RESEARCH PROTOCOL

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Feasibility of combined Focused Ultrasound and Radiotherapy treatment in patients with painful bone metastasis
- the PRE-FURTHER study -

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
BPI	Brief Pain Inventory
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DD	Device Deficiency
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
EBRT	External beam radiotherapy
EU	European Union
EM	Equivalent Minutes
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
Gy	Gray
H2020	European Commission Horizon 2020 Programme
IB	Investigator's Brochure
IC	Informed Consent
IDEAL	Innovation, Development, Evaluation, Assessment and Long term evaluation
KPS	Karnofsky Performance Score
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
MR	Magnetic Resonance
MR-HIFU	Magnetic Resonance Image guided High Intensity Focused Ultrasound
MRI	Magnetic Resonance Imaging
NRS	Numeric Rating Scale
PREM	Patient Reported Experience Measure
PRESENT	Prospective Evaluation of Interventional Studies on Bone Metastases
PRFS	Proton Resonance Frequency Shift
PSA	Procedural Sedation and Analgesia
QA	Quality Assurance

RCT	Randomized Controlled Trial
RT	Radiotherapy
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG
UMC	University Medical Center
USADE	Unanticipated Serious Adverse Device Effect
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Magnetic Resonance Image guided High-Intensity Focused Ultrasound (MR-HIFU) is a non-invasive technique, which may induce rapid induction of pain relief in patients with painful bone metastases. In 2019, an international, H2020 funded randomized controlled trial (FURTHER) will be started comparing MR-HIFU with the current standard of care, external beam radiotherapy (EBRT), and the combination of both modalities in terms of rapid and long lasting pain relief. For this purpose, feasibility and optimal logistics of the combined treatment need to be evaluated.

Objective The PRE-FURTHER project aims to evaluate the feasibility of the combined EBRT and MR-HIFU treatment for relief of metastatic bone pain, and to optimize the combined treatment logistics.

Study design: Prospective case series (n = 6 - 10), stage I and IIA study according to the Innovation, Development, Evaluation, Assessment and Long term evaluation (IDEAL) recommendations.

Study population: The study will be performed in male and female adult (≥ 18 years) cancer patients capable of giving informed consent and referred for EBRT of painful bone metastases (Numerical Rating Scale (NRS) ≥ 4).

Intervention: Following standard EBRT (single or multiple fraction), patients will receive one MR-HIFU treatment with the Profound Sonalleve MR-HIFU device on the most painful of their bone metastases. Patients will be followed up until 4 weeks after treatment. During follow-up they will be phoned around day 3, 7, 14, 21 and 28 to retrieve pain scores, pain medication and (serious) adverse events. At day 3 the patient's experience with the combined treatment will also be inquired.

Main study parameters/endpoints: The main outcome of this study is feasibility of the procedure, in terms of plannability as well as patient-tolerability of the combined treatment within a short time frame (3 hours - 4 days interval). In addition, pain relief and safety of the combined procedure will be monitored.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: In terms of benefits, patients participating in this study may experience a more rapid and longer lasting pain relief as a result of the MR-HIFU intervention. In terms of burden, patients in most cases will need to pay an extra visit to the hospital, undergo a rather lengthy additional intervention (MR-HIFU treatment), under conscious sedation. In addition, they are contacted regularly by phone. Serious adverse events due to the combined treatment are not to be expected.

1. INTRODUCTION AND RATIONALE

1.1 Bone metastases

Bone metastases are a common manifestation of advanced cancer. Due to rising cancer incidence rates and improved survival, the number of cancer patients living long enough to develop bone metastases is increasing rapidly. Depending on the location of the primary tumour approximately 30-80% of patients with advanced cancer develop bone metastases, with pain as a common and devastating consequence (Ripamonti, 2000, 2001; Portenoy, 2011; Lipton, 2010; Coleman 2006; Suva 2011). Metastatic bone pain strongly interferes with quality of life and daily functioning of patients and their families (Mantyh, 2014, Paice and Ferrell, 2011). Intermittent episodes of extreme pain, either occurring spontaneously or by movement of the affected limb, are often referred to as “breakthrough” pain, as it breaks through the opiate pain palliation regime, and is refractory to pharmacologic pain treatment. Metastatic bone pain affects mobility, productivity and independence, placing an increasing burden on health-care and social care systems.

1.2. Current standard of care: external beam radiotherapy (EBRT)

The current standard of care for patients with uncomplicated painful bone metastases includes palliative locoregional treatment using external beam radiotherapy (EBRT) (Ripamonti, 2010; Chow, 2014; Huisman, 2015), often in combination with systemic therapy and analgesics. EBRT alleviates pain through induction of deoxyribonucleic acid (DNA) damage, leading to tumour shrinkage, and through inhibition of the release of chemical pain mediators. Multiple randomized controlled trials and several systematic reviews over the past 30 years have demonstrated the efficacy of radiotherapy in palliating pain from uncomplicated bone metastases (Jones, 2014). Overall, approximately 25% of patients can expect to have complete pain relief whereas a total of 60-70% of patients can expect some response to radiotherapy. However, time to optimal symptom control, even after short courses of radiotherapy, is usually measured in weeks to months after radiation treatments are delivered, as clearly demonstrated in the case of pain relief from bone metastases. On average, it takes four weeks for EBRT to induce adequate pain relief. In the Dutch Bone Trial, including 1100 patients, only 71% of patients reported adequate pain response (van der Linden, 2004; Westhoff, 2015). In the large hospital based PRESENT (prospective evaluation of interventional studies on bone metastases; METC 13-261) cohort of unselected patients with bone metastases, 64% of patients experienced pain response following EBRT (van der Velden, 2018). Moreover, approximately 50% of responders experience recurrent pain. Radiotherapy retreatment of non-responders or those with recurrent bone pain is limited by cumulative doses of radiation delivered to sensitive structures surrounding the

bone metastases. In addition, re-irradiation is only effective in a small majority (58%) of patients (Huisman, 2012).
In summary, there is a clear clinical need for a treatment that provides rapid pain relief with a lasting effect, at least to bridge the time it takes for EBRT to take effect. In addition, since 30-40% percent of patients do not respond to EBRT, alternative treatment strategies could be of added value for the large group of patients that we are currently unable to treat effectively.

1.3. MR-HIFU treatment

Pain palliation may be substantially improved by including magnetic resonance image guided high intensity focused ultrasound (MR-HIFU) as alternative or in addition to EBRT. MR HIFU is a non-invasive outpatient treatment modality that delivers acoustic energy to heat lesions to ablative temperatures of more than 60°C. The combination of focused ultrasound with magnetic resonance imaging (MRI) enables physicians to perform localized tumor tissue ablation, with real-time temperature monitoring using magnetic resonance (MR) thermometry (Jolesz, 2008). The biological mechanism of pain relief induced by MR-HIFU treatment has not been completely elucidated, although it is generally assumed that periosteal denervation induced by cortical heating plays a major role. The importance of this therapy is that it offers a low-risk, non-invasive, focal therapy, avoiding side-effects to surrounding normal tissue that occur with radiation therapy. In contrast to EBRT, it does not require computed tomography (CT) for treatment planning or therapy.
Preliminary clinical studies on the use of MR-HIFU for palliation of painful bone metastases demonstrated excellent response rates and safety (Catane, 2007; Gianfelice, 2008; Napoli, 2013; Huisman, 2014). Hurwitz et al (2014) reported results of a multicenter randomized placebo-controlled trial to evaluate safety and efficacy of MR-HIFU for treating bone metastases in patients with persistent or recurrent pain. This study demonstrated that MR-HIFU is a safe and effective, non-invasive treatment for alleviating pain caused by bone metastases. Response to MR-HIFU was typically rapid, with about two-thirds of responses seen within days after treatment (Hurwitz, 2014). A recent single-centre matched-pair study showed that MR-HIFU provides a similar overall treatment response rate but faster pain relief compared with EBRT and thus has the potential to serve as the first-line treatment for painful bone metastasis in selected patients (Lee, 2017). University Medical Center Utrecht participated in a multicenter pilot study (METC 12-035) in which an early improvement in pain and quality of life in patients with painful bone lesions treated with MR-HIFU was shown (Harding, 2018). These studies were, however, performed in patients who were ineligible, or who failed or declined radiation. As such, there is a lack of evidence that supports the uptake of MR-HIFU as a standard (first-line) treatment option and alternative to

EBRT, even though these results show that MR-HIFU has the potential to provide added value in standard care.

1.4 The FURTHER study

Hitherto, no Phase III clinical trial has been conducted in which EBRT and MR-HIFU have been compared as a first-line treatment. Thus, strong evidence and context is lacking for wide-spread implementation of MR-HIFU into routine care.
A consortium of partners from 5 European countries and the Focused Ultrasound Foundation recently joined forces to provide the evidence base to stimulate the uptake of MR-HIFU as a first line treatment option in clinical guidelines for the treatment of cancer induced bone pain. Reaching this ambitious goal will require a demonstration of the added value of MR-HIFU in standard care with comprehensive outcome testing that will convince a wide variety of stakeholders of the added value of including and reimbursing MR-HIFU as part of standard care and a feasible alternative for the golden standard EBRT treatment.
The FURTHER consortium will undertake a three armed phase III multicenter randomized controlled trial (RCT) and a pain management pathway pilot. The multicenter RCT is designed to compare outcomes of EBRT, MR-HIFU alone and EBRT in combination with MR-HIFU, for palliation in patients that present with painful bone metastases. By combining the two modalities in one RCT arm the hypothesis can be tested whether the combined treatment has superiority over either modality alone with regard to overall pain response.

1.5 Combining EBRT and MR-HIFU: the PRE-FURTHER study

There are several hypotheses about the possible synergistic effect of EBRT and MR-HIFU. By combining both modalities, a substantial proportion of patients with painful bone metastases are expected to experience early pain relief and improved response durability, while all of the tumour tissue receives radiation.
Additionally, it is recognised that radiation and heat both induce tumour-specific immune responses (Wattenberg 2014; Udono 1993; Milani 2002; Hurwitz 2010).
The putative main mechanism of pain relief by EBRT involves the inactivation of osteoclasts to change the microenvironment of bone resorption followed by sterilization of cancer cells to reduce tumor-induced compression (Hartsell, 2007). The direct mechanism of action of EBRT is damage to DNA of tissues, including both single strand and double strand DNA breaks, originating mostly from different oxygen radicals. The mechanism of action of MR-HIFU is coagulative necrosis and apoptosis of tissue due to heat leading to rapid and durable pain relief from immediate periosteal nerve ablation

and thermal necrosis of the targeted bone tumor followed by remineralization of the trabecular bone and bone healing a few months later. Since the mechanism of action of EBRT and MR-HIFU differ, MR-HIFU provides an alternative means to overcome radioresistance and is recommended for patients with bone metastasis for whom radiotherapy (RT) is considered to have failed (Hurwitz, 2014).

Since the mechanism of action of EBRT and MR-HIFU differ, the two methods may be synergistic in first-line, or when applied nearly simultaneously. Heat-induced coagulative ablation is the main action of MR-HIFU, hence its pain palliation effect is expected to be rapid. However, heat distribution is often spatially heterogeneous in bone metastases because of the fact that absorption of ultrasound energy depends on many factors including the degree of bone lysis or formation, and incident ultrasound angle. Therefore, it might be that the, more long-term, systemic responses of EBRT of the tumor and its microenvironment, reduction of tumor-induced compression and inactivation of osteoclasts, can be augmented by local ablation of periosteal nerve ablation by MR-HIFU.

Some other effects should be mentioned:

- Hyperthermia (temperatures 42-45°C) beyond the ablated area results in complementary radiosensitization (reduction of hypoxia; inhibition of DNA repair mechanisms) (van der Zee, 2000; Dababou, 2018) thereby increasing the risk of damage to surrounding tissue.
- Coagulative ablation by MR-HIFU (temperatures around 60°C) also may lead to reduction/elimination of local perfusion leading to hypoxia of the treated area. This may render subsequent EBRT less efficient (less production of oxygen radicals).

Because of the above arguments, our patients will first undergo the EBRT treatment followed by MR-HIFU with an interval of at least three hours.

In the PRE-FURTHER study University Medical Center (UMC) Utrecht and Isala Zwolle will collaborate in determining the feasibility of the EBRT/MR-HIFU combination treatment. As part of the multicenter RCT design, both treatments should not be more than 4 days apart, but the aim is to minimize this time by optimizing hospital logistics. The benefits of the expected earlier pain relief when both modalities are combined, are substantial, considering the relatively short life expectancy of these patients.

Until now the combined EBRT and MR-HIFU treatment was only applied to patients with radiation refractory metastatic bone pain with an interval of at least several weeks between the two treatments. Hitherto, no information on feasibility is available when the two modalities are combined within a time frame of 4 days.

We may have to decide that we will not include the combined treatment in the FURTHER RCT, when hospital logistics hampers us from providing the combined treatment within a defined time frame, when patients are not willing to undergo the combined treatment or when the combined treatment leads to serious adverse events which are the result of combining EBRT and MR-HIFU,

1.6 IDEAL recommendations

This pilot study will be set up according to the IDEAL recommendations (McCulloch 2009; Verkooijen 2017). These recommendations provide direction for reporting and evaluation of innovative surgical procedures which are being undertaken for the first time, and for adoption of new procedures in other centers and by other teams. IDEAL is an acronym for the five stages that complex interventions go through, namely Innovation, Development, Evaluation, Assessment and Long term evaluation.
Stage 1 demonstrates feasibility and absence of unexpected detrimental effects. The initial patients are usually highly selected on an individual basis. Feasibility, duration and complication are reported for a small number of patients. These reports should contain clear anonymous details of the patient, their condition, the rationale and background for use of the procedure, exactly what was done, and adequate details of relevant outcomes.
After Stage 1 has shown technical feasibility, without major unexpected toxicities or complications, the technique enters Stage 2a.
Stage 2a aims to refine the technique and to optimize the work-flow. Outcomes of this stage are technical feasibility and safety. With practitioners maintaining confidence, the new approach becomes a practical alternative to the standard procedure. Reporting during this stage needs to include: selection criteria and proportion of eligible patients selected; a clear description of the procedure and each modification, with timing; and relevant outcomes, with recognized standard definitions of important categories, such as specific complications.
Transition to stage 2b (Evaluation or Exploration) is justified by improvements in procedure times and the avoidance of adverse events, with major refinements of the method completed. This stage consists of a larger series of consecutive patients. Stage 3 (Assessment) aims to answer the essential question: Is the clinical efficacy of this intervention better than the standard treatment? Comparative studies, preferably with a randomized component, are favored. Stage 4 (Long term evaluation) starts when the effectiveness of new intervention

has been demonstrated and the intervention is implemented in daily clinical practice. This pilot study is a combination of stage 1 (Idea) and stage 2a (Development).

2. OBJECTIVES

2.1 Primary objective

- To assess the feasibility of combining MR-HIFU and EBRT in a 4 day time window for the treatment of painful bone metastases from the perspective of
  1. the patient (patient tolerance)
  2. hospital logistics (standardisation of the procedure)

2.2 Secondary objectives

- To assess the pain reducing capabilities of the combined treatment:
  Pain response:
  - rapidity of pain relief
  - duration of pain relief
  - pain medication used
- To assess the safety profile of the combined treatment.

3. STUDY DESIGN

This study will be a prospective development study (IDEAL stage 1 and 2a) (McCulloch, 2009; Verkooijen, 2017) performed at the UMC Utrecht and Isala Zwolle. A group of 6-10 patients with painful bone metastases will be studied to evaluate feasibility and logistics of the combined EBRT MR-HIFU treatment within a 3 hours - 4 day time window.

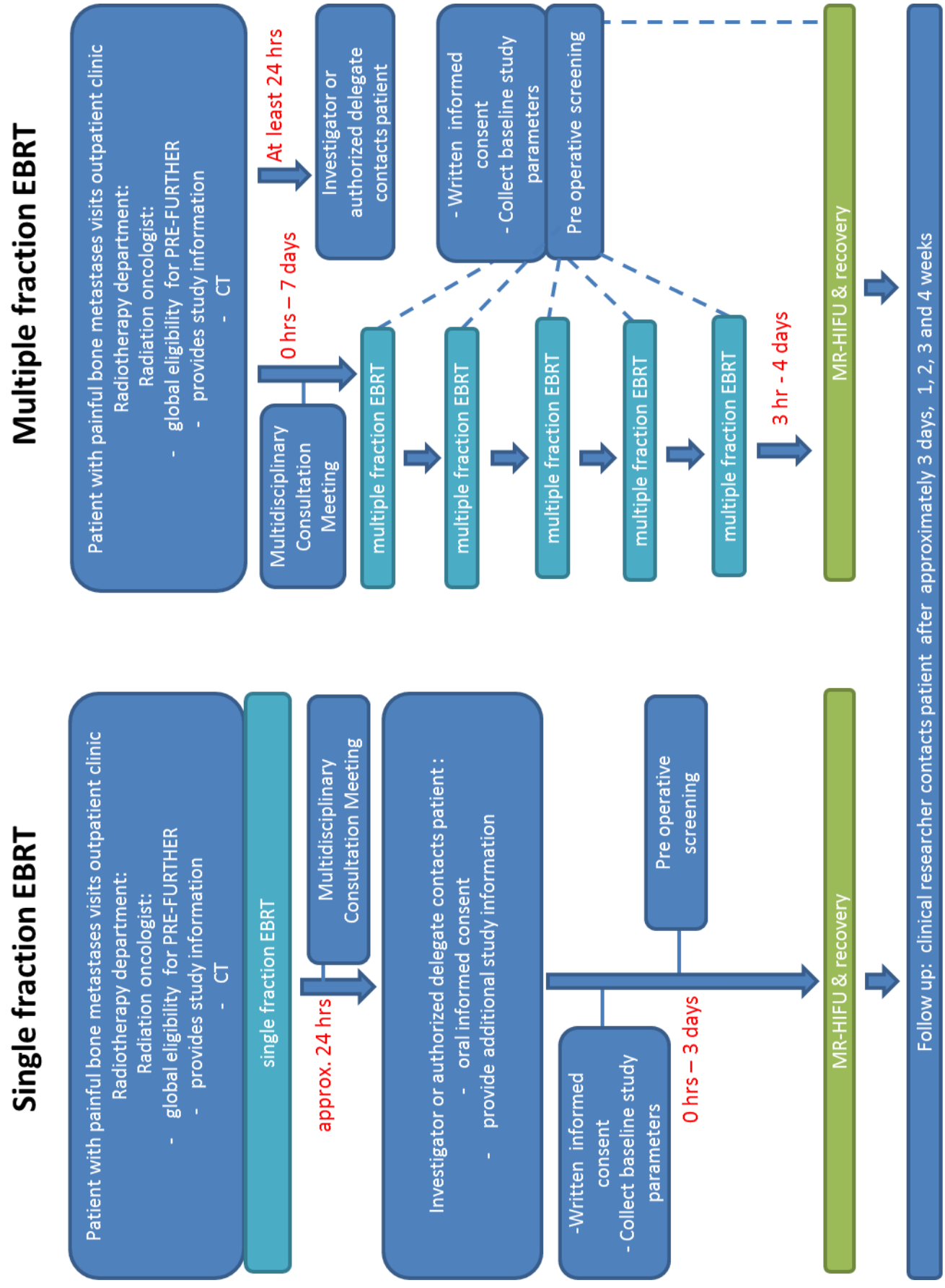
Participating doctors will be informed about the study and will be asked to inform possible eligible patients about its existence. If the patient is considered to be eligible for MR-HIFU by the treating physicians and investigators and when the patient is willing to participate, the investigator or an authorized delegate will take over and inform the patient in more detail about the study, explaining the study design and procedures and collecting informed consent and baseline data.
The inclusion preferably takes place shortly after the patient has been diagnosed and before treatment is started.

Patients who fulfil all inclusion criteria, none of the exclusion criteria, and sign an informed consent will first receive the standard of care, single or multiple fraction EBRT, followed by MR-HIFU within a 3 hours - 4 day time window.

The optimal logistic approach for administering both treatments will be assessed and protocolled. For this purpose, we will test several treatment schedules and make adjustments when needed. We will aim for the shortest time interval possible between the two treatments with a minimum interval of 3 hours and we set out to minimize additional hospital visits for participating patients.

During a follow-up period of 4 weeks, patients will be contacted by phone to retrieve information about their level of pain and pain medication around 3 days and 1, 2, 3 and 4 weeks after the MR-HIFU treatment.

A general flowchart of the study is given in the figure on the next page for both single and multiple fraction EBRT.


Multiple fraction EBRT
Patient with painful bone metastases visits outpatient clinic
Radiotherapy department:
Radiation oncologist:
- global eligibility for PRE-FURTHER
- provides study information
- CT
At least 24 hrs
Investigator or authorized delegate contacts patient
0 hrs – 7 days
Multidisciplinary Consultation Meeting
multiple fraction EBRT
multiple fraction EBRT
multiple fraction EBRT
multiple fraction EBRT
multiple fraction EBRT
3 hr - 4 days
- Written informed consent
- Collect baseline study parameters
Pre operative screening
MR-HIFU & recovery
Single fraction EBRT
Patient with painful bone metastases visits outpatient clinic
Radiotherapy department:
Radiation oncologist:
- global eligibility for PRE-FURTHER
- provides study information
- CT
single fraction EBRT
approx. 24 hrs
Multidisciplinary Consultation Meeting
Investigator or authorized delegate contacts patient :
- oral informed consent
- provide additional study information
-Written informed consent
- Collect baseline study parameters
0 hrs – 3 days
Pre operative screening
MR-HIFU & recovery
Follow up: clinical researcher contacts patient after approximately 3 days, 1, 2, 3 and 4 weeks

4. STUDY POPULATION

4.1 Population (base)

The study population will consist of male and female adults (age ≥ 18 years) with painful bone metastases who have given informed consent. This is a group of (often elderly) patients, with a limited life expectancy, in whom maintenance of quality of life and pain control is of utmost importance.

In the UMC Utrecht, the subjects will be recruited from the PRESENT cohort. In PRESENT, patients planned for radiation treatment of bone metastatic disease at the department of Radiation Oncology of the UMC Utrecht are included (around 400 per year).
In Isala patients will be recruited from patients that visit the outpatient clinic of the department of Radiation Oncology. In Isala, approximately 600 patients present annually to the department of Radiation Oncology for the treatment of painful bone metastases. In about one third of these patients the metastases are located outside the spine or the cranium. 36% of these 200 patients (72 patients annually) were estimated to be eligible for MR-HIFU treatment on the basis of a random sample of 50 patients.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

Criteria	How Measured
Men and women with age ≥ 18 years	Birth date
Patient capable of giving informed consent and able to attend study visits	Physician's interview
Uncomplicated painful bone metastases	Physician's examination / radiology
Weight < 140kg and able to fit in the MRI gantry	Physician's examination / patient history
Radiologic evidence of bone metastases from any solid tumor	Radiology
Pain is localized to the targeted area, or is likely to be referred pain arising from the targeted area	Physician's examination / patient history
Pain related to the target lesion is refractory to less invasive treatments for pain relief	Physician's interview and examination
Multiple metastatic lesions, with one predominantly painful lesion (>=2 points higher pain score than other lesions). The lesion should be clearly distinguishable from other painful lesions.	Radiology / patient history
Device accessible tumors: extremities (excluding	Radiology

joints), pelvis, shoulders, posterior vertebral spine below L5, in selected cases ribs and sternum	
Target lesion maximum dimension ≤ 8cm	Radiology
Intended target volume visible by non-contrast MR imaging	Radiology
Distance between target and skin ≥ 1cm	Radiology
Numeric Rating Scale (NRS) score >= 4 or equivalent	NRS
Life expectancy >3 months	Physician's examination

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

Exclusion Criteria	How Measured
Planned treatment lesion is a primary bone tumor or due to lymphoma, multiple myeloma, or leukemia.	Patient history
Communication barrier present	Physician's interview / patient history
Patient enrolled in another clinical study related to bone metastases treatment or pain relief treatment	Physician's interview / patient history
Unable to tolerate required stationary position during treatment despite adequate pain medication	Physician's interview / examination / positioning test in MRI before treatment
Need for surgery	Radiology
Pregnant woman	Pregnancy test / patient history
Pain related to target lesion is predominantly due to fracture or impending fracture	Physician's examination / radiology
Pain related to target lesion is due to involvement of a neighboring major nerve by the metastatic tumor (cord or nerve compression)	Physician's examination / radiology
Target < 3cm from bladder / bowel / nerve along the beam path and < 1cm in the plane orthogonal to the beam	Radiology
Target in contact with hollow viscera	Radiology
Target located in skull, joints, ribs (when HIFU beam overlapping with lung), spine (excluding sacrum which is allowed) or in most cases sternum	Radiology
Internal or external fixation device along the proposed HIFU beam path or at the target	Physician's examination / radiology
MRI contraindicated (e.g. paramagnetic implants, pacemaker, claustrophobia)	Patient history
MRI contrast agent contraindicated (e.g. previous	Laboratory tests / patient history

Exclusion Criteria	How Measured
anaphylaxis or Glomerular Filtration Rate < 20 ml/min/1.73m2)	
Sedation contraindicated	Laboratory tests / patient history
Previous surgery or minimally invasive treatment at targeted site within the last three months	Patient history
Clinically relevant medical history or abnormal physical findings that could interfere with the safety of the participant as judged by the treating physician or investigator	Physician's interview / patient history
Karnofsky performance score (KPS) < 60%	Physician's interview
Oligometastatic disease planned for curative treatment	Physician's interview / patient history
Indication for stereotactic radiotherapy (e.g. patients with radioresistent histology such as renal cell, melanoma, sarcoma metastases)	Physician's examination / radiology
History of photodermatoses (of the skin overlying the target area)	Patient history / physician's examination
Need for remineralisation	Physician's examination
Previous radiation to same site	Patient history

4.4 Sample size calculation

The total number of patients included in this pilot study will be 6-10 patients. The main objective of the current study is to determine feasibility of combining EBRT and MR-HIFU within a 3 hour - 4 day time window. As this is a first-in-man study there is no data present to perform a formal sample size calculation. We will closely monitor unexpected side effects. Changes in the protocol will be made where appropriate.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

The intervention that will be studied is single or multiple fraction EBRT in combination with MR-HIFU within a 3 hour - 4 day time window. The combined treatment is aimed at rapid and persistent relief of metastatic bone pain. For more information on the Sonalleve MR-HIFU Bone metastases Therapy System we refer to the Investigator's brochure.

5.2 Use of co-intervention

5.2.1 EBRT

In a first step, patients will undergo EBRT according to the standard of care on a priority base within maximally 7 days after they visit the outpatient clinic of the Department of Radiation Oncology. Patients undergo a planning CT scan, as part of standard care, in treatment position.

EBRT is provided as single fraction radiotherapy or multiple fraction radiotherapy. According to the American Society for Radiation Oncology (2012) evidence-based guidelines for the management of bone metastases, a single fraction of 8 Gray (Gy) has an equivalent pain relief quality indicator compared to longer courses of radiotherapy, including 5 or 6 fractions of 4 Gy and 10 fractions of 3 Gy (Lutz et al, 2014). However, multiple fraction radiotherapy may have a larger contribution to local tumor control and is therefore often used in patients with a longer life expectancy. The above dose fractionation schemes are recommended as quality indicators of palliative radiotherapy by the American National Quality Measures for EBRT for bone metastases. Acute and late side effects of radiotherapy for bone metastases are generally similar with single fraction versus multi fraction regimens, with some studies showing decreased acute side effects in patients receiving single-fraction radiotherapy. Time to pain relief also appears similar, with an optimal time to measure pain relief of 2 months after the completion of palliative radiotherapy.

5.2.2 Pain medication

Subjects should receive pain medication if and as required by their symptoms, both before and after the combined EBRT and MR-HIFU treatment. The amount of pain medication used is part of the secondary endpoints of the study, and should be recorded at baseline before treatment and during the follow-up after treatment.

Pain medication used for treatment-related pain shall be noted in a separate Data Element in the CRF and in Concomitant Medication Forms. The fact that the medication was used for

treatment related pain is marked on the Concomitant Medication Forms, and the use of this medication will not be considered in the assessment of the pain response.

Patients can continue to use chemotherapy, targeted therapies (e.g. angiogenesis inhibitors) or bisphosphonates if they are already using them. The treatment type and the date the treatment was started/stopped will be recorded.

During the MR-HIFU treatment the patient will be under conscious sedation. This will enable adequate pain control and ensure a stable patient position during treatment. The sedatives used are at the preference of the anaesthesiologist/sedation specialist.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product

The Profound MR-HIFU Sonalleve System integrates a high intensity phased array focused ultrasound transducer with a magnetic resonance (MR) imaging system and electromechanical transducer positioning system to deliver spatially and temporally controlled ultrasound energy and thermal heat to tissues non-invasively. The MR system is used to provide images to plan the therapy, and to guide and monitor the thermal ablation with thermal imaging during the treatment.
The MR-HIFU system consists of:

- HIFU Therapy Console, where treatment planning, treatment control and post-treatment operations are performed;
- Generator Cabinet that houses the control electronics and the 256-channel ultrasound generator with individually programmable amplitude and phase;
- Patient Tabletop that houses the electromechanical transducer positioning system, the phased array 256-channel ultrasound transducer immersed in a liquid bath, and integrated radiofrequency surface and wrap-around coils for MR imaging.

Patient contact materials are described in the Investigator's Brochure. The users are required to be trained for safety, system/treatment workflow and quality assurance (QA) procedures.

The Profound Sonalleve MR-HIFU system used in Isala and UMC Utrecht is a CE-marked device for pain palliation of bone metastases. They were manufactured by Philips Medical Systems Oy, Vantaa, Finland. The systems will be traceable by their serial number and the Device History Records maintained by the manufacturer. One Sonalleve MR-HIFU device is available at each study location.
Traditionally, the Profound Sonalleve MR-HIFU device allows physicians to heat and ablate tissue under MR image guidance. Bone metastases cause bone destabilization (due to destruction) leading to stimulation of the mechanosensitive receptors in the periosteum (outer bone covering). HIFU treatment will aim at ablating the periosteum and thus reducing the localized bone pain. Ablation can be performed with volumetric techniques, which are designed to allow heating of larger zones or cells in one sonication. During a sonication, the transducer applies heat in a continuous manner to adjacent points within the treatment cell. In the bone HIFU treatment, the treatment cells

are placed within a target treatment area to sonicate the targeted bone. Full treatment is performed by stepping through several treatment cells with cooling times between each sonication. Each HIFU ablation is performed with user selected ultrasound power set to achieve sufficient tissue heating to ablate the periosteal nerves, typically achieved in the temperature range 55-70°C. Heating of the surrounding tissue can be monitored by MR temperature mapping. The duration of the exposures linked with the cell size are fixed by the system.
Three different ablation approaches will be used to ablate the periosteum, i.e., the near-field approach, the direct approach and the soft-tissue approach. The main factors determining choice of ablation approach are the presence of cortical destruction, tissue in the far field and safety concerns. In patients with an intact cortex at metastasis level ablation of the metastasis is not possible. In that case the periost is ablated by heating the cortex. In patients with a (partly) destructed cortex it is unclear which part of the periost is still intact. The tumor itself and the overlying periost will be ablated. All three approaches aim for pain reduction.
The Profound Sonalleve MR-HIFU system displays real-time temperature data overlaid on anatomical MR images, accumulated thermal dose information, and the ultrasound therapy parameters such as transmitted output power, frequency, and timing. Additionally, the operator can select specific thermal areas to obtain temperature readouts. The temperature display is updated every 3 seconds with new information.

For more details about the system, please refer to the Investigator's Brochure.

6.2 Summary of findings from non-clinical studies

See Investigator's brochure for the summary of findings from non-clinical MR-HIFU studies (pages 17 - 24).

6.3 Summary of findings from clinical studies

See chapter 1.3 and Investigator's brochure for the summary of findings from clinical MR-HIFU studies (pages 25 - 30).

6.4 Summary of known and potential risks and benefits

The Profound Sonalleve MRI-HIFU system is able to elevate temperatures at the bone interfaces, inside the bone and inside the bone metastasis with fast acquisition of thermal maps covering a large volume (including the skin), and with continuous heating of adjacent points, which reduces the amount of energy deposed. The device provides the user with

sufficient information about the location of temperature elevation, volume of the ablation, and the temperature and thermal dose behavior of the heated tissue. With the device the temperature of the bone surface can be elevated and a part of the soft tissue ablated to the extent that provides a significant improvement to the symptoms experienced by the patient.

The risks are HIFU physics and clinical practice dependent rather than specific HIFU device dependent. The highest risk is unintended heating of tissue causing burns.
The Sonalleve device is equipped with several safety measures to reduce the risks.
The system offers e.g. real-time feedback to inform the operator of various safety parameters. The user can monitor for:

- Undesired temperature elevations in off-focal and focal areas.
- A significant drop in transmitted power.
- A significant drop in temperature versus time curve at the focus

The ultrasound system will automatically shut down if:

- The transducer heats to critical temperatures.
- The measured output power is higher or substantially lower than the requested power.
- High levels of reflected/backscattered power are detected in the amplifiers.
- Any system control element fails to respond correctly to a control request.

The sonication can also be shut down manually by the Patient Emergency Stop Button, the operator controlled Safety Device, or the stop button in the User Interface. A sonication shut down is indicated both by the user interface and by an indicator light on the operator console. A manual reset or other action by the operator is required to continue use of the system after a safety shutdown or use of the stop button by a patient.

The duration of the treatment is dependent on the area which needs to be ablated. In general, it takes one to two hours to treat the average patient with one or more painful bone metastases. Since EBRT only takes up to 20 minutes and there is no need for sedation, patients could experience the MR-HIFU treatment as more cumbersome. Based on the results from previous studies we have valid reason to tell our patients that, even though MR-HIFU is more cumbersome, it is expected to lead to much faster pain relief and perhaps even longer lasting pain relief in the majority of patients.

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

The main outcome of this study is the feasibility of the combined procedure in terms of

- Patient tolerance: assessed with a short patient reported experience measure (PREM).
- Optimal logistics and standardization of the procedure (treatment planning, extra hospital visits).

7.1.2 Secondary study parameters/endpoints

The secondary study endpoints of this study are:

- The pain reducing capabilities of the combined treatment:
  Pain scores related to the target lesion treated as measured by patient's self-assessment on a Numerical Rating Scale (NRS) in the Brief Pain Inventory (BPI) questionnaire (Cleeland 1994) post inclusion and post treatment by phone around day 3, 7, 14, 21 and 28 after the MR-HIFU treatment. The BPI is a well-established, thoroughly validated tool for pain self-assessment, which can be considered a gold standard. Patients will rate the worst and average pain that they felt from the treated area over the last three days, and the pain they feel currently.
- Safety of the combined treatment.

7.1.3 Other study parameters

Several patient and tumor related parameters will be assessed such as age, gender, primary tumor, Karnofsky performance score (KPS), location of targeted volume, number of symptomatic bone metastases, date of diagnosis of primary tumor, date of diagnosis of first symptomatic bone metastasis, prior systemic treatments received, current systemic therapy, prior radiotherapy received (including dose/fractionation schedule and dates) and MR-HIFU treatment data such as treatment duration (time in scanner, sonication time) and amount of sonications.

7.2 Randomisation, blinding and treatment allocation

This study is a non-randomized pilot study. All eligible subjects will first receive EBRT followed by MR-HIFU. As such, there will be no blinding of the study participants and their doctors.

7.3 Study procedures

At least one day after the visit to the outpatient clinic the investigator or an authorized delegate will phone the patient to inform him/her about eligibility for the study. In case of eligibility the investigator or an authorized delegate will ask the patient for oral informed consent. If the patient is willing to participate in the study the investigator or an authorized delegate will make an appointment with the patient when the informed consent will be signed. This will preferably coincidence with the patient's next visit to the hospital but latest before the preoperative screening and the MR-HIFU treatment. When written informed consent is given, the investigator or an authorized delegate will collect standard baseline demographic factors, disease history, and previous therapy for bone metastasis from participating patients and response to prior radiotherapy when applicable, as well as help the patient to fill out the BPI and record total analgesic consumption during the previous 24 hours.

Patients will be formally enrolled in the study following written informed consent, after inclusion criteria are met and none of the exclusion criteria apply. Patient screening and enrollment will be recorded on the Screening / Enrollment log. Information on withdrawal will also be recorded in this log. The Screening / Enrollment log will be used for subject accountability.

Treatment procedure

Usually single fraction EBRT is performed on the day of the patient's first visit to the outpatient clinic of the Radiation Oncology Department. The MR-HIFU treatment will be subsequently applied within the shortest time interval possible but at the latest 4 days after EBRT.

Multiple fraction EBRT is usually started within one to maximally seven days after the patient's first visit to the outpatient clinic of the Radiation Oncology Department. When multiple fraction EBRT is indicated, the MR-HIFU treatment will be minimally 3 hours and maximally 4 days after the last multiple fraction session.

Planning of MR-HIFU treatment is more challenging than planning of EBRT. Most of the time treatment planning can be done on the basis of the available (CT) images.
During the MR-HIFU treatment procedure, an intravenous catheter will deliver MR contrast media and medications (such as sedation and analgesics if required) within the MR room. The need for a urinary bladder cathether is determined by the treating physician. The body temperature of the patients will be measured prior to the procedure. In the MR room the

patients will be asked to lie still on the HIFU patient table inside the MRI magnet. The operator will locate the target tissue and mark the volume to be treated using MRI images. The operator starts the treatment and monitors the progress of the treatment with MR thermal and dose maps according to the Sonalleve Instructions for Use to ensure safety. Due to the pain associated with the MR-HIFU procedure, anaesthesiologists/sedation specialists need to be involved to provide procedural sedation and analgesia. The pre-operative screening will be preferably take place on a day that the patients is already in the hospital.
Patients will receive sedation during treatment administered by an anaesthesiologist or sedation specialist. Medication given will be a combination of pain medication (e.g. rapifen) and anesthetics (e.g. propofol in combination with lidocaine for injection) at the preference of the anaesthesiologist/sedation specialist. The use of medication for treatment-related pain shall be recorded.

Following the MR-HIFU procedure, a set of MR images of the target region will be acquired with the use of a MR contrast agent. When the whole planned volume has been treated, the operator stores the full treatment history and technical data as available from the Profound Sonalleve MR-HIFU device. The patients are then conducted to the recovery room for medical supervision. Before discharge, follow-up instructions will be given to the patient.

We expect that by gaining more clinical experience with the combined treatment, we will be able to provide the combined treatment in a faster, patient-friendly way.

Follow-up
Follow up will be approximately 3, 7, 14, 21 and 28 days after the MR-HIFU treatment. The investigator or an authorized delegate will contact patients by phone to ask them whether any possible complications/adverse events have occurred. He/she will also interview the patient about their pain medication use and fill in the BPI questionnaire. At the third day after the MR-HIFU treatment the investigator will also inquire about the patient’s experience with the combined treatment.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.4.1 Specific criteria for withdrawal

Patients will exit the study during the follow-up period if they have been referred to alternative palliative treatments of the treated metastasis for medical reasons (such as radiopharmaceuticals, surgery, cryotherapy or radio-frequency ablation).

7.5 Replacement of individual subjects after withdrawal

If a subject withdraws from the study for any reason prior to MR-HIFU treatment, the subject will not count towards total enrollment and may be replaced with another subject.

7.6 Follow-up of subjects withdrawn from treatment

Follow-up of withdrawn subjects will take place by their treating physician, according to standard clinical practice.

7.7 Premature termination of the study

The study will be prematurely terminated if any of the following predetermined conditions are met; a serious adverse event related to the study procedures resulting in death, a serious adverse event related to the study procedures that is life threatening, a serious adverse event related to the study procedures that results in persistent or significant disability or an obviously higher incidence of (wound) complications than normally anticipated.
Additionally, the study may be terminated for any other perceived safety concern based on clinical judgment, including but not limited to a higher than anticipated rate for any component of the primary or secondary endpoints or unexpected serious adverse events.

8. SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 Definitions in safety reporting

According to EU Directive 90/385/EEC, 93/42/EEC (last amended Directive 2007/47/EC) and the 'Guidelines on medical devices: MEDDEV 2.7/3 revision 3', the following definitions are used in the safety reporting:

8.2.1 Investigational medical device

Medical device being assessed for safety or performance in a clinical investigation. The investigational medical device in the PRE-FURTHER study is the Sonalleve MR-HIFU system.

8.2.2 Device deficiency (DD)

Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

8.2.3 Adverse event (AE)

Adverse events are defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.
This definition includes events related to the investigational device or the comparator or the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical device.

8.2.4 Adverse device effect (ADE)

Adverse event related to the use of the investigational medical device.
This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. This also includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

8.2.5 Serious adverse event (SAE)

Adverse event that:

a) led to a death, injury or permanent impairment to a body structure or a body function.

b) led to a serious deterioration in health of the subject, that either resulted in:

- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- in-patient hospitalization or prolongation of existing hospitalization, or
- a medical or surgical intervention to prevent life threatening illness.

c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

A planned hospitalization for a pre-existing condition, or a procedure required by the study protocol, without a serious deterioration in health, is not considered a serious adverse event.

8.2.6 Serious adverse device effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

8.2.7 Unanticipated serious adverse device effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

8.3 Safety reporting

8.3.1 Recording of adverse events

All adverse (device) events reported spontaneously by the patient or observed by the investigator or his staff will be recorded up to 1 month after the MR-HIFU treatment.

All complications and adverse events will be documented in detail according to the latest version of the Common Toxicity Criteria for Adverse Events (CTCAE). The physicians and investigators will evaluate reported (S)AEs for determination of seriousness and causal relationship with the fact that EBRT was combined with MR-HIFU. In those instances where it cannot be determined if the event is linked to the combined treatment, this will also be noted on the patient file event report. The following aspects will be recorded for each event:

- Grade according of the AE according to the CTCAE;
- Date of onset;
- Date of recovery;
- If possible, attribution factor;
- Intervention (action taken);
- If possible, the relationship of the AE to the combined treatment.

8.3.2 Reportable events

The following events are considered reportable events in accordance with Annex 7, section 2.3.5 and Annex X, section 2.3.5 of the above mentioned Directives (18):

- any SAE;
- any device deficiency that might have led to a SAE if:
  a) suitable action had not been taken or
  b) intervention had not been made or
  c) circumstances had been less fortunate.
- new findings/updates in relation to already reported events.

8.3.3 Report by whom

Reportable events will be reported by the sponsor (authorized representative or another person or entity).

8.3.4 Report to whom

Reportable events will be reported by the sponsor to the accredited METC that approved the study protocol.

8.3.5 Reporting timelines

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events. The sponsor will report the SAEs to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

8.3.6 Reporting standards

The METC will be notified through the web portal Toetsingonline.

8.4 Causality assessment

The relationship between the use of the medical device (including the medical - surgical procedure) and the occurrence of each adverse event will be assessed and categorized. Each SAE will be classified according to five different levels of causality. The following definitions to assess the relationship of the serious adverse event to the investigational medical device or procedures will be used:

1) Not related: relationship to the device or procedures can be excluded when:
   - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;

- the event has no temporal relationship with the use of the investigational device or the procedures;
- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
- the event involves a body-site or an organ not expected to be affected by the device or procedure;
- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment or other risk factors);
- harms to the subject are not clearly due to use error.

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

2) Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
3) Possible: the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
4) Probable: the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
5) Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:
    - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
    - the event has a temporal relationship with investigational device use/application or procedures;
    - the event involves a body-site or organ that the investigational device or procedures are applied to, or have an effect on;
    - the serious event follows a known response pattern to the medical device (if the response pattern is previously known);

- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use.

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

8.5 Follow-up of adverse events

All recorded AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

8.6 Data Safety Monitoring Board (DSMB) / Safety Committee

The investigators will perform continuous safety monitoring and will evaluate reported adverse events for agreement in determination of seriousness and causal relationship with the treatment (either procedure and/or device). In those instances where it cannot be determined if the event was linked to the treatment, this will also be noted on the patient file event report. If at any point during the study, the investigators conclude that continuation of the study will endanger the safety of the patients, the study shall be terminated.
Both EBRT and MR-HIFU have been proven to be safe when applied alone. A time window of minimally 3 hours between EBRT and MR-HIFU is taken into account to exclude possible detrimental synergistic effects between the two treatments. Moreover, the mechanism of action of MR-HIFU and EBRT differs. Therefore, we do not expect any SAE when the two treatments are combined.
However, representatives of the external advisory board of the FURTHER will act as a safety committee and evaluate the safety of the combined treatment after the first three patients. This committee consists of:

- Prof. Maurice van den Bosch, chairman OLVG Amsterdam and a MR-HIFU expert;
- Prof. Yvette van der Linden, radiation oncologist and head of Expertcentre of Palliative Care at Leiden University Medical Centre, Leiden;
- Dr. Jorrit-Jan Verlaan, Spine surgeon at Dept of Othopedic Surgery, UMC Utrecht.

9. STATISTICAL ANALYSIS

In order to reach the objectives, a two stage approach will be used following the IDEAL recommendations: IDEAL stage 1, i.e. innovation/proof of concept of EBRT followed by MR-HIFU within a 3 hours - 4 days time window, followed by IDEAL stage 2a, i.e. development of the new treatment strategy.

In the first stage, we will include three patients in whom the combined treatment will be applied and tested for the first time. In this stage, the main objective is to demonstrate the feasibility of the combined treatment strategy and describe it in detail. The report will contain clear anonymous details of the patient, exact description of the primary tumor, site of metastases, extent of the index lesion, rationale for the use of this procedure in these particular patients and a very detailed description of technical and clinical aspects of the procedures. For all patients, technical success, detailed pain scores (baseline and follow up), neurological symptoms (baseline and follow up), complications, toxicity, use of analgesics, and other relevant outcomes will be reported on an individual level. The patients reported experience will also be used to make adjustments to the logistics and treatment protocol. After stage 1, an interval of at least two weeks will be implemented before treating the next patient to allow identification of early major problems.

Progression to stage 2a (Development) will be justified after we have demonstrated feasibility of the combined procedure, without major technical problems or safety issues. In stage 2a, the main focus is safety and technical feasibility of the combined procedure, which will be measured in 3-7 consecutive patients meeting the inclusion criteria and none of the exclusion criteria.

For all patients, we will report toxicity and pain response. The patient-reported worst pain will be used. This is consistent with the latest version of the International Consensus for clinical trial endpoints on bone pain palliation with radiotherapy.

Pain responders are defined as patients with:

1. Pain score (numerical rating scale; NRS) at the treated site of zero without analgesic increase (complete response);
2. Reduction of pain score of at least 2 points at the treated site without analgesic increase (partial response);
3. Analgesic reduction of 25% or more without increase in pain (partial response).

In addition, pain medication pre- and post-procedure as reported by the patient and in medication records are documented. Opioid analgesics are expressed as the oral equivalent daily morphine use (OMED).

Results will be presented as descriptive statistics and no statistical tests will be performed. Early terminations and withdrawals, will also be reported.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (2013, www.wma.net) and in accordance with:

- All national and local laws of the pertinent regulatory bodies, including the Medical Research Involving Human Subjects Act (WMO) in the Netherlands,
- Internal Standard Operating Procedures,
  and
- This protocol.

10.2 Recruitment and consent

In the UMC Utrecht subjects will be recruited from the PRESENT cohort. In Isala patients will be recruited from patients that visit the outpatient clinic of the Department of Radiation Oncology.
The radiation oncologist will perform a first eligibility check on the basis of clinical parameters and images (PET-CT) which are usually already available when patients with painful bone metastases are referred to the Department of Radiation Oncology. If information on medical history, indication for treatment and capability to communicate with the physician indicate that the patient is likely to satisfy the inclusion and exclusion criteria (section 4.2 and 4.3), the radiation oncologist will inform the patient about the PRE-FURTHER study. Patients interested in participating in the study will receive a participant information letter including the informed consent form explaining the purpose and the details of the study, particularly the potential risks and burdens associated with the combined treatment. In case the patient is likely to give informed consent, eligibility of the patient is discussed in detail in a Multidisciplinary Consultation Meeting with the radiation oncologist and radiologist.
The investigator or an authorized delegate will conduct the informed consent process. He/she will contact the patient by phone at least one day after the initial hospital visit and in case of eligibility he/she will provide more details on the study if needed and will ask the patient for his/her oral consent to participate in the study.
The time window of minimally one day for an oral informed consent has been chosen as these procedures are almost always planned within one week after first presentation in the outpatient clinic. The one-day time window allows us to plan the combined treatment as soon as possible. In our opinion, with one day patients have a reasonable amount of time to consider this experimental combination without the risk on treatment delay.

The patients are requested to sign the informed consent form before the preoperative screening, the MR-HIFU treatment and before any other data are collected. Thus, patients also have the chance to revoke consent at this stage. Signature to the consent form should take place in the presence of the principal investigator or an authorized delegate.

10.3 Benefits and risks assessment, group relatedness

The PRE-FURTHER study is designed to assess the feasibility of the combined EBRT MR-HIFU treatment of painful bone metastases.

EBRT is the current standard of care. The most common adverse event of EBRT is a temporal increase of the pain after the treatment also known as pain flare (Mavrogenis, 2016). 'Pain flare' is observed in 2 to 44 percent of patients and can have an important impact on quality of life.
Pathologic fractures of weight-bearing bones occur in 10-20% of patients with bone metastases, with femoral metastases accounting for the largest part of these fractures (Body, 1992; Eastley, 2012) The risk of pathological fractures after radiotherapy has been well documented. In the most recent systematic review of palliative radiotherapy trials for bone metastases, comparing single versus multiple faction regimens, one of the secondary outcomes was pathological fracture rate after radiotherapy (Chow, 2007). Several studies reported data for pathological fracture rates (Bone Pain Trial Working Party, 1999; Cole, 1989; Hartsell, 2005; Kaasa, 2006, Nielsen, 1998; Price, 1986; Roos, 2005). The pooled pathological fracture rates ranged from 2.8% to 3.2% with no significant differences for treatment schedules. Most of these studies excluded patients with (impending) pathological fractures, which is also the case in this pilot study.

However, EBRT is only effective in part of the patients and it may take several weeks before pain reduction is achieved. The additional MR-HIFU treatment is expected to lead to a more rapid pain relief and may even prevent or reduce the pain flare. Besides occasional minor thermal skin burns, no serious adverse effects are expected as a result of the additional MR-HIFU treatment. A detailed summary of the results of the complete risk analysis performed by the Supplier is given in the Investigator's Brochure (chapter 10 and appendix 1).
The Investigator's Brochure summarizes the outcomes and reported adverse events of previous key MR-HIFU studies. The benefits and positive outcomes reported in these previous studies have been weighed against the identified risks. This weighing has led to CE labeling of the device in Europe.

In addition to those procedure- or device-related adverse events the following adverse events are anticipated in this patient population, but expected to be unrelated to the combined treatment procedure:

- Death due to progression of the underlying cancer or cancer-related complications;
- Hospitalization for cancer treatment or due to cancer-related complications;
- Fracture at site(s) of bone metastases unrelated to treatment requiring hospitalization and/or surgical intervention;
- Increase of cancer-related pain unrelated to treatment;
- Progression of the underlying disease.

For the combined treatment, patients will in most cases need to pay an extra visit to the hospital to undergo a rather lengthy additional intervention (MR-HIFU treatment), under conscious sedation.

There is no data available about the possible complications and risk of the combination of EBRT and MR-HIFU within 4 days. However, both treatments have proven to be safe when applied alone, their mechanism of action differs and the minimal interval of 3 hours between the two treatments has been chosen in such a way that a detrimental interaction between the two treatments is not to be expected.

10.4 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.
The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10.5 Incentives

Reasonable travel expenses and parking costs arising from an additional or prolonged hospital visit because of the MR-HIFU treatment will be reimbursed to enrolled subjects. Besides travel expenses and parking costs, there will be no extra compensation for study participants.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

A clinical database will be set-up using OpenClinica. As part of the data entry workflow, the OpenClinica software will assign a “study ID”. The reference between the Study ID and the hospital patient number is listed in the Subject Identification Log per site. The Subject Identification Log will only be accessible by authorized personnel. The study ID will also be used to tag the inbound technical patient data. Data will be pseudonymized according to the applicable regulations and rules. Each eCRF will be completed on site by the investigator or an authorized staff member. MRI and HIFU data will be stored on location.

All individual patient data records will be collected on confidential basis and according to the applicable national data protection, privacy, and secrecy laws (General Data Protection Regulation (GDPR) (In Dutch: Algemene Verordening Gegevensbescherming (AVG)). The investigators, auditors, monitors and employees of the ‘Inspectie Gezondheidszorg en Jeugd’ may have access to the medical and research data of the patients. It is the investigator’s responsibility to complete and approve all treatment related data.

Anonymized data collected from subjects treated under this protocol may be used in submissions to regulatory agencies, and for publications. Summaries of data and information from each patient data form may be used for reporting of the investigation's findings during the study.

Records of the study must be maintained at least as long as local document retention regulations require. In the event that the investigator withdraws or relocates, study records will be transferred to identified site personnel or to the sponsor. This transfer is subject to the sponsor’s approval.

Procedures for data management are detailed in a separate Data Management Plan.

11.2 Monitoring and Quality Assurance

Each site will be monitored by its own institutional monitor. The clinical monitor will be responsible for verifying adherence to the protocol, reviewing subject records and source data, maintaining records of all actions taken to correct protocol deficiencies during the investigation, and assuring that the data needed to complete the study is complete and accurate. Monitoring will be documented to the study files by monitor reports.
The monitor plan is attached as an addendum.

11.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

11.4 Annual progress report

The investigator will submit a summary of the progress of the pilot study to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events, other problems, and amendments.

11.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last follow-up moment 4 weeks after MR-HIFU.

The investigator will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.6 Public disclosure and publication policy

Data collected from subjects treated under this protocol will be used for conferences and publication according to the CCMO statement on publication policy (www.ccmo.nl). This statement contains the basic principles of the CCMO's position on the disclosure/publication of research results obtained from studies involving human subjects. It is the opinion of the CCMO that the results of scientific research involving human subjects must be disclosed unreservedly.

12. STRUCTURED RISK ANALYSIS

12.1 Potential issues of concern

In the PRE-FURTHER study patients with painful bone metastases will receive both (single or multiple fraction) EBRT and MR-HIFU within a rather short interval of 3 hours - 4 days. Since EBRT is the current standard of care for these patients this structured risk analysis focuses on any risks caused by the MR-HIFU treatment and by the combination of the two treatments.

a. Level of knowledge about mechanism of action

The putative main mechanism of pain relief by EBRT involves the inactivation of osteoclasts to change the microenvironment of bone resorption followed by sterilization of cancer cells to reduce tumor-induced compression (Hartsell et al 2007). The direct mechanism of action of EBRT is damage to DNA of tissues, including both single strand and double strand DNA breaks, originating mostly from different oxygen radicals. The mechanism of action of MR-HIFU is coagulative necrosis and apoptosis of tissue due to heat leading to rapid and durable pain relief from immediate periosteal nerve ablation and thermal necrosis of the targeted bone tumor followed by remineralization of the trabecular bone and bone healing a few months later. Since the mechanism of action of EBRT and MR-HIFU differ, MR-HIFU provides an alternative means to overcome radioresistance and is recommended for patients with bone metastasis for whom RT is considered to have failed (Hurwitz, 2014).

Since the mechanism of action of EBRT and MR-HIFU differ, the two methods may be synergistic in first-line, or when applied nearly simultaneously. Heat-induced coagulative ablation is the main action of MR-HIFU, hence its pain palliation effect is expected to be rapid. However, heat distribution is often spatially heterogeneous in bone metastases because of the fact that absorption of ultrasound energy depends on many factors including the degree of bone lysis or formation, and incident ultrasound angle. Therefore, it might be that the, more long-term, systemic responses of EBRT of the tumor and its microenvironment, reduction of tumor-induced compression and inactivation of osteoclasts, can be augmented by local ablation of periosteal nerve ablation by MR-HIFU.

Some other effects should be mentioned.

- Hyperthermia (temperatures 42-45°C) beyond the ablated area results in complementary radiosensitization (reduction of hypoxia; inhibition of DNA repair mechanisms) (van der Zee, 2000, Dababou 2018) thereby increasing the risk of damage to surrounding tissue.

- Coagulative ablation by MR-HIFU (temperatures around 60°C) also leads to reduction/elimination of local perfusion leading to hypoxia of the treated area. This may render subsequent EBRT less efficient (less production of oxygen radicals).

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

To date, MR-HIFU treatments of uterine fibroids, prostate cancer, breast cancer, bone metastases, brain tumors and pancreas-, liver- and kidney tumors are either a clinical application or in development. Currently HIFU is mostly used for the ablation of prostate cancer and uterine fibroids. Many HIFU treatments are performed under MR-guidance. MRI provides accurate guidance during HIFU treatment, as it offers good soft tissue visualization and enables treatment planning. Moreover MRI provides temperature maps for excellent therapy monitoring and evaluation of treatment results. For these reasons, MRI is considered the best and safest method for HIFU guidance.

Results of previous studies are presented in chapter 1.3 and the Investigator's Brochure.

The combined EBRT MR-HIFU treatment is applied for the first time within the relatively short interval of 3 hours - 4 days in human beings.

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

Animal studies were focused on:

- The Treatment Protocol for sonication on bone
- Safety Issues including skin, near field heating, cooling times, targeting accuracy
- Cavitation Detection: passive receive technique
- Full integrated HIFU system performance in a representative in vivo model

These studies confirmed the potential benefit but their relevance to the clinical situation is limited because of the following reasons:

- The origin of the primary tumor in the PRE-FURTHER and FURTHER projects varies (breast, prostate, etcetera), and hence also the genotype and phenotype of the bone metastasis.
- The anatomical location of the bone metastasis varies necessitating an individual planning and adaptation of both EBRT and MR-HIFU.

- The degree of bone lysis/bone growth differs affecting the ultrasound absorption necessitating specific MR-HIFU planning.
- EBRT efficacy varies with relation to the degree of hypoxia and perfusion.
- MR-HIFU efficacy differs with respect to ultrasound absorption, incidence angle of the ultrasound beam, and degree of bone lysis/bone growth.

In addition, pain scores are difficult to obtain in animal models. Also, the starting pain level in drug refractory patients in this trial is at such an elevated level that animal models are ethically questionable.

See for more detail page 21-24 of the Sonalleve Investigator's brochure.

To the best of our knowledge there are no data available from animal studies that combined EBRT and MR-HIFU.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

The mechanism of MR-HIFU thermal ablation does not depend on cell types, receptors or other biological characteristics, but merely on the targeted locations of the HIFU beam focal point. The targeting precision is in the range of millimeters. MR imaging is used for target definition and allows the physician to depict organs at risk of thermal damage (in the HIFU beam, i.e. in front of, or behind the focal point).

e. Analysis of potential effect

Thermal damage can be quantified with the thermal dose concept, which has been validated extensively ex vivo, in vivo and in the clinical setting (Chung, 1999; Dewhirst, 2003; McDannold, 2000 & 2006; Yarmolenko, 2011). A thermal dose of > 240 cumulative equivalent minutes (EM) at 43°C is generally considered lethal. In addition, tissue that is heated (for any duration) to > 60°C can be considered coagulated. This is regardless of whether malignant or (accidently) healthy tissue is targeted. During the MR-HIFU procedure, the thermal dose and temperature are visualized on the HIFU console in real-time. This allows the physician to continuously monitor the deposition of thermal energy, and to abort the sonication when a temperature elevation or thermal dose deposition is observed outside the targeted location. Thus, adjacent healthy organs can be monitored continuously for damage, and the physician can act immediately to prevent damaging these organs.

f. Pharmacokinetic considerations

Not applicable for this study.

g. Interaction with other products

Not applicable for this study.

h. Study population

The research subjects are male and female adults (age ≥ 18 years) with painful bone metastases. This is a group of (often elderly) patients, with a limited life expectancy. Since we will only include patients with a life expectancy longer than 3 months, the condition of these patients is expected to be good enough to undergo an additional treatment next to the standard EBRT treatment. Eligibility for the study will be assessed by the treating radiation oncologist and radiologist, the anesthesiologist and the investigator.

i. Predictability of effect

MR-HIFU tissue ablation has been demonstrated to have a high predictability of effect. Protein denaturation, causing cell death, occurs at temperatures ≥ 60°C, or when a cumulative thermal dose is reached of ≥ 240 EM. This mechanism has been demonstrated both ex vivo and in vivo in multiple studies, and has been validated in clinical studies on uterine fibroid ablation (Chung, 1999; Dewhirst, 2003; McDannold, 2000 & 2006; Yarmolenko, 2011). In addition, each treatment is preceded by a test sonication. This is a low-powered sonication that only causes a small increase in temperature. It is used to validate (and, if required, adjust) the HIFU beam targeting for optimal accuracy of the therapeutic shots.

j. Can effects be managed?

During MR-HIFU sonications, temperature development in the targeted and surrounding tissue is closely monitored with the proton resonance frequency shift (PRFS) method. The treating physician is able to follow the deposition of thermal energy in real-time. If needed, sonications are aborted in order to, for example, prevent lethal heating of surrounding healthy tissue. Abortion of the sonications is automatically done by the system or manually by the treating physician. Additionally an anesthesiologist will monitor the patient during treatments. He or she may abort or pause the treatment in case changes in the patient's vital signs indicate to do so.

After the MR-HIFU procedure, the patient will be allowed to recover from the procedural sedation and analgesia (PSA), after which he/she will be transferred to the ward. Local standard procedures, if applicable, will be followed. In principle, patients will stay in the

hospital at the nursing unit for a few hours after the procedure and will be discharged on the treatment day, unless clinical indications dictate otherwise. This allows (per)acute complications to become overt. In that case, adequate medical and/or surgical support is left at the discretion of the attending physician.

12.2 Synthesis

MR-HIFU ablation is a powerful technique that can rapidly increase the temperature in tissues to lethal temperatures. This makes it an useful tool for the treatment of a whole array of diseases. However, MR-HIFU can also potentially induce thermal damage to vital tissues and organs. For this reason, clinical studies focus on real-time treatment monitoring and optimizing the accuracy and precision of the ablation process. Previous MR-HIFU studies for painful bone metastases demonstrated that MR-HIFU is sufficiently safe and effective. The MR-HIFU procedures are performed under MRI guidance which means that the treated tissue is visualized during the entire treatment and that the temperature of the targeted region is continuously depicted in temperature maps.
In the presented literature, minor adverse events occurred in some patients and mainly consisted of mild skin burns and mild pain. No severe adverse events were reported. All minor adverse events subsided within a maximum of 10 days and had no sequelae.

The use of PSA for the MR-HIFU treatment has two major advantages over using local or no anesthesia. First, patients are able to lie still during the entire treatment, which decreases the risk of side effects and impaired treatment efficacy due to patient motion. Second, subjects experience less discomfort and pain during MR-HIFU treatment. The risks of the sedation used are very low.

We cannot fully exclude unexpected complications and (serious) adverse events due to the combination of EBRT and MR-HIFU. However, the minimal interval of 3 hours between the EBRT and MR-HIFU treatment was chosen in such a way that a detrimental interaction between the two treatments is not to be expected. Moreover, their mechanism of action differs and both treatments have proven to be safe when applied alone. Therefore, we do not expect any SAE.
Overall, it is deemed that the potential benefits of this study, both to the individual patient, as manifested by potential rapid and long lasting pain relief at the treated lesion, and in the end to the wider patient community, as manifested by potential wider availability of an additional non-invasive option for pain palliation in bone metastases, outweighs the potential risks.

13. REFERENCES

Body JJ. Metastatic bone disease: clinical and therapeutic aspects. Bone, 1992; 13 S1: S57-62.

Bone Pain Trial Working Party. 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. Radiother Oncol 1999;52(2):111-21.

Catane R, Beck A, Inbar Y, Rabin T, Shabshin N, Hengst S, et al. MR-guided focused ultrasound surgery (MRgFUS) for the palliation of pain in patients with bone metastases – Preliminary clinical experience. (2007)Ann Oncol (18) pp. 163–7

Chow E, Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol 2007 April 10;25(11):1423-36.

Chow E, van der Linden YM, Roos D, Hartsell WF, Hoskin P, Wu JS, Brundage MD, Nabid A, Tissing-Tan CJ, Oei B, Babington S, Demas WF, Wilson CF, Meyer RM, Chen BE, Wong RK. Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial. (2014) Lancet Oncol. 2014 15 (2) pp. 164-71.

Chung AH, Jolesz FA, Hynynen K. Thermal dosimetry of a focused ultrasound beam in vivo by magnetic resonance imaging. Medical physics. 1999;26(9):2017-26.

Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore. 1994 Mar;23(2):129-38.

Cole DJ. A randomized trial of a single treatment versus conventional fractionation in the palliative radiotherapy of painful bone metastases. Clin Oncol (R Coll Radiol) 1989;1(2):59-62.

Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res. 2006;12(20 Pt 2):6243s-9s.

Dababou S, Marrocchio C, Scipione R, Erasmus HP, Ghanouni P, Anzidei M, et al. High-Intensity Focused Ultrasound for Pain Management in Patients with Cancer. Radiographics. 2018:170129.

Dewhirst MW, Viglianti BL, Lora-Michiels M, Hanson M, Hoopes PJ. Basic principles of thermal dosimetry and thermal thresholds for tissue damage from hyperthermia. International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group. 2003;19(3):267-94.

Eastley N, Newey M, Ashford RU. Skeletal metastases – The role of the orthopaedic and spinal surgeon. Surg Oncol. 2012 21(3):216-22.

Gianfelice D, Gupta C, Kucharczyk W, Bret P, Havill D, Clemons M. Palliative treatment of painful bone metastases with MR imaging-guided focused ultrasound. Radiology 2008;249:355–63

Harding D, Giles SL, Brown MRD, Ter Haar GR, van den Bosch M, Bartels LW, Kim YS, Deppe M, deSouza NM. Evaluation of Quality of Life Outcomes Following Palliative Treatment of Bone Metastases with Magnetic Resonance-guided High Intensity Focused Ultrasound: An International Multicentre Study. (2018) Clin Oncol (R Coll Radiol). 30 (4), pp. 233-242.

Hartsell WF, Scott CB, Bruner DW, Scarantino CW, Ivker RA, Roach M, III et al. Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. J Natl Cancer Inst 2005;97(11):798-804.

Hartsell WF, Yajnik S. Chapter 92: palliation of bone metastases. In: Halperin EC, Perez CA, Brady LW, editors. Perez and Brady's principles and practice of radiation oncology. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2007. p 1986-99.

Huisman M, van den Bosch MA, Wijlemans JW, van Vulpen M, van der Linden YM, Verkooijen HM. Effectiveness of reirradiation for painful bone metastases: a systematic review and metaanalysis. Int J Radiat Oncol Biol Phys. 2012 Sep 1;84(1):8-14.

Huisman, M., Lam, M.K., Bartels, L.W., Nijenhuis, R.J., Moonen, C.T., Knuttel, F.M., Verkooijen, H.M., van Vulpen, M., van den Bosch, M.A. Feasibility of volumetric MRI-guided high intensity focused ultrasound (MR-HIFU) for painful bone metastases. (2014) Journal of Therapeutic Ultrasound, 2 (1), art. no. 16 .

Huisman, M., Ter Haar, G., Napoli, A., Hananel, A., Ghanouni, P., Lövey, G., Nijenhuis, R.J., Van Den Bosch, M.A.A.J., Rieke, V., Majumdar, S., Marchetti, L., Pfeffer, R.M., Hurwitz, M.D. International consensus on use of focused ultrasound for painful bone metastases: Current status and future directions. (2015) International Journal of Hyperthermia, 31 (3), pp. 251-259.

Hurwitz, M.D., Ghanouni, P., Kanaev, S.V., Iozeffi, D., Gianfelice, D., Fennessy, F.M., Kuten, A., Meyer, J.E., Leblang, S.D., Roberts, A., Choi, J., Larner, J.M., Napoli, A., Turkevich, V.G., Inbar, Y., Tempany, C.M.C., Pfeffer, R.M. Magnetic resonance-guided focused ultrasound for patients with painful bone metastases: Phase III trial results. (2014) Journal of the National Cancer Institute, 106 (5), art. no. dju082.

Hurwitz MD, Kaur P, Nagaraja GM, Bausero MA, Manola J, Asea A. Radiation therapy induces circulating serum Hsp72 in patients with prostate cancer. Radiother Oncol 2010;95:350–58.

Jolesz, F., McDannold, N., Clement, G., Kinoshita, M., Fennessy, F., Tempany, C. MRI-guided FUS and its clinical applications. (2008) Image-Guided Interventions: Technology and Applications, pp. 275-307.

Kaasa S, Brenne E, Lund JA, Fayers P, Falkmer U, Holmberg M et al. Prospective randomised multicenter trial on single fraction radiotherapy (8 Gy x 1) versus multiple fractions (3 Gy x 10) in the treatment of painful bone metastases. Radiother Oncol 2006;79(3):278-84.

McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, Nicholl J; Balliol Collaboration, Aronson JK, Barkun JS, Blazeby JM, Boutron IC, Campbell WB, Clavien PA, Cook JA, Ergina PL, Feldman LS, Flum DR, Maddern GJ, Nicholl J, Reeves BC, Seiler CM, Strasberg SM, Meakins JL, Ashby D, Black N, Bunker J, Burton M, Campbell M, Chalkidou K, Chalmers I, de Leval M, Deeks J, Ergina PL, Grant A, Gray M, Greenhalgh R, Jenicek M, Kehoe S, Lilford R, Littlejohns P, Loke Y, Madhock R, McPherson K, Meakins J, Rothwell P, Summerskill B, Taggart D, Tekkis P, Thompson M, Treasure T, Trohler U, Vandenbroucke J. No surgical innovation without evaluation: the IDEAL recommendations. Lancet. 2009 Sep 26;374(9695):1105-12.

Jones, J.A., Lutz, S.T., Chow, E., Johnstone, P.A. Palliative radiotherapy at the end of life: A critical review. (2014) CA Cancer Journal for Clinicians, 64 (5), pp. 295-310.

Lee, H.-L., Kuo, C.-C., Tsai, J.-T., Chen, C.-Y., Wu, M.-H., Chiou, J.-F. Magnetic resonance guided focused ultrasound versus conventional radiation therapy for painful bone metastasis: A matched-pair study.(2017) Journal of Bone and Joint Surgery - American Volume, 99 (18), pp. 1572-1578.

Lipton, A. Management of bone metastases in breast cancer (2005) Current Treatment Options in Oncology, 6 (2), pp. 161-171.

Lutz S, Berk L, Chang E, et al. Palliative radiotherapy for bone metastases: An ASTRO evidence-based guideline. Int J RadiatOncolBiolPhys 2011; 79:965-976.

Mantyh, P.W. Bone cancer pain: From mechanism to therapy (2014) Current Opinion in Supportive and Palliative Care, 8 (2), pp. 83-90

Mavrogenis AF, Angelini A, Vottis C, Pala E, Calabro T, Papagelopoulos PJ, et al. Modern Palliative Treatments for Metastatic Bone Disease: Awareness of Advantages, Disadvantages, and Guidance. Clin J Pain. 2016;32(4):337-50.

McDannold NJ, King RL, Jolesz FA, Hynynen KH. Usefulness of MR imaging-derived thermometry and dosimetry in determining the threshold for tissue damage induced by thermal surgery in rabbits. Radiology. 2000;216(2):517-23.

McDannold N, Tempany CM, Fennessy FM, So MJ, Rybicki FJ, Stewart EA, et al. Uterine leiomyomas: MR imaging-based thermometry and thermal dosimetry during focused ultrasound thermal ablation. Radiology. 2006;240(1):263-72.

Milani V, Noessner E, Ghose S, Kuppner M, Ahrens B, Scharner A, et al. Heat shock protein 70: Role in antigen presentation and immune stimulation. Int J Hyperthermia 2002;18: 563–75.

Napoli, A., Anzidei, M., Marincola, B.C., Brachetti, G., Ciolina, F., Cartocci, G., Marsecano, C., Zaccagna, F., Marchetti, L., Cortesi, E., Catalano, C. Primary pain palliation and local tumor control in bone metastases treated with magnetic resonance-guided focused ultrasound.(2013) Investigative Radiology, 48 (6), pp. 351-358.

Nielsen OS, Bentzen SM, Sandberg E, Gadeberg CC, Timothy AR. Randomized trial of single dose versus fractionated palliative radiotherapy of bone metastases. Radiother Oncol 1998;47(3):233-40.

Paice, J.A., Ferrell, B. The management of cancer pain (2011) CA Cancer Journal for Clinicians, 61 (3), pp. 157-182.

Portenoy, R.K. Treatment of cancer pain (2011). The Lancet, 377 (9784), pp. 2236-2247.

Price P, Hoskin PJ, Easton D, Austin D, Palmer SG, Yarnold JR. Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases. Radiother Oncol 1986;6(4):247-55.

Ripamonti, C., Fulfaro, F. Malignant bone pain: pathophysiology and treatments. (2000) Current review of pain, 4 (3), pp. 187-196.

Ripamonti C., Fulfaro, F. Pathogenesis and pharmacological treatment of bone pain in skeletal metastases.(2001) Quarterly Journal of Nuclear Medicine, 45 (1), pp. 65-77.

Roos DE, Turner SL, O'Brien PC, Smith JG, Spry NA, Burmeister BH et al. Randomized trial of 8 Gy in 1 versus 20 Gy in 5 fractions of radiotherapy for neuropathic pain due to bone metastases (Trans-Tasman Radiation Oncology Group, TROG 96.05). Radiother Oncol 2005;75(1):54-63.
Mantyh, P.W. Bone cancer pain: From mechanism to therapy (2014) Current Opinion in Supportive and Palliative Care, 8 (2), pp. 83-90.

Suva LJ, Washam C, Nicholas RW, Griffin RJ. Bone metastasis: mechanisms and therapeutic opportunities. Nat Rev Endocrinol. 2011;7(4):208-18

Udono H, Srivastava PK. Heat shock protein 70-associated peptides elicit specific cancer immunity. J Exp Med 1993;178: 1391–6.

van der Linden YM, Lok JJ, Steenland E, Martijn H, van Houwelingen H, Marijnen CA, Leer JW; Dutch Bone Metastasis Study Group. Single fraction radiotherapy is efficacious: a further analysis of the Dutch Bone Metastasis Study controlling for the influence of retreatment. Int J Radiat Oncol Biol Phys. 2004 59(2):528-37.

van der Velden J. Towards Personalised Treatment for Patients with Bone Metastases. Thesis. Utrecht University 2018. Utrecht the Netherlands ISBN 978-94-6361-068-1

van der Zee J, Gonzalez Gonzalez D, van Rhoon GC, van Dijk JD, van Putten WL, Hart AA. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: A prospective, randomised, multicenter trial. Dutch Deep Hyperthermia Group. Lancet 2000; 355(9210):1119–25.

Verkooijen HM, Kerkmeijer LGW, Fuller CD, Huddart R, Faivre-Finn C, Verheij M, Mook S, Sahgal A, Hall E, Schultz C. R-IDEAL: A Framework for Systematic Clinical Evaluation of Technical Innovations in Radiation Oncology. Front Oncol. 2017 Apr 3;7:59.

Wattenberg MM, Fahim A, Ahmed MM, Hodge JW. Unlocking the combination: Potentiation of radiation-induced antitumor responses with immunotherapy. Radiat Res 2014;182:126–38.

Westhoff PG, de Graeff A, Monninkhof EM, Pomp J, van Vulpen M, Leer JW, Marijnen CA, van der Linden YM; Dutch Bone Metastasis Study Group. Quality of Life in Relation to Pain Response to Radiation Therapy for Painful Bone Metastases.(2015) Int J Radiat Oncol Biol Phys. 93 (3) pp. 694-701.

Yarmolenko PS, Moon EJ, Landon C, Manzoor A, Hochman DW, Viglianti BL, et al. Thresholds for thermal damage to normal tissues: an update. International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group. 2011;27(4):320-43.