PAPER FOR CHIEF MEDICAL OFFICER, Scottish Office

1 Magnetic Resonance Guided Focused Ultrasound Surgery (MRgFUS): The Scottish Clinical Centre in Tayside

1.1 Background of MRgFUS in Dundee

Focused Ultrasound Surgery (FUS) is a non-invasive method of destroying a target tissue whilst sparing adjacent tissues and organs using real time imaging guidance and control. The treatments can be carried out under conscious sedation, often on an outpatient basis. The combination of magnetic resonance guidance with FUS (MRgFUS) provides the ability to plan and monitor treatments in real time, while increased patient safety is achieved through real time temperature mapping during treatment of the lesion, so that inadvertent damage to neighbouring normal tissues can be avoided[1]. This technology provides a personalised treatment, adjusted to the individual patient anatomy, pathology and treatment results (perfusion and temperature mapping) MRgFUS has been used very successfully in the treatment of uterine fibroids (in excess of 11,000 patients world wide at 140 centres) and has now been shown to be an effective treatment for painful bone metastases. Early studies on the use of MRgFUS for the treatment of breast cancer, prostate cancer, liver tumours, and pancreatic cancer have demonstrated encouraging results that support further research. It also shows great success in the treatment of facet joint disease and in various neurological conditions such as essential tremor and thalamic pain. New technical developments to solve the problem of respiratory motion mean that it will shortly be possible to target lesions in the kidneys and liver. Preclinical MRgFUS has also demonstrated the feasibility of targeted drug delivery, in which the acoustic beam is used to open biological membranes with the simultaneous release of drugs encapsulated in liposomes or microbubbles.

There is no doubt that this technique is established in clinical practice worldwide. It has been safely used on more than 12,000 patients in 150 centres. This document outlines a proposal for a Scottish Focused Ultrasound Centre, to be situated in Tayside to provide a service throughout Scotland.

The MRI guided focused ultrasound system installed in the Institute of Medical Science and Technology (IMSaT), adjacent to Ninewells Hospital in Dundee, Tayside, offers the state of the art MRgFUS system, currently in a research environment, with two systems, the ExAblate 2000 Body and 2100 conformal bone systems. This research facility has been approved for volunteer MR imaging and fulfils the NHS criteria for non-simple clinical imaging. It could be adapted to provide a national ambulatory outpatient treatment centre. There is substantial capital investment by NHS Tayside and the University of Dundee in the equipment and facility (£2.5m, with a further £4m in research funds). Building on the initial research experience over the last 5 years since installation and continued training of staff in using the equipment, it is an appropriate time to consider the conversion of the facilities to a clinical service for NHS patient benefit. The MRI component of the equipment is from GE Medical Systems and the focused ultrasound system, which is an integral part of the equipment installed in Dundee, is manufactured by InSightec Limited (Haifa, Israel).

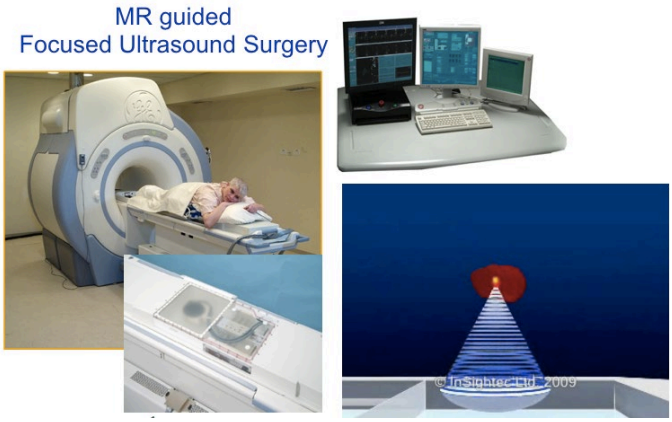

Figure 1. MRgFUS is an integrated planning and therapy system

Both suppliers have established collaborative world class research with IMSaT including 4 substantial EU grants (£10m).

This MRgFUS system is purpose built for clinical use with the appropriate regulatory approvals (FDA approval and CE mark). In addition, NICE guidelines from November 2011 support the clinical use of this technology for the treatment of uterine fibroids. The adaption of the facility in IMSaT for clinical usage has been worked up between both NHS Tayside and the University of Dundee. The standards of care and operating procedures will be under NHS Tayside quality assurance, clinical governance and operating procedures with shared staff. The clinical operations will be managed under NHS Tayside Clinical Governance procedures.

1.2 Underlying Principles of Treatment

The treatments are conducted with the patient lying on the modified MR table with transducers (the assembly that transforms electronic signals into the ultrasound beam) that are designed for particular applications in the body (bone, prostate and brain)[2]. Treatment planning takes into account the tissue to be targeted and the adjacent normal tissues to be avoided, such as bowel and nerves. The treatment is monitored in real time with MR thermal mapping, which allows controlled heating of the target tissue and permits the operator to monitor the tissue response. Total procedure time depends on the volume of tissue to be ablated and the specific disease condition and varies between 1½ hours to 4 hours. Patients are usually treated underconscious sedation or local anaesthesia.

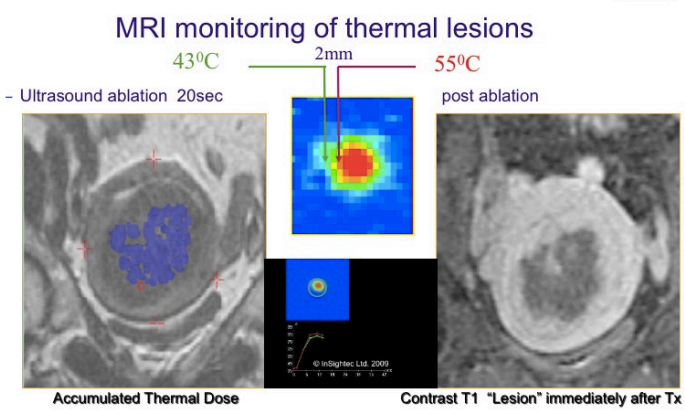

Figure 2: Realtime MR Monitoring of FUS therapy can be seen as colour map; on the targeted lesion being treated.

2 Approved Clinical applications of MRgFUS

2.1 MRgFUS treatment of Uterine Fibroids (CE, FDA approved and NICE recommended)

MRgFUS has been most widely applied to uterine fibroids with the aim of reducing symptoms.[3] These benign uterine tumours affect at least 25% of women of child-bearing age and cause menorrhagia and pressure symptoms with significant social and economic costs[4,5]. The conventional surgical treatment for fibroids is hysterectomy or myomectomy. Between 1989 and 2006, 37,120 Scottish women underwent hysterectomy and approximately 60% were for fibroids. A recent study carried out in Glasgow suggests that it is associated with significant morbidity in 3% of cases and minor morbidity in 14%, the total cost of operation being £2400[6]. It was observed in this study, that complications were more likely when hysterectomy involved the removal of a fibroid uterus. For women who desire future pregnancies or who wish to retain their uterus for other reasons, myomectomy is the operation of choice.

MRgFUS for fibroids has been shown to be a safe and effective treatment and is now offered by 140 hospitals worldwide. More than 11,000 women have had their fibroids ablated. Results have been published from phase 2 and 3 trials with a follow up between 6 and 36 months. The main outcome measures are the symptom severity scores. A 2007 paper analysing 24 month follow up of 359 patients demonstrated that when a large volume of fibroid had been ablated, the improvement in symptomatic scores was both significant and sustained, indicating that the effects of treatment are durable[6]. When the treatment volume was greater than

60%, less than 10% of patients sought alternative therapy within the 12 months following FUS. In the short term, MRgFUS appears to enable women to avoid surgery. The alternative techniques are uterine fibroid embolisation, myomectomy (both uterus-preserving) and hysterectomy. The main advantages of MRgFUS are: the very low incidence of adverse events, the lack of any percutaneous intervention or surgery, fast recovery and the ability to deliver treatment on an outpatient basis. Pregnancy is no longer a problem. Successful pregnancies after MRgFUS ablation have been reported[7,8] and an international registry has documented more than 100 successful full-term pregnancies. NICE has approved this procedure for NHS practice [9] (see Annex). MRgFUS for uterine fibroids has been shown to be equally cost-effective compared to embolization or myomectomy[10]. A recent meta-analysis has concluded that MRgFUS is a valuable non-invasive alternative to embolization, myomectomy or hysterectomy [11].

This approach will complement the minimally invasive interventional radiological uterine artery embolization treatments led by Prof Graeme Houston in Tayside. The integration of MRgFUS with a Scotland wide approach including interventional radiological techniques will be achieved through established networks.

2.2 MRgFUS treatment of bone metastases (CE and FDA approved)

Bone absorbs ultrasound energy, and it is possible to produce a broad area of heating at the periosteal margin with relatively low ultrasound energy in a short timeframe. This has enormous potential clinical benefit since the resultant local destruction of neural pain fibres by MRgFUS can result in excellent palliation of painful bone lesions such as metastases. Up to 30% of all cancer patients develop bone metastases and approximately 50% of these patients will develop pain from these lesions. Radiation therapy is the current primary treatment to such lesions but between 20 and 30% of patients do not gain any benefit from such treatments. Furthermore, pain recurs after radiotherapy in up to 20% of patients who are successfully treated. MRgFUS has been used in this setting in a number of trials on more than 500 patients in total. Rapid and significant pain relief has been observed. These treatments can be performed on an outpatient basis and the ExAblate system has received the CE mark and FDA approval for bone metastasis palliation and an extend CE mark for benign and malignant tumours and for rhizotomies in 2014[12].

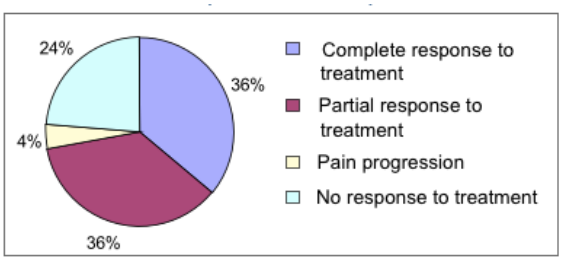

Figure 3. Initial clinical results of MRgFUS for metastatic bone pain.

MRI is used for treatment planning as well as for monitoring actual treatment. T2-weighted images are used to evaluate the tumour and surrounding anatomical structures and to define treatment volume and treatment path. Additionally, MR thermometry is performed with phase map imaging, which relies on subtle changes in resonance frequency of tissue at different temperatures, thus providing real-time temperature feedback during treatment. The focused ultrasound energy elevates temperature sufficiently to cause protein denaturation and cell death via coagulation necrosis. Immediately following treatment, contrast- enhanced MRI is performed to evaluate results. MRgFUS treatment of osteoid osteoma has also proven to be successful[13].

This service will be led by local clinicians Professor Houston, Dr Dougal Adamson (TBC), Mr Ghulam Nabi and Dr Raj Bhat. This will allow integration of palliative interventional radiological treatments of bone metastases including MRgFUS, vertebroplasty, RF ablation and cryotherapy. Research will be led by Prof Andreas Melzer for robotic positioning of FUS.

2.3 MRgFUS of the brain (CE marked, FDA pivotal trial)

Although the earliest clinical application of focused ultrasound, these early brain treatments required craniotomy. However there are now dedicated systems enabling penetration of the ultrasound beam through the intact skull to deliver very precise focused ultrasound treatments. Clinical trials in Switzerland, United

States and Canada have proven that this method can stimulate, detect and destroy targeted neural structures to interrupt selected pathways. Successful applications for this technique are essential tremor[14], chronic intractable pain, Parkinson's disease [15] and related conditions and other chronic benign conditions.

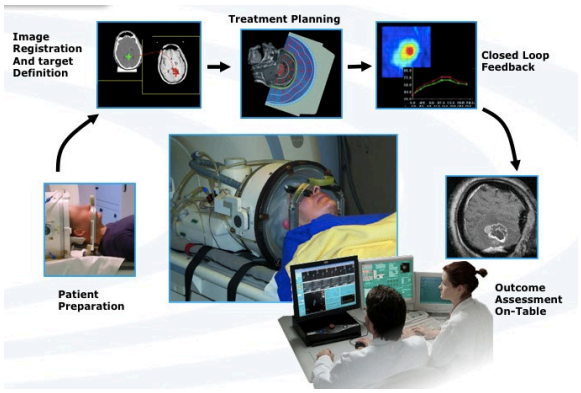

Figure 4. Workflow of MRgFUS of brain disease

The final FDA pivotal trial for FDA approval is ongoing and CE mark has been granted January 2013. The advantages of MgFUS are that it can be performed as outpatient procedure with as good results as alternative radiofrequency thalamotomy, pallidotomy, or cingulotomy. Radiofrequency procedures carry significant risk of CNS infection (5%), performed as inpatient procedure with an average stay in hospital of 4 days and theatre time of 4 hours on average for each procedure.

2.3.1 ***Essential tremor*** is one of the most common neurological disorders and is the most common movement disorder. Among the general population, the prevalence of essential tremor has been conservatively estimated at between 0.4 and 5 per cent, although it is expected that the true prevalence is much higher due to the existence of many undiagnosed patients. The wide range of these estimates is a result of an absence of uniform methodology by which to diagnose the disorder. Symptoms of essential tremor can develop at any age, from birth through to advanced age. The disorder, however, is clinically progressive in nature and as many as 4 to 5 per cent of people over the age of 40 are affected.

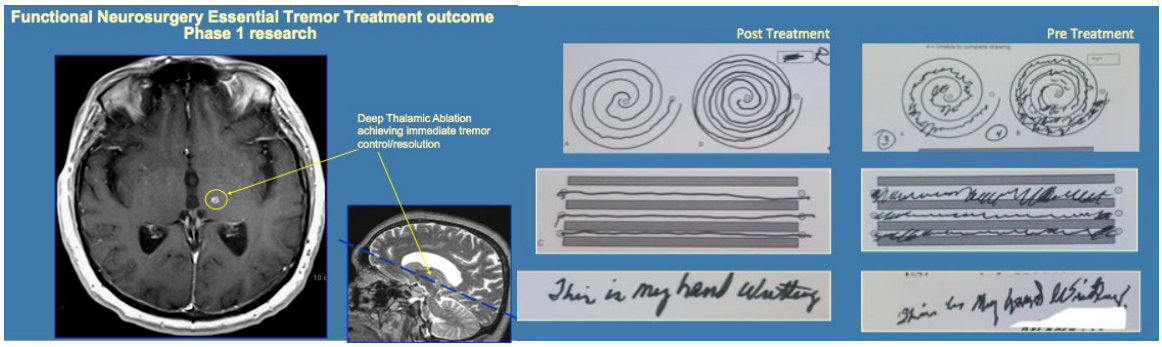

Figure 5: Essential Tremor 40 patients successfully treated Courtesy of: Jeff Elias, MD; University of Virginia, Department of Neurosurgery. For further details: https://www.youtube.com/watch?v=cWt6FPAz6xs

In Scotland at least 300,000 people suffer from essential tremor, with an estimated 50 patients per year potentially benefiting from surgery. If all these patients received deep brain stimulation at a cost of £20,000 each and replacements of batteries every 3-5 years at £10,000 each, a total cost in excess of £250,000 would be incurred in the long run, on top of an equally expensive follow up programme to monitor and adjust the stimulation. In MRgFUS there are no ongoing costs such as battery replacements and re-programming. If the efficacy and rate of non-infective complications are the same as DBS, there will be huge savings in the long run by using MRgFUS in this condition.

2.3.2 ***Idiopathic Parkinson's disease*** is an age-related neurodegenerative disorder, which is associated with a combination of asymmetrical bradykinesia, hypokinesia, and rigidity, sometimes combined with resting tremor and postural changes. The primary pathology is progressive loss of cells that produce the neurotransmitter dopamine from the substantia nigra in the brainstem. Treatment aims to replace or compensate for the lost dopamine. A good response to treatment supports, but does not confirm, the diagnosis. Several other

catecholaminergic neurotransmitter systems are also affected in Parkinson's disease. The mean age of onset is about 65. Overall age-adjusted prevalence is 1% worldwide, and 1.6% in Europe, rising from 0.6% at age 60–64 to 3.5% at age 85–89 years.

In Scotland PD affects over 500,000 patients, and an estimated 10-20% of these patients may be candidates for surgery, of which 50% might be suitable for pallidal surgery. Therefore MRgFUS could be used in about 50 patients per year. The cost of alternative DBS surgery in these patients would be in the region of £250,000.

2.3.3 ***Dystonia*** is a neurological disorder characterised by involuntary, abnormal muscle contractions that result in sustained abnormal postures, twisting, or both, and repetitive movements of body parts. It arises from dysfunction of the motor control system within the central nervous system. Dystonia is most simply classified by location: focal dystonia involves a single body part; multifocal dystonia involves two or more unrelated body parts; segmental dystonia affects two or more adjacent parts of the body; hemidystonia involves the arm and leg on the same side of the body; and generalised dystonia affects most or all of the body.; heterododegenerative dystonia where dystonia is a sign associated with neurological conditions, such as Parkinson's Disease and Huntington's Disease; and secondary dystonia where a cause (usually environmental) can be identified, such as head injury or use of drugs (e.g. neuroleptic drugs and metoclopramide).

In Scotland, about 10-15 patients per year may be candidates for surgery with an estimated cost of over £250,000.

In Scotland all neurosurgery for mental disorders such as depression or bipolar disorder are carried out at the National Centre for Advanced Interventions (CAI) in Dundee (about 5-10 cases per year). These patients would potentially be candidates for MRgFUS with significant savings.

3 Applications in Early Clinical Trials

3.1 MRI Guided Focused Ultrasound Treatment for Localised Prostate Cancer

Management of prostate cancer (PCa) remains one of the main uro-oncological challenges. At presentation, the majority of PCa are localised but up to 30% of patients have advanced or metastatic disease. The management of localised PCa remains controversial due to problem of over-diagnosis and the closely-linked issue of over-treatment. Over detection of PCa is particularly common in regions where PSA screening is in practice. For localised PCa, radical prostatectomy and radiotherapy are curative therapeutic options. However, these modalities can result in substantial side-effects due to collateral damage to surrounding structures. These include urinary incontinence (5 - 20%), erectile dysfunction (30–70%), and bowel toxicity (5–10%).

Ultrasound energy has been investigated for the treatment of both local and metastatic PCa. Combined with MRI for localisation of the cancer foci, focused ultrasound surgery is becoming more popular.

3.1.1. ***Rationale of focal therapy in prostate cancer*** Conventional therapeutic options for localised PCa are global in that they aim to treat the entire prostate gland based on presumption that it is filled with malignancy. Contrary to this belief, malignant processes do not always involving the prostate gland uniformly, thus conventional approaches may in fact be overly aggressive. Moreover, this can lead to significant side effects due to physiological and anatomical damage to the surrounding structures such as urinary sphincter and peri-prostatic neurovascular bundles. Targeted therapies, such as MR-guided Focused Ultrasound Surgery (MRgFUS), are aimed at achieving cancer control with minimal damage to surrounding structures. Furthermore, focal ablation such MRgFUS may be beneficial in patients needing salvage therapy after failed radiotherapy.

In recent years, organ preserving focal therapies have been investigated for the treatment of PCa. The aim of these therapies is to selectively eradicate cancer foci, thereby reducing the side-effects of radical therapies (radical prostatectomy and radical radiotherapy). Multiple modalities are capable of inducing irreversible cytotoxic damage such as; cryotherapy, high-intensity focused ultrasound (FUS), photodynamic therapy, and LASER-induced interstitial thermotherapy has been investigated for PCa. At present, FUS appears to be a valid alternative to active surveillance in low risk PCa and in older patients. FUS has proven short to medium term cancer control, with low rate of complications comparable with those of established therapies. Ultrasound guided FUS for treatment of patients with prostate cancer has been a reality for many years using the endorectal approach[16,17]. Modern state of the art MR imaging using advanced molecular imaging techniques such as diffusion weighted imaging and spectroscopy as well as tissue perfusion, can localise prostatic malignancy much more effectively than all other imaging modalities could in the past [18]. MRI has a number of important roles in focal therapies, especially for planning treatment sessions and more importantly to detect interval change. The rationale of image-guided prostate intervention is thus to use the images to guide the delivery of treatment accurately, to maximise the treatment to the clinical target volume and minimise the adverse effects to normal tissues nearby.

Although ultrasound guided HIFU has been investigated extensively, evaluation of MRgFUS is still in an early phase and current evidence is limited. Ahmed et al [16] reported on MR guided FUS for discrete areas of prostate cancer (unifocal and multifocal). Additionally, the treatment – related associated lower urinary tract symptoms were self-resolving. Increasingly positive experiences and result have been reported for MRgFUS for prostate cancer in North America[19,20].

3.1.2 MRgFUS focal treatment of prostate cancer Endorectal MRgFUS systems have been used in 10 centres for focal prostate cancer treatment with proven clinical safety. The possibility of targeted focal gland ablations under MRI guidance seems to significantly improve the outcome in comparison to the conventional ultrasound guided focused ultrasound ablation. The precise ablation technique, using MRgFUS, may be also suitable for radical prostatectomy and therefore may constitute a non-invasive alternative for the surgical technique including robotic assisted prostatectomy performed with the Da Vinci system. Due to the existing installation of the ExAblate main system the prostate FUS system could be installed in the Dundee centre for about £250k.

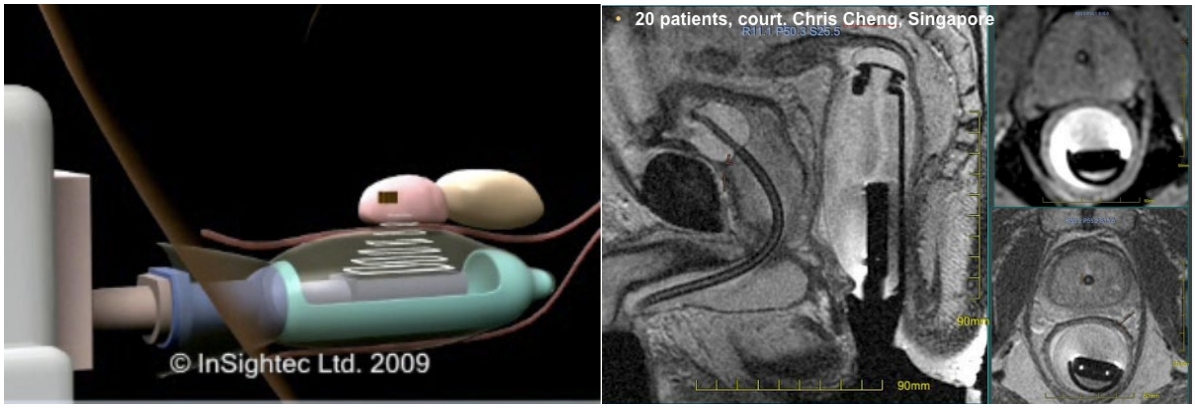

Figure 6: Schematic view and MR images of MRgFUS of prostate via a transrectal access

Research by Prof Andreas Melzer and Mr Nabi Ghulam would include ultrasound and MRI guided robotic assisted optical biopsy to assess MR visible focal lesions for an immediate FUS treatment.

Number of cases of localised prostate cancer eligible for MRgFUS treatment in Tayside

Local audit of MDT meetings over the past 3 years suggests that around 30-40 cases of localised prostate cancer (low risk category) could potentially benefit from MRgFUS treatment.

Prostate localised: 120

Metastatic: 50-60 and locally advanced: 40-45

3.2 MRgFUS treatment of liver tumours, renal and pancreatic cancers

Due to respiratory movement and the need to sonicate through the intercostal spaces to avoid the ribs, there are significant challenges for MRI guided FUS treatments of both liver and kidney. The only option is to perform the procedure under intubation and to stop respiration for the duration for the sonication, which has been done on limited numbers of patients. To solve this problem Dundee is working on a multicentre 3.6 m European collaborative project (www.fusimo.eu medical coordination by Prof Melzer) to develop the MRgFUS technology in relation to organs under respiratory motion and to liver treatments in particular. The follow on grant (€6.5m) starts 1 Jan 2014 and continues for 5 years for the translation of the research in to clinical application.

The currently developed real time MR organ tracking and FUS beam steering will be applicable both to primary liver tumours and also to the more common secondary liver tumours. We believe that successful application of this type of technology in the liver will potentially have the greatest immediate clinical impact of all MRgFUS applications because of their prevalence and the co-morbidities of patients with liver tumours, which preclude surgical interventions in a significant proportion of patients. In the field of renal tumours, the Small Renal Masses (SRMs) constitute an ongoing management problem, which often necessitates surgical excision of the lesion by partial nephrectomy. Mr Nabi and Prof Melzer have submitted a project proposal to CRUK to develop the MRgFUS technique on the Thiel soft embalmed cadavers as a preclinical model. MR guided focused ultrasound of pancreatic cancer has been performed in London and Rome and the early clinical results are promising.

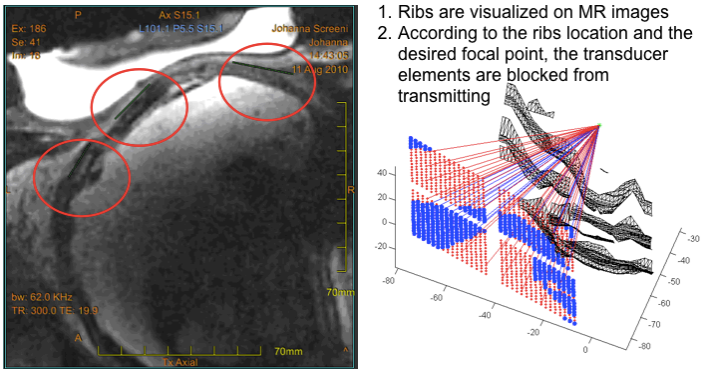

Figure 7: MRgFUS sonication sites avoid marked ribs and MR guided Beam steering to allow liver treatment under respiratory motion

Current research in Dundee is in the use of MRgFUS to focally ablate kidney tumours. Estimated numbers of patients would be: primary lesions: 60-70, metastatic: 30-40 patients per year.

This experimental work would be led clinically by Mr Ghulam Nabi (Kidney), Mr Ian Tait (Liver and Pancreas) TBC and Professor Graeme Houston with research led by Professor Andreas Melzer.

3.3 MRgFUS treatment of breast cancer

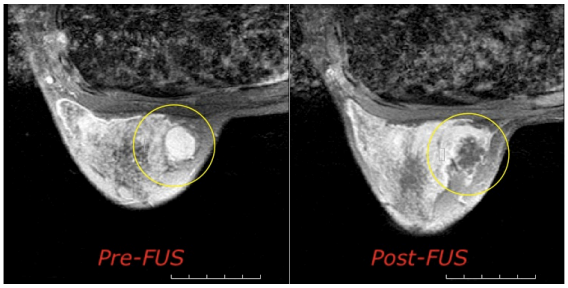

Figure 8: Axial MR images of MRgFUS of breast

With the ongoing scientific and public debate on the risks and benefits of national breast cancer screening programmes, there is increasing recognition of the problem of over-diagnosis and subsequent overtreatment of small low risk cancers, that might have remained undiscovered and never required treatment were it not for mammographic screening. Many screen-detected cancers are under 15mm in size, low grade and

have not involved the axillary lymph nodes at the time of diagnosis, but at present it is not possible to predict which cancers may safely be left untreated on an individual patient basis, so these low risk lesions are treated by surgery to the breast, with variable cosmetic results, an operation to sample the sentinel lymph node in the axilla, and subsequent radiotherapy to the breast as well as 5 years of oral endocrine treatment. Thus, there is widespread interest in the non-invasive treatment of small low grade breast cancers with techniques such as FUS, which can be done on an outpatient basis. Such a treatment would be particularly appealing for elderly patients with co-morbidities precluding surgical treatment.

3.3.1 Rationale for focal therapy in breast cancer It is established that breast conserving surgery is as good a treatment for breast cancer as mastectomy. The aim of local treatment is to completely remove the malignancy together with a margin of normal tissue that might harbour microscopic satellite foci of disease that are occult on clinical examination and conventional imaging. Screen-detected breast cancers are often impalpable and thus require image-guided localisation with ultrasound or mammography before surgical removal. Re-excision rates can be as high as 25% if surgical margins are not clear.

As with prostate cancer, small breast cancers can be destroyed through heating of the target tissue induced by a focused ultrasound beam. Since the breast is a superficial organ, there are no problems with respiratory motion or intervening bony structures such as the ribs. Breast tumours are readily visualised with ultrasound, which may be used for monitoring the procedure, but as MRI is the most sensitive technique available for the detection, diagnosis and, importantly, accurate sizing of breast cancer, it is logical to use MRgFUS in the treatment of breast cancers, since MR enables accurate targeting. Problems arise when the target is too superficial or too deep, when there is a risk of skin or rib burns respectively. Thermal mapping can be used to assess tissue heating and monitor the ablation as elsewhere in the body, though the frequent high fat content of breast tissue, especially in Western women with a high body mass index, can impede MR temperature mapping. Nonetheless there is the possibility of repeating the treatment until a satisfactory ablation has been achieved.

3.3.2 Clinical evidence for focal MRgFUS therapy in breast cancer The first work published on MRgFUS in the breast reported on a series of 9 successfully treated fibroadenomas[22] but there has been far more interest in treatment of early stage breast cancer. Most of the early phase 1 studies followed a treat-and-resect protocol so that the extent of ablation could be established. Published results for FUS in the treatment of breast cancers are highly encouraging, though long term follow-up is limited[23]. Early small scale studies suggest that a margin of at least 0.5 cm in all directions around the breast tumour should be built in to all MRgFUS procedures and establishing this can be problematic. In the largest series of patients treated without subsequent surgery, 63 lesions were treated successfully in 74 patients between June with a mean tumour size of 11mm. Median follow-up is now 50 months (range 1-81 months) and to date there have apparently been no local recurrences, though only 44 have been followed up for more than 24 months. No severe adverse events have been reported. Most published studies have used MRgFUS systems designed to treat bone metastases or fibroids, which can limit the numbers of lesions that can be safely treated for the reasons described above, but recently a number of groups have developed laterally mounted ultrasound transducers, which should theoretically increase the range of lesions that can be successfully targeted without skin or rib burns[24]. However, further research is needed to optimise transducer design and develop dedicated MRgFUS platforms. Finally, it is standard practice to base subsequent therapy on prognostic factors derived from histological examination of the resected specimen, so if the treated tissues are to be left in situ post MRgFUS, clinicians must be satisfied that adequate information has been obtained from the diagnostic tissue biopsy. Early information indicates that MRgFUS does not impair or interfere with any sentinel node procedures and that these can be carried out in the normal way.

Number of cases of early stage breast cancer eligible for MRgFUS treatment in NHS Tayside

On average, around 400 new cases of breast cancer are diagnosed in NHS Tayside each year. Of these, approximately 70 are screen detected, the total number of screen detected cancers in Scotland in 2012/13 being approximately 800. It is estimated that somewhere between 50-60% of these will be small (under 15mm), thus in NHS Tayside, as many as 40 cases per annum could potentially be suitable for MRgFUS treatment.

This experimental work would be led clinically by Dr Sarah Vinnicombe and Dr Dougal Adamson with research of improved MR temperature mapping and novel robotic assisted techniques for biopsy and FUS led by Professor Andreas Melzer.

4 Scottish Pre-clinical MRgFUS Research

4.1 MRgFUS mediated focal drug delivery

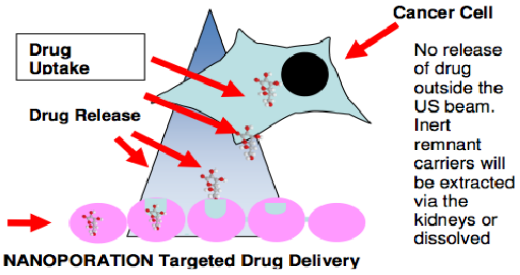

Figure 9: The combination of nanoporation and ultrasound could deliver targeted drug treatment using MRgFUS.

Recent preclinical results and research in Dundee (www.nanoporation.eu 2.8 m € grant coordinated by Prof Melzer) on MR guided focused ultrasound mediated targeted drug delivery is very promising and has the potential to further expand the applications of MRgFUS in the treatment of benign and malignant conditions. MRgFUS targeted drug delivery would provide a high initial focal concentration of potent chemotherapy agents in the area of tumour spread and could be applied after tumour debulking with ablation. The approach is two fold: focused ultrasound leads to an increase in cell membrane permeability through an effect called sonoporation, which has been visualized for the first time by the researchers of IMSaT, as a result of which 100% cell membrane permeability can be achieved. Secondly, focused ultrasound can mediate targeted release of potent chemotherapy drugs from drug encapsulating carriers, a technique developed at IMSaT. The current existing product Doxyl® is FDA approved and comprises liposomes encapsulating doxorubicin. The research team at IMSaT and their collaborators have proven the local release of doxorubicin from these carriers. Prof Melzer is a member of the core group for development of targeted drug delivery in the FUS foundation, which has brought together international leaders in this field. First clinical studies are under preparation and the possible candidates are breast cancer and prostate cancer, both of which have a diffusion barrier which potentially might be broken by the FUS technique to enhance drug uptake into the tumour cells and the respective lymph drainage. Initial very promising results of enhancing the delivery of doxorubicin have been reported by Chen et al[25].

The MRgFUS mediated drug delivery also has potential for the treatment of inflammatory and cardiovascular diseases such as treatment of arteriosclerotic diseases.

4.2 MRgFUS of haemorrhagic, ischaemic stroke and peripheral vascular occlusion

MRgFUS has shown feasibility in preclinical research as a tool capable of liquefying clotted blood in haemorrhagic brain lesions and thrombolysis of thrombosis in artificial and in-vivo vessels. The current research is focused on the development of: sonication protocols for stroke and peripheral arterial occlusions, venous thrombosis, targeted drug delivery of thrombolytic agents and safety envelopes e.g. defining the parameters that will allow clot lysis without triggering haemorrhage. This technique could potentially be used for treatment of arteriosclerotic plaques and intimal hyperplasia.

5 MRgFUS clinical centre in Scotland

Based on the progress of the clinical research, the local expertise and the extensive established facilities for performing these procedures adjacent to a major teaching hospital in Scotland, it would seem appropriate to consider establishing a national Scottish MRI focused ultrasound service for the provision of these numerous applications. The MRgFUS installation in Tayside is the second in the UK and the active and pioneering research undertaken has led to a high international visibility that resulted in the election of Prof Melzer as chair for the 2nd European Focused Ultrasound Therapy Symposium, which will be co-sponsored by the USA based FUS Foundation (www.fusfoundation.com). The FUS foundation joins about 150 centres world wide but in the UK, Dundee is the only research site. There is one single centre serving the population in England **(**MR Therapy Centre, St Mary's Hospital, London).

A new MR HIFU installation by Philips at the Institute of Cancer Research and The Royal Marsden Hospital in Brompton (Prof Gail ter Haar, Prof Nandita Da Souza) has been announced recently and awarded as Centre of Excellence of the FUS Foundation. The same offer has been made to Dundee in 2009 but due lack of clinical work is has not yet materialized.

5.1 The Proposal

It is proposed that the Scottish MR focused ultrasound facility should be situated within Wilson House, in the grounds of Ninewells Hospital Dundee, Tayside, managed under the NHS Tayside clinical Governance scheme, and adapted as a national centre for such service in a phased manner over 4 years.

The initial two year period will comprise introduction of the applications of treatment of uterine fibroids and bone metastases. This would establish the clinical service and the appropriate delivery of outpatient care pathways. Access to the service would be open on a national basis and run under appropriate direct NHS Tayside clinical guidance. The second phase is proposed as an extension of clinical applications into emerging are as for patient benefit as evidence and practice becomes established.

5.2 Costs

The following is an outline estimate of annual running costs:

Phase 1:

5.2.1 Initial clinical staffing level which allows clinical activity for 7 clinical sessions per week:

Consultant Radiologist – 0.7WTE	£73,000
Radiology Fellow	£55,000
Surgery Fellow	£55,000

MRI Radiographers 1.5 WTE Band 7		£ 58,000
MRI Medical Physicist – 0.5 WTE Band 7		£ 37,000
Nurse – 1.25 WTE Band 6		£ 32,000
Clerical – 0.5 WTE Band 5		£ 11,000
Annual Staffing	**TOTAL**	**£320,000**

This provision of service would allow 4 sessions for uterine fibroid treatments to undertake 300 treatments per year, and 3 sessions per week to undertake 450 other treatments per year, 1500 outpatient attendances for pre-procedure and post-procedure care.

5.2.2 MRgFUS Facility Running Costs Year 1&2

Service costs of MRI and MRgFUS	£110,000 per annum
Overheads	£120,000 per annum
Recurring Costs: **TOTAL**	**£ 550,000**

5.2.3 Initial Costs:

Clinical facility conversion £ 75k: This comprises IT integration into NHS clinical data systems and conversion of the MRgFUS facility for increased patient throughput.

5.3 Income as National MRgFUS Centre – Sustainable Business Model

Phase 1: Appropriate service level agreements for NHS Scotland across the range of these initial clinical applications with the existing equipment would cost the assessment and treatments at a cost of:

Uterine fibroid treatments:	£ 2,200 per patient
Bone Metastases treatment:	£ 1,750 per patient

Based on caseload from year 3 it is estimated that national SLA annual income would be £1.5m.

Phase 2: Based on the success of the initial phase a further development of the facility to undertake emerging applications such as MRgFUS of the brain, prostate and breast will take place. It is envisaged that this service would also be on a national basis.

5.3.1 The second phase of the development would require:

1 Acquisition of new equipment for advanced treatments:

Breast option	£100,000
(ExAblate Brain System (has been offered on loan to Prof Melzer)	
Prostate	£250,000

Liver and Kidney new system for moving organs (has been offered to Prof Melzer)

2 Further extension of staff complement

3 Integration of a brain or prostate MRgFUS system with the existing MRI unit under collaborative agreement and reduced costs

4 Enhanced service level agreements for NHS Scotland across the range of these advanced clinical applications

5.3.2 Estimated new clinical procedures in phase 2:

Breast: £2,200 early stage breast cancer - 40-50 patients per year

Brain: £10,000 per case
Essential tremor and Parkinson's - 50-70 patients per year
Dystonia around 10 – 15 patients per year
Mental disorders – 15-20 patients per year

Prostate: £3,200 localised prostate cancer (low risk category)
30-40 cases per year

Pancreas: £5,200 per case
Non-resectable tumours, MRgFUS to improve quality of life - 20-30 patients per year

Liver: £6,200 per case
Resectable lesions for a randomised prospective trial MRgFUS versus surgery - 30 to 50 patients per year

SLA annual income including new applications and trials: from year 4 £ 2.6-3.6m

6 Collaborations and National Relationships

This proposal has been developed in collaboration between NHS Tayside, the University of Dundee, GE Healthcare, InSightec and the respective NHS clinicians in Gynaecology, Oncology and Neurosciences. We have invited colleagues in other NHS and Universities in Scotland in the fields of Interventional Radiology, Clinical Specialties and in the relevant research networks such as SINAPSE, SUPA, and Northern Research Partnerships, to participate.

7 Conclusion

Focused Ultrasound therapy is becoming well established across the EU and North America. Whilst England has access to a single centre, the Scottish population is being denied a safe, effective and often less invasive treatment due to lack of a Scottish site. This proposal indicates that Tayside has not only the facilities for this work, but the clinical expertise, and through its relatively central position, it is well placed to supply focussed ultrasound treatments to a Scotland-wide population.

We request permission to prepare a formal feasibility document for such a Centre, to serve the whole of Scotland.

8 Scottish MRgFUS Service team

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Jill Belch, Professor of Cardiology and Director TASC (NHS Tayside Academic Heath Science Centre)

Dundee, June 2014

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