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

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Relationship with other trial committees.

This joint oversight committee was formed following a number of the original committee members no longer being eligible to sit on the individual Data

(Consultant Interventional Radiologist)	Monitoring & Trial Steering committees. Given the late stage of FEMME the funders (NIHR HTA) agreed that the roles of both the TSC and DMC could be replaced with a single oversight committee which has the functions of both. This single, combined committee is referred to as the Joint Oversight Committee (JOC).

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Amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version

Protocol Amendment	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
1	*19/10/11*	*1.1*	*Minor*	*Appendices removed*
2	*12/12/11*	*1.2*	*Substantial*	*All centres now blood centres, blood sampling periods modified, no longer undertaking inhibin assay*
3	*01/02/12*	*1.3*	*Minor*	*Harmonisation of time points*
4	*05/03/12*	*1.4*	*Minor*	*Inserting ISRCTN*
5	*16/05/12*	*1.5*	*Minor*	*Amendment to blood centres in Figure 2*
6	*15/08/12*	*1.6*	*Minor*	*Change of DMC member and Data Manager contact details*
7	*28/02/13*	*1.7*	*Minor*	*Reflect changes in Questionnaire completion sequence, and other ethics approved changes*
8	*18th October 2013*	*1.8*	*Substantial*	*Insertion of new recruitment end date, sample size and Accrual &*

				Analysis section
9	*15th January 2014*	*1.9*	*Minor*	*Removal of the Data Manager and their contact details. Change of delivery address*
10	*14th March 2014*	*1.10*	*Minor*	*Clarification of the stratification criteria*
11	*19th September 2014*	*1.11*	*Substantial*	*Increasing sample size to 250. Extending the recruitment date 'till this total is reached, and correcting minor typos*
12	*13th February 2019*	*2.0*	*Substantial*	*Detailing the members of the FEMME Joint Oversight Committee which the funder has agreed can replace the individual TSC & DMC. Clarification of outcome measures. Insertion of GDPR compliance statement.*

Abbreviations

AE	Adverse event
AMH	Anti-Mullerian Hormone
BCTU	Birmingham Clinical Trials Unit at the University of Birmingham
CEMRI	Contrast Enhanced Magnetic Resonance Imaging
CI	Chief Investigator
CLRN	Comprehensive Local Research Network
DMC	Data Monitoring Committee
E2	Oestradiol
GCP	Good Clinical Practice
GP	General Practitioner
ISRCTN	International Standard Randomised Controlled Trial Number
JOC	Joint Oversight Committee
MREC	Multicentre Research Ethics Committee
NIHR	National Institute for Health Research
OR	Odds Ratio
PI	Principal Investigator – the lead clinical investigators for the FEMME Study
PIS	Participant Information Sheet
RCR	Royal College of Radiologists
RCOG	Royal College of Obstetricians and Gynaecologists
RR	Relative Risk
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
TVUS	Trans-Vaginal Ultrasound
UAE	Uterine Artery Embolisation

CONTENTS

1. BACKGROUND AND EXISTING RESEARCH

1.1. Clinical Context and Epidemiology

Uterine fibroids are the most common tumour in women of reproductive age and increase in prevalence as the woman gets older. A survey in the US, using transvaginal sonography, estimated the prevalence of fibroids to be 70% among whites and 80% among African-Americans by the time they are 50 years old[1]. Fibroids grow more quickly for a given age among black women[2]. Approximately half of women with fibroids experience significant symptoms which include heavy menstrual bleeding (HMB), abdominal pain and pressure, all of which impact significantly on their quality of life. In addition some women with fibroids may also have difficulty conceiving, whilst others may be at risk of miscarriage. Fibroids vary considerably in position, size and number and this may influence the symptoms experienced and the effect of different treatments. 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. Submuscosal fibroids project into the uterine cavity, cause heavy menstrual bleeding and potentially impacts on fertility. Hospital Episode Statistics report over 28,000 diagnosed cases of fibroids for 2008/09.

Women with symptomatic fibroids often respond poorly to drug management or risk unacceptable side effects from hormonal preparations[3]. The choice for many has been between hysterectomy and, where available, Uterine Artery Embolisation (UAE). If women wish to preserve their uterus, hysterectomy is not an option and myomectomy (surgical removal of the fibroids) has been the surgical intervention of choice[4]. Alternative techniques such as fibroid destruction by MRI guided high frequency ultrasound and laparoscopic laser myomectomy are not supported by robust evidence and are considered experimental[5,6].

Myomectomy involves the surgical removal of fibroids from the uterus whilst reconstructing the normal myometrium. This can be difficult if fibroids are large or very numerous. Myomectomy can be performed through an incision in the abdominal wall (open myomectomy), or by keyhole techniques through the abdomen or via the cervix. Myomectomy is normally only offered to those wishing to maintain fertility since hysterectomy (where the uterus and fibroids are removed) is often technically easier.

UAE is a minimally invasive interventional radiology procedure in which blood vessels supplying the uterus are occluded. The fibroids fail to regain a new blood supply and die (infarct). The myometrium avoids infarction by developing a collateral circulation from the vaginal and ovarian vessels.

Average length of stay for hysterectomy is 4.4 days, for myomectomy 3.6 days and UAE 1 day, and studies have shown that UAE offers a faster return to normal life. UAE is more cost effective than surgery in the short term, although recent evidence suggests this advantage is lost at five years due to the higher re-intervention rate associated with UAE[7]. The HOPEFUL observational study showed similar results, but compared UAE with hysterectomy.

Although there were initially concerns regarding the impact of UAE on fertility, this less invasive procedure is also now often considered alongside myomectomy as an option amongst women wanting to preserve their fertility. However, both of these treatments can in principle compromise fertility: myomectomy by the formation of adhesions and UAE by interfering with the blood supply to the ovaries. Births in women over the age of 40 years are increasing with 24,000 in England and Wales in 2006, twice as many as ten years before[8]. As this trend for later births progresses, the proportion of women experiencing

sub-fertility who are diagnosed with fibroids is expected to increase, raising inevitable questions about appropriate treatment for which there is insufficient reliable evidence. The prevalence of sub-fertile women with fibroids, whether the fibroids are implicated or not, will rise. If untreated this may lead to an adverse effect on fertility and pregnancy outcomes as well as menstrual problems.

1.2. Women's perspective on treating their fibroids

Fibroid Network Online (www.fibroidnetworkonline.com) is a public website through which women can obtain high quality information regarding fibroids. Surveys undertaken among women with fibroids indicate preservation of fertility is the main patient outcome that women seek when looking for an alternative to hysterectomy[9]. A general poll of 2,000 women with fibroids of all ages reported that over 95% were seeking an alternative to hysterectomy. Yet specialists recommended 77% of the poll participants undergo a hysterectomy, primarily to control heavy bleeding. (www.fibroidnetworkonline.com)

Many women still report difficulty in finding hospitals which provide alternatives to hysterectomy and some may delay or cancel surgical treatments because they wish to maintain their fertility. Most women are either employed or looking after their families and may prefer to undergo a surgical procedure which quickly allows them to return to their normal lives, otherwise they are may feel forced to delay treatment until such time that their symptoms become unbearable.

1.3. Evidence of effectiveness of proposed interventions

1.3.1 Evidence of the effectiveness of UAE compared with hysterectomy

A Cochrane review[10] initially included two trials (EMMY and a study by Pinto *et al*) comparing UAE with hysterectomy[11,12]. Since this Cochrane review was published, a third study, REST, has reported[13] and comprehensive follow-up has become available for EMMY[14]. These later studies reported an improved post-procedure quality of life at 1 and 5 years yet no difference between the treatments. Meta-analyses did not report any statistically significant difference in patient satisfaction (OR 0.6; 95%CI 0.2-1.4; p=0.2) between those undergoing hysterectomy or myomectomy, but favoured hysterectomy for rates of reintervention (OR 3.2; 95%CI 1.4-7.1; p=0.004). Other outcomes were not consistently reported in all three studies, but generally proposed UAE as a viable alternative to hysterectomy, achieving relief of symptoms not related to fertility and a 50% decrease in fibroid volume. The HTA funded HOPEFUL cohort study[15,16] compared UAE with hysterectomy and concluded that UAE is safe with a lower major complication rate than surgery.

1.3.2 Evidence of effectiveness of UAE compared with myomectomy

For women with fibroids who wish to retain their uterus, the choice lies between myomectomy and UAE. There has been one small (n=121) single centred randomised clinical trial from the Czech Republic, comparing myomectomy with UAE in women with intramural fibroids[17]. The eligibility criteria included women with 'unfinished reproductive plans' or 'planned pregnancy'. The authors assessed the safety and efficacy of the two procedures, with surgical outcomes being the main outcome measures. 15% of eligible patients approached declined to participate in the trial. The authors concluded that UAE was less invasive, but as effective and safe as myomectomy for treating symptoms of fibroids, but that myomectomy appears to have superior reproductive outcomes in the first two years of follow up. When comparing UAE and myomectomy, complication rates were 7% and 9%, hospital stays 60 and 86 hours and recovery period 12 and 22 days respectively. Of the 63 women who underwent a myomectomy 40 tried to conceive. Of the 58 women who underwent a UAE 26 tried to conceive. This produced significantly

imbalanced groups in which there were 33 pregnancies in women who received a myomectomy and 17 pregnancies in women who underwent a UAE. Miscarriages occurred in 6 patients in the myomectomy arm and 9 in the UAE arm[18]. Whilst these results appear significant the study was not sufficiently powered for any outcomes and Mara *et al* suggested that their work needed to be repeated in a larger patient population and with a longer follow up period.

The REST trial did follow up participants for a longer period and reported that comparative MRI performed on participants at five years post-procedure reported a 34% incidence of new fibroid formation following myomectomy compared with 14% after UAE[7].

A pilot study for FEMME has recently been conducted at St George's Hospital, London. 160 women not planning on becoming pregnant were randomised to UAE or myomectomy over a 24 month period[19]. Women with pedunculated fibroids, predominantly submucosal fibroids and fibroids which on clinical examination extended beyond the level of the umbilicus, were excluded. The primary outcomes measure was health-related quality of life. This pilot study reported equivalent improvements in quality of life in both groups, with a 40 point improvement (on a scale of 100) from myomectomy and 32 points from UAE, (p=0.1). Of the 74 women randomised to UAE, 6 chose to have a myomectomy after randomisation. The study found hospital stay was shorter for the UAE group (two days compared with six days). During the first year major complications were lower with UAE (2.9% vs. 12.2%).

Meta-analysis of these two trials shows re-intervention rates are substantially greater in the UAE group (OR 6.9; 95%CI 3.1-15.4; p<0.001).

1.3.3

Evidence on the safety of myomectomy and uterine artery embolisation

Myomectomy may be associated with significant complications, including a risk of hysterectomy and possible adhesion formation, although robust data are unavailable. A similar lack of data for hysterectomy was the case until the 1990s when large trials and audits were completed[20]. The incidence of salvage hysterectomy is low and confined to women with large or multiple fibroids in awkward positions. Clearly measuring adhesions and their effect on fertility is too invasive to assess systematically, although data are available after laparoscopic myomectomy[21],but the risk of uterine rupture following myomectomy is considered small and lower than that after caesarean section[22]. Approaches have been developed to decrease bleeding since excessive blood loss is more likely to result in hysterectomy. Blood loss is related to uterine size, the volume of the fibroid removed and operating time. Steps taken to decrease blood loss include mechanical methods as well as intra-operative and pre-operative drug use and occasionally pre-myomectomy UAE.

UAE was first reported in 1994. Since then it has been subjected to two NICE reviews[22, 23] and is considered as a safe and effective treatment for uterine fibroids which should be offered to women as an alternative to hysterectomy. Complications do occur but several RCTs have shown UAE to have a similar or lower complication rate when compared with hysterectomy. The HOPEFUL study found embolisation is associated with a fifth of the risk of serious complications when compared with hysterectomy (OR=0.21, 95%CI=0.11-0.40), or half the risk of hysterectomy when compared to all complications (OR =0.48, 95%CI=0.26-0.89)[16]. Significant complications of UAE are usually a result of infection and rarely (0.05-0.1%) require a salvage hysterectomy. There have been five deaths reported worldwide from several hundred thousand procedures.[25] Complications of UAE, although very rare, usually appear beyond the standard 30 day surgical window[13].

1.3.4 Evidence of the impact of fibroids and their treatment on fertility

1.3.4.1The role of fibroids in sub-fertility

It is believed by many that fibroids may interfere with the mechanism and likelihood of embryo implantation, an effect which may be mediated by alteration of the uterine cavity, either anatomically or because of abnormal function in the myometrium or endometrium. Recently Farquhar discussed the evidence of the extent to which fibroids cause infertility[26], and adopted the uncertain position of NICE[27] that a connection has not been established. Farquhar cites a review of observational studies[28] which suggested women with submucosal fibroids have decreased fertility and a greater rate of pregnancy loss compared with those without fibroids, although the quality of the studies was generally poor. The role of intramural fibroids was less clear.

1.3.4.2 The impact of treatment on sub-fertility in the presence of fibroids

Meta-analysis of observational studies comparing women's fertility outcomes after open, laparoscopic or hysteroscopic surgery for all types of fibroid and the sole randomised controlled trial of myomectomy found removal of submucosal fibroids led to improved pregnancy rates but no statistically significant differences in other pregnancy outcomes, nor was there a significant difference when intramural fibroids were surgically removed[29].These data support the view that submucosal fibroids which significantly distort the uterine cavity may need to be removed from infertile women but intervention for intramural fibroids remains controversial. Proponents of laparoscopic methods claim high success rates although results are less consistent than with the hysteroscopic procedures as there is less certainty of the relationship between intramural or subserosal fibroids and subfertility symptoms in these cases. In addition, the results from many procedures go unreported, there is significant selection bias and the net impact of the fibroids themselves is uncertain.

Farquhar quotes the randomised controlled trial as reporting no difference in fertility between myomectomy and no treatment regardless of the location of the fibroids,[30] and concurs with Pritt's conclusion regarding removal of intramural fibroids. Magos[31] disagrees since he considers the Casini trial was 'grossly' underpowered, had recruited a restricted population and included errors in the description, confusing submucosal with subserosal fibroids, and thus lead to erroneous conclusions. Whilst Pritts and Farquhar recommend further high quality randomised controlled trials to address the uncertainty, Magos believes women with submucosal fibroids and subfertility should be offered hysteroscopic myomectomy. Such debate emphasises the need for rigorous assessment of interventions.

1.3.4.3 Evidence of the impact of interventions on ovarian reserve

The impact of UAE and hysterectomy on ovarian reserve in younger women who wish to become pregnant in the future can be quantified by measuring ovarian hormones including gonadotrophins, Oestradiol (E2)and anti-mullerian hormone (AMH), the latter being particularly useful. A subset of the EMMY trial looked at AMH levels in women following UAE (n=30) and hysterectomy (n=33). Although in this cohort participants were nearly all over 40 years of age when their levels of AMH would be expected to be low anyway, it is perhaps unsurprising that the authors found it difficult to assess any change[32].The trial found AMH falls in both groups but with some recovery in the hysterectomy arm. There is no information on AMH levels following myomectomy.

1.3.5 The impact of interventions on obstetric outcomes

A recent systematic literature review has studied 227 completed pregnancies in UAE patients and compared various pregnancy outcomes with a matched group of untreated

women of similar age and profile of fibroid locations[33]. Miscarriage rates were higher in the UAE group (OR=2.8, 95%CI=2-2.9) and the pregnancies were more likely to be delivered by Caesarean section. Rates of preterm delivery, intrauterine growth restriction and malpresentation were similar in both groups. The most important fibroid characteristic for miscarriage is the location, with intramural and submucosal fibroids demonstrating a greater risk[28].The initial concerns regarding the effect of UAE on obstetric outcomes now appears to relate mainly to early pregnancy loss[34].

1.4 Evidence on cost effectiveness of embolisation and myomectomy

REST includes a myomectomy arm but the numbers were small (n=8) and the cost effectiveness analysis comparing UAE with surgery are dominated by the majority cases of hysterectomy[13]. UAE was clearly more cost-effective at 1 year principally because of the decrease in the length of hospital stay. At five years, REST showed no cost benefit with UAE due to the significant re-intervention rate[7]. The HOPEFUL study argues that quality of life outcomes favour embolisation against hysterectomy in short term. For younger women, subject to recurrence, this may not be true. This has been confirmed by subsequent studies which found UAE improved quality of life and is cost-effective when compared with hysterectomy[35, 36].

1.5 National Guidelines

Joint guidelines from the Royal College of Radiologists (RCR) and Royal College of Obstetricians and Gynaecologists (RCOG) say that “myomectomy itself generates strongly held opinions and centres in the UK vary widely in their activity levels.”[37] This is partly skill related in that it can be a more difficult procedure than a hysterectomy particularly in the presence of multiple fibroids.

Their recommendations on UAE are:

1. It is at least as safe as surgical alternative
2. For symptomatic fibroids it should be considered as one treatment option with surgical treatments
3. For infertile patients it should only be offered with fully informed consent
4. It is contraindicated among women with an infection and women unwilling to have a hysterectomy in any circumstances
5. Embolisation patients should be seen by a gynaecologist and an MRI is recommended
6. It should be undertaken by a radiologist with appropriate training
7. The responsibilities of both gynaecologist and radiologist should be established prior to treatment
8. These recommendations apply to the NHS and private sector

The RCR and RCOG advocate a multi-centred randomised control trial (RCT) comparing embolisation and myomectomy, ideally with pregnancy outcome as the primary endpoint and further comparative research into the effect of UAE on ovarian function.

The NICE clinical guidelines[24] for heavy menstrual bleeding recommend either UAE or myomectomy for women with fibroids who want to retain their fertility, without favouring one technique over the other. Hysterectomy should only be considered for women with large fibroids (>3cm) and bleeding that is having a large impact on their life quality. NICE does not support the routine use of laparoscopic laser myomectomy[6] and MRI guided percutaneous laser ablation[5]. Overall, the management of women considering myomectomy for fibroid-associated fertility should be individualised, with specific

counselling about the risks of myomectomy and risks of pregnancy in the presence of fibroid(s).

A recent survey of members of the British Fertility Society confirmed that few consider that myomectomy need be performed routinely unless the fibroids are associated with other symptoms. In addition, many women with sub-fertility have multiple contributing factors of which fibroids are only one, making interpretation of studies very difficult.

1.6 Rationale and demand for the FEMME Study

Both myomectomy and UAE appear to improve quality of life, but with little randomised data for these very different options[13,38,39,40]. For symptom control the choice is currently very uncertain and indications and clinical preferences for either modality are currently varied. Since the options are so different, requiring very different hospital stays with very different outcomes including fertility, sexual function and recurrence, a fair and comprehensive comparison is both overdue and complex.

Both NICE and the RCR/RCOG guidance emphasise the need for a randomised comparison. The NICE clinical guidelines on heavy menstrual bleeding highlight unanswered questions regarding interventions for uterine fibroids, including the effect on long term fertility and ovarian function, the impact on psychosexuality and the long term recurrence rate[24]. A rigorous evaluation of UAE and myomectomy in women wishing to avoid hysterectomy has been called for by the RCR and the RCOG[37]. Several other publications addressing the issues basic to this proposal have concluded that a randomised trial is strongly indicated[41].

In the USA in 1999 the research and education foundation of the Society for Interventional Radiology Foundation commissioned an evidence report which recommended four important research needs[42]:

1. Development of a disease-specific quality of life instrument
2. Establishing a registry for prospective collection of outcomes data
3. Undertaking a randomised trial against standard surgery

and

4. Undertaking a comparative cost analysis.

The first two of these aims have been achieved through this initiative[43,44,45], but to date, no randomised comparison of UAE and myomectomy has commenced. Comparisons against MRI guided ultrasound surgery are ongoing (NCT00995878).

Understanding better the impact on fertility of fibroids and their treatment is of fundamental importance. The NICE recommendations on assessment and treatment for infertility also indicate a need for randomised controlled trials to evaluate the role of these interventions on pregnancy outcome[27]. The extent to which fertility is retained or improved as a result of either treatment is also uncertain but due to the number of confounding and extraneous factors influencing conception and delivery, is difficult to assess. The FEMME Study will adopt an intermediate strategy to assess quality of life as a primary endpoint, while collecting comparable data on pregnancy outcomes. Women who wish to avoid hysterectomy do so largely to avoid irreversible infertility. Women may also consider the uterus as an important aspect of their feminine identity, even if the family is complete, and may be concerned about the impact of treatments on sexual function[46]. Surveys conducted by the Fibroid Network consistently highlight the lack of reliable information on fertility provided to women when faced with treatment choices.

Good, robust data are required so that women can make an informed choice between treatment options on the basis of hard evidence. Thus a comparison of UAE with myomectomy is increasingly fundamental to the choices many women who are concerned about their fibroids will have to make. The number of such women is set to increase because the tendency to delay first pregnancy is increasing to ages when fibroids are increasingly prevalent but where hysterectomy may be considered too radical a treatment for heavy menstrual bleeding. If fertility retention is explicitly sought, the current treatment of choice is myomectomy, but UAE is cheaper and associated with a shorter hospital stay and a quicker recovery and could be an attractive alternative if robust data on quality of life and some comparable information on subsequent fertility were available.

The pilot study carried out at St George's Hospital suggests that this trial is feasible, and pilot studies have shown that FEMME is both desirable and acceptable to women. The exclusion criteria imposed by the ethics committee at the initiation of the pilot meant that for every woman that was randomised, at least three were excluded. Since then more observational information has accrued on pregnancies following UAE, giving rise to less concern[47]. The FEMME Study, with wider entry criteria will have a greater population to draw upon and be more generalisable.

The study must be done now before it is too late. With an increase in delayed pregnancies, fibroids are becoming of increasing concern as a cause of sub-fertility in women. Women need to be empowered to make an informed choice as to the best method of treatment which maximises their chances of conceiving and carrying the pregnancy to term. In the current state, the evidence that may support such a choice is surrounded with uncertainty, which will remain until a large pragmatic randomised comparison is accomplished. This proposal aims to provide such evidence at a time when the uncertainty is greatest and the question most pressing.

1.7 Aim and Objectives of the FEMME Study

The aim of the FEMME Study is to examine the effectiveness of uterine artery embolisation (UAE) in comparison to myomectomy in the treatment of symptomatic fibroids.

This will be met through the following objectives:

1. Conduct a large, multicentre, open randomised controlled trial of UAE compared with myomectomy using quality of life as the primary outcome
2. Conduct an economic evaluation to determine the relative cost-effectiveness of the two interventions
3. Explore the relative effectiveness of the interventions on symptoms
4. Explore difference between the two groups of women in pregnancy rates and outcomes following the interventions
5. Compare adverse events and complications of the two interventions
6. Compare re-intervention rates
7. Investigate whether presenting characteristics can predict outcomes of the intervention

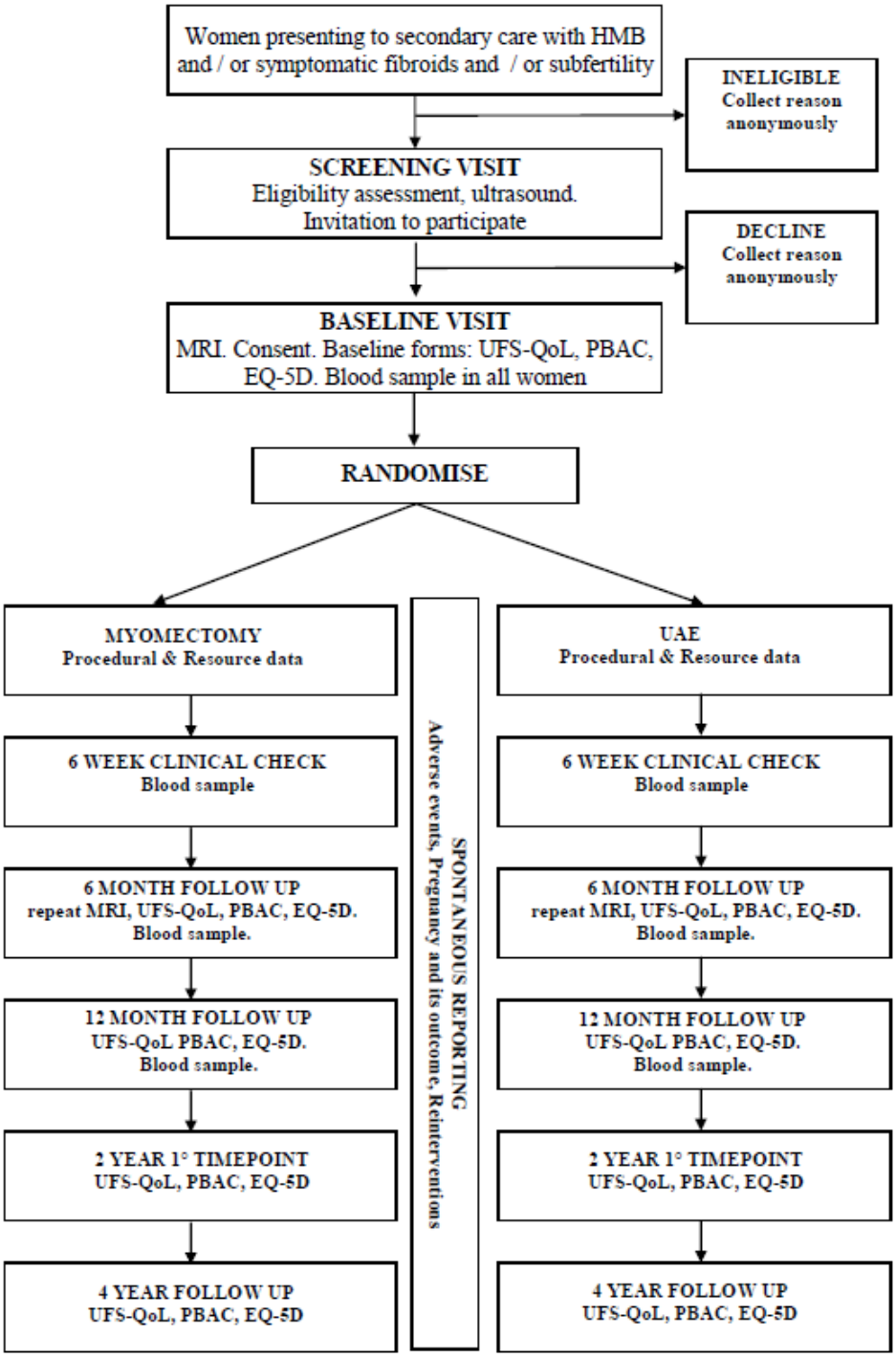
2 TRIAL DESIGN

2.1 Summary

The FEMME Study is a multicentre randomised trial comparing uterine artery embolisation (UAE) with myomectomy in women with symptomatic fibroids wishing to retain fertility

potential (Figure 1). 250 eligible women will be randomised in a 1:1 ratio to myomectomy or embolisation. The primary outcome of quality of life will be assessed by use of a disease specific questionnaire (UFS-QOL) at two years. Effectiveness will also be assessed at six months and one and four years after treatment and as a repeated measure over time. Secondary outcomes include effect on menstrual bleeding, pregnancy outcomes, further treatment and adverse events. Ovarian function and reserve will be assessed. Data on resource use will be collected to allow a concurrent economic evaluation.

Figure 1 FEMME Study Schema



2.2 Study population

The trial seeks inclusion for all women for whom uncertainty exists about treating their fibroids, who have troublesome symptoms and who wish to retain their uterus. There is less concern whether fertility is a dominant issue or not, since the importance of fertility among women avoiding a hysterectomy has an unpredictable time course[48]. Although clinicians will be asked to designate whether the woman is seeking to conceive to ensure balanced groups at baseline, we are not attempting to conduct this trial in two separate populations, as any designation will inevitably be artefactual in time.

In view of these considerations, this trial adopts a pragmatic approach and eligibility is based not on rigid entry criteria but on the "uncertainty principle". That is, if the clinical team is uncertain which treatment (myomectomy or embolisation) a particular patient should be offered, that patient is eligible to be included in the randomised trial. However, should the specialist strongly prefer one intervention over the other in order to provide the woman with what they believe is the most effective treatment for their fibroids then that women would not be suitable for inclusion in FEMME. Similarly, should a women have a strong preference for the procedure they wish to undergo to treat their fibroids, they too would **not** be suitable for inclusion in this trial. Eligibility based on uncertainty has been used in many previous surgical trials (e.g. the MRC's Carotid Endarterectomy Trial and the PD SURG trial) and has been shown to facilitate large-scale recruitment of an appropriately heterogeneous group of patients from a clinical community with a range of opinions.

3 ELIGIBILITY

Women will be identified primarily from menorrhagia or general gynaecology clinics, although a few may also be referred directly to interventional radiologists. Randomising centres should use existing referrals networks for their source of potential participants.

3.1 Screening of potential participants

The path to a diagnosis of uterine fibroids will follow routine practice for their centre, but will generally follow that shown in Figure 2 (Recruitment of participants into the FEMME study). A full gynaecological and general history will be taken and a general and pelvic examination performed. The diagnosis of fibroids will be made by transabdominal or transvaginal ultrasound (TVUS) in the first instance, with a hysteroscopy in some instances. This is likely to be supplemented by contrast enhanced magnetic resonance imaging (CEMRI) in most women. CEMRI scans will be saved in a format to allow independent review by a second radiologist. The patient will be given an explanation of the purpose of the trial, the treatment options and the requirements for follow-up. An information sheet and consent form will be provided and the patient will have time to consider participation. The participant will also receive the baseline questionnaire, part of which needs to be completed during a menstruation. There will be an interval whilst the MRI scan is performed that will allow for at least one menstrual period to occur prior to the woman attending the second clinic.

3.2 Inclusion and Exclusion Criteria

Individual gynaecologists, in consultation with the women and their collaborating interventional radiologist, will decide their own level of treatment uncertainty corresponding to the general criteria given below. Contact details (land line, email, mobile number) and NHS numbers will be collected from eligible consenting women to allow future contact.

This is a pragmatic study and there will be no limitation regarding site, size or number of fibroids. Women will be randomised into the FEMME study provided they meet all of the inclusion criteria below and none of the exclusion criteria.

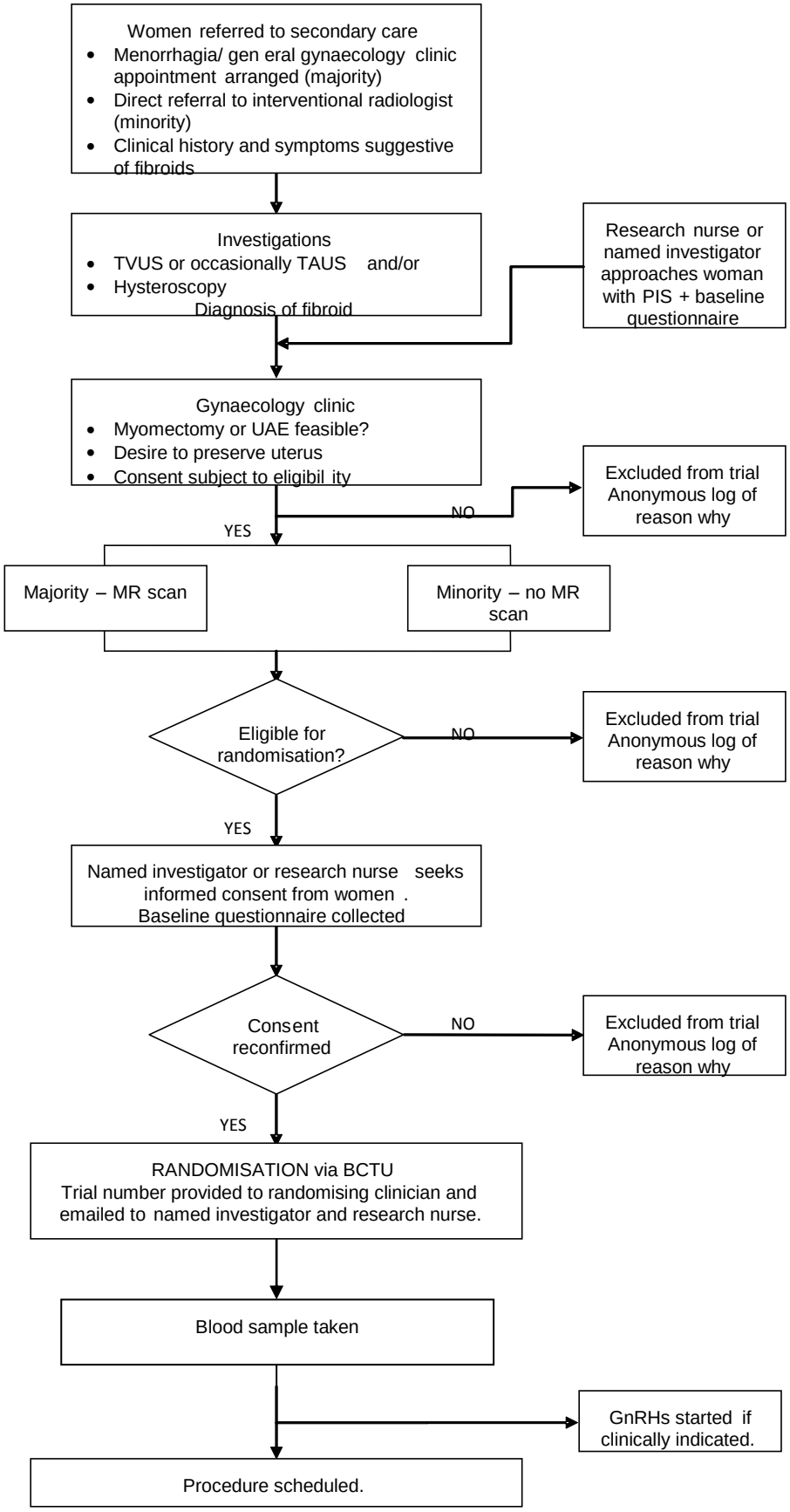
3.2.1 Inclusion

- Women with symptomatic fibroids who do not wish to have a hysterectomy
- Women with symptomatic fibroids who would ordinarily be offered a myomectomy
- Women must be considered suitable for either treatment (myomectomy or embolisation)
- Clinical team uncertain as to which treatment is indicated
- Written informed consent

3.2.2 Exclusion

- Refusal to accept hysterectomy, even as a result of an intra-operative complication
- Recent or ongoing pelvic inflammatory disease
- Significant adenomyosis, as identified by TVUS or CEMRI. Concurrent adenomyosis where fibroids are believed to the predominant cause of symptoms will be eligible
- Positive pregnancy test
- Refusal to accept surgery or embolisation as treatment option
- Post menopausal, as defined as greater than one year since previous menstrual period
- Suspected malignancy
- Women aged under 18 years old
- Unable to provide informed consent due to incapacity (as defined by Mental Capacity Act 2005 or Adults with Incapacity (Scotland) Act 2000)
- A non-English speaker where translation or interpretation facilities are insufficient to guarantee informed consent
- A previous myomectomy *via* a laparotomy or a previous embolisation

Figure 2 Recruitment of participants into the FEMME Study



3.3 Ineligible women

We will collect basic, anonymous information, including the age of women who are screened but found to be ineligible before randomisation, or who decline participation, to assess the prevalence of fibroids in this setting and the generalisability of the findings. Women found to be ineligible after randomisation will be treated appropriately but not withdrawn and will be followed-up as per the protocol.

3.4 Obtaining consent

The patient's written informed consent to participate in the trial must be obtained before randomisation and after a full explanation has been given of the treatment options and the manner of treatment allocation. Patient information sheets and consent forms will be provided so that patients can find out more about the trial before deciding whether or not to participate. Consent subject to confirmation of eligibility should be obtained as early as possible to enable the baseline questionnaire to be given to the women with sufficient time for completion. Consent must be confirmed prior to randomisation.

3.5 Informing the participant's GP

The patient's GP should be notified, with the patient's consent, and a specimen "Letter to GP" is supplied.

4 RANDOMISATION

4.1 Randomisation

Patients are entered in the trial by contacting the randomisation service either by

- Telephone (Freephone **0800 9530274**)
- fax (**0121 415 9136)**

or

- internet (**https://www.trials.bham.ac.uk/femme**)

Telephone randomisation is available Monday-Friday 0900-1700 hrs UK time. Randomisation out of these hours is obtained by logging on to the FEMME website. Each centre and each randomiser will be provided with a unique log-in and password to do this. Randomisation notepads are provided in the FEMME Site File and should be used to collate the necessary information prior to randomisation. After all the necessary details have been provided, the treatment allocation will be specified at the end of the telephone call, by return of fax or in the final screen of the website program.

4.2 Randomisation method and stratification variables

Randomisation can only occur once all eligibility criteria are confirmed, consent obtained and stratification variables determined. To prevent potential bias, following consent women will complete the baseline Quality of Life questionnaire which will be returned to the clinical staff prior to randomisation. The participant will be given the menstrual blood loss diary to take away and complete when they start their next period. At randomisation a 'minimisation' procedure using a computer-based algorithm will be used to avoid chance imbalances in important stratification variables.

Stratification variables will be:

- Longest dimension of largest uterine fibroid: <=7cm - >7cm (determined by ultrasound or magnetic resonance imaging).

- Numbers of fibroids: 1-3, 4-10, >10 (determined by ultrasound or magnetic resonance imaging).
- Fertility: currently desiring pregnancy or not

The choice of subgroups has been informed by data from the UK Fibroid Registry that indicates 45% of women have less than 4 fibroids and in 50% of women, the dominant fibroid was <=7cm at time of intervention[49]. To avoid any possibility of foreknowledge, the randomised allocation will not be given until all eligibility and stratification data have been given. The clinical team will assign a date for the procedure and inform the woman.

5 TREATMENT ALLOCATIONS

5.1 Trial interventions

The participant will be randomised to either embolisation or myomectomy in a 1:1 ratio. Additional treatments (pre- and peri-operative) will be documented. A proforma will be completed by the specialist and any additional information regarding procedure and inpatient stay collected from the case notes by the research nurses or research fellow.

5.1.1 Embolisation

This procedure will be performed by an interventional radiologist experienced in the technique. Bilateral selective catheterisation and embolisation of the uterine arteries will be performed under fluoroscopic guidance, either in a single procedure or two staged unilateral procedures. The embolic agent will be at the discretion of the interventional radiologist, provided the brand bears a European CE mark. The name and size of particles used will be recorded.

5.1.2 Myomectomy

Myomectomy will be carried out using the route preferred by the operating gynaecologist (open, hysteroscopic, laparoscopic). Gonadotrophin releasing hormone analogue (GnRH) pre-treatment can be initiated at the discretion of the gynaecologist but are not recommended.

5.1.3 Co-interventions

The trial will not seek to restrict concurrent procedures being undertaken e.g. adhesiolysis but will record basic details.

5.2 Withdrawal before treatment or protocol violation

Withdrawal of participants before the randomised treatment allocation has been performed is undesirable. Interventional radiologists should refer all MRI scans for a second review within their centres to ensure incidental pathologies are identified. Women should be counselled as to the nature of the procedure to which they have been allocated to reduce the risk of refusal or withdrawal.

6 SAFETY MONITORING PROCEDURES

6.1 Serious Adverse Event Reporting

The collection and reporting of Adverse Events (AEs) will be in accordance with the Research Governance Framework for Health and Social Care and the requirements of the National Research Ethics Service (NRES). The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the protocol. Serious Adverse Events

(SAEs) are those that are attributable to the study protocol or study interventions and causes or result 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 should be provided:

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

Assessment of causality and expectedness must be made by an Investigator at the randomising centre. If the SAE occurs at another hospital or in the community, initial reports without causality assessment should be submitted to the FEMME Study Office by a healthcare professional. The information will be assessed by one of the clinical Lead Principal Investigators. The local Principal Investigator and others responsible for patient care should instigate any supplementary investigations of SAEs based on their clinical judgement of the likely causative factors and provide further follow-up information as soon as available. An SAE judged by the Local Principal Investigator to have a reasonable causal relationship with the trial intervention will be regarded as a related SAE. If a participant dies as a result of the study protocol or study interventions, any post-mortem findings must be provided to the FEMME Study Office.

Women will also be provided with contact details for the FEMME Study Office to report hospitalisations, which will be followed up in conjunction with the randomising centre to ascertain if the event constituted an SAE. The outcome of pregnancies known to the study will be collected by the research nurse, with any reported congenital anomalies being assessed for causality by the participant's obstetrician and the randomising centre.

6.2 Reporting Period

Details of all protocol or intervention derived SAEs will be documented and reported from the date of commencement of protocol defined treatment until four years post randomisation.

6.3 Reporting SAEs

An SAE form should be completed for each episode and returned to the FEMME Study Office.

All SAEs forms should be faxed to the FEMME Study Office on 0121 415 9136 within 24 hours of the research staff becoming aware of the event. The Local Principal Investigator (or other nominated clinician) should assign seriousness, causality and expectedness to the SAE before reporting.

On receipt of an SAE Form, seriousness and causality will be determined independently by a Lead Principal Investigator. SAEs still present at the end of the trial must be followed up at least until the final outcome is determined, even if it implies that the follow-up continues after the end of the planned period of follow-up.

The FEMME Study Office will report all SAEs to the Joint Oversight Committee (JOC) . The JOC will view data with knowledge of treatment. If a participant dies as a result of the study protocol or study interventions, any post-mortem findings must be provided to the FEMME Study Office, who will report all deaths to the JOC for continuous safety review. The FEMME Study Office will also report all related and unexpected SAEs to the main REC annually, and to the Trial Steering Committee every six months. Local Investigators are responsible for reporting SAEs to their host institution, according to local regulations, but they do not need to inform the main REC as this will be done by the FEMME Study Office as detailed above.

6.4 Safety Reporting Responsibilities

6.4.1 Local Principal Investigator (or nominated individual in PI's absence):

- To identify **all** AEs that occur in the trial participants. This includes non-serious, serious, expected or unexpected adverse events
- Medical judgement in assigning seriousness and causality with respect to the study intervention or protocol, and to report any SAEs that are related and complete SAE form as required
- To fax SAE forms to FEMME Study Office within 24 hours of becoming aware, and to provide further follow-up information as soon as available
- To report SAEs to Trust R&D office, in line with local arrangements
- To sign an Investigator's Agreement accepting these responsibilities

6.4.2 Clinical Lead Principal Investigator:

- To assign causality of SAEs where it has not been possible to obtain local assessment
- To review all events assessed as SAEs in the opinion of the local investigator

6.4.3 FEMME Study Office:

- To report any related and unexpected SAEs to main REC
- To prepare annual progress reports to the main REC and TSC
- To prepare SAE safety reports for the JOC every . The JOC will be able to review unblinded data
- To report all fatal SAEs to the JOC for continuous safety review
- Note: The JOC has combined the roles of both the TSC and DMC, namely;

6.4.4 TSC (Trial Steering Committee) roles:

- To provide independent supervision of the scientific and ethical conduct of the trial on behalf of the Trial Sponsor and funding bodies
- To review data, patient compliance, completion rates, adverse events (during treatment and up to end of follow-up)

6.4.5 DMC (Data Monitoring Committee) roles:

- To review overall safety and morbidity data to identify safety issues which may not be apparent on an individual case basis

- To recommend to the TMG and the Funders whether the trial should continue unchanged, continue with protocol modifications, or stop

7 FOLLOW-UP AND OUTCOME MEASURES

7.1 Timeframe for measurement of outcomes

The trial will address outcomes over three timeframes, with with all timepoints taking place at specified intervals post-randomisation.

- Short-term: Operative details will be collected prior to hospital discharge and at six weeks post-operationto collect the immediate post-operative adverse events, resources used in diagnosis and intervention. The immediate impact on fertility potential will be measured using markers of ovarian reserve at 6 weeks after the procedure.
- Medium term: up to two years for symptom specific and generic quality of life outcomes and initial cost-effectiveness, and pregnancy rates. The first publication of results will be once all participants have reached the two year post-randomisation timepoint, but will include all outcomes collected at 6 months, 1 and 2 years. Ovarian reserve will also be measured at 6 months and 12 months post-procedure.
- Long term: up to four years for pregnancy and further treatment rates, together with quality of life outcomes. A further publication will report on these outcomes

Table 1 Timing of outcome measures collected

Timepoint **Outcome measure**	**Prior to randomisation**	**Before discharge**	**6 weeks**	**6 months**	**1 year**	**2 year**	**4 year**
UFS-QoL	X			X	X	X	X
EQ-5D and VAS	X			X	X	X	X
Pregnancy				X	X	X	X
Outcomes of pregnancy					As reported by participant		
PBAC	X			X	X	X	X
Fertility potential*	X		X	X	X		
Resource usage (clinical)	X	X		X			
Technical success				X			
Serious adverse					As reported by clinician/ participant		

events							
Further treatment				X	X	X	X

7.2 Primary endpoints/ outcome measures

The primary outcome will be assessment of quality of life using the Uterine Fibroid Symptom and Quality of Life (UFS-QoL) tool that combines assessment of symptoms as well as general quality of life[43]. The health-related quality of life (HRQoL) domain will be the primary outcome, whilst the symptom domain will be a secondary outcome. The HRQoL score at two years of follow-up will be the considered the primary timepoint. The instrument demonstrates face, construct and discrimination validity and has been demonstrated to be responsive to change[50]. Scores range from zero indicating worst HRQoL to 100 indicating the best. Combined assessment of symptoms as well as HRQoL is not possible with the UFS-QoL and moreover, symptom scores will be redundant if the woman is pregnant.

We have chosen not to use the SF-36 Health Survey in addition to the UFS-QoL. Although SF-36 has been validated for use in gynaecology and its wide use allows comparison of information between studies, it fails to capture the impact of a treatment on specific symptoms such as menstrual problems, unlike the UFS-QoL. This avoids the need for multiple questionnaires. Assessing QoL where subfertility is concerned or during pregnancy is extremely difficult and no well validated questionnaires are available. However, the outcome is likely to be reflected in the HRQoL items of the UFS-QoL and also the EuroQoL EQ-5D.

7.3 Secondary endpoints/ outcome measures

- HRQoL domain from the UFS-QoL at the other timepoints (see Table 1)
- Symptom severity domain from the UFS-QoL. Scores range from zero (no symptoms) to 100 (worst symptoms)
- EuroQoL EQ-5D-3L score (on the scale -0.59 [worst] to 1.0 [perfect]).[51]
- EuroQoL health thermometer score (on the scale 0 [worst] to 100 [perfect]).[51]
- Menstrual blood loss – The Pictorial Blood loss Assessment Chart (PBAC)[52] will be used (scores range from 0 [no bleeding] as a minimum but have no fixed upper limit). This is a validated and well used assessment of menstrual blood loss in women with uterine fibroids, which will also be used to generate rates of amenorrhea and non-heavy bleeding.
- Pregnancy outcomes – specifically pregnancy (overall and in the population desiring pregnancy at the time of randomisation) and outcomes (live birth, miscarriage, still birth and termination. Pregnancy will be reported by the women in the first instance.
- Adverse events – all adverse outcomes considered to be related to the study protocol or intervention will be collected (see Section 6). Since adverse outcomes may occur many months after intervention, these data will continue to be collected throughout the study
- Participant responses to ‘would you have your operation again?’
- Participant responses to ‘would you recommend operation to a friend?’
- Length of hospital stay

- Further treatment for incomplete removal or recurrence of symptoms, including hysterectomies
- Ovarian reserve will be measured at six weeks, six months and at one year after the initial procedure.

7.4 Fertility potential

The primary focus of the trial is to assess the impact of embolisation and myomectomy on the quality of life and not fertility, although of course maintenance of fertility and conception will be important to many women. Since women recruited to this trial will be randomised, all exogenous influences on fertility will be reasonably balanced, although we will not be collecting information on an exhaustive list of such factors e.g. male fertility potential.

In addition to collecting information on confirmed pregnancies and live birth, we also plan to explore "the potential for a woman to conceive " – in particular her ovarian reserve, by measuring the serum levels of anti-Mullerian factor (AMH) and Oestradiol (E2). If the blood sample is taken on days 2,3 or 4 of the woman's menstrual period then we will also measure the levels of the day 2-4 gonadotrophins follicle stimulating hormone (FSH) and luteinising hormone (LH) before randomisation and then again at six weeks, six months, one year after intervention. Blood samples will be drawn at the site into Serum Separator Vacutainers (SST).

These SSTs will be labelled with the participant's trial number before being sent directly to the Biobank at the University of Birmingham. Upon receipt, the Biobank will log the sample then spin out and store the serum until all the blood samples have been collected. The Biobank will inform the FEMME Trials Co-ordinator each time a FEMME blood sample arrives and the FEMME Trial Co-ordinator or Data Manager will update that patient's record on the FEMME database.

Once the final blood sample has been collected the serum will be transferred on dry ice to Prof. Lumsden at the University of Glasgow. All assays for FSH, LH, E2 and AMH will be carried out in the laboratories of the University of Glasgow under the supervision of Professor Lumsden. Blood samples will be considered as a gift to the University of Oxford.

7.5 Timing of assessments

7.5.1 Baseline Visits

The woman will be checked to ensure that they meet all the criteria for inclusion. The women will be given opportunity to discuss the trial, after which they will be asked to give informed consent and provided with contact details in case questions arise. The patient baseline quality of life questionnaire will be given to the woman who will be asked to complete it and return it to the local clinical team prior to randomisation. The participant will be given a copy of the menstrual blood loss diary and asked to complete it when they start their next period.

An MRI scan will be organised for most participants to establish the site, size and number of fibroids.

Blood will be taken for assessment of ovarian function.

7.5.2 Treatment Visit

A pregnancy test will be performed immediately prior to treatment. Information collected at the time of procedure will include details of the method of treatment, problems encountered and length of in-patient stay.

7.5.3 Follow-up visits

The patient will routinely be seen at six weeks and six months after treatment to assess recovery from treatment. At six months a second MRI will also be performed and a brief review visit performed by the research nurse or research fellow. The patient completed follow-up forms will be collected at this time.

7.5.4 Subsequent follow-up

The patient will then be followed by post and/ or telephone at 12 months, two and four years thereafter. Participants will be asked to contact the FEMME Study Office should they become pregnant. Details of the outcome of the pregnancy will be collected by the coordinating research nurse following contact with the patient and examination of the case notes where possible. Research nurses will be encouraged to keep regular contact with the patients in order to minimize drop out.

Any serious adverse events, requiring or prolonging hospitalisation, or that are fatal or potentially life-threatening, will be reported by the clinical team to the FEMME Study Office as they occur until the woman has reached the four year follow-up timepoint.

7.6 Resource usage information

Data on health care resource use in each arm of the trial will be collected alongside the trial, these include:

- Tests and investigations received
- Time in the operating and recovery rooms
- Total length of stay in hospital
- Surgical treatment of uterine fibroids
- The number, frequency and duration of out-patient visits and primary care consultations
- Additional inpatient stays
- Type and volume of medications received
- The number and duration of hospital readmissions and re-treatments.

These data will be collected prospectively from health care providers using a post-operative case report form. At the 12 months, two and four year follow-ups, participants will also be asked to report further surgical procedures which will be validated against hospital records.

8 ACCRUAL AND ANALYSIS

8.1 Sample size

The sample size for the trial is based around the primary outcome measure of total health-related quality of life score taken from the UFS-QoL questionnaire, and is informed by the results of the pilot study at St. George's Hospital[19]. The mean difference seen here from the 118 patients who provided questionnaire responses at twelve months was 12 points in favour of myomectomy with a standard deviation of 22 points (using an analysis of covariance approach). This is equivalent to approximately 0.5 standard deviations (rounded downwards to be conservative). To detect a difference of this size (a moderate effect[53]) with 90% power (p=0.05) would require 86 patients in each group (172 in total). Whilst the number of women expected to become pregnant before the primary outcome

time of 2 years is expected to be low (10% or less), some provision needs to be made for these women as not all questions on the UFS-QoL will be still relevant. Additionally, a further 10% has also been added to account for loss to follow-up (including withdrawals). Thus, the target sample size has been inflated to 216 patients. We do expect a number of cross-overs in this study. To allow for these and ensure that the results still remain sufficiently powered to detect any differences in the primary outcome between the two treatment arms the sample size has been inflated to a total of 250.

8.2 Projected accrual and attrition rates

Projecting forward the recruitment data obtained over the period of 1st June 2013 to 31st August 2014 predicts that a sample size of 250 should be attained (with a 95% certainty) between the end of November 2014 and the End of January 2015. To allow for a decrease in the recruitment rate typically seen over the Christmas and New Year period, FEMME will continue to recruit until the end of March 2015 or the number of women randomised to the trial reaches 250, depending on whichever is reached first.

8.3 Statistical Analysis

8.3.1 Primary analysis

In the first instance, follow-up at two years will be considered the principal time for analysis of the primary outcome measure (HRQL domain score from UFS-QoL). This score will be analysed using a linear model (analysis of covariance), with estimates of difference between groups adjusting for the baseline score. Results of the primary outcome score at other time points, along with the results of other continuous-type measurements (e.g. symptom severity score from the UFS-QoL questionnaire, EQ-5D, PBAC scores) will be analysed in a similar fashion. Further analysis of continuous measures will be undertaken using a repeated measure multilevel model to examine any differential effect over time[54]. Dichotomous measures (e.g. pregnancy or re-intervention rates) will be analysed using relative risks and chi-squared tests at each time point. Variables including pregnancy and reintervention will also be explored using standard time-to-event analysis methods (log-rank test). All analyses will be performed using the intention-to-treat principle with effect sizes presented as point estimates and corresponding 95% confidence intervals. Further details on analysis will be given in the statistical analysis plan to be agreed with the Data Monitoring (DMC).

8.3.2 Interim analyses

An interim report including the analysis of major endpoints will be provided in strict confidence to a Joint Oversight Committee as to a timetable agreed by the JOC. See Section 9.4 for further details on trial data monitoring.

8.3.3 Handling missing data

In the first instance analysis will be completed on received data, with every effort made to follow up participants even after protocol treatment violation to minimise any potential bias. Sensitivity analysis of the primary outcome measure including imputed values for missing responses will be carried out to determine the robustness of the results obtained. Methods based on multiple imputation will be used.

8.4 Sub-group analysis

Subgroup analyses are limited by statistical power and can produce spurious results particularly if many are undertaken. For this reason any subgroup analysis will be limited to the stratification variables pre-specified in Section 4.2. Effects within subgroups will only be investigated further if suitable tests for interaction (i.e. by including the relevant interaction parameter in the regression model) are of statistical importance.

8.5 Economic evaluation of embolisation compared with myomectomy

An economic evaluation will be conducted alongside the clinical trial to determine the relative cost effectiveness of embolisation compared to myomectomy from the perspective of the NHS and the personal social services[55]. Health utility values associated with each arm of the trial will be calculated from the responses to the EQ-5D. Information relating to health care resource use associated with the procedures and associated complications and events during the trial period will be collected (see Section 7.6). Unit costs for all health care resource used will be obtained from routinely collected data and the literature to estimate the total costs associated with resource use in each arm of the trial. All costs and QALYs will be discounted at the currently recommended rate. Cost-utility analyses will be carried out at two and four years post randomisation. Cost effectiveness will be expressed as incremental cost per quality adjusted life years (QALY) gained. The 95% confidence limits for the difference in mean costs between arms and for the incremental cost effectiveness ratios will be calculated using non parametric bootstrap methods. In addition the long term cost effectiveness of the intervention will be estimated by modelling. The probabilistic decision model will be developed to estimate the subsequent health status and costs beyond the period of the trial, until menopause. The model will be populated primarily by data extrapolation from this trial. Extensive sensitivity analyses will be conducted to explore areas of structural uncertainty in the analyses. Parameter uncertainty, including that relating to heterogeneity of the pre-specified subgroups, will be handled by using probabilistic sensitivity analysis and presented using cost-effectiveness curves.

9 DATA MANAGEMENT AND QUALITY ASSURANCE

9.1 Completion of Data Collection Forms

All data collection forms will be available in paper and web-based formats, with identical questions and data items. Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. All forms must be completed and returned to the FEMME Study Office, or directly input by the local Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log) within appropriate timeframes. Entries on paper data collection forms should be made in ballpoint pen, in blue or black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. The FEMME Study Office will query all missing and ambiguous data. If it is not obvious why a change has been made, an explanation should be written next to the change. The web-based forms will highlight incorrect, inconsistent or missing data and will contain an audit tracking system for corrections.

In all cases it remains the responsibility of the Investigator to ensure that the data collection forms are been completed correctly and that these data are accurate.

Participant completed forms will be posted to the last known address with a pre-paid return envelope. Women will also be given the option of completing the form on a data-enabled PDF or, eventually, via a web-based form.

Trial forms may be amended by the FEMME Study Office, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the form must be implemented by participating sites immediately on receipt.

9.2 Confidentiality and data protection

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do

so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic databases. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

Personal data and sensitive information required for the FEMME Study will be collected directly from trial participants and hospital notes. Participants will be informed about the transfer of this information to the FEMME Study Office at the BCTU and asked for their consent. With the patient's consent, their full name, date of birth, National Health Service (NHS) number, or in Scotland the Community Health Index (CHI), address, post code, hospital number and general practitioner details will be collected at trial entry. This will allow direct contact with the participant and also enable tracing of non-responders via the NHS Information Centre for Health and Social Care (service formally provided by the Office of National Statistics) and to assist with long-term follow-up via other health care professionals (e.g. patient's GP). Patients will be identified using only their unique trial number, and date of birth to verify identify on the Data Collection Forms and correspondence between the FEMME Study Office and the participating site.

Consent forms will be collected by the FEMME Study Office to perform in-house monitoring of the consent process. Participants will be asked to acknowledge their consent to this transfer. The consent form may also been forwarded to other health care professionals involved in the treatment of the participant eg their GP, if needed to verify consent to participation in the study.

The data will be entered onto a secure computer database, either directly via the internet using secure socket layer encryption technology or indirectly from paper by FEMME Study Office staff.

Blood samples, which have been transferred from local centres to the central laboratory, will only be identified by their trial number. Central laboratory staff will not have access to personal or clinical trial data.

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the 2018 General Data Protection Regulations and other relevant legislation.

Participants will always be identified using their unique trial identification number on questionnaires measuring the quality of life, and in any correspondence between BCTU and the trial site.

The Investigator must maintain documents not for submission to BCTU (e.g. Participant Screening Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

BCTU will maintain the confidentiality of all participants' data and will not disclose information by which participants may be identified to any third party, other than those directly involved in the treatment of the participant, or organisations for which the participant has given explicit consent to view their records. Representatives of the FEMME trial team, sponsor, and other oversight organisations may be required to have access to participant's notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.The FEMME Study Office will maintain the confidentiality of all participants' data and will not disclose information by which patients may be identified to any third party except to those directly involved in the treatment of the participants.

9.2.1 Monitoring and Audit

Investigators and their host Trusts will be required to permit trial-related monitoring and audits to take place by the FEMME Study Coordinator or by the sponsor, providing direct access to source data and documents as requested. Trusts may also be subject to inspection by the Research and Development Manager of their own Trust and should do everything requested by the Chief Investigator in order to prepare and contribute to any inspection or audit. Study participants will be made aware of the possibility of external audit of data they provide in the participant information sheet.

9.2.2 On-site Monitoring

Monitoring will be carried out as required following a risk assessment. Additional on-site monitoring visits may be triggered for example by poor data collection form return, poor data quality, low SAE reporting rates, excessive number of patient withdrawals or protocol deviations. If a monitoring visit is required the FEMME Study Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the FEMME study staff access to source documents as requested.

9.2.3 Central Monitoring

FEMME study staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Study staff will check incoming data collection forms for compliance with the protocol, data consistency, missing data and timing. Sites will be contacted to request missing data or clarification of inconsistencies or discrepancies.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/ or GCP, and/ or poor recruitment. Any major problems identified during monitoring may be reported to the JOC. This includes reporting serious breaches of GCP and/ or the study protocol to the main Research Ethics Committee (REC).

9.2.4 Statistical monitoring throughout the study

The study will also adopt a centralised approach to monitoring data quality and compliance. A computer database will be constructed specifically for the trial data and will include range and logic checks to prevent erroneous data entry. Independent checking of data entry will be periodically undertaken on small sub-samples. The trial statistician will regularly check the balance of allocations by the stratification variables.

9.3 Independent Joint Oversight Committee

Until October 2018, FEMME has been overseen by a Data Monitoring Committee (DMC) (which ensures the safety, well-being and dignity of participants in clinical studies as well as determining if and when a meaningful result can be obtained), and a Trial Steering Committee (TSC) (which provides independent supervision for the trial) Numerous relocations and retirements have depleted the original TSC and DMC memberships. Given the late stage of FEMME the funders (NIHR HTA) have agreed that FEMME can be overseen by a single committee which combines the roles of the DMC and the TSC. This committee is referred to as the “Joint Oversight Committee (JOC)”.If the Chief and Principal Investigators are unable to resolve any concern satisfactorily, Principal Investigators, and all others associated with the study, may write through the FEMME Study Office to the chairman of the JOC, drawing attention to any concerns they may have about the possibility of particular side-effects, or of particular categories of patient requiring special study, or about any other matters thought relevant.

9.4 JOC: determining when clear answers have emerged

Previously the FEMME DMC advised the chair of the Trial Steering Committee if, in their view, any of the randomised comparisons in the trial have provided both (a) “proof beyond reasonable doubt” that for all, or for some, types of patient one particular treatment is definitely indicated or definitely contraindicated in terms of a net difference in the major endpoints, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. The TSC then advised the TMG and the funders whether to close or modify any part of the trial. During this process the TMG, , the investigators and all of the central administrative staff (except the statisticians who supplied the confidential analyses) remained unaware of the interim results.

The JOC will be run along similar lines. The JOC will be convened and operate according to the recommendations arising from the DAMOCLES project. A trial specific charter has been drawn up to define the remit and terms of reference of the JOC, which will be agreed by the Chief Investigator and the JOC members before the first meeting of the JOC. The JOC will report their recommendations back to the funders and the TMG.

9.5 Long-term storage of data and Archiving

Once data collection is complete on all participants, all data will be stored for at least 15 years (but ideally not less than 25 years). This will allow adequate time for review and reappraisal. Any queries or concerns about the data, conduct or conclusions of the trial can also be resolved in this time. Limited, anonymous data on the participants and records of any adverse events may be kept for longer if recommended by an independent advisory board.

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source records (e.g. signed Informed Consent Forms, Investigator Site Files, patients’ hospital notes, copies of data collections forms etc.) at their site are securely retained for the required timeframe. No documents should be destroyed without prior approval from FEMME Study Office.

Long-term offsite data archiving facilities will be considered for storage of the Trial Master File after 5 years. The BCTU has standard processes for both hard copy and computer database legacy archiving.

9.5.2 Data Sharing

In line with the MRC’s policy on data sharing, the FEMME Study dataset will be made available to other researchers proposing high quality secondary research, e.g. individual patient data meta-analysis. Anonymised data can be shared in legacy formats.

9.6 End of Trial Definition

The end of the intervention period of the trial will reached when the last participant has undergone the initial trial treatment. The end of the observational phase of the study will be when the last participant has reached the four year follow-up timepoint. The FEMME Study Office will notify the main REC when each phase of the trial has ended and a summary of the clinical trial report will be provided within 12 months of the end of trial observational period.

10 ORGANISATION AND RESPONSIBILITIES

10.2 Site Set-up and Initiation

All sites will be required to sign a “Clinical Study Site Agreement” with the Sponsor (University of Oxford) prior to participation. In addition all lead local investigators will be asked to sign an Investigator Agreement and supply a current CV and evidence of GCP

training to the FEMME Study Office. All members of the site research team will also be required to sign the Site Signature and Delegation Log which should be returned to the FEMME Study Office and a copy retained in the Investigator Site File. Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, serious adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The FEMME Study Office must be informed immediately of any change in the site research team.

To ensure the smooth running of the trial and to minimise the overall procedural workload, it is proposed that each participating centre should designate individuals who would be chiefly responsible for local co-ordination of clinical and administrative aspects of the trial.

10.3 Centre eligibility

Any centre capable of offering both myomectomy and UAE, either directly or through local referral networks, will be eligible to participate. Investigators will be asked to provide details of their current practice and number of procedures performed.

10.4 Local Principal Investigator at each centre

Each centre should nominate a consultant gynaecologist **or** interventional radiologist to act as the local Principal Investigator and bear responsibility for the conduct of research at their centre. Close collaboration between all clinical teams is particularly important in FEMME in order that patients for whom embolisation is an option can be identified sufficiently early for entry. The responsibilities of the local Principal Investigator will be to ensure that all medical and nursing staff involved in the care of women with uterine fibroids are well informed about the study and trained in trial procedures, including obtaining informed consent. The local Principal Investigator should liaise with the Trial Coordinator on logistic and administrative matters connected with the trial.

10.5 Nursing Co-ordinator at each centre

Each participating centre should also designate one nurse as local Nursing Coordinator. This may be a nurse specifically appointed, by the hospital Trust or Local Comprehensive Research Network, to act as a FEMME research nurse. This person would be responsible for ensuring that all eligible patients are considered for the study, that patients are provided with participant information sheets and have an opportunity to discuss the study if required. The nurse will be responsible for collecting the baseline patient data and for assisting the FEMME Study Office with follow-up questionnaires, including ascertaining outcomes of pregnancy. Again, this person would be sent updates and newsletters, and would be invited to training and progress meetings.

10.6 The FEMME Trial Office

The FEMME Study Office at the University of Birmingham Clinical Trials Unit (BCTU) is responsible for providing all trial materials, including the Investigator Site Files containing printed materials and the update slides. These will be supplied to each collaborating centre, after relevant Trust research governance approval has been obtained. Additional supplies of any printed material can be obtained on request. The FEMME Study Office also provides the central randomisation service and is responsible for collection and checking of data (including reports of serious adverse events thought to be due to trial treatment), for reporting of serious and unexpected adverse events to the main REC and JOC and for analyses. The FEMME Study Office will help resolve any local problems that may be encountered in trial participation.

10.7 Research Governance

All Investigators are responsible for ensuring that any research they undertake follows the agreed protocol to ensure that participants receive appropriate care while involved in research, the integrity and confidentiality of clinical and other records and data generated by the research are protected, and for reporting any failures in these respects, serious adverse events and other events or suspected misconduct through the appropriate systems.

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care for the relevant UK countries.

Before any patients are enrolled into the trial, the Principal Investigator at each site is required to obtain local Trust research governance approval. Sites will not be permitted to enrol patients until written confirmation of such approval is received by the FEMME Study Office.

It is the responsibility of the Chief Investigator to ensure that all subsequent amendments gain the necessary protocol approvals and that local investigators are informed of the nature and effective date of the amendment. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

All participating Trusts will be required to sign a Clinical Study Site Agreement, detailing their commitment to accrual, compliance, Good Clinical Practice, confidentiality and publication. Deviations from the agreement will be monitored and the JOC will decide whether any action needs to be taken, e.g. withdrawal of funding, centre suspension, etc. The FEMME Study Office will ensure researchers not employed by an NHS organisation hold an NHS honorary contract for that organisation. Staff at the FEMME Study Office required to visit many hospitals will obtain a NHS research passport.

10.7.2 Ethical and Trust Management Approval

The Trial has a favourable ethical opinion from Coventry and Warwickshire Research Ethics Committee (MREC) approval, determining that the trial design respects the rights, safety and wellbeing of the participants.

The Local Comprehensive Research Network will conduct global governance checks. The Trust R&D Office will assess the facilities and resources needed to run the trial in order to give host site permission. The FEMME Study Office is able to help the local Principal Investigator in the process of the site specific assessment by completing much of Site Specific Information section of the standard IRAS form as possible. The local Principal Investigator will be responsible for liaison with the Trust management with respect to locality issues and obtaining the necessary signatures at their Trust.

As soon as Trust research governance approval has been obtained, the FEMME Study Office will send an Investigator Site File to the local Principal Investigator. Potential trial participants can then start to be approached.

10.8 Funding and Cost implications

The research costs of the trial are funded by a grant from the National Institute for Health Research Health Technology Assessment Programme awarded to the University of Oxford. Subcontracts, coordinating centre agreements and central laboratory agreements will be created between the University of Oxford, St George's Medical School and Universities of Birmingham and Glasgow respectively.

The trial has been designed to minimise extra 'service support' costs for participating hospitals, with no extra visits to hospital above routine post-procedural follow-up. The 6

month MRI scan will be an additional trial related procedure for women allocated to myomectomy and in some centres where post-embolisation MRI scans are not routine. Additional costs service support costs associated with the trial, e.g. gaining consent, aliquoting extra blood samples etc, are estimated in the Site Specific Information section of the standard IRAS form. These costs should be met by accessing the Trust's Support for Science budget via the Local Comprehensive Research Network.

10.9 Indemnity

The University of Oxford has arrangements in place to provide for harm arising from participation in the study for which the University is the research sponsor. NHS indemnity operates in respect of the clinical treatment which is provided.

The University of Oxford has arrangements in place to provide for non-negligent harm arising from participation in the study for which the University is the research sponsor.

10.10 Publication

A meeting will be held after the end of the study to allow discussion of the main results among the collaborators prior to publication. The success of the study depends entirely on the wholehearted collaboration of a large number of doctors, nurses and others. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all those who have collaborated in the study. Centres will be permitted to publish data obtained from participants in the FEMME Study that use trial outcome measures but do not relate to the trial randomised evaluation and hypothesis.

10.11 Ancillary studies

It is requested that any proposals for formal additional studies of the effects of the trial treatments on some patients (e.g. special investigations in selected hospitals) be referred to the Trial Management Group for consideration. In general, it would be preferable for the trial to be kept as simple as possible, and add-on studies will need to be fully justified.

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FEMME STUDY SCHEMA