Australian Government

Department of Health and Ageing

Australia and New Zealand Horizon Scanning Network

ANZHSN

AN INITIATIVE OF THE NATIONAL, STATE AND TERRITORY GOVERNMENTS OF AUSTRALIA AND THE GOVERNMENT OF NEW ZEALAND

Horizon Scanning Technology Prioritising Summary

MRI guided high intensity focused ultrasound for the non-invasive treatment of symptomatic uterine fibroids

May 2007

AHTA

Adelaide Health Technology Assessment

[add ISSN]
[add Publications Approval Number]

Electronic copies can be obtained from http://www.horizonscanning.gov.au

Enquiries about the content of this summary should be directed to:

HealthPACT Secretariat
Department of Health and Ageing
MDP 106
GPO Box 9848
Canberra ACT 2606
AUSTRALIA

The production of this *Horizon scanning prioritising summary* was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from health departments in all states and territories, the Australia and New Zealand governments; MSAC and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

This *Horizon scanning prioritising summary* was prepared by Linda Mundy and Janet Hiller from the National Horizon Scanning Unit, Adelaide Health Technology Assessment, Discipline of Public Health, Mail Drop 511, University of Adelaide, South Australia, 5005.

PRIORITISING SUMMARY

REGISTER ID: **000301**

NAME OF TECHNOLOGY: **MRI GUIDED HIGH INTENSITY FOCUSED ULTRASOUND**

PURPOSE AND TARGET GROUP: **NON-INVASIVE TREATMENT OF SYMPTOMATIC UTERINE FIBROIDS**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- ☐ Yet to emerge
- ☐ Experimental
- ☒ Investigational
- ☐ Nearly established
- ☐ Established
- ☐ Established *but* changed indication or modification of technique
- ☐ Should be taken out of use

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- ☐ Yes — ARTG number
- ☒ No
- ☐ Not applicable

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
United States		✓	
Germany	✓		
United Kingdom	✓		

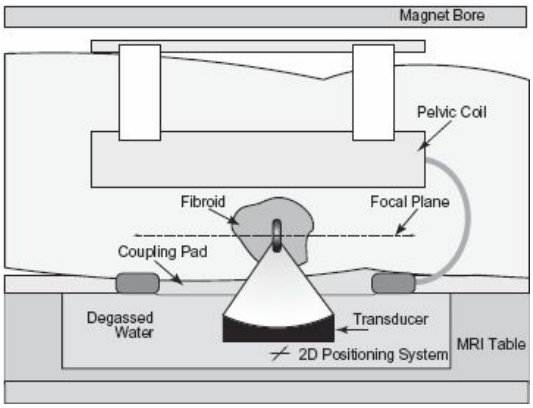
IMPACT SUMMARY:

Several systems are available for use in high intensity focused ultrasound (HIFU). ASERNIP-S has previously reported on the Sonablate® 500 system for the treatment of localised prostate cancer, without the use of MR guidance (ANZHSN 2006). InSightec Ltd (Haifa, Israel) provides the ExAblate® 2000 system, an MRI guided focussed ultrasound system (MRgFUS) with the aim of targeting and ablating uterine fibroids. The technology does not have TGA approval but was approved by the FDA in October 2004 and received CE marking in 2002. ExAblate® would be made available through specialist hospitals with interventional radiology facilities for pre- or peri-menopausal women with symptomatic uterine fibroids who desire a uterine sparing procedure.

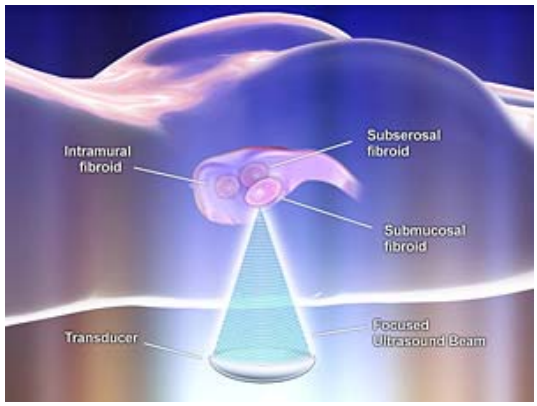
BACKGROUND

Uterine fibroids[1] are benign tumours composed of smooth muscle cells and collagenous fibrous tissue that develop within or near the wall of the uterus. Although the majority of fibroids are asymptomatic, approximately 25 per cent are associated with severe symptoms including pelvic pain, menorrhagia, dysmenorrhagia, dyspareunia, pelvic fullness, urinary frequency and infertility (Fennessy & Tempany 2005; Hesley et al 2006).

HIFU is essentially a thermal ablation technique which utilises sound waves focussed at a point to deliver heat (65-95°C) to tissue, resulting in tissue necrosis, apoptosis and cell death (Fennessy & Tempany 2005). MRgFUS combines MRI and high intensity focussed ultrasound. A specialised table is required that is capable of docking into conventional MRI units. The patient lies in a prone position on the table which houses the focussed ultrasound phased array transducer and its positioning system, held in a cooling water bath (Figure 1a). The patient's abdominal wall is positioned over the water tank, protected by a plastic membrane which allows the ultrasound beam to penetrate within the pelvic area. The transducer array controls the location of the ultrasound focal spot and ultrasound waves are focussed through the abdominal wall, causing high temperature deposition at the focal point for a few seconds, resulting in the thermal ablation of the fibroid (Figure 1b) (FDA 2005; Fennessy & Tempany 2005).



1a



1b

Figure 1a MRgFUS set up of specialised table in MRI unit (Hynynen & MacDannold 2004)
Figure 2b The focussed ultrasound beam on the uterine fibroid (printed with permission SightLine Houston)

MRgFUS is conducted as a day surgery procedure. Patients undergo MRI treatment planning the day before the MRgFUS procedure, to identify and confirm the location of the fibroids (FDA 2005; Fennessy & Tempany 2005). As ultrasound interacts with gases, patient preparation prior to the procedure is important. All hair needs to be removed from the pelvic area to prevent the formation of gas bubbles which may cause burns. In addition, any skin lotions must be removed with alcohol as these may

[1] Also known as leiomyomas, leiomyofibromas, fibromyomas and myomas –

reduce the acoustic coupling (Hynynen & MacDannold 2004). To reduce motion and discomfort, patients are consciously sedated, allowing the patient to provide feedback on pain experienced during the procedure. The ExAblate® 2000 System software uses the pre-treatment MRI images to calculate the number and type of sonications required. Treatment typically consists of 20-50 separate sonications, lasting between 10-30 seconds each, followed by a 90 second cooling period. Post-treatment imaging, before and after administration of contrast agent, is conducted immediately to calculate the necrotic volume (FDA 2005; Fennessy & Tempany 2005).

The ExAblate® 2000 system is contraindicated for use in women who have:

- obstructions in the treatment beam path such as a scar, skin fold, bowel, intrauterine device or any hard implants;
- fibroids that are close to sensitive organs such as the bowel or bladder; and
- MRI related issues such as an allergy to contrast agent or metallic implants (FDA 2004).

CLINICAL NEED AND BURDEN OF DISEASE

Uterine fibroids are one of the most common disorders of the uterus and the most prevalent tumour in women (one in four women are affected). However, uterine fibroids are predominantly asymptomatic and do not require treatment in approximately 60-90 per cent of the women affected. Ethnicity may have an impact on the incidence of fibroids, with a higher incidence documented in African American women (Broder 1999; Technology Evaluation Center 2002; Topfer 2002).

The number of public hospital separations relating to uterine leiomyoma for Australian women in 2004–05 was 13,140, which represents a total of 41,654 patient days. Many of these women may wish to have their fibroids treated whilst at the same time sparing their uterus, especially those of a child bearing age. Of the total number of women with the principle diagnosis of leiomyoma of the uterus, 5,329 (40.6%) were women under the age of 44 years (AIHW 2007). These figures may underestimate the true burden of disease because only severe symptomatic uterine fibroids are treated with hospital procedures (usually hysterectomy or myomectomy), whereas less severe symptoms would be treated in an outpatient setting.

DIFFUSION

MR guided HIFU for the treatment of uterine fibroids is currently not practiced in Australia. There is, however, considerable interest in this technology but the high capital outlay required may be hindering the establishment of this technique in Australia (personal communication, Vascular and Interventional Radiology, Alfred Hospital).

COMPARATORS

There are two categories of treatment for symptomatic uterine fibroids – uterine-removing and uterine-conserving. If there is no desire for future childbearing, the

standard treatment for symptomatic uterine fibroids is hysterectomy. Abdominal or vaginal hysterectomy involves the surgical removal of the uterus and is the most certain cure of fibroids as there is no possibility of fibroid recurrence. Hysterectomy is the most common invasive treatment for symptomatic uterine fibroids (Broder 1999).

A large range of uterine-conserving, but *not necessarily* fertility-preserving, treatments are also available. The type of treatment may depend on the location, size and number of uterine fibroids and whether the treatment is aimed at the fibroid itself or the control of symptoms associated with the fibroid (Smith 2000).
In younger women, myomectomy[2] is a common alternative to hysterectomy and involves the surgical removal of uterine fibroids. Myomectomy may be indicated for women with symptomatic uterine fibroids who have experienced infertility or repeated miscarriage, or have a desire for future childbearing (Braunwald et al 2001; Pugh 2000).

A recent MSAC report assessed the safety and effectiveness of uterine artery embolisation (UAE), a uterine-conserving, minimally invasive technique that treats symptomatic uterine fibroids. UAE achieves its aim by blocking blood supply to the dominant fibroid via the injection of embolic material into the uterine arteries. The dominant fibroid undergoes cell death and necrosis due to a lack of blood supply, resulting in a reduction in size of the fibroid and relief in the primary patient-relevant symptoms of menorrhagia, pelvic pain and pelvic bulk. The MSAC recommended that UAE received interim funding on the Medicare Benefits Schedule for 5-years (MSAC 2006).

Fibroids can also be treated medically through the administration of progesterone or progesterone-like drugs or gonadotropin releasing hormone (GnRH) antagonists which cause fibroid shrinkage. Hormone therapy may produce menopausal symptoms, increase the risk of osteoporosis and may result in a rapid return of symptoms once treatment has ceased (InSightec Ltd 2007; MSAC 2006).

EFFECTIVENESS AND SAFETY ISSUES

Safety and effectiveness data were reported in the original submission (the pivotal study) to the FDA from a multi-centre trial on women with symptomatic fibroids enrolled in two separate (non-randomised) treatment arms: MRgFUS with ExAblate® (n=109) and hysterectomy (n=83) (level III-2 intervention evidence). There was no difference in the demographic and baseline characteristics of the two groups (FDA 2005).

The primary endpoint for the women enrolled in the MRgFUS arm was a symptom severity score (SSS) relating to quality of life questions, in particular symptoms of bulk and bleeding. At 6-months follow-up, a 10-point improvement in the SSS was reported in 77/109 (70.6%) women, which was defined as a clinically significant

[2] Also known as fibroidectomy, leiomyomectomy, fibromectomy or hysteromyomectomy

improvement, with the remaining patients reporting unchanged or worsened symptoms. The mean baseline SSS value of all women was reported to be 61.0 ± 16.3, and at 6-months the mean was significantly reduced at 37.3 ± 21.4, $p<0.0001$. At 6-month follow-up, 102 women were available for MRI to evaluate fibroid shrinkage. Baseline volume of fibroids was 334.4 ± 240.4 compared to the volume at 6-months of 295.4 ± 256.4, a reduction of 15.3 ± 30.4 per cent (not reported to be a significant reduction). It should be noted that the standard deviations for all measurements were large. These results were not reported for the hysterectomy group as they were considered to no longer have fibroid related symptoms once their uterus was removed. By 6-months the hysterectomy group reported significant improvements in the following SF-36 quality of life categories compared to the ExAblate® treated women: role physical, bodily pain, general health, vitality and mental health.

A total of 17 (15.6%) women in the ExAblate® group reported clinically significant complications compared to 63 (75.9%) in the hysterectomy group. For the ExAblate® and hysterectomy groups, respectively, rehospitalisation rates were 7.3 vs 9.6%, fever >38°C for two consecutive days 2.8 vs 14.5%, transfusion rates were 2.8 vs 7.2%, unintended surgical procedure related to treatment 0 vs 4.8%, and interventional treatment 0 vs 2.4%. Antibiotic use was high in the hysterectomy group compared to the ExAblate® group 24-hours post-treatment (36.1 vs 2.8%). In addition, 14 (12.8%) patients treated with ExAblate® experienced leg pain or nerve tingling, eight of which were deemed to be sonication-related. Symptoms resolved after 3-days in all but one patient, who reported severe sciatic pain which did not resolve until 11-months post-treatment. There were five cases of first or second degree skin burns in the ExAblate® group, the majority resulted from hair being present in the sonication pathway and one case resulted from patient movement (FDA 2005).

Stewart et al (2006) reported 12-month follow-up data on 82/109 (75.2%) of the same ExAblate® treatment group. Of the initial 109 women, 23 (21%) sought an alternative treatment for their fibroids ie hysterectomy, myomectomy or UAE. At 12-months 42/82 (51.2%) women met the targeted 10-point improvement in SSS, however if considered on an intention-to-treat basis then this proportion is reduced markedly to 38.5 per cent (42/109). The mean SSS score at 12-months was still significantly below that observed at baseline (38.8 vs 61.1) (Stewart et al 2006).

A small MRgFUS study was conducted on 42 women (mean age 46 years, range 38-54) with symptomatic fibroids by the Mayo Clinic (level IV intervention evidence). One patient (2.4%) with large fibroids was treated on two consecutive days, two patients (4.7%) received less than one third the required number of sonications due to discomfort and three patients (7.1%) required re-treatment 12-18 months after initial treatment to further reduce symptoms. One patient (2.4%) who underwent additional MRgFUS treatment was diagnosed with deep vein thrombosis and remains on anticoagulation therapy. One patient (2.4%) reported sciatic pain which resolved over

the 12-months post-treatment. No skin burns were reported. Before treatment 29/42 (69%) women reported excessive menstrual bleeding. This number was reduced to 13/42 (30.9%) at 6-months follow-up. Of the 37 (88%) patients experiencing pressure symptoms before treatment, only one (2.7%) reported no improvement after treatment, with 18 (48.6%) reporting improvement and 18 (48.6%) reporting complete relief from pressure symptoms. Nocturia[3] was reported in 25 women pre-treatment and was completely resolved in 17 (68%) women with the remaining women reporting some (24%) or no (8%) improvement. Of the 42 women enrolled, 17 (40.5%) sought either re-treatment with MRgFUS (n=6) or an alternative fibroid treatment: hysterectomy (n=6), myomectomy (n=2), UAE (n=1), or endometrial ablation (n=2) (Hesley et al 2006).

Other studies have reported on that the administration of gonadotrophin releasing hormone agonist potentiates the thermal effects of MRgFUS (Smart et al 2006) and that phase of the menstrual cycle does not influence MRgFUS treatment outcome (So et al 2006).

In summary, although MRgFUS is a non-invasive treatment option for women with symptomatic fibroids who wish to maintain their fertility, it appears to have a high failure rate with 21 and 26 per cent of women seeking an alternative treatment for their fibroids. However, this may be a reflection on the severity of symptoms before treatment. In addition, adverse events such as deep vein thrombosis and transfusion, although not common, are considered severe.

COST IMPACT

No cost information was available at the time of writing this summary, however costs would include the purchase of the specialised MR table and the image interpreting software.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

A non-invasive procedure to treat uterine fibroids may be an attractive option for women with symptomatic fibroids who may wish to retain their uterus for future child bearing.

OTHER ISSUES

The FDA approved the ExAblate® 2000 system in 2004 under the proviso that InSightec provide three year follow-up data on the women enrolled in their pivotal study (n=109) and the continued access study (n=250) which were the basis of the company's successful application to the FDA (FDA 2004).

[3] Excessive urination at night

CONCLUSION:

A number of treatment options, including uterine conserving, are currently available for the treatment of symptomatic uterine fibroids. MRgFUS may be attractive option for many women due to the non-invasive nature of the procedure, however, it appears that this technology is still in the "learning curve" phase of introduction, with the number of adverse events reported and a large proportion of women seeking treatment alternatives.

HEALTHPACT ACTION:

As MRgFUS offers women a non-invasive and uterine conserving option for the treatment of uterine fibroids, HealthPACT have recommended that this technology be monitored in 12 months time.

SOURCES OF FURTHER INFORMATION:

AIHW (2007). *AIHW National Hospital Morbidity Database* [Internet]. Australian Institute of Health and Welfare. Available from: http://www.aihw.gov.au/cognos/cgi-bin/ppdscgi?DC=Q&E=/ahs/principaldiagnosis9899-0405 [Accessed 2nd April 2007].

ANZHSN (2006). *Sonablate 500 system for prostate cancer,* Medical Services Advisory Committee, Canberra, http://www.horizonscanning.gov.au/internet/horizon/publishing.nsf/Content/2E6BEDBA8F538999CA25714E00200B64/$File/Sonablate%20500%20System%20for%20prostate%20cancer.pdf.

Braunwald, E., Hauser, S. L. et al (Eds.) (2001). *Harrison's principles of internal medicine,* McGraw-Hill, New York.

Broder, M. S., Harris, K., Morton, S.C., Sherbourne, C., Brook, R.H. (1999). *Uterine artery embolization: a systematic review of the literature and proposal for research,* RAND Corporation, USA,

FDA (2004). *ExAblate® 2000 System - P040003 - New device approval* [Internet]. Food and Drug Administration. Available from: http://www.fda.gov/cdrh/mda/docs/p040003.html [Accessed 2nd April 2007].

FDA (2005). *Summary of safety and effectiveness data* [Internet]. Food and Drug Administration. Available from: http://www.fda.gov/cdrh/PDF4/p040003b.pdf [Accessed 3rd April 2007].

Fennessy, F. M. & Tempany, C. M. (2005). 'MRI-guided focused ultrasound surgery of uterine leiomyomas', *Acad Radiol,* 12 (9), 1158-1166

Hesley, G. K., Felmlee, J. P. et al (2006). 'Noninvasive treatment of uterine fibroids: Early mayo clinic experience with magnetic resonance imaging-guided focused ultrasound', *Mayo Clinic Proceedings,* 81 (7), 936-942

Hynynen, K. & MacDannold, N. (2004). 'MRI guided and monitored focused ultrasound thermal ablation methods: A review of progress', *International Journal of Hyperthermia,* 20 (7), 725-737

InSightec Ltd (2007). *EXABLATE - Non-Invasive Treatment for Uterine Fibroids* [Internet]. InSightec Ltd. Available from: http://www.exablate.net/html/index.htm [Accessed 2nd April 2007].

MSAC (2006). *Uterine artery embolisation for the treatment of symptomatic uterine fibroids,* Medical Services Advisory Committee, Canberra, http://www.msac.gov.au/internet/msac/publishing.nsf/Content/AD35ED216E990FC7CA2571420004A192/$File/MSAC%201081%20-%20UAE.pdf.

Pugh, M. (2000). *Stedman's medical dictionary*. 27th edition, Lippincott Williams & Wilkins, Philadelphia.

Smart, O. C., Hindley, J. T. et al (2006). 'Magnetic resonance guided focused ultrasound surgery of uterine fibroids--the tissue effects of GnRH agonist pre-treatment', *Eur J Radiol,* 59 (2), 163-167

Smith, S. J. (2000). 'Uterine fibroid embolization', *American Family Physician,* 61, 3601-3607, 3611-3602

So, M. J., Fennessy, F. M. et al (2006). 'Does the phase of menstrual cycle affect MR-guided focused ultrasound surgery of uterine leiomyomas?' *Eur J Radiol,* 59 (2), 203-207

Stewart, E. A., Rabinovici, J. et al (2006). 'Clinical outcomes of focused ultrasound surgery for the treatment of uterine fibroids', *Fertil Steril,* 85 (1), 22-29

Technology Evaluation Center (2002). *Uterine artery embolization for treatment of symptomatic uterine fibroids,* Blue Cross and Blue Shield Association, Chicago, Illinois,

Topfer, L., Hailey, D. (2002). *Issues in Emerging Health Technologies: Uterine artery embolization for the treatment of fibroids.,* Canadian Coordinating Office for Health Technology Assessment, Ottawa, www.ccohta.ca.

LIST OF STUDIES INCLUDED

Total number of studies	
Level IV intervention evidence	2

SEARCH CRITERIA TO BE USED:

Female
Leiomyoma
Magnetic Resonance Imaging
Ultrasonic Therapy
Uterine Neoplasms