In response to an enquiry from NHS National Services Scotland

Number 55 October 2015

Is magnetic resonance guided focused ultrasound surgery (MRgFUS) for the treatment of uterine fibroids clinically effective, safe and cost effective compared with uterine artery embolisation, myomectomy and hysterectomy?

What is an evidence note

Evidence notes are rapid reviews of published secondary clinical and cost-effectiveness evidence on health technologies under consideration by decision makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions and are produced in an approximately 3-month period. Evidence notes are not comprehensive systematic reviews. They are based on the best evidence that Healthcare Improvement Scotland could identify and retrieve within the time available. The reports are subject to peer review. Evidence notes do not make recommendations for NHSScotland, however the Scottish Health Technologies Group (SHTG) produce an Advice Statement to accompany all evidence reviews.

Definitions

Uterine fibroids: benign tumours in the wall of the uterus, which can result in symptoms including bleeding, pain, abdominal pressure and urinary incontinence, and may be associated with infertility and miscarriage.

Magnetic resonance guided focused ultrasound surgery (MRgFUS): a non-invasive procedure that uses magnetic resonance imaging (MRI) to plan, guide and monitor tissue ablation using focused ultrasound. MRI enables thermal mapping during the procedure while high-intensity ultrasound generates intense heat that destroys abnormal cells at the focal point without damaging adjacent normal tissue.

Hysterectomy: surgical removal of the uterus.

Myomectomy: surgical removal of uterine fibroids.

Key points

- There are currently no published randomised controlled trials comparing magnetic resonance guided focused ultrasound surgery (MRgFUS) with alternative treatment options for symptomatic uterine fibroids.
- Evidence comparing MRgFUS with other uterine-preserving treatments is limited to two non-randomised studies suggesting that UAE results in better outcomes.
- Evidence on the safety of MRgFUS from uncontrolled observational studies suggests that major complications are rare.
- The effects of the procedure on fertility and future pregnancy are uncertain.
- Overall, the evidence is inconsistent and inconclusive surrounding the cost effectiveness of MRgFUS.
- One United Kingdom (UK) study demonstrated MRgFUS to be cost-effective, up to the age of 45 years. However, the robustness of the results is compromised owing to an absence of head to head trial data, a large number of assumptions in the model, and the use of unpublished data.
- Two of three appraised American studies concluded MRgFUS to be cost-effective and a Canadian health technology assessment (HTA) estimated UAE to be cost-effective. It should be noted that the results of these studies were sensitive to changes in the model assumptions, and it is difficult to draw any clear conclusions from the studies. Furthermore, the generalisibility of the results to Scotland is limited as the studies were carried out from a United States (US) and Canadian societal perspective.
**Uterine artery embolisation (UAE):** Fluoroscopic imaging is used to guide insertion of a catheter into the uterine artery and injection of embolic agents (small particles) into the arteries that supply blood to the fibroids, which reduces blood flow resulting in shrinkage and necrosis of the fibroids.

**Literature search**
A systematic search of the secondary literature was carried out between 29 January and 6 February 2015 to identify systematic reviews, health technology assessments (HTA) and other evidence based reports. Medline, Medline in process, Embase and Cinahl databases were also searched for systematic reviews and meta-analyses. The primary literature was systematically searched between 29 January and 6 February 2015 using Medline, Medline in process, Embase and Cinahl. Results were limited to English language. Both searches were updated on 27 March 2015.

Key websites were searched for guidelines, policy documents, clinical summaries, economic studies and ongoing trials.

Concepts used in all searches included: magnetic resonance guided focused ultrasound surgery (MRgFUS), high-intensity focused ultrasound (HIFU) ablation, uterine fibroid, uterine myoma and uterine leiomyoma. The updates also included focused searches for ExAblate and Sonalleve.

A full list of resources searched and terms used are available on request.

**Introduction**
MRgFUS is a non-invasive treatment for symptomatic uterine fibroids typically performed on an outpatient basis by an interventional radiologist. MRgFUS treatment is currently available in the United Kingdom (UK) in only one tertiary referral centre at St Mary’s Hospital in London. MRgFUS is being evaluated in research centres elsewhere in the UK, including the Institute of Medical Science and Technology (IMSaT) in Dundee.

The St Mary’s centre accepts referrals only from consultant gynaecologists and has no pre-defined patient pathway (GJ Houston, Consultant Radiologist, NHS Tayside. Personal Communication, 19 May 2015). A retrospective review of 280 women with complete data who underwent MRgFUS at the centre between 2003–2011, reported that 202 (72%) had no previous treatment, 12 (4.3%) had previous myomectomy, 12 had transcervical resection of fibroid, 7 (2.5%) had UAE, and 47 (16.8%) had IUS (meaning intrauterine system, a contraceptive device placed in the uterus). It is anticipated that any provision of MRgFUS in Scotland would be a more integrated service based on existing NHS infrastructure (GJ Houston, Consultant Radiologist, NHS Tayside. Personal Communication, 19 May 2015). It is expected that MRgFUS would be offered to patients in Scotland with uterine fibroids who are considering intervention for symptomatic menorrhagia (abnormal heavy and prolonged menstrual bleeding) and in particular those patients requesting uterus preserving treatment with UAE or myomectomy (GJ Houston, Consultant Radiologist, NHS Tayside. Personal Communication, 19 May 2015).

**Health technology description**
The technology comprises a specialised HIFU transducer coupled with an MRI scanner. Two manufacturers currently produce MRI-guided HIFU systems, namely Insightec’s ExAblate 2000 system and upgraded ExAblate 2100 conformational system (Insightec Haifa, Israel) and Philips’ Sonalleve (Philips Medical Systems, The Netherlands). The ExAblate 2000 system received a CE Mark for the treatment of symptomatic uterine fibroids in 2002, followed by ExAblate 2100 in 2012. The ExAblate system is compatible with General Electric Healthcare MRI systems. The ECRI Institute determined the cost of the ExAblate at US $750,000 to US $1.5 million. IMSaT in Dundee is equipped with the ExAblate body and conformal system. The Sonalleve system received a CE mark for treatment of uterine fibroids in 2002, followed by ExAblate 2100 in 2012. The Sonalleve system uses a volumetric ablation strategy in contrast to ExAblate’s point-by-point ablation method. The Sonalleve system is compatible with Philips MRI scanners. In both systems, the HIFU device is embedded within a specially designed table that fits into the MRI scanner so that the scanner can be used for other purposes.
The procedure is performed with the patient lying prone inside the MRI scanner, usually under conscious sedation, with the head of the HIFU device in contact with the patient’s abdominal skin. High-intensity focused ultrasound is passed through the front of the abdomen to converge on a precise point within the fibroid causing a temperature rise to 55°C–90°C that induces coagulative necrosis (cell death) within seconds without damaging adjacent normal tissue. Concurrent MRI provides continuous imaging throughout the procedure, which facilitates accurate targeting and gives real-time temperature feedback thereby enabling controlled localised ablation of the fibroid. Treatment is delivered as a series of pulses (sonications) targeting different areas of the fibroid, each ablating a small volume of tissue until the entire fibroid is ablated. Treatment typically consists of 20–50 separate sonications lasting between 10–30 seconds each, followed by a 90 second cooling period, hence the treatment time can be long, depending on the amount of fibroid tissue to be ablated. Consequently, the patient is required to lie still for up to 3–4 hours. Technical success is assessed by the volume of fibroid tissue ablated as indicated by the non-perfused volume (NPV) visualised on MRI. MRgFUS treatment protocols have evolved over time largely reflecting relaxation of initial technical restrictions imposed by the US Food and Drug Administration (FDA) to optimise safety in early trials. Prior to April 2004 the FDA allowed only one procedure and ablation was limited to 33% or 100 ml for a single fibroid and the maximum procedure time allowed was 120 minutes. From April 2004 up to April 2009, the ablation limit was increased to 50% fibroid volume up to 150 ml per patient, the maximum treatment time was increased to 180 minutes, and second or staged procedures (when there was insufficient time to ablate the entire target volume in a single session) were allowed. In April 2009 restrictions on target volume and treatment time were lifted to allow 100% ablation of the target fibroid. The original FDA criteria stated that women must have completed child bearing, which was modified in 2009 to should have completed child bearing.

**Epidemiology**

Uterine fibroids (also called myomas or leiomyomas) are benign tumors of the uterus and one of the most common gynaecological problems among women in the UK. They develop in women of reproductive age with an estimated incidence of 20–40% among women of child-bearing age and increasing prevalence with age until the menopause. The incidence of uterine fibroids is reportedly similar among Caucasian, Asian and Hispanic women whereas the risk is estimated to be two to three times higher among black women. Fibroids can be single or multiple, vary in size from a few millimetres to greater than 10 cm in diameter, and are classified by their location in the wall of the uterus as subserous, intramural or submucous. Most women with uterine fibroids do not have symptoms and do not require treatment. An estimated 10–20% of women do experience symptoms including menorrhagia, pelvic pressure, pain, and urinary incontinence and constipation due to compression of adjacent structures. Fibroids may also be associated with infertility and miscarriage. Fibroid growth is believed to be promoted and maintained by exposure to the hormones oestrogen and progestogen hence fibroids typically shrink and symptoms improve after menopause.

Management of symptomatic fibroids is individualised based on the severity of symptoms, the size and location of the fibroids, the woman’s age, and her desire to retain her uterus for future child-bearing or for other reasons. Hysterectomy used to be standard treatment and remains the only definitive treatment to resolve symptoms and prevent recurrence. Minimally invasive treatments (myomectomy, UAE) and non-invasive treatments (MRgFUS, radiofrequency and other ablation techniques) are now available or in various stages of development as options for women who wish to preserve their uterus. These techniques have restrictive eligibility criteria largely dependent on the number, size and location of the fibroids to be treated.
MRgFUS is not suitable for women with six or more fibroids, fibroids larger than 10 cm, fibroids located more than 12 cm beneath the anterior abdominal wall or close to the sacral spine. Other contraindications include obstructions in the path of the ultrasound beam such as an intrauterine device or structures such as the bladder and bowel loops that cannot be circumvented or manipulated out of the beam pathway, as well as contraindications to MRI such as being overweight, metallic implants and allergy to contrast agent. Based on a review of outcomes up to 5 years post-treatment, the St Mary’s Hospital centre suggested treating women with five or fewer fibroids, fibroids with low signal intensity on MR imaging, and following pre-treatment with a gonadotropin-releasing hormone (GnRH) analogue to reduce the fibroid volume. The effect of MRgFUS on fertility and future pregnancy remains uncertain and although the British Fibroid Trust say the procedure is not recommended for women who still want children the desire for future pregnancy does not preclude eligibility for MRgFUS treatment in England. It is anticipated that women offered MRgFUS in Scotland would be given the same advice currently given to those considering UAE, namely that caution is advised for patients wishing to retain their fertility (G Houston, Consultant Radiologist, NHS Tayside. Personal Communication, 19 May 2015).

The number of women in Scotland who would potentially be eligible for MRgFUS is estimated at 100–200 cases per year at most, based on clinical expert opinion. Presently, the St Mary’s Hospital centre treats 30–40 women per year in England (SD Quinn, Consultant Obstetrician and Gynaecologist, St Mary’s Hospital, Imperial College London NHS Healthcare Trust. Personal Communication, 1 June 2015).

Clinical effectiveness

The secondary literature search identified Interventionsal Procedure Guidance (IPG) published by The National Institute for Health and Clinical Excellence (NICE) in 2011. An HTA published by Health Quality Ontario in 2015, two systematic reviews published in 2014, and an ECRI Institute rapid review updated in 2013. The search for primary literature published to March 2015 identified one subsequently published comparative study and a published retrospective review of 280 women who underwent MRgFUS at the St Mary’s Hospital centre between January 2003 and January 2011 that were not included in the secondary sources.

Secondary evidence

NICE issued IPG on magnetic resonance image-guided transcutaneous focused ultrasound for uterine fibroids in November 2011. The supporting evidence was based on a literature search to October 2010. The assessment of efficacy included quality of life outcomes from one international non-randomised study published in 2009 comparing MRgFUS with abdominal hysterectomy and seven uncontrolled case series (2007–2011) reporting on quality of life or symptom relief (four studies), fibroid volume/NPV ratio (three studies), reintervention for failed symptom control or recurrence (two studies), and pregnancy outcomes (one study). All of the studies used the ExAblate 2000 system.

NICE concluded that the evidence on the efficacy of MRgFUS for uterine fibroids in the short term was adequate, although further treatment may be required and the effect on subsequent pregnancy was uncertain.

The guidance stated that:

- Patient selection should be carried out by a multidisciplinary team including a gynaecologist and an appropriate imaging specialist.
- The procedure should only be carried out by clinicians with specific training in this technique.
- Clinicians should inform patients that their symptoms may not be relieved, that their symptoms may return, and that further procedures may be required.
- Patients contemplating pregnancy should be informed that the effects of the procedure on fertility and on pregnancy are uncertain.
- NICE encourages further research on the efficacy of MRgFUS for uterine fibroids and studies should report long-term outcomes, and data on the incidence and outcomes of subsequent pregnancy are particularly important.
The Canadian HTA of MRgFUS treatment of symptomatic uterine fibroids was based on a literature search to March 2014\textsuperscript{14}. It found no published randomised controlled trials (RCTs). The only comparative studies identified were the non-randomised study reviewed by NICE comparing MRgFUS with abdominal hysterectomy\textsuperscript{12} and one other non-randomised study conducted in Germany comparing MRgFUS (ExAblate 2000) with UAE\textsuperscript{23}. The HTA concluded that lack of evidence comparing MRgFUS with other uterine-preserving treatments, such as UAE and myomectomy, limits informed decision making about these treatment options\textsuperscript{14}. Evaluation of the clinical effectiveness of MRgFUS was based primarily on uncontrolled observational studies variously reporting on fibroid reduction, symptom relief, health-related quality of life (HRQoL), and reintervention for persistent or recurrent symptoms. The HTA differentiated studies using earlier restricted ablation protocols from those using complete or near complete ablation protocols, observing that reported technical success (excluding outliers) was generally higher in the near-complete ablation studies (range 93% to 100% of patients treated) than in the restricted ablation studies (89% to 95%) whereas reintervention rates at 12 months were generally higher in restricted ablation studies (range 4.9% to 33%) than in near-complete ablation studies (range 3.8% to 13.7%)\textsuperscript{14}. Based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria, the evidence was rated as moderate for technical success and short-term symptom reduction, but low for symptom reduction beyond 1 year\textsuperscript{14}. Further, the treatment advantages of MRgFUS are potentially offset by restrictive eligibility and lengthy procedure time\textsuperscript{14}. The quality of the available evidence on fertility (pregnancy) was rated as very low\textsuperscript{14}. The HTA noted that while clinical studies to date had not been designed to evaluate the effect of MRgFUS on fertility, the fact that pregnancies and uneventful term deliveries following the procedure have been reported suggested that it may have a role in fertility preservation\textsuperscript{14}. Overall, the HTA concluded on the basis of evidence from uncontrolled studies that MRgFUS was an effective treatment for women failing medical therapy seeking alternatives to hysterectomy, and one from which they rapidly recover\textsuperscript{14}.

The two systematic reviews published in 2014 were based on literature searches to February 2013\textsuperscript{19} and September 2013\textsuperscript{20} and reported only MRgFUS outcomes without comparator data, primarily from case series and case reports\textsuperscript{19,20}. The quality of reporting of these reviews is poor and neither of them assessed the potential for bias in the studies that they included which, together with the lack of comparator data, raises concerns about the reliability of their conclusions. One review pooled the results from 10 publications (apparently from eight studies) to obtain an average mean improvement in symptom severity score (Uterine Fibroid Symptom and Quality of Life (UFS-QoL) scale) of 31.0 (95% Confidence Interval (CI) 23.9 to 38.2) at 6 months following MRgFUS\textsuperscript{20}. This meta-analysis needs to be interpreted with caution for several reasons in addition to the lack of comparator data and information on the potential for bias, including evident marked heterogeneity and lack of reassurance on non-overlap in the study populations\textsuperscript{20}.

The ECRI Institute’s updated rapid review on MRgFUS for ablating uterine fibroids was based on a systematic literature search to July 2013\textsuperscript{16}. It summarised the NICE IPG\textsuperscript{18}, an earlier technology assessment by the Australia and New Zealand Horizon Scanning Network\textsuperscript{24}, the German non-randomised study comparing MRgFUS with UAE\textsuperscript{23}, and five uncontrolled case series published in 2012–2013. ECRI concluded that the evidence on the efficacy of MRgFUS using the ExAblate 2000 system was of small quantity and low quality\textsuperscript{16}.

### Comparative primary studies

The three published comparative studies are summarised in table 1 (see page 12). The earliest study compared 109 premenopausal women who underwent MRgFUS (ExAblate 2000) for symptomatic uterine fibroids at seven centres in the US, UK (St Mary’s Hospital), Germany and Israel with 83 women who underwent abdominal hysterectomy contemporaneously at seven different centres in the same countries\textsuperscript{22}. Although myomectomy and UAE were available at the time, hysterectomy was chosen as the comparator treatment for this study at the request of the US FDA\textsuperscript{22}. The authors acknowledged that a limitation of the study was that the two groups differed in clinically
important parameters at baseline: women treated with MRgFUS had less severe symptoms and better function than those who underwent hysterectomy. The total MRgFUS treatment time was limited to 3 hours and the ablation volume restricted to 100 ml per treated fibroid or 150 ml per patient with multiple treated fibroids (most women had a single fibroid treated)\(^2\),\(^2\)\(^5\). As a result of these FDA restrictions, the volume of treated fibroid ablated was on average less than 10\%\(^2\),\(^5\). The study showed improvements in all Short Form-36 (SF-36) quality of life domains in both treatment groups, but women treated by hysterectomy had statistically significantly better scores for five of the eight domains at 6 months. Four women (3.7\%) in the MRgFUS group required surgical or other interventional treatment (three hysterectomies, one UAE) for continued or recurrent fibroid-related symptoms before completing the 6-month follow up. While women who underwent MRgFUS reported significantly fewer lost work days and days kept from usual activities than those who underwent hysterectomy 1 and 3 months after treatment, there was no difference between the groups at 6 months. The authors concluded that while MRgFUS compared favourably as a treatment alternative to hysterectomy, an RCT comparing MRgFUS with other less invasive alternatives was needed to inform decision making on fibroid treatment\(^2\),\(^2\).

The German study compared 50 premenopausal women who underwent MRgFUS (ExAblate 2000) for symptomatic uterine fibroids with 30 women, judged to be equally eligible for MRgFUS, who underwent UAE at a single centre between 2002–2009\(^2\),\(^3\). Both groups had similar symptom severity and HRQoL scores at baseline but women who underwent UAE had a significantly larger entire fibroid volume and were older than women who underwent MRgFUS. Most women in the MRgFUS group (47/50) were treated in accordance with the FDA protocol that allowed ablation of 50\% of the treated fibroid, a maximum of 150 ml treated fibroid volume per patient, and maximum treatment time of 3 hours; a second treatment within 12 weeks was however regarded as a single treatment contrary to the FDA stipulated interval of 2 weeks. Three women were treated according to the original more restrictive FDA protocol. Overall, the median ablated treated fibroid volume was 41.2\% (based on NPV data available for 45 cases)\(^2\),\(^3\). At median follow up of 13.3 months (reported as midterm results), the reintervention rate was significantly greater following MRgFUS (15/50 (30\%)) comprising seven repeat MRgFUS, five myomectomy, two hysterectomy, one UAE) compared with UAE (2/30 (6.7\%): one hysterectomy and one endometrial ablation) (\(p=0.002\)). Total HRQoL scores (UFS-QoL) improved significantly from baseline in both groups; while the median score at follow up was statistically significantly greater in the UAE group compared with the MRgFUS group (\(p=0.032\)) analysis of the difference in terms of change from baseline was not reported. Symptom severity scores decreased in both groups with no statistically significant difference in median scores at follow up (\(p=0.061\))\(^2\),\(^3\).

A second publication from the German centre reported long term results based on 77 women of whom 36 underwent MRgFUS (original FDA protocol \(n=1\), modified protocol \(n=35\)) and 41 underwent UAE (the extent of the study population overlap between the reports of midterm and long term results was not mentioned in either publication)\(^2\),\(^6\). The median ablated treated fibroid volume was 36.4\% (based on NPV data available for 33 cases). At a median follow up of 60.7 months (MRgFUS) and 61.9 months (UAE) the rate of reintervention for persistent or recurrent symptoms was significantly greater following MRgFUS (24/36, 67\%) compared with UAE (5/41, 12\%). At follow up, the median symptom score was statistically significantly lower (better) and the median HRQoL score significantly higher (better) in the UAE group than in the MRgFUS group (based on 42 (12 MRgFUS, 36 UAE) and 46 (11 MRgFUS, 35 UAE) women, respectively). Again, analysis of the difference in terms of change from baseline was not reported. Nine women in the MRgFUS group reported 10 pregnancies that led to seven live births and three miscarriages; no pregnancies were reported in the UAE group (women in the UAE group had older median age at baseline (42.7 years, range 33.6 to 52.2) compared with the MRgFUS group (36.2 years, range 29.2 to 41.0))\(^2\),\(^6\). The authors of these studies concluded that UAE seems to be the better treatment option and that MRgFUS seems to be a promising bridging treatment for women planning future pregnancy\(^2\),\(^3\),\(^6\).
The study conducted in The Netherlands compared 51 premenopausal women who underwent MRgFUS (Sonalleve) for symptomatic uterine fibroids at one centre with 68 women, theoretically eligible for MRgFUS, who underwent UAE at a different centre between 2010–2013. At baseline, women treated with MRgFUS had a significantly lower median total symptom score, older median age, greater maximum fibroid diameter, dominant fibroid volume and uterine volume, and higher total HRQoL (UFS-QoL) scores than the UAE group. MRgFUS was considered successful if the NPV ratio (NPV divided by total fibroid volume) achieved was at least 0.5. The overall median post-treatment NPV ratio actually achieved was 0.38 (interquartile range (IQR) 0.26 to 0.62) and 35/51 (68.6%) women had limited treatment (NPV ratio ≤ 0.5). Women treated with MRgFUS had a 7.1 (95% CI 2.00 to 25.3) times higher risk of reintervention within 12 months (18/51 versus 3/68 UAE). While both treatments resulted in clinically significant symptom relief and HRQoL improvement at 3 months, regression analysis showed greater improvement following UAE. The authors concluded that, for now, UAE is preferred to MRgFUS but, given new MRgFUS protocols and growing levels of experience, an RCT is warranted.

Ongoing trials
Two ongoing RCTs were identified: the FIRSTT study comparing MRgFUS (ExAblate 2000) with UAE and the SOFIA study comparing MRgFUS (Sonalleve) with a sham procedure. These are summarised in table 2 (see page 14).

UK centre data
A published retrospective review of 280 women who underwent MRgFUS (ExAblate 2000) at the St Mary’s Hospital centre between January 2003 and January 2011 reported an overall reintervention rate of 42.8% (77/180) at 3-years and 59.3% (96/162) at 5-years. The reintervention rate for women who received GnRH analogue pre-treatment was 36.0% at 3-years compared with 48.7% in those who did not (p=0.048), and at 5-years 51.2% versus 65.7% (p=0.047). When asked if they would recommend MRgFUS to a friend, 54.2% (124/229) of women said yes, 35.8% were not sure and 10% said no. The UK centre started using the newer Exablate 2100 system in January 2011. Findings of an improvement in the mean NPV achieved with the new 2100 system compared with women treated in previous years using the Exablate 2000 system were based on very few data (34 women had been treated with ExAblate 2100).

Safety
Secondary evidence
NICE IPG concluded that there are well-recognised complications associated with MRgFUS but the evidence on safety was adequate to support the use of the procedure provided that normal arrangements are in place for clinical governance and audit. The supporting evidence comprised events reported in the non-randomised study comparing MRgFUS with abdominal hysterectomy, four case series and three case reports (2005–2011). These events included minor skin burns (1–2.5% of patients in two case series), full-thickness burn (one case report), sciatic nerve damage (one event), deep vein thrombosis (one event), post-procedural pain (62% MRgFUS versus 95% abdominal hysterectomy in the non-randomised study), abdominal, lower back and leg pain ranging from single event reports up to 11% in four case series, paraesthesia (one event), endometritis (one event), and vaginal expulsion of treated fibroid tissue requiring hysteroscopic removal (one event). The guidance stated that during the consent process clinicians should inform patients about the risk of skin burns.

The Canadian HTA, using evidence from three published case reports (2005–2011), 21 published uncontrolled case series (2004–2014), incident reports on the FDA national safety database (2004–2014), and a survey of clinicians attending the first international symposium on MRgFUS in 2008, concluded that major complications were rare and MRgFUS provides a safe treatment. In the 21 case series, involving 1,594 patients, while minor complications were common only 26 (1.6%) major complications were reported. The reported major complication rate associated with earlier experience using restricted ablation criteria was higher at 4.1% (22/534) than the 0.4% (4/1,060) with later experience using complete or near-complete ablation protocols. The major adverse events included deep vein thrombosis,
non-target thermal injury (such as skin burns and sciatic nerve palsy), transfusions and rehospitalisation. Using GRADE criteria, the evidence for safety (major adverse events) was rated as moderate.14

A systematic review that extracted data on complications from 22 uncontrolled case series and case reports published to February 2013 concluded that skin burns, abdominal pain or discomfort, sciatic nerve paresthesia and leg pain were the most commonly reported events.19

**Comparative primary studies**

The MRgFUS data used in the comparative study against hysterectomy were the basis for FDA approval of the ExAblate 2000 system for treatment of uterine fibroids in 2004.25 Therefore, strict reporting of adverse events was adhered to in compliance with the Standard Code of Federal Regulations.22,25,29 One woman treated with MRgFUS suffered sciatic nerve palsy due to absorption of ultrasound energy by bone, which resolved clinically by the 12 month follow up visit. The risk of transfusion, rehospitalisation and skin burns was 3%, 7% and 5%, respectively.25

Compared with the hysterectomy cohort, fewer women reported at least one adverse event following MRgFUS (88/109 versus 82/83; p<0.0001) but there was no difference with regard to serious adverse events at 6 months (9/109 MRgFUS and 8/83 hysterectomy).22

Fewer significant clinical complications (including fever, transfusion, unintended major surgical procedures, hospital discharge with a drain/catheter, outpatient interventional treatment and rehospitalisation) were recorded in the MRgFUS group (14/109) compared with the hysterectomy group (33/83; p<0.0001).22

Of the two non-randomised studies that compared MRgFUS with UAE, the German study reported only that there were no complications during either MRgFUS or UAE therapy.23 The study conducted in The Netherlands reported no serious complications or adverse events during or after MRgFUS whereas in the UAE group two patients (3%) were treated with antibiotics for endometritis, two patients reported an amenorrhea as a result of premature ovarian failure, one patient (1.5%) described an infected haematoma at the arterial puncture site, one patient developed a vulvar abscess due to non-target embolisation, and seven patients (10%) described painful spontaneous expulsion of part of the treated fibroid 6–12 weeks after the procedure.21

**UK centre data**

The retrospective review of women who underwent MRgFUS at the St Mary’s Hospital centre between January 2003 and January 2011 reported that 249/280 women (88.9%) reported no adverse events, 6.4% reported mild to moderate pain lasting up to 5 days, and 3.9% experienced minor complications. Three women (1.1%) suffered severe complications, which were fibroid expulsion, a major skin burn requiring surgical repair, and one case of persistent neuropathy. Treatment of 34 women with the new Exablate 2100 system introduced in 2011 resulted in no skin burns; only one woman required analgesia to take home; and there were no reported major adverse events, hospital admissions, urinary tract infections, persistent neurological problems or other complications.

**Cost effectiveness**

Five cost effectiveness studies were identified as relevant. The first of these was a cost-utility analysis published in 2008 and conducted from a UK NHS perspective. The study addressed the cost effectiveness of treatment strategies for symptomatic uterine fibroids, specifically MRgFUS compared with current treatment comprising of UAE, myomectomy and hysterectomy.30 The patient population in the study was women for whom surgical treatment for uterine fibroids was being considered. The model was based over a 17 year time horizon and assumed that proportion of women receiving current treatment was as follows; 25% received UAE, 25% received myomectomy and 50% received hysterectomy. The base-case results estimated that MRgFUS was the dominant treatment strategy. That is to say that it was associated with a lower cost (cost saving per woman approximately £295) and better outcomes (one-hundredth of a Quality Adjusted Life-Year (QALY) gain per woman, which equates to 3.65 days). It is worth highlighting that the QALY gains estimated per women were small and translated to a very small impact on patients’ life expectancy. Furthermore, the paper suggested MRgFUS was only cost-effective up until the age of 45 years; thereafter the current treatment strategies were cost-effective.
There are a number of weaknesses associated with the analysis. Uncertainty is introduced into the model since, owing to a paucity of data, it was heavily based upon assumptions and inferred comparisons. Thus the model estimates were subject to bias and confounding. In addition, the paper was published in 2008 and therefore the model inputs, such as the sources for the effectiveness assumptions and the cost data, are outdated. The model assumed that there would be no minor or major complications at year 1 or any long term complications with MRgFUS, but yet there are assumed to be complications with the comparators. As detailed above in the safety section, there is evidence to suggest the assumption of no complications associated with MRgFUS treatment is not accurate, which may question the appropriateness of the model. Finally, it is worth noting that the costs of MRgFUS are based upon a costing exercise conducted in one hospital only, and the clinical efficacy data were taken from unpublished trial data and thus cannot be verified. Overall, although this study indicates that MRgFUS may be cost effective, there are a number of weaknesses with the analysis that undermine the results. The results here are also contradictory to main results of the studies conducted in the US and Canada, as discussed below.

The second cost-utility analysis, published in 2009, was conducted in the US to examine the cost effectiveness of MRgFUS compared with current treatment comprising of UAE, myomectomy, hysterectomy and pharmacotherapy for symptomatic uterine fibroids. Women were assumed to be previously untreated for their symptomatic fibroids, and premenopausal\textsuperscript{31} for which surgical treatment for uterine fibroids was being considered.

The base case analysis was from a societal perspective conducted over a lifetime time horizon. It is worth noting at this stage that a societal perspective incorporates factors beyond those that directly impact upon patients’ health and the healthcare provider, for example productivity losses and impact upon relatives or carers. Such factors are not included within the context of a NHS assessment, since the inclusion of these societal factors could be considered inequitable, as they are unlikely to be equal across all patients. This can include the benefits and cost of other factors affected by a patients’ health for example productivity losses and gains and the effects on carers. This estimated an incremental cost effectiveness ratio (ICER) of US $41,400 (£26,986) for MRgFUS compared to hysterectomy (note: all reported costs converted to GBP using the exchange rate as 20 May 2015). The paper estimated an ICER of US $54,200 (£35,330) for UAE compared to MRgFUS. Even with the wider benefit inclusion of the productivity gains the ICERs are at the upper end of the commonly accepted UK cost effectiveness threshold. Myomectomy was estimated to be dominated, that is to say it was more expensive than MRgFUS and also less effective. The results are analysed incrementally, see table 3 below.

The model was heavily based upon assumptions and very sensitive to varying those assumptions, which limited the robustness of the results, the authors’ stated that any of the treatments could be cost-effective. The model inputs were specific to the US and thus there are issues with the generalisibility of the results to Scottish practice. Therefore no clear conclusion can be drawn from this study.

### Table 3 Cost-effectiveness results of treatments

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Total cost ($)</th>
<th>Incremental cost</th>
<th>Total QALYs</th>
<th>Incremental QALYs</th>
<th>ICER ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacology</td>
<td>9,207</td>
<td>-</td>
<td>16.699</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>19,799</td>
<td>10,592</td>
<td>17.182</td>
<td>0.485</td>
<td>21,800</td>
</tr>
<tr>
<td>MRgFUS</td>
<td>27,285</td>
<td>7,486</td>
<td>17.364</td>
<td>0.181</td>
<td>41,400</td>
</tr>
<tr>
<td>UAE</td>
<td>28,892</td>
<td>1,607</td>
<td>17.394</td>
<td>0.030</td>
<td>54,200</td>
</tr>
<tr>
<td>Myomectomy</td>
<td>35,057</td>
<td>-</td>
<td>17.305</td>
<td>-</td>
<td>Dominated</td>
</tr>
</tbody>
</table>
Thirdly, a cost-utility analysis published in 2014 and conducted in the US aimed to establish the cost effectiveness of MRgFUs compared with current treatment comprising of UAE, myomectomy and hysterectomy in premenopausal women who wished to preserve their uterus\textsuperscript{32}, over a five year time horizon. Although the main focus was from a societal perspective, the paper did present an analysis excluding the loss of productivity, estimating results using a decision threshold of US $50,000 (£32,592). The results estimated an ICER for MRgFUS compared to myomectomy of US $46,250 (£30,147) based on a lower cost of US $210 (£137), but also had lower QALYs of 0.004. This represents a situation where MRgFUS was cheaper but also less effective. Combining these figures showed that myomectomy was the preferred treatment strategy as the savings per QALY given up did not exceed the decision threshold, ie the QALYs lost were not justified by the costs saved. UAE was dominated by all of the other comparator treatments, that is UAE was more costly and less effective than the other treatment strategies. In terms of limitations with the analysis, any QALY gain estimated in the base case was small and would not equate to a considerable long term benefit in a patient’s quality of life. The model was heavily based upon assumptions which weaken the results validity. In addition the data used to populate the model was specific to the US and thus affects the transferability and generalisability of the results to Scotland.

Another US cost utility analysis published in 2014 set out to assess the cost effectiveness of MRgFUS, this time compared to UAE and hysterectomy as first-line treatment options for symptomatic uterine fibroids\textsuperscript{33}. In this analysis, a decision analytic model was used, based on a lifetime time horizon and carried out from a societal perspective. In the base case, first line UAE was the most effective and costly strategy (22.75 QALYs and $22,968 (£15,048)) followed by MRgFUS (22.73 QALYs and $20,252 (£13,269)) and then hysterectomy (22.54 QALYs and $11,253 (£7,373)). The paper reported that MRgFUS was cost effective compared to hysterectomy since MRgFUS generated an additional 0.19 QALYs alongside an additional cost of $8,999 (£5,896), resulting in an ICER of approximately $47,000 (£30,793). The ICER for UAE compared to MRgFUS was above $100,000 (£65,518), with UAE generating only 0.02 additional QALYs at an added cost of $2,716 (£1,779). As such, MRgFUS was said to be the cost effective option. From a Scottish NHS perspective, the main limitation with the analysis was that it included societal costs, which may have an important effect upon the overall conclusions. For example, the number and cost of missed work days associated with each treatment was included in the analysis, and the figures vary widely across treatments. MRgFUS was said to lead to only 2 days lost, while hysterectomy was assumed to result in 39.8 days lost. At a daily cost of $145 (£93), the inclusion of societal costs may have an important impact upon the overall conclusions.

The final cost-utility analysis was an HTA published in 2015 in Ontario, Canada\textsuperscript{34}. The HTA aimed to examine the cost-effectiveness of Magnetic Resonance Guided High-Intensity Focused Ultrasound (MRgHIFU) as a treatment strategy compared to hysterectomy, myomectomy and UAE for premenopausal women aged between 40 and 51 years (nine year time horizon) for whom pharmacologically therapy has been unsuccessful in treating symptomatic uterine fibroids. The base case results estimated that UAE was the cost-effective option. Specifically, compared to hysterectomy, UAE was estimated as having an ICER of $46,480 (£30,297) per QALY. The MRgHIFU strategy was not cost-effective in relation to a combination of UAE and hysterectomy, and myomectomy was dominated by MRgHIFU and UAE. The model was heavily based upon assumptions which limit the validity of the results. The model inputs were specific to the Canada and thus there are issues with the generalisibility of the results to Scottish practice.

**Conclusion**

There is currently insufficient published evidence to support definitive conclusions on the clinical effectiveness and safety of MRgFUS compared with UAE, myomectomy or abdominal hysterectomy for the treatment of uterine fibroids. There are currently no published RCTs and only three non-randomised studies that compared results following MRgFUS with results following hysterectomy or UAE in clinically
dissimilar groups of patients. Most studies published to date are uncontrolled case series that report on short term outcomes achieved using first generation ExAblate MRgFUS technology and treatment protocols with historical restrictions on ablation volume and procedure duration.

NICE guidance that women should be informed that their symptoms may not be relieved, that their symptoms may return, that further procedures may be required, that patients contemplating pregnancy should be informed that the effects of the procedure on fertility and on pregnancy are uncertain, and, the need for future studies to report long-term outcomes, appropriately reflects the available evidence on clinical effectiveness. There is a reasonable quantity of moderate quality evidence from uncontrolled observational studies suggesting that major complications and severe adverse events are rare, but the potential for publication bias remains unknown.

As a whole, the results of the cost effectiveness studies are inconsistent and inconclusive. Generally the US and Canadian studies – including the broader societal perspective – conclude that MRgFUS is not cost effective as even with the wider perspective included the ICERs are typically approaching or exceeding accepted UK cost-effectiveness thresholds. In addition, MRgFUS was not always identified as the most cost-effective treatment option. In particular, one UK study demonstrated MRgFUS to be cost effective compared to UAE, myomectomy and hysterectomy. However, the results were based heavily upon a number of assumptions and unpublished data which affect the robustness of the conclusions.

Two US studies – one comparing MRgFUS to hysterectomy, and one comparing MRgFUS to UAE and hysterectomy – reported that MRgFUS and myomectomy were the cost effective treatment options. However, not only were the ICERs at the upper end of the commonly accepted cost effectiveness threshold, the studies were carried out from a US societal perspective which limits the generalisability of the results to Scotland. Furthermore, in another US study comparing MRgFUS to UAE, myomectomy and hysterectomy, myomectomy was found to be the most cost effective treatment option. Finally, a Canadian HTA estimated that UAE was the cost-effective option. In addition, it is not know if the treatment pathway in the paper is reflective of current Scottish clinical practice which introduces some uncertainty.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The process for producing evidence notes has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on www.healthcareimprovementscotland.org

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This evidence note will be considered for review 2 years post-publication, and at 2-yearly intervals thereafter. For further information about the evidence note process see http://www.healthcareimprovementscotland.org/our_work/clinical__cost_effectiveness/shtg/standard_operating_procedures.aspx

To propose a topic for an evidence note, email evidencenotes.HCIS@nhs.net

References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network http://www.knowledge.scot.nhs.uk, or by contacting your local library and information service.
### Table 1 Comparative primary studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taran et al., 2009&lt;sup&gt;22&lt;/sup&gt;</td>
<td>14 centres in US, UK, Israel, Germany (7 MRgFUS, 7 hysterectomy)</td>
<td>192 premenopausal women with symptomatic uterine fibroids and no plans for future pregnancy; 21/109 in MRgFUS group had prior surgical myoma treatment&lt;sup&gt;25&lt;/sup&gt;</td>
<td>MRgFUS (ExAblate 2000) n=109</td>
<td>Improvement in all SF-36 quality of life domains in both groups, but women treated by hysterectomy had statistically significantly better scores for 5 of the 8 domains at 6-month follow up. Lost work days: MRgFUS 1.2 days versus hysterectomy 19.2 days at 1 month (p&lt; 0.0001); 0.2 versus 1.7 at 6 months (not statistically significant) Days kept from usual activities: MRgFUS 2.7 days versus hysterectomy 17.4 days (p&lt; 0.0001) at 1 month; 1.4 versus 1.7 at 6 months (NS) 4/109 women treated with MRgFUS pursued surgical or interventional treatment (3 hysterectomies, 1 UAE) for continued or recurrent fibroid-related symptoms before completing 6 month follow up 14 significant complications and 9 serious adverse events in the MRgFUS group compared with 33 and 8 in the hysterectomy group.</td>
<td>Women treated with MRgFUS had less severe disease at baseline than those who underwent hysterectomy. MRgFUS protocol: maximum ablation volume 100 ml per fibroid or 150 ml per patient, maximum treatment time 3 hours. Mean time in MR scanner 202 minutes (range 90 to 370 minutes, SD 56)&lt;sup&gt;29&lt;/sup&gt;</td>
</tr>
<tr>
<td>Froeling et al., 2013&lt;sup&gt;23,26&lt;/sup&gt;</td>
<td>1 centre in Germany 2002–2009</td>
<td>80 premenopausal women with symptomatic uterine fibroids and no plans for future pregnancy; previous treatment not reported</td>
<td>MRgFUS (ExAblate 2000) n=50</td>
<td>Reintervention to control persistent or recurrent fibroid related symptoms (primary outcome) 2/30 (6.7%) following UAE versus 15/50 (30%) MRgFUS (p&lt;0.002) at median follow up 13.3 months Total HRQoL scores (UFS-QoL) improved significantly from baseline in both groups; median score at follow up statistically significantly greater in the UAE group compared with the MRgFUS group (p=0.032); comparative analysis of changes from baseline not reported Symptom severity scores decreased in both groups with no statistically significant difference in median scores at follow up (p=0.061); comparative analysis of changes from baseline not reported.</td>
<td>Symptom severity and HRQoL scores similar at baseline but women who underwent UAE had significantly larger median fibroid volume and were older than women who underwent MRgFUS MRgFUS protocol: maximum ablation volume 50%, 150 ml per patient, treatment time 3 hours (n=47); maximum ablation volume 33%, 150 ml per patient, treatment time 2 hours (n=3). Study population overlap between midterm&lt;sup&gt;23&lt;/sup&gt; and long term&lt;sup&gt;26&lt;/sup&gt; results cohorts is unclear.</td>
</tr>
</tbody>
</table>
| Ikink et al., 2014 | 2 centres in The Netherlands (1 MRgFUS, 1 UAE) 2010–2013 | Non-randomised, retrospective, follow up 3 months (HRQoL) or 12 months (reintervention rate) | 119 premenopausal women with symptomatic uterine fibroids; plans for future pregnancy not reported; previous treatment not reported | MRgFUS (Sonalleve) n=51 | UAE n=68 | Clinically significant symptom relief and HRQoL improvement in both groups at 3-months, but multivariate analysis showed that UAE had a stronger effect than MRgFUS. Women treated with MRgFUS had a 7.1 (95% CI 2.00 to 25.3) times higher risk of reintervention within 12 months (18/51 versus 3/68). | Women treated with MRgFUS had significantly lower median total symptom score, older median age, larger maximum fibroid diameter, dominant fibroid volume and uterine volume, and higher total HRQoL scores at baseline than the UAE group. | IQR–interquartile range; CI–confidence Interval; SD–standard deviation
### Table 2 Ongoing RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>FIRSTT (NCT00995878)</td>
<td>Premenopausal women, symptomatic uterine fibroids, age ≥25 years; exclusion criteria include prior myomectomy, UAE or MRgFUS, and actively trying for pregnancy or currently pregnant n=180</td>
<td>MRgFUS (ExAblate 2000)</td>
<td>UAE</td>
<td>Primary outcome is need for an additional intervention for fibroid symptoms; secondary outcomes include adverse events and impact on reproductive function</td>
<td>Ongoing but not recruiting, estimated primary completion date December 2014 (however Stewart 2015 notes that enrollment was recently completed)</td>
</tr>
<tr>
<td>SOFIA (NCT01504308)</td>
<td>Pre- or perimenopausal women, symptomatic uterine fibroids, age 18–50 years; exclusion criteria include desire for future pregnancy n=224</td>
<td>MRgFUS (Sonalleve)</td>
<td>Sham MRgFUS</td>
<td>Primary outcomes are need for alternative intervention and menstrual blood loss; secondary outcomes are return to activity within 72 hours and Symptom Severity Score of UFS-QoL questionnaire</td>
<td>Recruiting, estimated primary completion date April 2017</td>
</tr>
</tbody>
</table>
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3. Professor Gail ter Haar, Team Leader, Therapeutic Ultrasound Team, Joint Department of Physics, Division of Radiotherapy & Imaging, Royal Marsden Hospital : Institute of Cancer Research, Independent topic reviewer

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References


References continued


References continued


