAEs without disaggregation of procedural complications reported in *Tables 15* and *16*.

TABLE 15 Procedure complications: ITT groups

Complication	Number of partipants (%)	
	UAE group	Myomectomy group
Perioperative or postoperative complications		
Sample size	113	118
Access artery occlusion	1 (1)	0
Post-embolisation syndrome resulting in a delay in discharge[a]	2 (2)	0
Haematoma	3 (3)	0
Major haemorrhage	2 (2)	6 (5)
Infection	0	5 (4)
Other[b]	1 (1)	3 (3)
Post discharge to 6 weeks complications[c]		
Sample size	109	114
Access artery occlusion	1 (1)	0
Post-embolisation syndrome resulting in re-admission	3 (3)	0
Haematoma	0	2 (2)
Infection	15 (14)	17 (15)
Other[d]	10 (9)	8 (8)

a Clinically characterised by low-grade fever, pain, fatigue, nausea and vomiting, typically by 48 hours after UAE and resolving within 1 week.
b UAE group details: episode of hypotension in recovery. Myomectomy group details: persistent oozing requiring ligation of internal iliac vessels, constipation and anaesthetic awareness.
c Post-discharge complications recorded from discharge from hospital to 6 weeks post discharge.
d UAE group details: anaemia ($n = 2$), sciatica, constipation, atypical cells found in fibroid histology, left upper thigh pain, fibroid expulsion, suspected infection and re-admitted with pain ($n = 2$). Myomectomy group details: norovirus, abdominal pain, upper gastrointestinal tract bleeding with *Helicobacter pylori* infection, chest pain, dyspnoea and tachycardia, gaping wound/wound leakage ($n = 2$), leiomyosarcoma and constipation.

TABLE 16 Procedure complications: actual procedure undertaken

Complication	Number of participants (%)	
	UAE group	Myomectomy group
Perioperative or pre-discharge complications		
Sample size	98	105
Access artery occlusion	1 (1)	0
Post-embolisation syndrome delaying discharge[a]	2 (2)	0
Haematoma	0	3 (3)
Major haemorrhage	0	4 (4)
Blood transfusion	0	11 (10)
Infection	0	4 (4)
Other[b]	1 (1)	3 (3)

continued

TABLE 16 Procedure complications: actual procedure undertaken (*continued*)

Complication	Number of participants (%)	
	UAE group	Myomectomy group
Post-discharge complications[c]		
Sample size	96	103
Access artery occlusion	1 (1)	0
Post-embolisation syndrome requiring re-admission	3 (3)	0
Haematoma	0	2 (2)
Infection	13 (14)	17 (17)
Other[d]	8 (8)	6 (6)

a Clinically characterised by low-grade fever, pain, fatigue, nausea and vomiting, typically by 48 hours after UAE and resolving within a week.
b UAE group details: episode of hypotension in recovery. Myomectomy group details: persistent oozing requiring ligation of internal iliac vessels, constipation and anaesthetic awareness.
c Post-discharge complications recorded from discharge from hospital to 6 weeks post discharge.
d UAE group details: anaemia ($n = 2$), sciatica, constipation, left upper thigh pain, fibroid expulsion and re-admitted with pain ($n = 2$). Myomectomy group details: norovirus, upper gastrointestinal tract bleeding with *Helicobacter pylori* infection, chest pain, dyspnoea and tachycardia, gaping wound/wound leakage ($n = 2$) and constipation.

TABLE 17 Serious adverse events within 2 years

SAEs reported	Number of participants (%) ($N = 127$)		*p*-value
	UAE group	Myomectomy group	
Total number of women experiencing a SAE	38 (30)	31 (24)	0.32
Total number of SAEs	52 (41)	40 (31)	

Chapter 4 Clinical effectiveness results: 4-year follow-up data

Women were sent UFS-QOL, PBAC and EQ-5D-3L questionnaires to be completed 4 years after undergoing their procedure. Further questions to the participants captured information regarding acceptability, pregnancy and associated outcomes, and further procedures for fibroids, in the same format as at 2 years.

Participant flow within 4 years

Compared with return rates at 2 years, a further 25 women in the myomectomy group and 33 women in the UAE group did not return questionnaires and/or were uncontactable, with 67 (53%) and 81 (64%) women, respectively, returning complete UFS-QOL quality-of-life scores. Interpretation should take this level of missing data into account because it may limit the generalisability of the results.

Participant-reported outcomes within 4 years

Health-related quality of life within 4 years

The estimated mean difference in HRQoL using observed (UFS-QOL) data at the 4-year follow-up time point can be seen in *Table 18*.

Symptom severity and quality-of-life questionnaire results within 4 years

There was no evidence of any difference between the groups in symptom severity at 4 years. General quality-of-life scores were higher in the myomectomy group than in the UAE group (*Table 19*).

Menstrual bleeding outcomes within 4 years

At 4 years, there were fewer women completing the PBAC diary and reporting on their menstrual cycle regularity than at 2 years (*Table 20*). A larger proportion of women were amenorrhoeic at 4 years than at the 2-year time point (*Table 21*).

TABLE 18 Health-related quality-of-life domain scores from the UFS-QOL within 4 years

	Mean (SD) score, *n*		
Outcome	UAE group	Myomectomy group	Estimated mean difference (95% CI)
HRQoL[a,b]	86.6 (20.5), 67	90.2 (19.7), 81	5.0 (−1.4 to 11.5)

a Least-square mean differences are estimated from the regression mode described in *Chapter 2, Statistical methods*. Estimates were adjusted for baseline value and minimisation variables.
b Scores ranged from 0 (worst outcome) to 100 (best outcome). Differences of > 0 favour myomectomy.

TABLE 19 Symptom severity and quality-of-life questionnaires within 4 years

Outcome	Mean (SD) score, *n*		Estimated mean difference (95% CI)[a]
	UAE group	Myomectomy group	
UFS-QOL symptom severity domain score[b]	18.8 (18.8), 70	14.5 (17.5), 80	−5.0 (−10.8 to 0.8)
EQ-5D-3L score[c]	0.79 (0.30), 70	0.90 (0.16), 83	0.13 (0.06 to 0.20)
EQ-5D VAS score[d]	75.3 (19.4), 71	82.8 (17.5), 82	8.7 (3.5 to 13.8)

a Least-square mean differences are estimated from the regression mode described in *Chapter 2, Statistical methods*. Estimates were adjusted for baseline value and minimisation variables.
b Uterine fibroid symptom and HRQoL questionnaire: scores range from 0 (no symptoms) to 100 (worst symptoms). Differences of < 0 favour myomectomy.
c EQ-5D-3L quality-of-life scores range from −0.59 (worse outcome) to 1.00 (best outcome). Differences of > 0 favour myomectomy.
d EQ-5D VAS scores range from 0 (worse outcome) to 100 (best outcome). Differences of > 0 favour myomectomy.

TABLE 20 Menstrual cycle regularity within 4 years

Menstrual cycle regularity	Number of participants (%)	
	UAE group	Myomectomy group
Currently having periods	48	39
Cycle regularity		
Regular	13 (27)	12 (31)
Fairly regular	23 (48)	18 (46)
Irregular	11 (23)	9 (23)
Bleeding on and off	1 (2)	0

TABLE 21 Pictorial blood assessment chart bleeding scores and categories within 4 years

PBAC score/category	UAE group	Myomectomy group	Estimated relative risk (95% CI)
Total score, median (IQR)	28 (0–75)	29 (0–81)	
Total score (log-transformed), mean (SD)[a]	2.8 (2.0)	2.6 (2.0)	−0.01 (−0.4 to 0.4)
Amenorrhoea, *n* (%)	14 (27)	15 (35)	1.3 (0.7 to 2.3)[b]
Light bleeding, *n* (%)	3 (6)	1 (2)	
Normal bleeding, *n* (%)	26 (51)	21 (49)	
Heavy bleeding, *n* (%)	8 (16)	6 (14)	0.9 (0.4 to 2.4)
Total, *n*	51	43	

a For PBAC scores of 0 to be included for log-transformed scores, all responses have been transformed by adding 1 and then taking the log.
b Unadjusted model used as adjusted model failed to converge.

Pregnancy and associated outcomes within 4 years

At 4 years, pregnancies, and their outcomes, continued to be reported by the participants or members of the local study team. The number of women getting pregnant, reported as cumulative rates, is shown in *Table 22*. Appropriate denominators cannot be presented here because of the high levels of drop-out between 2 and 4 years. Data are also reported for the per-protocol (i.e. only those who went on to receive the randomised intervention) and treatment-received populations. *Figure 6* presents the ITT data as Kaplan–Meier estimates and takes into account the lack of full follow-up for all women.

The cumulative pregnancy rate was 15% in the UAE group and 6% in the myomectomy group (hazard ratio from ITT data 0.48, 95% CI 0.18 to 1.28) (see *Figure 6*).

Participant satisfaction

There were no apparent differences in the participants' rating of their operation by 4 years, which remained high overall (*Table 23*).

TABLE 22 Pregnancy outcomes within 4 years

Outcome	Number of women (number of events)	
	UAE group	Myomectomy group
Pregnancy by ITT		
Women reporting pregnancy[a]	12 (15)	6 (7)
Pregnancy (in population desiring pregnancy at time of randomisation)	12 (15)	6 (7)
Live birth	7 (9)	5 (6)
Miscarriage	4 (5)	0
Termination	1	1
Pregnancy by per protocol		
Women reporting pregnancy[b]	7 (8)	6 (7)
Live birth	4 (5)	5 (6)
Miscarriage	2	0
Termination	1	1
Pregnancy by treatment received		
Women reporting pregnancy[c]	7 (8)	8 (10)
Live birth	4 (5)	6 (7)
Miscarriage	2	1 (2)
Termination	1	1

a UAE group: one participant had two pregnancies that both ended in miscarriage and two participants had two pregnancies that both ended in live birth. Myomectomy group: one participant had two pregnancies that both ended in live birth. These events have been primarily included once in this table, with repeat events in the same woman shown in brackets. All other events occurred in separate women. Percentages of the total population cannot be calculated, as women withdrew from the trial or were lost to follow-up at different intervals up to 4 years.

b UAE group: one participant had two pregnancies that both ended in live birth. Myomectomy group: one participant had two pregnancies that both ended in live birth. These events have been primarily included once in this table, with repeat events in the same woman shown in brackets. All other events occurred in separate women. Percentages of the total population cannot be calculated, as women withdrew from the trial or were lost to follow-up at different intervals up to 4 years.

c UAE group: one participant had two pregnancies that both ended in live birth. Myomectomy group: one participant had two pregnancies that both ended in live birth and one participant had two pregnancies that both ended in miscarriage. These events have been primarily included once in this table, with repeat events in the same woman shown in brackets. All other events occurred in separate women. Percentages of the total population cannot be calculated, as women withdrew from the trial or were lost to follow-up at different intervals up to 4 years.

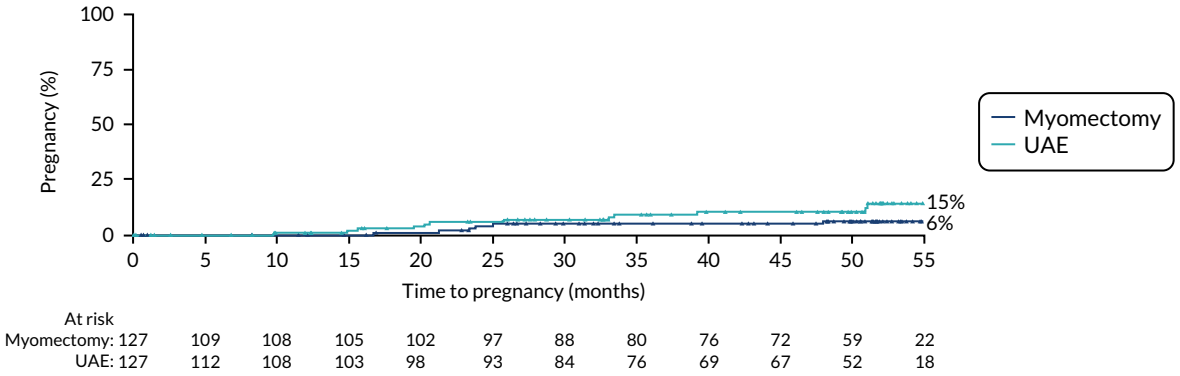

FIGURE 6 Time to pregnancy.

TABLE 23 Participant rating of operation within 4 years

Satisfaction question	Proportion, *n/N* (%)		Estimated risk (95% CI)[a]
	UAE group	Myomectomy group	
Would you have your operation again?	50/66 (76)	59/78 (76)	1.0 (0.8 to 1.2)
Would you recommend operation to a friend?	51/64 (80)	69/76 (91)	1.1 (0.9 to 1.3)

a Estimates of > 1 favour myomectomy. An unadjusted model was used because the adjusted model failed to converge.

Further procedures for fibroids within 4 years

The cumulative number of further procedures for treatment of fibroids was 22 in the UAE group and 13 in the myomectomy group (*Table 24*), which were hysterectomies for 11 and 8 women, respectively. Again, appropriate denominators are not presented here because of the high level of drop out between 2 and 4 years. *Figure 7* presents these data as Kaplan–Meier estimates and takes into account the lack of full follow-up for all women.

The cumulative repeat procedure rate was 24% in the UAE group and 13% in the myomectomy group (hazard ratio 0.53, 95% CI 0.27 to 1.05).

TABLE 24 Further procedures for fibroids within 4 years

Procedure	Number of participants, (*n*)	
	UAE group	Myomectomy group
Any further procedure	22	13
Method		
Hysterectomy	11	8
Myomectomy	6	2
Transcervical resection	5	3

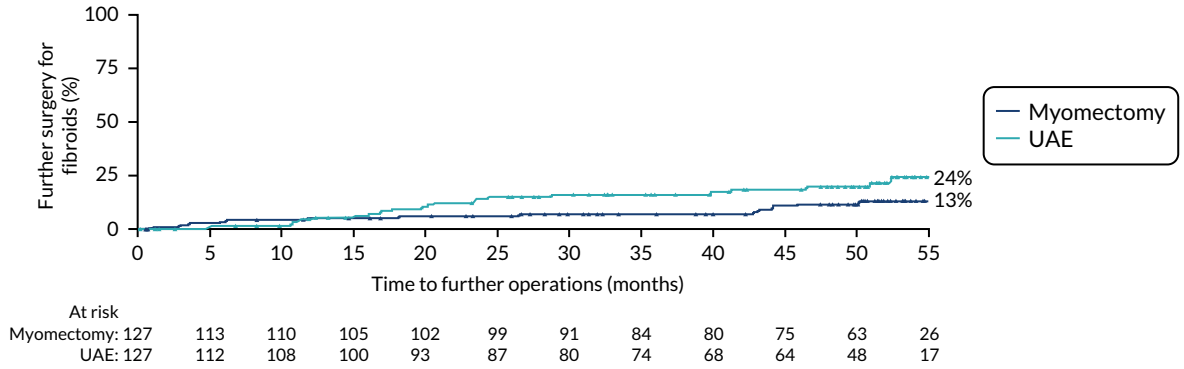

FIGURE 7 Time to further procedure for treatment of fibroids. Operation dates were estimated to be half-way between follow-up times if exact dates were not available.

Chapter 5 Methods for economic evaluation

An economic evaluation was conducted from the perspective of the UK NHS over the time horizons of 2 and 4 years. Within-trial analysis was conducted based on individual participant-level data on resource use and HRQoL. The items of resource use and data on HRQoL (EQ-5D-3L) that were collected during the study period are illustrated in *Figure 8*.

The methodology adopted in this evaluation adhered to good practice guidelines set out by NICE.[67] All costs and outcomes were discounted at the rate of 3.5%.

Resource use and costs

Direct health-care resource use data collected during the treatment and follow-up periods of the trial include items related to diagnostic procedures, interventions, medication, GP visits, outpatient attendance and inpatient admissions (*Table 25*). The resource use items were categorised into two parts: (1) treatment-related resource use items and (2) post-treatment resource use items. Treatment-related resource use items referred to items that were recorded from the time of pre-procedure fibroid assessment to the time that participants were discharged following the initial treatment. This period included any imaging performed to assess fibroids, actual interventions received, immediate repeat procedures, excess bed-days and medications that were prescribed on discharge. Post-treatment resource use items were recorded during the period from post discharge from initial treatment to the first follow-up at 6 months and, subsequently, to follow-ups at 1, 2 and 4 years.

All unit costs were collected from routine sources, including the NHS reference costs,[68] the Personal Social Services Research Unit[69] and the *British National Formulary* (BNF).[70] All costs were expressed in GBP (£) for the price year 2018/19 (*Table 26*). Costs associated with all resource use were summed as the total cost for each participant.

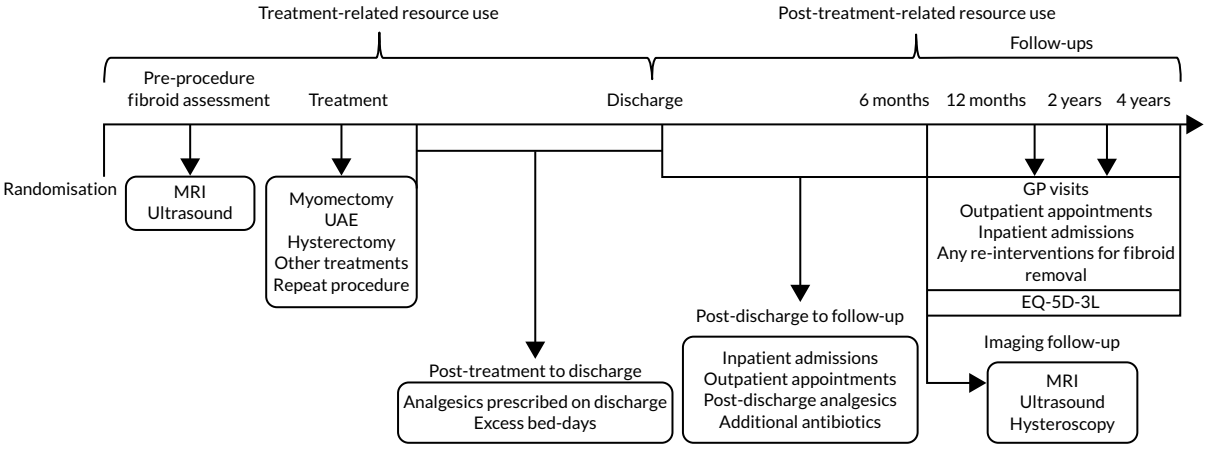

FIGURE 8 Data on resource use and outcome collected during the study period. Reproduced with permission from Rana *et al.*[66] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

TABLE 25 Resource use items and unit of measurement

Resource use item	Resource use measurement
Treatment-related items	
Pre-procedure fibroid assessment	Type and number of imaging procedures
Myomectomy	Number of patients receiving the intervention
UAE	Number of patients receiving the intervention (including repeat procedures)
Any other intervention	Number of patients receiving the intervention
Excess bed stay	Number of extra days in ward
Medications	Number of medicines prescribed during the period, including frequency, dose and duration
Post-treatment-related items	
Fibroid assessment	Type and number of imaging procedures
Reintervention[a]	Number of patients who had repeat or additional interventions
Medications[a]	Number of medicines prescribed during the period, including frequency, dose and duration
GP visits[a]	Number of visits to the GP
Outpatient visits[a]	Number of outpatient clinic attendance
Inpatient admissions[a]	Number of re-admissions to the hospital as an inpatient

a Recorded at 6 months and at 1, 2 and 4 years.

TABLE 26 Unit costs and sources

Resource use item	Unit	Cost (£) per unit applied[a]	Source and additional details
Imaging			
MRI	Per procedure	345.00	NHS reference costs;[68] average of HRG codes RD01A and RD03Z
Ultrasound	Per procedure	229.00	NHS reference costs;[68] average of HRG codes MA36Z, RD40Z and RD41Z
CEMRI	Per procedure	204.00	NHS reference costs;[68] HRG code RD03Z
Non-CEMRI	Per procedure	141.00	NHS reference costs;[68] HRG code RD01A
TVUS	Per procedure	169.00	NHS reference costs;[68] HRG code MA36Z
Transabdominal ultrasound	Per procedure	60.00	NHS reference costs;[68] average of HRG codes RD40Z and RD41Z
Hysteroscopy	Per procedure	405.00	NHS reference costs;[68] HRG codes RD41Z and MA31Z
Myomectomy			
Elective inpatient	Per procedure	3023.00	NHS reference costs;[68] average of unit costs for HRG codes MA09A and MA09B
	Per excess bed-day	244.00	NHS reference costs;[68] average of elective inpatient excess bed-day cost
UAE			
Elective inpatient	Per procedure	2037.00	NHS reference costs;[68] HRG code YR55Z
	Per excess bed-day	584.00	NHS reference costs;[68] elective inpatient excess bed-day

TABLE 26 Unit costs and sources (*continued*)

Resource use item	Unit	Cost (£) per unit applied[a]	Source and additional details
Hysterectomy			
Elective inpatient	Per procedure	3962.00	NHS reference costs;[68] average of unit costs for HRG codes MA08A and MA08B
	Per excess bed-day	530.00	NHS reference costs;[68] average of elective inpatient excess bed-day
Other treatment			
Endometrial ablation	Per procedure	1876.00	NHS reference costs;[68] average of elective inpatient for HRG code MA12Z
Transcervical resection of fibroids	Per procedure	1876.00	NHS reference costs;[68] elective inpatient cost for HRG code MA12Z
Other	Per procedure	2917.00	NHS reference costs;[68] weighted average of all the treatments
	Per excess bed-day	530.00	NHS reference costs;[68] average of elective inpatient excess bed-day
Re-admission as inpatient			
Long stay (> 2 days)	Per admission	3189.00	NHS reference costs;[68] average of overall HRG non-elective short stay and long stay
Short stay (≤ 2 days)	Per admission	630.00	NHS reference costs;[68] average of overall HRG non-elective short stay and long stay
Inpatient admissions for follow-ups	Per admission	1909.00	NHS reference costs;[68] average of overall HRG non-elective short stay and long stay
Outpatient appointment	Per appointment	217.00	NHS reference costs;[68] average of non-admitted face-to-face attendances with HRG codes WF01A and WF01B for gynaecology
GP visits	Per visit	28.00	PSSRU;[69] GP per surgery consultation lasting 9.22 minutes
Analgesics prescribed on discharge			
Paracetamol-based analgesics	Per dose	0.05	[b]BNF;[70] cost of paracetamol (500 mg)
Non-steroidal anti-inflammatories	Per dose	0.38	[b]BNF;[70] cost of codeine phosphate (30 mg)
Opiates	Per dose	0.83	[b]BNF;[70] cost of diclofenac sodium (150 mg)
Additional antibiotics[b]			
Amoxicillin	Per dose	0.06	[b]BNF;[70] 500 mg
Cefalexin	Per dose	0.13	[b]BNF;[70] 500 mg
Cefuroxime	Per dose	1.27	[b]BNF;[70] 250 mg
Ciprofloxacin	Per dose	0.08	[b]BNF;[70] 750 mg
Clarithromycin	Per dose	0.11	[b]BNF;[70] 500 mg
Clavulanic acid	Per dose	0.06	[b]BNF;[70] 500 mg
Clindamycin	Per dose	0.31	[b]BNF;[70] 600 mg
Dalteparin sodium	Per dose	5.12	[b]BNF;[70] 120 units/kg
Erythromycin	Per dose	0.36	[b]BNF;[70] 500 mg
Flucloxacillin	Per dose	0.38	[b]BNF;[70] 500 mg

continued

TABLE 26 Unit costs and sources (*continued*)

Resource use item	Unit	Cost (£) per unit applied[a]	Source and additional details
Gentamicin	Per dose	0.28	[b]BNF;[70] 7 mg
Metronidazole	Per dose	1.87	[b]BNF;[70] 400 mg
Nitrofurantoin	Per dose	0.30	[b]BNF;[70] 100 mg
Penicillin	Per dose	0.38	[b]BNF;[70] 250 mg
Piperacillin	Per dose	0.38	[b]BNF;[70] 250 mg
Tetracycline	Per dose	0.36	[b]BNF;[70] 250 mg
Trimethoprim	Per dose	0.03	[b]BNF;[70] 200 mg

HRG, Healthcare Resource Group; PSSRU, Personal Social Services Research Unit.
a All unit costs were inflated using the NHS Cost Inflation Index for 2018/19.[71]
b All unit costs for additional medicines were adjusted to account for the different dose, frequency and duration prescribed to each participant.

Note
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A number of assumptions related to resource use and unit costs were made. In the case of treatment-related resource use, all interventions were assigned unit costs according to the Healthcare Resource Group (HRG). All participants were assumed to be admitted as elective inpatients. Repeat interventions were assumed to incur the same resource use and cost as the initial intervention. Length of stay (LOS) was calculated as the difference between admission date and discharge date. In the case of LOS exceeding the 'trim points' (i.e. the expected LOS for each HRG), an additional per-diem cost was assigned to estimate costs associated with these excess bed-days.[72] Medications used during the procedure or during the time in a ward were assumed to be included in the HRG episode cost. Any additional medications prescribed on discharge were costed separately using unit costs from the BNF.

In the case of post-treatment resource use, all re-admissions from post discharge to first follow-up were assigned an average cost of non-elective short stay and long stay. Stays of ≤ 2 days were considered to be short stays and stays of > 2 days were considered to be long stays. All participants who did not report hospital re-admissions but had complications, infections or medications during the follow-up period were assumed to attend outpatient clinics. It was assumed that all reinterventions for fibroid removal during the follow-up period were performed on an elective inpatient basis. Resource use data captured in hospital records from post discharge to follow-up and data separately recorded by the participants at their first follow-up (i.e. 6 months) were cross-checked to avoid double-counting.

Health outcomes

Patient-reported HRQoL was measured using the EQ-5D-3L. The EQ-5D-3L was completed by the participants at baseline, 6 months, 1 year, 2 years and 4 years. The EQ-5D-3L describes health status of a patient in five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and there are three levels of response for each dimension.[73] Responses to the five health domains were used to calculate health utilities using a standard UK value set. The area under the curve method was used to estimate quality-adjusted life-years (QALYs) for each participant by adjusting the life-years gained by the quality of life experienced over the study period.[74] The method considers the utilities obtained at different time points because it assumes a linear relationship between these utilities. Subsequently, QALYs from baseline to 2 years and from baseline to 4 years were estimated.

Handling missing data

For the purpose of analysis, the following assumptions were made:

- With regard to medication, the median duration of treatment was assumed where data were missing and standard BNF doses were assumed where data on dosages were missing.
- In the case of participants with initial fibroid assessment scans who did not undergo any procedure, but remained in the trial and had cost/utility follow-up data (nine participants in the UAE group and four in the myomectomy group).
    - We did not make assumptions on additional resource use for participants with no resource use data throughout the study period (six in total); participants who had no other resource use data apart from those collected during the follow-up (three in the UAE group); nor participants who had additional fibroid imaging but no fibroid removal reintervention during the follow-up (two in the myomectomy group).
    - We assumed that all participants who had reintervention, but no other imaging related resource use, received fibroid imaging (two in UAE group).

The association between missingness, baseline variables and observed outcomes was also explored. A binomial logistic regression was carried out to investigate which variables and outcomes were associated with probability of missingness. We assumed that the data were missing at random.[75] Multiple imputation was performed using multiple imputation by chained equations.[76] Ten imputation data sets were generated with predictive mean matching (the mean of five nearest values). Imputation was performed for total costs at a subaggregate level of treatment and non-treatment costs, whereas QALYs were imputed at aggregate level of the total QALYs level and not on a health utilities level.

Cost-effectiveness analysis

The base-case analysis followed an ITT strategy and was conducted post multiple imputation. Generalised linear models were used to analyse cost and QALY data because of their non-normal distribution, which would otherwise render the calculation of a simple mean as inappropriate.[77] Generalised linear models accommodate this non-normal distributions of cost and QALY data by allowing specification of a more appropriate distributional family and link function through the modified Park test and other tests.

The cost model was analysed using a gamma family and log-link. It was adjusted for minimisation variables used in the clinical analysis (i.e. the participant's desire to be pregnant at the time of randomisation, the longest dimension of largest fibroid and the number of fibroids). The QALY model was analysed with Gaussian family and identity link. It was adjusted for minimisation variables, as well as the statistically significant predictors of QALYs (i.e. baseline utilities and body mass index). Baseline utilities are usually highly correlated with the patient's QALY gain, and any imbalance of baseline utility level between treatment groups may lead to misleading cost-effectiveness estimates.[74] The models were then used to predict the marginal mean costs and mean QALYs, which were then used to calculate their cost and QALY differences.

Cost-effectiveness was expressed as incremental cost per QALY gained [incremental cost-effectiveness ratio (ICER) = $\Delta C/\Delta Q$)], where appropriate. Incremental mean cost ($C_{UAE} - C_{Myomectomy} = \Delta C$) is the difference in mean costs between the two treatment groups, and incremental QALY ($Q_{UAE} - Q_{Myomectomy} = \Delta Q$) is the difference in QALYs gained between the two treatment groups. The ICER provides the additional cost of achieving 1 perfect year of health and can be compared against the NICE willingness-to-pay (WTP) threshold of £20,000.[67] In addition, incremental net monetary benefit (NMB), a measure of the health

benefit expressed in monetary terms, was also estimated. The NMB was calculated using the following formula:

$$\text{NMB} = (\Delta Q \times \lambda) = \Delta C, \quad (1)$$

where ΔQ is the incremental QALY, λ is the WTP threshold (i.e. £20,000 in the UK) and ΔC is the incremental cost.[77] An intervention is generally considered cost-effective compared with the alternative if the incremental NMB is positive.

To quantify the uncertainty around incremental costs and QALYs, a 1000-iteration bootstrap was performed. The results were presented on cost-effectiveness planes. Cost-effectiveness acceptability curves were used to present uncertainty in the decision regarding cost-effectiveness over a range of WTP thresholds.[78] All analysis was carried out using Stata (StataCorp LP, College Station, TX, USA) version 16.0.

Sensitivity analyses

The second scenario involved varying the unit cost applied to the procedures during initial intervention and any reinterventions for fibroid removal. In the base-case analysis, costs were estimated using a top-down approach, which emphasises national average costs. The English NHS reference costs incorporate costing on the basis of HRG, which is a measure of case mix, demonstrating groups of clinically similar treatments that utilise a common set of health-care resources.[72] Therefore, the HRG tariffs are a reflection of NHS average costs and may not capture the difference in practice across different FEMME trial sites. Therefore, we performed a sensitivity analysis to test the robustness of our results according to variations in unit costs that may have resulted from difference in practices. A 20% cost increment and decrement were applied to cost of initial intervention, as well as to the cost of reinterventions for fibroid removal that happened during the study period.

Chapter 6 Results for economic evaluation

Health-care resource use and costs

Overall, 127 women were randomised to each treatment group (*Table 27*). The majority of women underwent pre-procedure imaging prior to UAE and myomectomy. Across both groups, the majority of women received MRI (UAE group, 71%; myomectomy group, 79%). In the UAE group, 98 women received UAE, 14 received myomectomy and one received endometrial ablation (in addition, 14 women did not receive treatment or withdrew from the study). In the myomectomy group, 105 women received myomectomy, six received UAE and eight received hysterectomy (in addition, eight women did not receive treatment or withdrew from the study). UAE was associated with a median LOS of 2 (IQR 2–3) days, compared with 4 (IQR 3–5) days for myomectomy. Across both groups women were prescribed analgesics on discharge (UAE group, 87%; myomectomy group, 97%).

TABLE 27 Treatment-related resource use

Resource use	UAE group ($N = 127$)	Myomectomy group ($N = 127$)
Pre-procedure fibroid assessment		
Sample size, (*n*)	126	126
MRI		
Total, *n* (%)	89 (70.63)	99 (78.57)
Missing, *n* (%)	0 (0.00)	0 (0.00)
Ultrasound		
Total, *n* (%)	36 (28.57)	27 (21.43)
Missing, *n* (%)	0 (0.00)	0 (0.00)
Not mentioned, *n* (%)	1 (0.79)	0 (0.00)
LOS (days) during treatment		
Sample size, (*n*)	112	117
Mean (SD)	2.65 (1.34)	4.24 (1.53)
Median (IQR)	2 (2–3)	4 (3–5)
Medications		
Sample size, (*n*)	118	118
Total number of analgesics prescribed on discharge		
Total, *n* (%)	103 (87.29)	114 (96.61)
Missing, *n* (%)	2 (1.69)	1 (0.85)

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Post-treatment-related resource use is shown in *Table 28*. During the period from discharge to first follow-up (at 6 months), UAE was associated with a slightly higher proportion (16%) of women with re-admissions than myomectomy (11%). Similar patterns were observed for the mean number of re-admissions from discharge to 2 and 4 years. Resource use associated with outpatient appointments and medications prescribed was similar between the UAE and the myomectomy treatment groups and this pattern was consistent at 2 and 4 years. A larger number of women in UAE group ($n = 18$) than in

TABLE 28 Post-treatment-related resource use

Resource use	UAE group ($N = 127$)	Myomectomy group ($N = 127$)
Re-admission as inpatient after discharge to first follow-up		
Sample size, (*n*)	109	114
Number (%) of inpatient re-admissions	17 (15.60)	13 (11.40)
Missing, *n* (%)	0 (0.00)	0 (0.00)
Re-admission as inpatient after discharge to 2 and 4 years		
Mean ± SD number of re-admissions at 2 years	5.87 ± 6.41	4.96 ± 7.16
Median (IQR) number of re-admissions at 2 years	3 (1–8)	3 (2–5)
Mean ± SD number of re-admissions at 4 years	5.69 ± 6.30	5.24 ± 6.67
Median (IQR) number of re-admissions at 4 years	3 (2–8)	4 (2–5)
Outpatient appointment after discharge to first follow-up		
Sample size, (*n*)	109	114
Number (%) of outpatient appointments	92 (84.40)	101 (88.60)
Missing, *n* (%)	0 (0.00)	0 (0.00)
Outpatient appointments as inpatient after discharge to 2 and 4 years		
Mean ± SD number of outpatient appointments at 2 years	5.73 ± 13.29	5.22 ± 13.85
Median (IQR) number outpatient appointments at 2 years	3 (1–6)	2 (1–4)
Mean ± SD number of outpatient appointments at 4 years	6.12 ± 13.30	5.51 ± 12.73
Median (IQR) number of outpatient appointments at 4 years	3 (1–6)	3 (1–6)
Medicines prescribed after discharge to first follow-up		
Sample size, (*n*)	92	101
Total number (%) of analgesics prescribed on discharge	26 (28.26)	23 (22.77)
Missing, *n* (%)	0 (0.00)	0 (0.00)
Number (%) of patients prescribed antibiotics	11 (11.96)	15 (14.85)
Missing, *n* (%)	0 (0.00)	0 (0.00)
Imaging follow-up		
Sample size, (*n*)	105	94
CEMRI, *n* (%)	76 (72.38)	72 (76.60)
Non-CEMRI, *n* (%)	17 (16.19)	13 (13.83)
TVUS, *n* (%)	4 (3.81)	6 (6.38)
Transabdominal ultrasound, *n* (%)	2 (1.90)	1 (1.06)
Hysteroscopy, *n* (%)	0 (0.00)	0 (0.00)
Missing, *n* (%)	7 (6.67)	3 (3.19)

TABLE 28 Post-treatment-related resource use (*continued*)

Resource use	UAE group ($N = 127$)	Myomectomy group ($N = 127$)
GP visits		
Mean ± SD number of GP visits at 2 years	6.24 ± 12.51	4.91 ± 4.72
Median (IQR) number GP visits at 2 years	3 (2–6)	4 (2–6)
Mean ± SD number of GP visits at 4 years	6.86 ± 12.72	7.40 ± 12.47
Median (IQR) number of GP visits at 4 years	4 (2–7)	4 (2–8)

the myomectomy group ($n = 8$) received reintervention within the first 2 years. At the end of 4 years, 22 women from the UAE group had reintervention compared with 13 women in the myomectomy group.

Table 29 provides a breakdown of average costs according to resource use categories. In the case of most resource use categories, the costs incurred are very similar in both treatment arms. The minimal

TABLE 29 Average cost breakdown according to resource use categories

	Average cost (£) (SE)	
Resource use category	**UAE group**	**Myomectomy group**
Pre-procedure fibroid assessment	312 (53)	320 (48)
Treatment	2176 (373)	3036 (330)
Post-treatment to discharge	811 (563)	636 (433)
Cost for patients with excess bed-days	849 (544)	682 (409)
Post-discharge analgesics cost	7 (7)	6 (5)
Post-discharge to first follow-up (i.e. 6 months)	518 (859)	424 (716)
Inpatient re-admissions	2135 (1298)	2008 (1328)
Outpatient appointments	217 (0)	217 (0)
Post-discharge analgesics	6 (5)	4 (4)
Additional antibiotics	7 (7)	12 (17)
Follow-up over 6 months post discharge	3225 (6064)	1768 (3014)
Follow-up over 1 year post discharge	4011 (9003)	3419 (8999)
Follow-up over 2 years post discharge	4889 (9817)	4020 (9418)
Follow-up over 4 years post discharge	5403 (10,569)	4830 (9630)
GP visits		
Over 6 months	150 (452)	75 (76)
Over 1 year	137 (357)	110 (110)
Over 2 years	175 (350)	137 (132)
Over 4 years	192 (356)	207 (349)

continued

TABLE 29 Average cost breakdown according to resource use categories (*continued*)

Resource use category	Average cost (£) (SE)	
	UAE group	Myomectomy group
Outpatient appointments		
Over 6 months	1722 (5046)	506 (423)
Over 1 year	1122 (3383)	1301 (3663)
Over 2 years	1243 (2882)	1131 (3003)
Over 4 years	1327 (2894)	1195 (2761)
Inpatient admissions		
Over 6 months	7128 (6058)	5728 (2887)
Over 1 year	10,328 (11,144)	9069 (14,097)
Over 2 years	11,210 (12,233)	9479 (13,665)
Over 4 years	10,873 (12,022)	10,010 (12,728)
Imaging follow-up for fibroid assessment	191 (34)	195 (29)
Fibroid removal		
Over 6 months	3649 (542)	3128 (1142)
Over 1 year	3088 (865)	3083 (937)
Over 2 years	3092 (824)	3046 (967)
Over 4 years	3194 (806)	3306 (872)

SE, standard error.

difference in pre-procedure fibroid assessment can be attributed to the type of scans that these women received at the beginning. Most women in the myomectomy group received MRI rather than ultrasound, and MRI is slightly more expensive. The same explanation is applicable for the cost of imaging follow-up for fibroid reassessment. The average cost of treatment is higher in the myomectomy group, given that myomectomy is a more expensive procedure and requires a longer stay in the hospital. By contrast, costs incurred during the period from post treatment to discharge were higher in the UAE group. This reflects the unit cost applied for UAE excess bed-days (see *Table 26*), which was almost double the excess bed-days unit cost for myomectomy. Mean costs during post discharge to 6-month follow-up period were higher in the UAE group than in the myomectomy group. Women in the UAE group, again, incurred higher mean costs during the follow-up, which included the cost of GP visits, outpatient appointments and inpatient admissions.

Health outcomes

The proportion of responding participants and their corresponding responses to five health domains at baseline, 6 months, 1 year, 2 years and 4 years are presented in *Table 30*. Across the two treatment groups, at baseline, only a minority of women reported any problems with mobility (UAE, 16%; myomectomy, 17%) and self-care (UAE, 4%; myomectomy, 2%). Twenty-nine per cent of women in the UAE group and 33% of women in the myomectomy group reported some problems with usual activity. However, in both groups, 79% of women reported any problems with pain/discomfort, and 50% of women in the UAE group and 55% in the myomectomy group reported any problems with anxiety/depression.

TABLE 30 Percentage of respondents with responses on each EQ-5D-3L domain at baseline and different follow-up points

	Number of participants (%)									
	UAE group					Myomectomy group				
EQ-5D-3L domain	Baseline	6 months	1 year	2 years	4 years	Baseline	6 months	1 year	2 years	4 years
Mobility										
Level 1	105 (84.00)	87 (86.14)	86 (87.76)	88 (88.00)	63 (88.73)	105 (82.68)	93 (94.90)	89 (90.82)	102 (96.23)	77 (92.77)
Level 2	20 (16.00)	14 (13.86)	12 (12.24)	12 (12.00)	8 (11.27)	22 (17.32)	5 (5.10)	8 (8.16)	4 (3.77)	6 (7.23)
Level 3	0	0	0	0	0	0	0	1 (1.02)	0	0
Total	125	101	98	100	71	127	98	98	106	83
Self-care										
Level 1	120 (96.00)	97 (96.04)	95 (96.94)	92 (92.93)	65 (91.55)	125 (98.43)	98 (100.00)	96 (97.96)	105 (99.06)	83 (100.00)
Level 2	5 (4.00)	4 (3.96)	3 (3.06)	6 (6.06)	6 (8.45)	2 (1.57)	0	2 (2.04)	1 (0.94)	0
Level 3	0	0	0	1 (1.01)	0	0	0	0	0	0
Total	125	101	98	100	71	127	98	98	106	83
Usual activities										
Level 1	84 (67.20)	82 (82.00)	76 (77.55)	84 (84.00)	58 (81.69)	79 (62.20)	85 (85.86)	88 (89.80)	94 (88.68)	74 (89.16)
Level 2	36 (28.80)	12 (12.00)	20 (20.41)	13 (13.00)	11 (15.49)	42 (33.07)	14 (14.14)	9 (9.18)	12 (11.32)	9 (10.84)
Level 3	5 (4.00)	6 (6.00)	2 (2.04)	3 (3.00)	2 (2.82)	6 (4.72)	0	1 (1.02)	0	0
Total	125	100	98	100	71	127	99	98	106	83

continued

TABLE 30 Percentage of respondents with responses on each EQ-5D-3L domain at baseline and different follow-up points (*continued*)

	Number of participants (%)									
	UAE group					Myomectomy group				
EQ-5D-3L domain	Baseline	6 months	1 year	2 years	4 years	Baseline	6 months	1 year	2 years	4 years
Pain/discomfort										
Level 1	27 (21.60)	45 (44.55)	46 (46.94)	50 (50.51)	40 (57.14)	27 (21.26)	53 (53.54)	65 (66.33)	76 (71.70)	64 (77.11)
Level 2	72 (57.60)	47 (46.53)	42 (42.86)	43 (43.43)	25 (35.71)	73 (57.48)	44 (44.44)	28 (28.57)	26 (24.53)	18 (21.69)
Level 3	26 (20.80)	9 (8.91)	10 (10.20)	6 (6.06)	5 (7.14)	27 (21.26)	2 (2.02)	5 (5.10)	4 (3.77)	1 (1.20)
Total	125	101	98	99	70	127	99	98	106	83
Anxiety/depression										
Level 1	63 (50.40)	65 (64.36)	62 (63.27)	68 (68.00)	46 (64.79)	58 (45.67)	69 (70.41)	71 (72.45)	76 (71.70)	64 (77.11)
Level 2	45 (36.00)	30 (29.70)	30 (30.61)	26 (26.00)	19 (26.76)	60 (47.24)	28 (28.57)	26 (26.53)	28 (26.42)	18 (21.69)
Level 3	17 (13.60)	6 (5.94)	6 (6.12)	6 (6.00)	6 (8.45)	9 (7.09)	1 (1.02)	1 (1.02)	2 (1.89)	1 (1.20)
Total	125	101	98	100	71	127	98	98	106	83

The EQ-5D-3L consists of five dimensions (mobility, self-case, usual activities, pain/discomfort and anxiety/depression) where each dimension has three levels of problems: 1 (no problem), 2 (some problems) or 3 (extreme problems).

Note

The table includes minor additions and formatting changes to the original table.

In the UAE group, the proportions of women reporting any problems with mobility and self-care were consistent over time. There were substantial improvements in the usual activities and pain/discomfort domains, and a modest improvement in the anxiety/depression domain. In the myomectomy group, there were modest improvements in the mobility and self-care domains over time, and substantial improvements in the remaining three domains. In particular, the improvement in the pain/discomfort and anxiety/depression domains was greater than that observed in the UAE group.

Cost-effectiveness analysis

Participants who withdrew, were lost to follow-up, had missing resource use at the main time points or had any missing health utilities data were considered to be missing. EQ-5D-3L data were missing for 32% and 45% of participants at the 2- and 4-year follow-up, respectively. The proportion of participants with missing resource use data was low at both time points (4% and 8%, respectively).

The cost-effectiveness results for the FEMME trial are presented in *Table 31*. Predicted total mean costs were estimated separately based on resource use from baseline to 2 years and from baseline to 4 years. Each of these costs constituted cost components (i.e. treatment cost, as well as post-treatment costs up to 2 and 4 years).

TABLE 31 Cost-effectiveness analysis results

Predicted mean cost	UAE group, point estimate (95% CI)		Myomectomy group, point estimate (95% CI)	
	Cost (£)	*95% CI*	*Cost (£)*	*95% CI*
Treatment cost[a]	3064	2906 to 3222	3862	3667 to 4056
Post-treatment cost over 2 years[a]	4918	3076 to 6759	3431	2191 to 4671
Post-treatment cost over 4 years[a]	5288	3445 to 7131	4151	2745 to 5557
2 years				
Mean total cost (£) (95% CI)	7958 (6304 to 9612)		7314 (5854 to 8773)	
Mean total QALY (95% CI)	0.74 (0.70 to 0.78)		0.83 (0.79 to 0.87)	
Incremental cost (ΔC) (95% CI)	645 (−1381 to 2580)			
Incremental QALYs (ΔQ) (95% CI)	−0.09 (−0.11 to −0.04)			
ICER[b] (ΔC/ΔQ) (95% CI)	−7167 (−39,597 to 19,764)			
NMB[b] (ΔQ × λ) − ΔC, λ = £20,000 (95% CI)	2445 (−4319 to 15)			
4 years				
Mean total cost (£) (95% CI)	8362 (6640 to 10,083)		8010 (6422 to 9598)	
Mean total QALY (95% CI)	0.73 (0.69 to 0.76)		0.82 (0.79 to 0.87)	
Incremental cost (ΔC) (95% CI)	352 (−1825 to 2528)			
Incremental QALYs (ΔQ) (95% CI)	−0.09 (−0.12 to −0.05)			
ICER[b] (ΔC/ΔQ) (95% CI)	−3911 (−31,357 to 23,566)			
NMB[b] (ΔQ × λ) − ΔC, λ = £20,000 (95% CI)	−2152 (−4350 to 221)			

a Cost component of total cost.
b ICERs and NMB are not normally calculated when an intervention is dominated by its comparator. However, we present them for completeness.

Notes
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The mean treatment costs were lower in the UAE group than in the myomectomy group (£3064 vs. £3862). Conversely, the UAE group was associated with a higher post-treatment cost than the myomectomy group over 2 years' follow-up (£4918 vs. £3431) and over 4 years' follow-up (£5288 vs. £4151). The total mean cost incurred over 2 years was £7958 in the UAE group compared with £7314 in the myomectomy group. The total mean cost over 4 years was £8362 in the UAE group compared with £8010 in the myomectomy group.

Over the period of 2 years, the QALY gain was 0.74 (95% CI 0.70 to 0.78) in the UAE group compared with 0.83 (95% CI 0.79 to 0.87) in the myomectomy group. UAE was associated with higher costs (i.e. a £645 difference in cost, but this was not statistically significant) and lower QALYs (i.e. a −0.09 difference in QALYs) than myomectomy. UAE is dominated by myomectomy.

Similar results were observed over the 4-year time horizon. The QALY gain was 0.73 in the UAE group (95% CI 0.69 to 0.76) compared with 0.82 (95% CI 0.79 to 0.87) in the myomectomy group. UAE was associated with higher costs (i.e. a £352 difference in cost, but this was not statistically significant) and lower QALYs (i.e. a −0.09 difference in QALYs). Again, UAE is dominated by myomectomy. Compared with the 2-year follow-up, the cost difference between the UAE and the myomectomy group at 4 years' follow-up was slightly lower, while the QALY gain remained the same.

The cost-effectiveness planes for 2 and 4 years are presented in *Figure 9*. The lines represent the WTP thresholds (i.e. £20,000 per additional QALY gained). The bootstrapped replications were displayed in the north- and south-west quadrants. Most replications were concentrated in the north-west quadrant. Regardless of the time horizons, there is little difference in costs between UAE and myomectomy. The deterministic estimate is close to zero. There is little uncertainty that UAE has lower health benefits than myomectomy. There is some uncertainty relating to the magnitude of the difference in costs between the two groups at 4 years.

Both of the cost-effectiveness acceptability curve figures (*Figure 10*) showed that myomectomy had a higher probability of being cost-effective than UAE at WTP thresholds of ≥ £20,000. At a £20,000 WTP threshold, the probability of myomectomy being cost-effective is 98% at 2 years and 96% at 4 years.

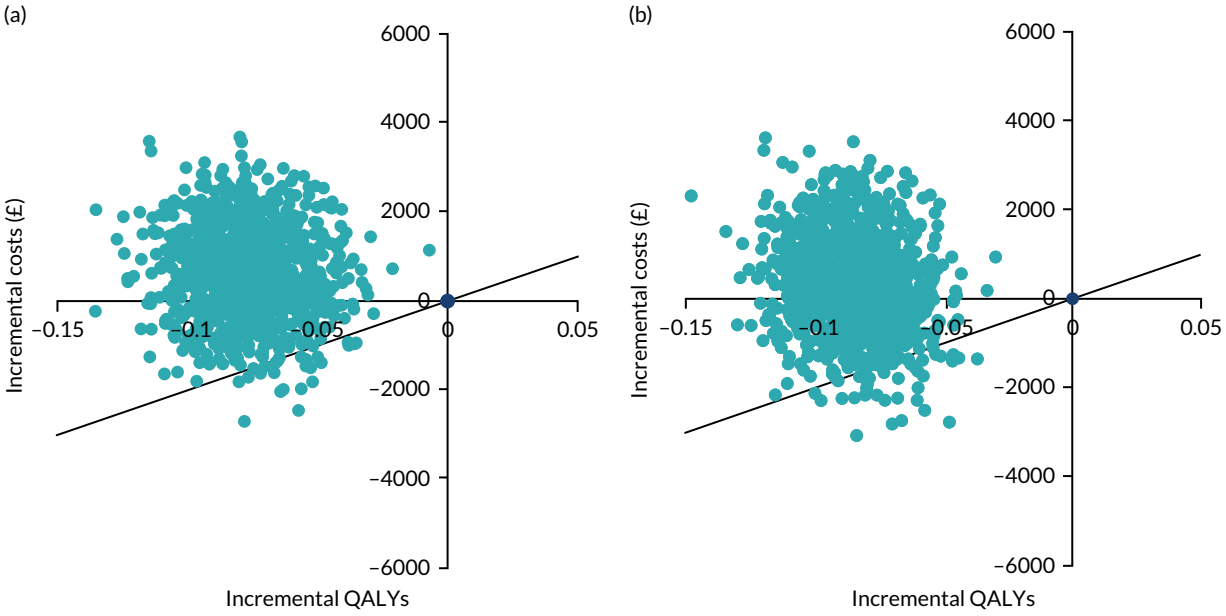

FIGURE 9 Cost-effectiveness plane for (a) 2 years and (b) 4 years. Reproduced with permission from Rana *et al.*[66] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

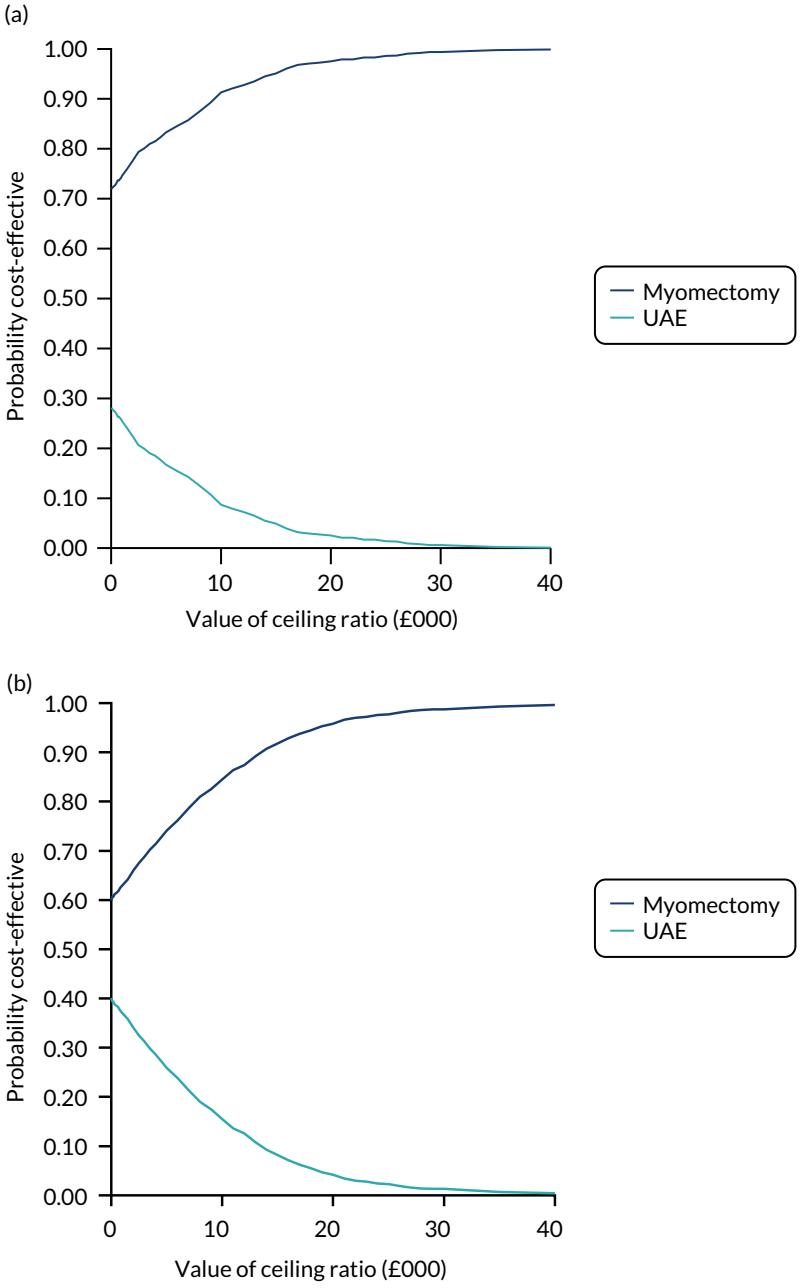

FIGURE 10 Cost-effectiveness acceptability curves for (a) 2 years and (b) 4 years. Reproduced with permission from Rana *et al.*[66] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

Sensitivity analysis

The results from the scenario in which we performed a complete-case analysis are presented in *Table 32*. Similar to the base-case analysis, analysis of cost components showed that women in the UAE group had lower treatment costs than women in the myomectomy group (£3073 vs. £3870, respectively). Women in the UAE group also incurred higher post-treatment costs over 2 years than women in the myomectomy group (£4663 vs. £3384, respectively) and 4 years (£5057 vs. £4127, respectively). UAE was associated with higher costs (i.e. a £456 difference in cost, but this was not statistically significant) and a lower QALY gain (difference of −0.06) over a time horizon of 2 years. Similar results were observed over a 4-year time horizon. The cost difference was slightly lower than at the 2-year

TABLE 32 Results of complete-case analysis

Predicted mean cost	UAE group, point estimate (95% CI)		Myomectomy group, point estimate (95% CI)	
	Cost (£)	*95% CI*	*Cost (£)*	*95% CI*
Treatment cost[a]	3073	2920 to 3227	3870	3678 to 4063
Post-treatment cost over 2 years[a]	4663	2889 to 6438	3384	2112 to 4657
Post-treatment cost over 4 years[a]	5057	3280 to 6835	4127	2678 to 5576
2 years				
Mean total cost (£) (95% CI)	7665 (6068 to 9262)		7209 (5714 to 8704)	
Mean total QALY (95% CI)	0.76 (0.72 to 0.79)		0.82 (0.79 to 0.85)	
Incremental cost (ΔC) (95% CI)	456 (−1823 to 3164)			
Incremental QALYs (ΔQ) (95% CI)	−0.06 (−0.11 to −0.02)			
ICER[b] ($\Delta C/\Delta Q$) (95% CI)	−7600 (−68,356 to 45,346)			
NMB[b] ($\Delta Q \times \lambda$) − ΔC, λ = £20,000 (95% CI)	−1656 (−4695 to 856)			
4 years				
Mean total cost (£) (95% CI)	7990 (6323 to 9658)		7802 (6178 to 9426)	
Mean total QALY (95% CI)	0.76 (0.73 to 0.80)		0.83 (0.79 to 0.86)	
Incremental cost (ΔC) (95% CI)	188 (−3435 to 3290)			
Incremental QALYs (ΔQ) (95% CI)	−0.06 (−0.11 to −0.01)			
ICER[b] ($\Delta C/\Delta Q$) (95% CI)	−3133 (−52,975 to 101,463)			
NMB[b] ($\Delta Q \times \lambda$) − ΔC, λ = £20,000 (95% CI)	−1388 (−5045 to 2610)			

a Cost component of total cost.
b ICERs and NMB are not normally calculated when an intervention is dominated by its comparator. However, we present them for completeness.

Note
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follow-up, but the QALY difference remained the same. A 6% decrease in ICER was observed when we compared the 2-year follow-up ICERs obtained from the base-case analysis with those obtained from the sensitivity analysis. Relatedly, an increase in ICER of 20% was observed for the 4-year follow-up. It is imperative to note that ICERs are not normally calculated when an intervention is dominated by the comparator.

The results of the sensitivity analysis on the impact of varying unit cost of procedures on mean total costs show that costs were higher in UAE group than in the myomectomy group (*Table 33*). Overall, varying cost of interventions had an overall effect on the magnitude of the ICERs (*Figure 11*). However, the overall results remained consistent with the base-case analysis. UAE was associated with higher costs and lower QALYs gained when compared with myomectomy across the two time horizons. Therefore, myomectomy dominated UAE.

TABLE 33 Impact of varying unit cost of procedures on mean total cost for treatments

	20% decrement		20% increment	
Treatment	**Mean total cost (£) (SD)**	**95% CI (£)**	**Mean total cost (£) (SD)**	**95% CI (£)**
2 years				
UAE	7238 (840)	5590 to 8885	8221 (833)	6587 to 9855
Myomectomy	6531 (730)	5101 to 7961	7816 (773)	6302 to 9330
4 years				
UAE	7536 (863)	5843 to 9228	8546 (873)	6834 to 10,259
Myomectomy	7123 (796)	5562 to 8683	8387 (832)	6757 to 10,017

Notes
All monetary units have been rounded to the nearest pound.
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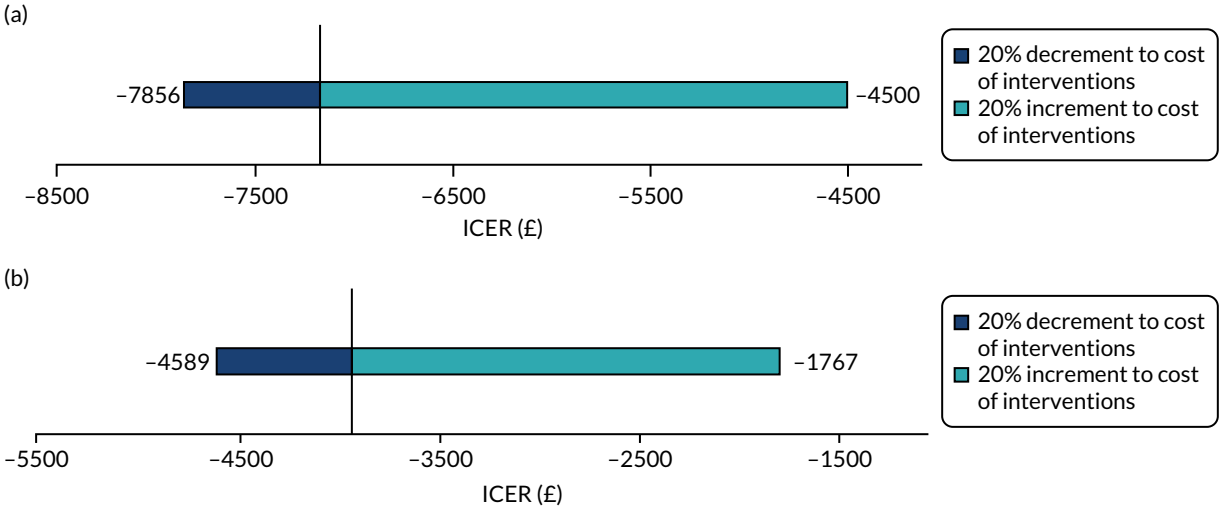

FIGURE 11 Sensitivity analysis on cost of interventions. (a) ICERs at 2 years and (b) ICERs at 4 years. ICERs are normally not presented when an intervention is dominated by its comparator. However, we present them for completeness. The mean incremental QALY for the ICER was −0.09, which is consistent with the base case, as we only varied the unit cost of procedures in sensitivity analysis. Reproduced with permission from Rana *et al.*[66] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

Chapter 7 Discussion

Principal findings

Although both myomectomy and UAE improved participant-reported HRQoL scores, women assigned to the myomectomy group reported higher scores than those assigned to the UAE group. Menstrual bleeding scores appeared similar in both groups. Overall complication rates from all initial procedures occurred in a similar proportion of women in both groups. The need for additional treatments was higher and hospital stay was shorter in the UAE group than in the myomectomy group. There were no consistent differences between groups in biomarkers of ovarian reserve. In total, there were 15 pregnancies in the UAE group and seven pregnancies in the myomectomy group, but these numbers were too small draw a conclusion on the effect of the procedures on fertility. The economic evaluation showed that UAE was associated with higher costs and lower QALYs than myomectomy. At a £20,000 WTP threshold, the probability of myomectomy being cost-effective is 98% at 2 years and 96% at 4 years.

Interpretation

Doubling of the UFS-QOL quality-of-life score from baseline to each time point shows that, on average, both treatments are effective, with an additional 8-point benefit accrued from myomectomy, equating to a small to moderate standardised treatment benefit at 2 years.[79] In a review of the use of EQ-5D in 11 varied populations, a mean minimally important difference of 0.07 was derived.[80] This is consistent with the difference in EQ-5D score observed in this study, corroborating the between-group difference observed for UFS-QOL.

There were substantially more surgical reinterventions in the UAE group in the first 2 years of follow-up, possibly reflecting the higher residual impact on quality of life observed in the UAE group and the marginal patient-reported preference for myomectomy. However, the number of hysterectomies performed as the initial procedure was higher in the myomectomy group because of either patient preference or clinical decision.

Our results show that UAE is associated with higher costs and lower QALYs than myomectomy (£645 and £352 over the 2- and 4-year time horizons, respectively). This incremental cost should be interpreted with caution, as the difference was small and not statistically significant. The difference in QALYs over both the 2- and the 4-year time horizons was 0.09, and this is equivalent to 33 days of perfect health. The cost drivers were GP visits, outpatient appointments and inpatient admissions during the follow-ups and the associated reinterventions for fibroid removal. The key driver for this QALY difference was the substantial improvements associated with pain/discomfort and anxiety/depression observed with the myomectomy group.

Findings in the context of the existing effectiveness literature

The only comparable randomised trial using UFS-QOL[29] suggested a between-group difference of 12.1 (95% CI 4.0 to 20.2) points in the HRQoL domain at 1 year, following our reanalysis of their individual patient data, which is consistent with our observation of a 10.8-point difference (95% CI 4.2 to 17.5 points) at the same time point. The changes in score from baseline to 1 year are substantial: an improvement of at least 33 points (maximum score for domain is 100 points) in both the FUME[29] and the FEMME trial and following either treatment. Similar large improvements in UFS-QOL scores have been reported following various fibroid treatments.[81,82]

In a study from Czechia,[27,28] the rate of reintervention within 2 years was 33% in the UAE group and 3% in the myomectomy group, but these rates are not directly comparable with the FEMME results, as the protocol of the former study recommended myomectomy if improvements were not seen 6 months after UAE. Only one participant had a subsequent hysterectomy following myomectomy in the other RCT,[29] although the reintervention rate was 15% (i.e. nine participants) more than 1 year after an initial UAE.

There were substantially more pregnancies in the study from Czechia,[27,28] with 13 out of 26 women who attempted conception becoming pregnant in the UAE group and 30 out of 40 women in the myomectomy group achieving pregnancy within a mean follow-up period of around 2 years. Half of those women who became pregnant in the UAE group had a subsequent myomectomy. Comparing their pregnancy and pregnancy outcome data with data from the FEMME trial is difficult because of the different proportions of women intending to get pregnant and differences in the age profile of participants.

Previous randomised trials that measured FSH, and used varying thresholds for ovarian failure, also found no evidence of harm from UAE over short and longer time frames.[35] To the best of our knowledge, no other randomised studies have assessed AMH.

Findings in the context of the existing economic literature

To identify the main driver of total mean costs, the costs were categorised according to treatment-related cost and post-treatment cost. The treatment cost of UAE was lower than that of myomectomy. This can be attributed to the fact that the observed LOS was longer for myomectomy than for UAE (i.e. a median of 4 days vs. a median of 2 days), and this is consistent with the literature.[81,83] Women in the UAE group incurred greater post-treatment costs than women in the myomectomy group. The main driver of post-treatment costs was utilisation of health-care resources (e.g. GP visits, outpatient appointments and inpatient admissions), as recorded during the follow-ups associated with reinterventions for fibroid removal. Over the 4 years' follow-up, the rate of reintervention was higher in the UAE group than in the myomectomy group (hazard ratio 0.53, 95% CI 0.27 to 1.05). Our findings are in line with existing studies that reported on UAE continuously accruing costs in the long term[40] and higher reintervention cost than myomectomy.[38] In our study, the majority of the post-treatment costs were accrued within 2 years and only a small amount of additional post-treatment costs incurred between the 2-year and the 4-year follow-up.

Strengths and limitations of the randomised trial

To the best of our knowledge, this study is the largest ever randomised clinical trial to report on treatment of symptomatic fibroids by UAE and myomectomy. The robust study design ensures internal validity, enabling the results to be interpreted with confidence. Randomisation via computer-generated allocation sequence was effective in achieving balanced groups with respect to important prognostic factors.

In the absence of a minimally important difference for between-group comparisons on the UFS-QOL scale,[58] the size of the study was driven by a small to moderate standardised effect. This was derived from the published results of the FUME study.[29] Later, we reanalysed the individual participant UFS-QOL data of the FUME study using more appropriate regression methods, accounting for baseline imbalances. This reanalysis generated a larger potential difference and a smaller pooled-group SD. This enabled us to reduce the FEMME trial's sample size from the original projection, which we were then able to achieve. However, this cannot be considered data driven, as the recalculation was performed before any interim analysis and ratified by the TSC and Data Monitoring Committee, which were blind to any contemporary outcome data.

Our trial design offered a number of other strengths with respect to data collection and analysis. The primary outcome measure and many secondary outcome measures focused on the participants' report of their symptoms and quality of life. In addition, the primary outcome was fibroid specific and co-developed with women with fibroid symptoms. This ensured that the outcomes reflect the aspects of the condition of most importance to women.

The techniques used for both myomectomy and UAE were determined by the fibroid presentation and the preference of the operating clinician. This enabled a diverse range of fibroid diagnoses to be included in the study, but limits the interpretation of the results to a class comparison of myomectomy with UAE (i.e. the trial did not analyse operative subgroups, e.g. laparoscopic myomectomy vs. UAE, and we did not balance the randomisation by intended myomectomy approach).

We consider the trial design and conduct to have been methodologically robust, but there are some limitations of our study that should be considered. Nineteen per cent of participants failed to return the UFS-QOL questionnaire at 2 years, despite our attempts to retrieve this information. Our analytical approach involved imputation of missing responses using a recognised method, but assumed that data were missing at random and that the reason for non-response was not related to these participants' quality of life. Any deviation from this assumption could give rise to inconclusive results, given that the lower end of our CIs around effect estimates were close to zero.

A substantial number of women were not recruited because of their preference for a particular treatment option and expectations of treatment benefit were not captured pre randomisation. As with all surgical or interventional procedure trials, not every participant ultimately undergoes the allocated procedure, either for clinical reasons or because of patient preference The proportion of women who did not undergo their allocated procedure differed between groups (UAE group, 20%; myomectomy group, 15%). The numbers undergoing different types of alternative treatment also varied; for example, the number of women undergoing no immediate procedure was nine in the UAE group and four in the myomectomy group. All participants were analysed in the groups to which they were allocated and the per-protocol analysis gave a treatment effect very similar to ITT population analysis, suggesting little impact of non-adherence to the allocation.

The two procedures have considerably different recovery periods, which may be reflected in the first outcome measures reported by participants at 6 months. The duration from randomisation to the procedure averaged around 13 weeks in both groups, and the primary outcome was at 2 years post procedure, as this is a realistic time point at which to compare quality of life.

Some blood samples were unable to be analysed for FSH and LH, as they were not obtained within 5 days of the start of the last menstrual period, reducing the data available to corroborate the AMH results. Despite randomisation, there was a small difference in participant age between the two groups, prompting a post hoc-adjusted analysis of the ovarian reserve markers.

Our statistical analysis plan did not include correction for multiplicity of statistical testing. We have not carried out multiplicity correction for the secondary outcomes in terms of size of CI (*p*-values were not reported).

Strengths and limitations of the economic evaluation

The economic evaluation is based on robust data collected alongside, to the best of our knowledge, the largest RCT that evaluated this comparison and adhered to good practice guidelines set out by NICE.[67] In accordance with the guidance,[67] we took into account relevant resource use and estimated costs, and we estimated health benefits based on the EQ-5D. Robust methods were used in the analysis to explore uncertainties.

A limitation of the analyses is the number of missing health utility data. However, incomplete participant data is an expected feature of trials with long follow-up periods and is attributable to participants being withdrawn or lost to follow-up or non-compliance. We performed sensitivity analysis to examine the impact of missing data. Another limitation is that the health outcomes were assessed using the EQ-5D-3L, rather than the EuroQol-5 Dimensions, five-level version, which is considered to be a more sensitive and precise measure of health status. The former has a tendency to underestimate health utilities by overestimating health problems.[84] Moreover, one inherent limitation of this approach is that it does not take into account patient preference, despite that the literature that suggests that there is no statistically significant difference between UAE and surgery (hysterectomy or myomectomy) in terms of health-related quality of life.[81] Furthermore, this suggestion is supported by the substantial number of women who were not recruited into the trial because of their preference for a particular treatment option. A larger number of participants with similar resource use and outcomes would have decreased uncertainty in our results. Based on the cost–utility framework, the potential trade-off between the additional QALYs gained associated with myomectomy and the potential benefits of avoiding a surgical procedure associated with UAE is not known.

Generalisability

Unlike previous comparisons[27–29] of myomectomy and UAE, the FEMME trial was a multicentre clinical trial and did not include or exclude women based on their pregnancy intentions. The generalisability of the findings is increased by the inclusion of multiple centres, gynaecological surgeons and interventional radiologists, allowing both interventions' impact to be evaluated without confounding by individual variance in clinical practice and skill, although nearly two-thirds of participants were recruited from just three hospitals. A substantial number of participants were of African-Caribbean ethnicity and presented with a wide range of fibroid diagnoses.

Patient and public involvement

We have been supported throughout the project by the Fibroid Network, in particular, and also FEmISA and the British Fibroid Trust. Public and patient involvement was crucial in improving the acceptability of the FEMME trial, in providing authenticity for the trial among women and in promoting recruitment. We engaged with the Fibroid Network founder throughout, developing an appreciation of the lack of choice often presented to women around the treatment of fibroids and uncertainty surrounding UAE and myomectomy among women, as well as the opinions of clinicians and barriers to accessing UAE that the chairperson had encountered. This prompted us to work harder to engage with clinicians to reiterate the uncertainty around both treatments, in particular for women desiring pregnancy.

We will engage with the Fibroid Network and British Fibroid Trust regarding the dissemination of our findings (FEmISA has ceased activity), providing a plain English summary of the findings and the uncertainties around the evidence we have discussed here. This will be distributed via their respective websites and via Twitter (Twitter, Inc., San Francisco, CA, USA; www.twitter.com). Any future research groups taking forward the research recommendations from this project would benefit from engaging with these groups and women directly via social media.

Chapter 8 Conclusions

In conclusion, both UAE and myomectomy are effective treatments for improving the quality of life of women with symptomatic uterine fibroids. UAE is cheaper than myomectomy, but it generates lower health benefits. At a £20,000 WTP threshold, the probability of myomectomy being cost-effective is 98% at 2 years and 96% at 4 years. Based on a cost–utility assessment, UAE is dominated by myomectomy and would not be considered a cost-effective alternative to displace myomectomy. However, this does not take into account any potential preference for a less invasive procedure. In this context, given the small difference in costs between the two procedures, fully informed patient preference should be taken into account and women should have the option to choose between the two procedures.

Implications for health care

Myomectomy and UAE are both established procedures within the repertoire of many gynaecologists and interventional radiologists, respectively, and training of junior doctors should continue to include these procedures. Services should continue to offer both procedures to women where both are potential options. Women, including those desiring a future pregnancy, should be provided with the evidence generated by the FEMME trial to enable them to make a fully informed decision regarding their fibroid treatment.

Research recommendations

The FEMME trial provides high-quality evidence on the clinical effectiveness and cost-effectiveness of UAE compared with myomectomy and, in our opinion, further clinical trials addressing this pragmatic question around quality of life are not required. An individual patient data meta-analysis is under way (PROSPERO CRD42018098676), which aims to identify which patients have the highest risk of unchanged or worsened quality of life and reintervention by 1 year.

Recommendations for further research encompass fertility concerns, long-term outcomes and technical aspects of the interventions. These may be prioritised as follows:

- The impact of myomectomy, compared with UAE, on live birth rates is the most urgent unanswered question. A comparable trial[36] to the FEMME trial, specifically for women with fibroids and no other infertility factors, commenced in France (NCT02577055); however, this trial struggled to recruit in the face of the same concerns regarding the impact of UAE on ovarian function and was terminated after 15 participants were enrolled.[36] The lack of compelling evidence for adverse effects of myomectomy and UAE from the FEMME trial and other sources[37] should reduce the barriers to a new randomised trial in women seeking to get pregnant naturally or undergoing assisted reproduction treatment. The effectiveness of hysteroscopic myomectomy of submucosal fibroids in women seeking treatment for infertility or who have had recurrent miscarriages, compared with deferred surgery, is being addressed in a UK randomised trial (URL: https://fundingawards.nihr.ac.uk/award/NIHR128969). The extent of uterine cavity distortion from submusocal fibroids and its impact on the success of fertility following myomectomy may also be revealed from this trial.
- Long-term follow-up of women who have undergone myomectomy or UAE using routine data to capture further reinterventions in the FEMME cohort would be of benefit.
- If and when the emerging drug classes of progesterone receptor modulators and oral gonadotropin-releasing hormone receptor antagonists gain marketing authorisation for use by women with uterine fibroids, then these drugs should be evaluated both against standard medical treatments, such the levonorgestrel-releasing intrauterine-releasing system, and against myomectomy or UAE.

- Adenomyosis is another common menstrual disorder, with symptoms that overlap with those of fibroids, that can often co-exist with fibroids, but is relatively overlooked. A randomised trial of UAE compared with hysterectomy is under way in the Netherlands (URL: www.trialregister.nl/trial/5471; accessed 15 December 2021). Many of the drugs that potentially provide benefit for fibroids or endometriosis could also help with the symptoms of adenomyosis and should also be evaluated in RCTs.
- Comparison of the surgical approaches to myomectomy may be considered, but the number, size and location of the fibroids are key determinants to the decision to operate hysteroscopically, laparoscopically or by open laparotomy. Outcome data, such as those collected in the FEMME trial and fibroid registries, may help to define and revise the criteria for deciding which types of fibroids require open myomectomy and which can be removed laparoscopically.
- There are opportunities for further research into some of the technical aspects of myomectomy (e.g. the minimisation of blood loss through the use of tranexamic acid or vasopressin[85]) and in pain control. Morcellation of fibroid tissue remains a controversial issue and, although modifications to the technique, such as in-bag morcellation, have been compared with uncontained power morcellation,[86] the theoretical risk of dissemination of leiomyosarcoma will remain a barrier to further investigation of the value of morcellation.
- The choice of embolic agent for UAE has generally been at the discretion of the interventional radiologists, although randomised comparisons have been undertaken.[87,88] Further trials could help to refine the endovascular techniques and determine the impact of embolic agent not only on radiological features, such as the extent of infarction, but also on symptom and patient-reported outcomes.
- Post-embolisation syndrome is a common AE following UAE, particularly associated with larger fibroids, and, although self-limiting, can delay discharge and may mask infection. Identification of risk factors and optimisation of antipyretic and antiemetic therapy would improve the patients' experience.
- There are few data on how widely thermal and microwave ablation, and ultrasound-guided high-intensity transcutaneous-focused ultrasound and MRgHIFU techniques, are being used in the UK, as routine data sources do not distinguish between modalities. Anecdotally, these techniques do not appear to be gaining traction in the UK, but if any become more mainstream then their clinical effectiveness and cost-effectiveness should be established against both myomectomy and UAE.

There is also scope for methodological research around the evaluation of fibroid treatments. A core outcome set of the most important outcomes to be measured and reported in clinical trials of fibroid treatment is under development.[89] This initiative will reduce research waste, but will define only the main domains not the actual outcome measures. The UFS-QOL is validated, but was developed from responses from women who had completed their family and, therefore, does not refer to the fertility and pregnancy concerns that women may have. Evaluation of the validity of generic fertility quality-of-life or anxiety questionnaires specifically among women with fibroids desiring pregnancy would be valuable and, if necessary, a new outcome measure for this population could be developed.

Cost–utility analyses using health utilities valued using a generic measure of HRQoL do not take into account patient preference. It is conceivable that some women may place additional value on a non-surgical procedure over a surgical alternative. Further research on how such fully informed patient preference may be quantified and incorporated into subsequent economic analyses of medical, surgical and non-surgical interventions for fibroids would be worthwhile. For example, patient preferences may be elicited through discrete choice experiments as a supplement to QALY measurement.

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Publications

McPherson K, Manyonda I, Lumsden MA, Belli AM, Moss J, Wu O, *et al.* A randomised trial of treating fibroids with either embolisation or myomectomy to measure the effect on quality of life among women wishing to avoid hysterectomy (the FEMME study): study protocol for a randomised controlled trial. *Trials* 2014;**15**:468.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available 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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