HBB-SABR: A feasibility study investigating the effect of hyoscine butylbromide injections on cone beam CT quality when delivering abdomino-pelvic stereotactic ablative radiotherapy (SABR)

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# List of abbreviations

**AE: adverse event**

**AR: adverse reaction**

**BPM: beats per minute**

**CBCT: cone beam computed tomography**

**CT: computed tomography**

**CTCAE: Common Toxicity Criteria for Adverse Events**

**Gy: Gray**

**HBB: hyoscine butylbromide**

**IMRT: intensity modulated radiotherapy**

**MR: magnetic resonance**

**MRI: magnetic resonance imaging**

**PET-CT: positron emission tomography-computed tomography**

**PTV: planning target volume**

**SABR: stereotactic ablative radiotherapy**

**SAE: serious adverse event**

**SAR: serious adverse reaction**

**SABR: stereotactic ablative body radiotherapy**

**SBRT: stereotactic body radiotherapy**

**SRS: stereotactic radiosurgery**

**SUSAR: serious unexpected serious adverse reaction**

**UAE: unexpected adverse event**

**VMAT: volumetric modulated arc therapy**

# Study team:

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# Trial summary:

## Title:

HBB-SABR: A feasibility study investigating the effect of hyoscine butylbromide injections on cone beam CT quality when delivering abdomino-pelvic stereotactic ablative radiotherapy (SABR).

## Background:

SABR can be used to treat oligometastatic disease in the abdomen and pelvis. Image quality of cone beam CT used for treatment verification is affected by bowel gas motion resulting in streaking artefacts. Intra-fractional bowel motion occurs close to the planning target volume (PTV) during abdomino-pelvic SABR. Diagnostic radiological studies routinely employ anti-peristaltic agents such as hyoscine butylbromide (HBB) to induce aperistalsis and improve image quality. HBB can be delivered by intravenous or intramuscular route. Intramuscular injection may be more convenient than intravenous injection in radiotherapy departments.

## Objectives:

This study will investigate if administration of intramuscular HBB is associated with better cone beam CT image quality for abdomino-pelvic SABR. It will also determine if addition of intramuscular HBB is feasible within a clinical abdomino-pelvic SABR workflow and is tolerated by patients.

## Design:

Feasibility study with patients acting as own controls.

## Intervention schedule:

Intramuscular HBB administered and not administered on alternate fractions to permit evaluation of image quality and bowel motion. Patients act as internal controls to reduce confounding from individual unique bowel motion. Twenty patients to be recruited.

## Inclusion criteria:

* Age ≥ 18
* WHO performance status 0-2
* Histologically or radiologically confirmed lymph node or bone oligometastatic disease in the abdomen or pelvis limited to ≤3 lesions in total
* All metastases must be visible on imaging and be suitable for treatment with SBRT in accordance with the dose fractionation options specified in the standard clinical protocol specified by NHS England Commissioning through Evaluation
* Predicted life expectancy >6 months
* No co-morbid conditions likely to impact on the advisability of SABR (e.g. previous inflammatory bowel disease, previous abdominal or pelvic surgery, significant bladder instability or urinary incontinence, clinically significant renal or hepatic impairment)
* No comorbidities likely to impact on safety of administration of HBB (for example severe cardiac disease, recent cardiac event, cardiac tachyarrhythmias, angle closure glaucoma, myasthenia gravis, pyloric stenosis, severe ulcerative colitis, paralytic ileus, obstructive uropathy or allergy to HBB)
* No bilateral prosthetic hips- this would prevent use of volumetric modulated arc therapy (VMAT) solution for SABR
* Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol; those conditions should be discussed with the patient before registration in the trial
* Written informed consent

## Endpoints:

Primary endpoints:

* Improvement in cone beam CT image quality when HBB administered. This will be determined by proportion of images with improved Likert-type scale results.

Secondary endpoints:

* Demonstration that administration of intramuscular HBB is feasible within a clinical abdomino-pelvic SABR workflow.
* Demonstration of patient and radiotherapy department staff acceptability of intramuscular HBB injection using questionnaire at time of final fraction.

## Study schema:

20 patients assessed for suitability for study and recruited from stereotactic radiotherapy (SABR) clinic

20 patients receive injection of hyoscine butylbromide into muscle of buttock before first, third and fifth radiotherapy treatment (or first and third if only three treatments given)

Cone beam computed tomography (CT) before each radiotherapy treatment

Cone beam computed tomography (CT) after each radiotherapy treatment

End of treatment patient questionnaire and assessment of side effects (how acceptable was it to have hyoscine butylbromide injection?)

End of treatment radiotherapy department staff questionnaire (how practical was it to include butylbromide injection?)

Cone beam CT image quality scored using Likert-type scale

# Background and introduction

## Oligometastatic disease

Oligometastatic disease describes a state between a local tumour and widely disseminated metastatic disease. The implication of this diagnosis is that treating the limited sites of metastases with local metastasis-directed therapy may result in long term survival for patients previously considered incurable (Weichselbaum, 2011; Macdermed, 2008). Evidence exists for improved survival and, in some circumstances, cure of patients who undergo resection of liver metastases in colorectal cancer (Pawlik, 2005) and resection of lung metastases from a variety of primary tumour sites (Pastorino, 1997). The evidence is less clear regarding the benefits of surgical resection of lymph node metastases in some pelvic malignancies and there are high risks of post-operative side effects (Franzese, 2017; Kobayashi, 2009; Min, 2008). Systemic anticancer therapies may risk toxicity without symptomatic benefit for low volume metastatic disease and are generally not curative for solid tumours. Radiotherapy represents an alternate local therapy to surgery but metastatic lesions often regrow over time if conventional dose fractionations are used (Cheung, 2016).

## Stereotactic ablative radiotherapy (SABR)

SABR is a technique of delivering high doses of therapeutic radiation with high accuracy and precision to a highly-conformal target volume (Martin, 2010). SABR can deliver an ablative dose that has equivalent or greater biological effectiveness than conventional radiotherapy. It aims to eradicate the metastatic deposit and thus provide longer term control than conventional radiotherapy, without some of the risks associated with surgery (Cheung, 2016; Martin, 2010; Sahgal, 2012; Tree, 2013). To safely deliver SABR, effective patient preparation and immobilisation as well as accurate target localisation and treatment delivery with millimetre tolerances using image guidance and online correction for inter-fraction patient internal motion and set up errors are required. Complex inverse treatment planning system software and the use of intensity modulated radiotherapy (IMRT), especially VMAT, permits the delivery of radiation to the target with steep dose gradients sparing critical normal organs and tissues (Desai, 2017; Martin, 2010; Musunuru, 2014).

## SABR to treat oligometastatic disease

Much of the clinical evidence for SABR for the treatment of oligometastatic disease has been derived from retrospective observational studies with small numbers of patients. Confounding factors therefore limit interpretation of its true clinical benefit. In many centres patients may be considered for SABR where either patient or disease-related factors preclude surgical resection. Few randomised studies have been performed and many published outcomes are from single centre institutions and lack a comparator arm with other local therapies such as surgery or the standard of care for metastatic disease in the tumour site of interest (Palma, 2015). Randomised studies are currently in progress to try to more clearly define the benefit of SABR for the treatment of oligometastatic disease including the CORE trial of SABR or standard of care for oligometastatic lung, breast and prostate cancer (ClinicalTrials.gov Identifier: NCT02759783); the SABR-COMET study of SABR or conventional palliative radiotherapy for oligometastatic cancer (Palma, 2012); the ORIOLE study of SABR versus observation in prostate cancer (Radwan, 2017); and the STORM trial of SABR or surgery for oligometastatic prostate cancer with and without whole pelvis radiotherapy (NCT03569241).

## Image guidance using cone beam CT (CBCT)

Small inter and intra-fraction deviations in the patient position or position of the target or internal organs may result in a geographic miss with the potential for undercoverage of the target and overdose of critical organs at risk. Given the highly conformal volumes and high doses per fraction used for SABR, the use of 3D image guidance with correction for set up and internal organ motion discrepancies is of critical importance (Martin, 2010).

CBCT is commonly used for image-guided radiotherapy. CBCT combines an x-ray source with a flat panel detector and is mounted on a linear accelerator gantry perpendicular to the treatment head and portal image detector. As the gantry rotates images are acquired during a 180-360 degree gantry rotation over 40 seconds to two minutes. Reconstruction into volumetric images permits evaluation of bone and soft tissue structures. These images can be registered with the planning CT scan and any discrepancy in the position of the target can be observed and a match applied (Jaffray, 2002; Sykes, 2005).

## Bowel organ motion

Pelvic organs are subject to changes in position, shape and volume over time and the appearance of both the target and organs at risk may differ between a radiotherapy planning scan and images obtained during treatment (Jadon, 2014). Bowel motion is under neurological and hormonal control and results in complex peristaltic waves of dilatation and relaxation (Husebye, 1999). Small bowel peristaltic waves have been shown to occur 11 times per minute with average amplitude of 7mm. In addition to this oscillating motion, large changes in bowel position and volume occur as a consequence of faeces and gas within the bowel as well as the influence of bladder volume (Froehlich, 2005). There is considerable variation in the appearance of the small bowel both within and between patients and a single CT image represents only an arbitrary shape and position of a mobile organ. The volume of bowel seen in a single scan may be larger than the average volume seen throughout a course of radiotherapy (Hysing, 2006; Kvinnsland, 2005). Bowel volume has been observed to vary by 20% compared to the planning CT scan on weekly cone beam CT images for bladder radiotherapy treatments with the volume of bowel close to the bladder correlating with bladder volume (Muren, 2003). It may be that only 20% of bowel occupies the same position throughout treatment (Hysing, 2006; Sanguineti, 2008). The position of small bowel has been seen to vary by up to 2.7cm in the anterior-posterior direction and 1.6cm in the superior-inferior direction for patients receiving adjuvant radiotherapy for rectal cancer. An increased bladder volume has also been shown to be associated with reduced amount of small bowel close to the radiotherapy target in rectal cancer (Nuyttens, 2001; Nuyttens, 2004).

## Impact of bowel organ motion on CBCT quality

Image quality of CBCT is limited in comparison to diagnostic helical CT scanners for a number of reasons. Large quantities of scattered radiation reach the flat panel detector and this reduces image contrast and increases image noise, which negatively impacts on image quality (Endo, 2001; Graham, 2007; Siewerdsen, 2001).

Bowel motion negatively impacts on diagnostic image quality and anti-peristaltic agents have been used routinely for several decades, especially for abdomino-pelvic magnetic resonance imaging (MRI), CT colonography, mesenteric angiography and barium studies (Dyde, 2008; Goei, 1995; Johnson, 2007; Maher, 1999). During MRI, motion causes blurring and ghost artefacts resulting from a spreading out of the signal from an object and this causes deterioration in image quality. These artefacts impact on MRI rather than diagnostic CT because of the long scan acquisition times (Bellon, 1986; Dosda, 2003; Martí-Bonmatí, 1996). The prolonged period of time it takes for the CBCT gantry to rotate (in comparison to a helical fan beam CT scanner where one rotation takes around one second) means any internal organ motion, including respiratory and cardiac motion, bowel peristalsis and arterial pulsation, may create significant motion artefacts during image reconstruction including blurring, streaking, doubling and distortion (Smitsmans, 2005; Xing, 2006). It is gas moving within the bowel that appears to result in streak artefacts during image reconstruction of CBCT (Nijkamp, 2008; Smitsmans, 2005).

## Assessment of CBCT image quality

CT image quality can be determined by physical measurements or observer assessments. Physical measurements include spatial resolution, image uniformity and contrast to noise ratio. While these might provide an objective measure of a particular technology’s performance, observer scored methods of image quality such as visual grading analysis may be more clinically relevant.

Assessments can also be performed in relation to the task for which the imaging was performed, for example identification of anatomical structures in diagnostic radiology or soft tissue matching in IGRT (Bath, 2010). Use of Likert-type rating scales for visual grading analysis has been used in diagnostic radiology studies, where observers scored the visibility of particular structure and they have also been used to assess CBCT image quality for target matching in radiotherapy studies (Johnson, 2007; Kember, 2016). An example of a scale used by Sweeney *et al* for a study comparing 4D with 3D CBCT for lung SABR was a three point score summarised as: score 1: “clearly visible tumour, no difficulty in matching”; score 2: “visible tumour but some difficulty in matching”; score 3: “tumour not visible for matching” (Sweeney, 2012). Scores with different numbers of points have been used in previous studies. Kember *et al* chose an even number scale with the points ‘very clearly visible’, ‘clearly visible’, ‘unclear’ and ‘not visible’ to avoid observers choosing the middle value by default (Kember, 2016). Measurement of intra and inter-observer agreement for several assessors of image quality can be performed to validate results (Demehri, 2015).

## Use of anti-peristaltic agents in imaging

Hyoscine butylbromide (HBB) (also known as scopamine butylbromide, butylscopolaminebromide or N-butyl scopolammonium and marketed under the trade name Buscopan® (Boehringer Ingelheim Ltd, Germany)) is an anticholinergic quaternary ammonium compound with limited systemic absorption when administered via the enteral route. It can however be delivered by intravenous or intramuscular routes. By binding to muscarinic receptors located in smooth muscle cells of the gastrointestinal tract results it results in inhibition of bowel motility (Tytgat, 2007).

A study investigated the onset of action following administration, duration of action and effectiveness for intravenous and intramuscular HBB and glucagon for cessation of peristalsis in healthy volunteers undergoing small bowel MRI. Aperistalsis occurred on average after 85 seconds (±25 seconds) and 65 seconds (±25 seconds) for intravenous HBB and glucagon and 310 seconds/5.1 minutes (±110 seconds) and 696 seconds/11.6 minutes (±610 seconds) for intramuscular HBB and glucagon respectively. Duration of action was 1260 seconds/21 minutes (±739 seconds) and 1397 seconds/23.3 minutes (±842 seconds) for intravenous HBB and glucagon and 1060 seconds/17.7 minutes (±1406 seconds) and 1690 seconds/28.2 minutes (±1614 seconds) for intramuscular HBB and glucagon respectively. There was significant variation in the timing of onset and duration of action between individuals and the investigators reported more variability between subjects in the degree of aperistalsis after intramuscular administration of both HBB and glucagon. They speculated that this could be due to slower systemic availability of the drugs following intramuscular injection (Gutzeit, 2012).

In Europe HBB is used more frequently than glucagon for inhibition of bowel peristalsis for radiological procedures because it is less expensive and can be stored at room temperature (Dyde, 2008).

A study of intravenous HBB in pelvic MRI using Likert-type scales for qualitative image analysis found significantly improved image quality, organ identification and tumour visualisation following administration of HBB. There was a reduction in the proportion of images scored as having significant motion artefact and an increase in the proportion judged to have no motion artefact. Tumour identification post HBB was felt to be improved and fewer images permitted very limited lesion assessment. Identification of the bladder, rectum, pelvic bowel, prostate, seminal vesicles, uterus and vagina was felt to be significantly improved post HBB (Johnson, 2007).

## Safety of hyoscine butylbromide (HBB)

Along with glucagon, HBB is routinely used as an anti-peristaltic agent for radiological procedures including abdomino-pelvic MRI, CT colonography, mesenteric angiography and barium studies (Dyde, 2008; Goei, 1995; Johnson, 2007; Maher, 1999). It is well tolerated, and adverse events generally appear mild and self-limiting in studies that used HBB for radiological procedures. No toxicities attributable to subcutaneous HBB were observed in a study of 25 patients undergoing abdominal MRI (Dosda, 2003).

A study of HBB in 35 patients undergoing pelvic MRI found seven patients reported blurred vision, 22 patients reported dry mouth, four patients reported dizziness and two reported palpitations. All toxicities resolved within 15 minutes except blurred vision which persisted for up to one hour (Johnson, 2007). In another study of HBB for small bowel MRI two of ten healthy volunteers experienced a short period of dizziness following administration of intravenous HBB (Froehlich, 2009). Transient visual disturbance occurred in a proportion (exact numbers not reported) of ten health volunteers administered 40mg of intravenous HBB as part of a study of bowel motility (Froehlich, 2005). Another study of intravenous HBB in abdominal MRI reported blurred vision in two of 33 patients (Laniado, 1997). Another study compared intravenous HBB, glucagon and placebo for barium enema examinations. Five of 109 (4.6%) of patients who received HBB reported blurred vision compared to no patients who received glucagon or placebo but no significant changes in visual accommodation were observed between the three groups. The authors recommended that patients who receive HBB should wait in the department until any visual disturbance has resolved before they drive home (Goei, 1995). Other authors recommended that patients should be told to expect blurred vision and not to drive for 45 minutes after the injection (Dyde, 2008).

Although anticholinergic drugs such as HBB may precipitate acute angle closure glaucoma it is undiagnosed and therefore untreated patients who are at greatest risk of this condition and therefore previous authors have recommended that all patients are advised to seek urgent medical attention if they develop painful blurred vision within 12 hours of the injection (Dyde, 2008; Fink, 1995).

Other contraindications to administration of HBB are a history of myasthenia gravis, porphyria, paralytic ileus, obstructive uropathy and a history of allergic reaction to HBB (Dyde, 2008).

A Medicines and Healthcare products Regulatory Agency (MHRA) drug safety update was published in February 2017 following reports of eight patients who died as a result of myocardial infarction or cardiac arrest following procedures that included administration of intravenous or intramuscular HBB (Medicines and Healthcare Products Regulatory Agency, 2017). HBB may induce tachycardia as a result of anticholinergic inhibition of vagal tone and can lead to angina and cardiac ischaemia in susceptible individuals. It has been recommended not to administer HBB in patients with unstable cardiac disease such as recent acute coronary syndrome, recurrent angina especially at rest, uncontrolled left ventricular failure and cardiac tachyarrhythmias (Dyde, 2008; Joint position statement from The Royal College of Radiologists and the British Society of Gastrointestinal and Abdominal Radiologists, 2017; Maher, 1999; Medicines and Healthcare Products Regulatory Agency, 2017). Dyde et al recommended however that a small increase in pulse rate of 20 beats per minute (bpm) for around one hour and small increase in diastolic blood pressure is unlikely to be clinically significant in patients without significant cardiac disease (Dyde, 2008). There is the suggestion that pulse rate elevation may be dose-related with 40mg intravenous HBB leading to an increase of 30 bpm but the standard dose for HBB during radiological procedures is 20mg (Dyde, 2008; Mui, 2004).

## Adaptive SABR workflow

Adaptive radiotherapy (ART) involves adjusting the treatment plan based on anatomical changes that are observed during pre-treatment imaging, ideally prior to that day’s treatment. Previous studies in the pelvis have used different ART strategies. These include an offline replanning strategy whereby a new plan is produced after treatment is delivered, based on tumour shrinkage and pelvic internal organ motion in cervical cancer. Alternatively a library of plans can be produced to allow selection of the most appropriate ‘plan of the day’ based on bladder volume and daily online plan re-optimisation in bladder and prostate cancers (Ahunbay, 2010; Oh, 2014; Vestergaard, 2013). Abdomino-pelvic SABR would likely especially benefit from ART strategies. As described above there is considerable internal organ motion in the pelvis, especially for bowel, and previous studies have shown that the volume of small and large bowel receiving higher doses of radiotherapy correlates with development of gastrointestinal toxicities (Fokdal, 2005; Roeske, 2003). Given the significant hypofractionation used with SABR, ART for abdomino-pelvic SABR based on position of the target and the surrounding loops of bowel would ideally be performed daily and be performed immediately prior to delivery of treatment. However there is the potential for intrafraction bowel motion and patient discomfort during the time taken to re-optimise the plan, and bowel gas can negatively affect recontouring of bowel loops (Lim-Reinders, 2017; Vestergaard, 2013). Deformable image registration has the potential to rapidly facilitate recontouring of relevant structures on pre-treatment CBCT, but artefacts generated during acquisition of the CBCT images may introduce significant error into the process. In addition, deformable image registration strategies for small and large bowel loops are not well developed (Lim-Reinders, 2017; Perna, 2016; Schulze, 2011). Our study aims to investigate whether administration of intramuscular HBB could reduce the streak artefacts seen on CBCT images associated with moving gas. If successful this would help contribute towards development of an adaptive workflow for abdomino-pelvic SABR. The future of ART may be in MR-guided radiotherapy, for example utilising an MR linear accelerator or cobalt machine, with deformable image registration of the MR images to the planning scan and automatic recontouring of targets and organs at risk (Acharya, 2016; Bohoudi, 2017; Kupelian, 2014). Potential for intrafraction bowel motion would exist during both the acquisition of MR sequences and replanning process, and therefore a wider application of HBB could be used to both reduce bowel motion MR artefacts and stabilise bowel position prior to delivery of an adapted radiotherapy treatment.

## Conclusions

Streak artefacts from moving bowel gas negatively impact image quality of CBCT images used for abdomino-pelvic SABR. HBB is routinely used in diagnostic radiology, especially for abdomino-pelvic MRI, to reduce bowel motion artefacts and improve image quality. The hypothesis for our study is that use of intramuscular HBB will reduce streak artefacts and improve image quality of CBCT in the process of target matching prior to delivery of SABR. Likert-type scales will be used to assess image quality. We also hypothesise that implementation of intramuscular HBB will be feasible within a clinical abdomino-pelvic SABR workflow and that it will be tolerated by patients. If successful we anticipate that this strategy will be a useful component in the development of an adaptive SABR workflow.

# Study objectives

## Primary objective

* To determine the impact of intramuscular HBB in reducing bowel motion artefacts on CBCT images used for image guidance of abdomino-pelvic SABR. The aim is to demonstrate an improvement in image quality as assessed by better scores on a Likert-type scale when HBB is administered.

## Secondary objectives

* To demonstrate that implementation of intramuscular HBB into a clinical abdomino-pelvic SABR workflow is feasible and does not negatively impact on radiotherapy department scheduling.
* To determine if an intramuscular HBB injection is acceptable to both patients and radiotherapy department staff by use of an end of SABR treatment questionnaire.

## Endpoints

1. Primary endpoints:

* Improvement in CBCT image quality with administration of intramuscular HBB determined by proportion of images with better scores on a Likert-type scale.

2. Secondary endpoints:

* Feasibility of implementation of intramuscular HBB into a clinical SABR workflow determined by absence of delays to radiotherapy department scheduling as a result of administering intramuscular HBB.
* Acceptability of intramuscular HBB to both patients and radiotherapy department staff determined by end of SABR treatment questionnaire covering tolerance for receiving an injection, toxicity of HBB and convenience for departmental staff in administering the injection within clinical workflows.

# Patient selection criteria

## Inclusion criteria

* Age ≥ 18
* WHO performance status 0-2
* Histologically or radiologically confirmed lymph node or bone oligometastatic disease in the abdomen or pelvis limited to ≤3 lesions in total
* All metastases must be visible on imaging and be suitable for treatment with SBRT in accordance with the dose fractionation options specified in the standard clinical protocol specified by NHS England Commissioning through Evaluation
* Predicted life expectancy >6 months
* No co-morbid conditions likely to impact on the advisability of SABR (e.g. previous inflammatory bowel disease, previous abdominal or pelvic surgery, significant bladder instability or urinary incontinence, clinically significant renal or hepatic impairment)
* No comorbidities likely to impact on safety of administration of HBB (for example severe cardiac disease, recent cardiac event, cardiac tachyarrhythmias, angle closure glaucoma, myasthenia gravis, pyloric stenosis, porphyria, severe ulcerative colitis, paralytic ileus, obstructive uropathy or allergy to HBB)
* No bilateral prosthetic hips- this would prevent use of volumetric modulated arc therapy (VMAT) solution for SABR
* Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol; those conditions should be discussed with the patient before registration in the trial
* Written informed consent

# Trial design

* This is a prospective, non-randomised feasibility study of intramuscular HBB administered on alternate SABR fractions in the management of oligometastatic disease in the lower abdomen and pelvis. The rationale for giving HBB is to try to improve image quality of CBCT by reducing bowel motion artefacts. Patients will act as their own controls to try to account for individual variation in bowel motion.
* The trial will be performed in Leeds Cancer Centre and other radiotherapy centres within the Cancer Research UK Advanced Radiotherapy Technologies Network (ART-NET) will be invited to participate. These centres are: Institute of Cancer Research/The Royal Marsden Hospital, Manchester Cancer Research Centre, (Leeds), Oxford and University College London.
* The primary endpoint is an improvement in CBCT image quality with administration of intramuscular HBB determined by proportion of images with better scores on a Likert-type scale.
* The secondary endpoints are demonstrating feasibility of incorporating intramuscular HBB into a clinical SABR workflow and demonstrating acceptability of intramuscular HBB to both patients and radiotherapy department staff determined by means of an end of SABR treatment questionnaire.

# Clinical evaluation of HBB in SABR workflow

## Prior to treatment

* Of note, local trial activities will be coordinated by the local trial clinical research fellow. Within this protocol, where there are activities relating to the Clinical Research Fellow (and Chief Investigator) at the central trial site in Leeds the prefix ‘Leeds’ is used.
* Patients will be assessed in outpatient clinic to determine suitability for SABR and HBB within this study. This will be done by documentation of patient history, clinical examination and review of relevant biochemical, histological and radiological investigations. Documentation of past medical history and drug history will be used to exclude patients not suitable for HBB.
* Specific contraindications are severe cardiac disease, recent cardiac event, cardiac tachyarrhythmias, angle closure glaucoma, myasthenia gravis, pyloric stenosis, porphyria, severe ulcerative colitis, paralytic ileus, obstructive uropathy or allergy to HBB.
* Patients will be approached by their clinical team at a clinic visit and if they appear potentially suitable the rationale, practicalities and risks of the trial will be discussed. If interested in participating the patient information sheet will be provided and contact details obtained. Participant name, date of birth, NHS number, and telephone number will be obtained to facilitate recruitment into the study by one of the trial investigators. Verbal consent will be obtained for this process to take place. This process will take place internally within each of the trial sites. Patients will be contacted by the local clinical research fellow within 1 week to arrange for assessment for recruitment into the study if the patient remains interested. They will be offered at least 24 hours to consider their decision to enter the trial. The process for consent and registration into the study will most likely take place in the radiotherapy department when the patient attends for their SABR planning CT scan, to try to avoid participants returning for a separate consent visit.

## During treatment

* Patients will receive intramuscular HBB 20mg (into upper outer quadrant of gluteal muscle) on fractions 1, 3 and 5 of a five-fraction SABR treatment (or fractions 1 and 3 of a three-fraction regimen). On fractions 2 and 4 (or fraction 2) no injection of HBB will be given. The injection will be administered following check of the drug name, dose and expiry date. Patient identity (by means of name and date of birth) and allergy status will be confirmed prior to administration. An aseptic non-touch technique will be used.
* Following delivery of intramuscular HBB patients will proceed with pre-treatment CBCT, target matching and set up adjustment, delivery of SABR fraction and post-treatment CBCT as per departmental protocol.

## After treatment

* Following delivery of SABR fraction patients will be asked not to drive for 60 minutes following administration of HBB. This is to allow any blurred vision that may occur with HBB to settle. They will be asked to attend hospital immediately if they develop painful blurred vision in one or both eyes after receiving HBB, as this may be a symptom of previously undiagnosed acute angle closure glaucoma.
* Patients will be asked to seek medical advice in the event of any other side effect that may be secondary to HBB including acute urinary retention, chest pain, breathlessness, dizziness, palpitations, rash, angio-oedema, abdominal pain or vomiting. Patients in Leeds Cancer Centre will be provided with the contact details for the on call oncology nurse practitioner for any clinical advice. At other trial sites participants should be provided with contact details for their respective on call oncology advice line.
* After the final fraction patients and radiographer staff involved in their care will be asked to complete an end of treatment questionnaire (see Appendix D). The patient questionnaire includes questions relating to tolerance for receipt of HBB intramuscular injection. Toxicity will be assessed by a member of the trial team using CTCAE version 5 criteria. The staff questionnaire includes questions about acceptability of including a HBB injection within a clinical SABR workflow and impact on department scheduling.
* Following completion of SABR treatment analysis of CBCT images with and without HBB will be performed by multiple experienced observers using a four-point Likert-type scale (see Appendix H).

# Statistical considerations

## Study design

* This is a prospective, non-randomised feasibility study of intramuscular HBB administered on alternate SABR fractions in the management of oligometastatic disease in the lower abdomen and pelvis. The rationale for giving HBB is to try to improve image quality of CBCT by reducing bowel motion artefacts. Patients will act as their own controls to try to account for individual variation in bowel motion.
* The null hypothesis of the primary endpoint is that administration of HBB does not result in increased proportion of images with an improved Likert-type scale score.
* The null hypotheses of the secondary endpoints are that incorporation of intramuscular HBB into a clinical SABR workflow is neither feasible within the radiotherapy department schedule nor is it acceptable to patients because of toxicity or lack of tolerance for receiving an intramuscular injection.

## Significance level and sample size

* This is a feasibility study and therefore does not aim to demonstrate statistical significance.
* No published informative data exist upon to guide sample size calculation.
* Sample size required for feasibility study is minimum of 30, as recommended by Lancaster et al (Lancaster, 2004). Other authors have suggested a smaller sample size of 12 where there is no prior information to guide sample size calculation (Julious, 2005). Since patients are acting as their own controls 20 patients will permit analysis of 40 groups- 20 set of CBCT images acquired with and 20 without HBB.

## Study accrual

* On average one patient referred to Leeds Cancer Centre per week for consideration of SABR for lower abdomen/pelvic oligometastatic disease therefore it is anticipated to recruit 20 patients over 12-24 months.
* All of the patients registered in the study will be accounted for. The number of patients who were not evaluable, who died or withdrew before treatment began will be specified. Final evaluation of patients will take place at the time of their last SABR fraction. Since patients will not be followed up within the context of this study no description of follow up time is required and there would be no impact from loss to follow up.

## Safety monitoring

Toxicity will be assessed at the time of final SABR treatment by means of trial clinician assessment. Grading of toxicity will be performed using CTCAE version 5 (see Appendix B). Both events related and unrelated to treatment will be captured.

## Statistical analysis

* Data will be analysed using IBM SPSS (IBM, New York, USA)
* The number of patients accrued will be described.
* Safety analysis will be based on the number of patients accrued. All analyses of safety will be descriptive and will consist of frequency tables for binary and categorical variables and summary statistics (mean, median and range) for continuous variables.
* The adherence to the theoretical main protocol treatment (dose, schedule and modifications to administration of HBB) and the reasons for non-adherence by, as well as the reasons why administration of HBB was stopped will be described.
* Proportions of CBCT images with better or worse Likert-type scales scores for target matching will be described with confidence intervals to indicate the likely true proportion in the population. This is a feasibility study and therefore not expected to demonstrate statistical significance of differences between proportions to a p value of ≤0.05, therefore no comparative statistical tests will be performed and no p value will be described.
* Analysis of Likert-type scale score data will be represented graphically to show the proportions of patents with each Likert-type scale score and proportions of images with better/worse scores with and without HBB.
* Assessors of image quality will be blinded to which SABR fraction the CBCT images are related to, to avoid confounding from knowledge of which fraction HBB was administered on. This will be performed by use of coded image file names.
* Measurements of inter and intra-observer variation may be performed to validate assessment of image quality using Cohen’s kappa statistic. This ranges from -1 to +1. Agreement will be interpreted as: ≤0 (none); 0.01-0.2 (slight); 0.21-0.4 (fair); 0.41-0.6 (moderate); 0.61-0.8 (substantial); 0.81-1.0 (almost perfect). The process of intra-observer variation will likely be determined by including a copy of an image obtained with and without HBB within the set of images for the assessors to score.
* Feasibility of clinical use of HBB in SABR workflow will be based on responses to end of treatment staff questionnaire. All analyses of feasibility will be descriptive and will consist of frequency tables for binary and categorical variables and summary statistics (mean, median and range) for continuous variables.

# Investigator authorisation procedure

* This trial concept was discussed at the CTRad Proposals Guidance Meeting on 05.07.2018 and it was felt to be both feasible and achievable. This meeting included patient and public involvement and input into the trial design and methodology.
* The trial will be approved by St James’s Institute of Oncology Clinical Trials Review Approval Board (CTRAB), Leeds Teaching Hospitals Research and Development and the Local Research Ethics Committee.
* This trial will be conducted in accordance with the professional and regulatory standards required for non-commercial research in the NHS under the Research Governance Framework for Health and Social Care and ICH GCP.
* This trial will comply with the protocol and the protection of patients’ rights as detailed in the Declaration of Helsinki adopted by the 18th World Medical assembly, Helsinki, Finland, 1964 and later revisions (last revised Edinburgh 2000).

# Patient registration

Patients will be registered to the trial after they have provided written informed consent.

The local ART-NET Clinical Research Fellow may be contacted by NHS telephone or NHS e-mail during office hours. The following information should be provided:

* Patient name
* Patient date of birth
* Local hospital number
* NHS number
* Date and result of relevant radiological imaging (CT or PET-CT scan)
* Performance status
* Information about any potential contraindications to administration of HBB (severe cardiac disease, recent cardiac event, cardiac tachyarrhythmias, angle closure glaucoma, myasthenia gravis, pyloric stenosis, porphyria, severe ulcerative colitis, paralytic ileus, obstructive uropathy or allergy to HBB)
* This process will take place within each of the participating trial sites (for example, Leeds clinical research fellow will contact participants treated in Leeds)

# Forms and procedures for collecting data

Data will be collected on dedicated case report forms and stored on a trial-specific secure database. Data will be collected by the ART-NET Clinical Research Fellow and other Investigators. Data will be analysed using IBM SPSS (IBM, New York, USA).

The following forms will be available:

* Serious Adverse Events forms
* Patient end of treatment questionnaire
* Patient end of treatment toxicity assessment
* Radiotherapy department staff end of treatment questionnaire
* Cone beam CT image quality assessment form

## Trial forms and procedure for completion

The following forms will be completed for all participants:

* Consent form
* All original Consent Forms are dated and signed by both the patient and investigator, and are kept in a central log at the participating trial site.
* End of treatment patient and staff questionnaires and patient toxicity assessment
	+ End of treatment patient and staff questionnaires and patient toxicity assessment form should be completed at the time of the patient’s final SABR fraction
	+ These should be completed for all patients and should not be made available to third parties. Each questionnaire should be photocopied. The original copy must be sent by the hospital to the clinical research fellow as soon as it is due. One other copy must be filed in the patients’ notes. If information is not known it must be clearly stated.
	+ All non-serious adverse events, adverse reactions and unexpected adverse events should be should be graded by a member of the trial team using CTCAE version 5, and recorded in the end of treatment toxicity assessment form. These should be recorded and reported as per the adverse event section of the trial protocol.
	+ Completed end of treatment patient, staff and toxicity assessment forms should be sent to the Leeds Clinical Research Fellow within 28 days of the form being due.
	+ The Chief Investigator reserves the right to amend or add to the end of treatment patient and staff questionnaires as appropriate. Such changes do not constitute a protocol amendment, and revised or additional forms should be used by centres with immediate effect.
	+ End of treatment patient and staff questionnaires should be returned as soon as possible by fax or by post to the following address: Dr Finbar Slevin, Radiotherapy Research Office, Level 4 Bexley Wing, St James’s University Hospital, Beckett Street, Leeds LS9 7TF.
	+ The Leeds Clinical Research Fellow will monitor receipt of end of treatment patient and staff questionnaires. They will also check incoming end of treatment patient and staff questionnaires for compliance with the protocol, inconsistent and missing data.
* Cone beam CT image quality assessment form.
	+ To be completed for every patient.
	+ Trial sites are using both X-ray volume imaging (XVI) (Elekta®, Stockholm, Sweden) and On-Board Imager® (OBI) (Varian, California, USA). Image quality assessment forms should be completed at the trial site treating the patient. This is to avoid problems with evaluation of imaging from one image guided radiotherapy platform on a different system. Form should be returned to the following address: Dr Finbar Slevin, Radiotherapy Research Office, Level 4 Bexley Wing, St James’s University Hospital, Beckett Street, Leeds LS9 7TF.

The following forms may be required:

* Serious adverse event (SAE) forms
	+ To be completed in the event of an SAE
	+ **The SAE form MUST be completed and the clinical research fellow must be notified of all non-exempt SAEs within one working day. The telephone number is 0113 206 8891**
	+ The SAE form MUST be completed and the clinical research fellow must be notified of all SAEs that occur up to 30 days from the completion of radiotherapy, and all SARs and SUSARs indefinitely
	+ An SAE form must be completed and signed by the investigator for all SAEs, SARs and SUSARs, including the information regarding grading, causality and expectedness. A member of the site trial team may complete and sign the SAE on behalf of the investigator if the specific responsible investigator is unavailable. When the responsible investigator becomes available they must check the SAE, make any necessary changes and sign and re-send the form to the clinical research fellow as soon as possible.
	+ Completed SAE forms should be faxed to the clinical research fellow within one working day of the investigator becoming aware of the SAE, SAR or SUSAR. The telephone number is: 0113 206 8891.

## Data flow

Data will be collected on dedicated case report forms and stored on a trial specific password secure NHS database. Serious Adverse Events forms must also be completed as necessary. Details from SAE forms will also be stored on the dedicated secure database.

Data will be collected by the clinical research fellow and other trial investigators.

**The Leeds Chief Investigator/Clinical Research Fellow will monitor receipt of CRFs. They will also check incoming CRFs for compliance with the protocol, inconsistent and missing data. All SAE reports will be reviewed by the clinical research fellow. The causality as assessed by the investigator cannot be overruled by the clinical research fellow. In cases where there is disagreement, both opinions will be recorded on subsequent reports.**

**The Clinical Research Fellow will maintain the confidentiality of all subject data and will not reproduce or disclose any information by which subjects could be identified, with the exception of the reporting of serious adverse events.**

**Sufficient data will be recorded for all participating patients to enable accurate linkage between hospital records and trial activities (for example, arranging consent appointment at the same time as participants attend for their radiotherapy planning scan)- this process will be undertaken within each trial site by their clinical research fellow. No specific clinical information from medical records is required for the purposes of this trial.**

**Source data and all trial related documentation will be accurate, complete, maintained and accessible for monitoring and audit visits;**

**All original Consent Forms will be dated and signed by both the patient and investigator, and will be kept together in a central log together with a copy of the specific patient information sheet(s) they were given at the time of consent.**

**Copies of CRFs will be retained for 5 years to comply with international regulatory requirements.**

# Reporting adverse events

## Definitions

An **Adverse Event (AE)** is defined as any untoward medical occurrence or experience in a patient or clinical investigation subject which occurs following the administration of the trial medication regardless of the dose or causal relationship. This can include any unfavourable and unintended signs (such as rash or enlarged liver), or symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment. (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), 2016).

An **Adverse Drug Reaction (ADR)** is defined as any response to a medical product, that is noxious and/or unexpected, related to any dose. (ICH-GCP).

**Response to a medicinal product** (used in the above definition) means that a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

An **Unexpected Adverse Drug Reaction** is any adverse reaction for which the nature or severity is not consistent with the applicable product information (e.g., Investigators’ Brochure). (ICH-GCP).

A **Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or**

**Suspected Unexpected Serious Adverse Reaction (SUSAR):** is defined as any undesirable experience occurring to a patient, whether or not considered related to the protocol treatment. A Serious Adverse Event (SAE) which is considered related to a protocol drug treatment is defined as a **Serious Adverse Drug Reaction (SADR).**

Adverse events and adverse treatment related reactions which are considered as **serious** are those which result in:

* death
* a life threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
* hospitalization or prolongation of hospitalization
* persistent or significant disability/incapacity
* a congenital anomaly/birth defect
* any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above) (ICH-GCP)

Medical judgment should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

The Leeds **Clinical Research Fellow** must be notified of all non-exempt SAEs within one working day, and the SAE from completed.

The Leeds **Clinical Research Fellow** must be notified of all SAEs that occur up to 30 days from the completion of radiotherapy, and all SARs and SUSARs indefinitely.

## Exceptions specific to this trial in expedited SAE Notification and Reporting

Although meeting the definition of a ‘serious’ event, patients who are hospitalised:

* Purely to simplify treatment delivery (e.g. due to large geographical distance to travel for treatment)
* As a result of pre-existing conditions that, in the opinion of the investigator, have not been exacerbated by treatment are exempt from expedited notification as an SAE.

**Institutional requirements**

All non-serious AEs, ARs and UAEs should be recorded in the toxicity section of the CRF. Completed forms should be sent to the Leeds **Clinical Research Fellow** within 28 days of the form being due.

All AEs, ARs and UAEs, whether serious or not, should be graded using CTCAE version 5.

**Investigator requirements**

In the event of an AE or AR, expected or unexpected, the investigator responsible for the care of the patients must judge whether the event is considered serious or non-serious (see definitions and exceptions above). All non-exempt serious events must be immediately reported to the Leeds **Clinical Research Fellow** (within one working day) and recorded on an SAE form.

**Causality**

The investigator must also judge the causality of all serious events and reactions with regard to their relationship to the trial treatment. Causality can be defined as follows:

**Unrelated:** There is no evidence of any causal relationship- considered SAE

**Unlikely:** There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient’s clinical condition, other concomitant treatment) - considered SAR

**Possible:** There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient’s clinical condition, other concomitant treatments) - considered SAR

**Probable:** There is evidence to suggest a causal relationship and the influence of other factors is unlikely- considered SAR- considered SAR

**Definite:** There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out- considered SAR

**Expectedness**

The investigator must assess whether the event is expected or expected (see definitions above). All unexpected SARs are considered SUSARs and are reported as such.

**Reporting procedure**

**The Leeds Clinical Research Fellow must be notified within one working day of the investigator becoming aware of any non-exempt SAE, SAR or SUSAR**. The Leeds **Clinical Research Fellow** must be notified of all SAEs that occur up to 30 days from the completion of radiotherapy, and all SARs and SUSARs indefinitely.

An SAE form must be completed and signed by the investigator for all SAEs, SARs and SUSARs, including the information regarding grading, causality and expectedness. A member of the site trial team may complete and sign the SAE on behalf of the investigator if the specific responsible investigator is unavailable. When the responsible investigator becomes available they must check the SAE, make any necessary changes and sign and re-send the form to the Leeds **Clinical Research Fellow** as soon as possible.

Completed SAE forms should be faxed to the Leeds **Clinical Research Fellow** within one working day of the investigator becoming aware of the SAE, SAR or SUSAR. The telephone number is 0113 206 8891.

The Leeds **Clinical Research Fellow** will inform the sponsor of all SAE, SAR or SUSARs within one working day of being made aware of the event.

**Follow-up following Adverse events or reactions**

Patients who have experienced a SAE, SAR or SUSAR must be followed up until complete clinical recovery and blood results have returned to baseline, or until the event has stabilised. Information regarding follow up should be recorded on a further SAE form and the box marked ‘Follow-up’ should be ticked. Completed forms should be faxed to the Leeds **Clinical Research Fellow**. Additional information may be provided separately. The patients should be identified by trial number, date of birth and initials only. The patient’s name should not be used on any trial documentation.

**Leeds Clinical research fellow Responsibilities**

All SAE reports will be reviewed by the Leeds **Clinical Research Fellow**. The causality as assessed by the investigator cannot be overruled by the **Clinical Research Fellow**. In cases where there is disagreement, both opinions will be recorded on subsequent reports.

The Leeds **Clinical Research Fellow** is responsible for the reporting of all SARs and SUSARs to the research ethics committees and regulatory authorities as appropriate.

The Leeds **Clinical Research Fellow** will keep all investigators informed of any safety issues arising during the trial.

# Quality assurance

This trial will be conducted in accordance with the professional and regulatory standards required for non-commercial research in the NHS under the Research Governance Framework for Health and Social Care and ICH GCP.

The centre may be monitored by Health Authorities to carry out source data verification, and confirm compliance with the protocol and the protection of patients’ rights as detailed in the Declaration of Helsinki adopted by the 18th World Medical assembly, Helsinki, Finland, 1964 and later revisions (last revised Edinburgh 2000). By participating in this trial the Chief Investigator is confirming agreement with his/her local NHS Trust to ensure that:

* Sufficient data is recorded for all participating patients to enable accurate linkage between hospital records and CRFs;
* Source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit visits;
* All staff who are involved with the trial are trained appropriately;
* All original Consent Forms are dated and signed by both the patient and investigator, and are kept together in a central log together with a copy of the specific patient information sheet(s) they were given at the time of consent.
* Copies of CRFs are retained for 5 years to comply with international regulatory requirements;
* Staff will comply with the Standard Operating Procedures for this trial.

 The Leeds **Clinical Research Fellow** will monitor receipt of CRFs. They will also check incoming CRFs for compliance with the protocol, inconsistent and missing data.

# Ethical considerations

## Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), 2016).

The protocol will be approved by the NHS Ethics Committee.

## Subject identification

The patient’s full name, date of birth, hospital number and NHS number will be collected at registration to allow tracing through local medical records. This will be done to clarify suitability for the trial and permit identification of correct dates and times for trial team interactions with the participant during their radiotherapy treatment (for example, arranging appointment for consent when participant attends for their radiotherapy planning scan). The personal data recorded on all documents will be regarded as confidential. Only initials and date of birth will be recorded on Case Report Forms. The code linking identifiable data to the allocated study number is to be stored electronically within password protected database on a secure NHS server at each participating trial site.

The dedicated trial computer database where patient information is stored is password protected. The database is stored with the secure, password protected NHS computer system.

The local Principle Investigator must keep a separate log of patients’ trial numbers, names, and hospital numbers. This log will be kept within a secure locked filing cabinet, within a locked office and access to the office area is with swipe card only. This is situated within Leeds Cancer Centre, within St James's University Hospital. Equivalent arrangements will be present in any of the other ART-NET centres who participate in the study. The investigators must maintain in strict confidence trial documents, which are to be held in the local hospital (e.g. patients' written consent forms). The investigators must ensure the patient's confidentiality is maintained.

The research team will maintain the confidentiality of all subject data and will not reproduce or disclose any information by which subjects could be identified, with the exception of the reporting of serious adverse events. Representatives of the trial team will be required to have access to patient notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times. In the case of special problems and/or competent authority queries, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

Radiotherapy department staff (who are asked to complete an end of treatment questionnaire) will be identified only by their name on the consent form and no other identifiable information will be collected. Only initials will be recorded on the end of treatment questionnaire.

## Informed consent

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

It is the responsibility of the central trial site in Leeds to translate the enclosed informed consent document. The translated version should be dated and version controlled.

The bold sections of the enclosed informed consent document are the sections that **must** appear in the translation.

The translated informed consent form is part of the documents to be submitted to the ethics committee for approval. The competent ethics committee for each institution must validate local informed consent documents before the centre can join the study. It is the responsibility of the NHS ethics committee to guarantee that the translation is conforming to the ICH-GCP guidelines.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient’s subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered in the study. This must be done in accordance with the national and local regulatory requirements.

All healthcare staff approached to complete end of treatment staff questionnaire will be informed of the aims of the study. It is not anticipated that any possible adverse events will result from completion of the questionnaire. It will be emphasized that the participation is voluntary and that the staff member is allowed to refuse further participation in the protocol whenever he/she wants. Documented informed consent must be obtained for all patients included in the study before they are registered in the study. This must be done in accordance with the national and local regulatory requirements.

For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that the written informed consent form should be signed and personally dated by the patient.

# Administrative responsibilities

Chief investigator: Dr Finbar Slevin

The person above accepts the responsibilities as outlined previously.

# Trial sponsoring and financing

The trial sponsor is the University of Leeds.

C/o Claire E Skinner

Faculty NHS Research Ethics Officer

Faculty Research Office

Room 9.29, Level 9, Worsley Building

Clarendon Way

Leeds

LS2 9NL

Telephone: 0113 343 7587

The trial is financed within a Cancer Research UK Accelerator award to the UK Advanced Radiotherapy Technologies Network (ART-NET).

# Trial insurance

Insurance is provided under the NHS indemnity scheme.

# Publications policy

All publications and presentations relating to the trial will be authorised by the Chief Investigator. Authorship will be determined by the Chief Investigator and will include the Chief Investigator and trial statisticians. Further authorship will be determined by centre accrual. All participating centres will be acknowledged in the manuscripts according to patient accrual.

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# Appendix B: CTCAE version 5 scoring for toxicity

|  |  |
| --- | --- |
| **Adverse Event** | **Grade** |
|  | 1 | 2 | 3 | 4 | 5 |
| Abdominal distension | Asymptomatic; clinical or diagnostic observations only; intervention not indicated | Symptomatic; limiting instrumental ADL | Severe discomfort; limiting self care ADL | - | - |
| Allergic reaction | Systemic intervention not indicated | Oral intervention indicated | Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated | Life-threatening consequences; urgent intervention indicated | Death |
| Abdominal pain | Mild pain | Moderate pain; limitinginstrumental ADL | Severe pain; limiting self care ADL | - | - |
| Anaphylaxis | - | - | Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related oedema/angioedema; hypotension | Life-threatening consequences; urgent intervention indicated | Death |
| Bloating | No change in bowel function or oral intake | Symptomatic, decreased oral intake; change in bowel function | - | - | - |
| Blurred vision | Intervention not indicated | Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL | Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL | Best corrected visual acuity of 20/200 or worse in the affected eye | - |
| Bruising (intramuscular injection site) | Localized or in a dependent area | Generalized | - | - | - |
| Cardiac arrest | - | - | - | Life-threatening consequences; urgent intervention indicated | Death |
| Cardiac disorders - Other, specify: Dizziness | Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated | Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL | Life-threatening consequences; urgent intervention indicated | Death |
| Chest pain- cardiac | Mild pain | Moderate pain; pain on exertion; limiting instrumental ADL; haemodynamically stable | Pain at rest; limiting self care ADL; cardiac catheterization; new onset cardiac chest pain; unstable angina | - | - |
| Constipation | Occasional or intermittentsymptoms; occasional use of stool softeners, laxatives, dietary modification, or enema | Persistent symptoms withregular use of laxatives orenemas; limiting instrumental ADL | Constipation with manual evacuation indicated; limiting self care ADL | Life-threateningconsequences; urgentintervention indicated | Death |
| Diarrhoea | Increase of <4 stools per day over baseline; mild increase in stoma output compared to baseline | Increase of 4 - 6 stools perday over baseline; moderate increase in stoma output compared to baseline | Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated;severe increase in stomaoutput compared to baseline; limiting self care ADL | Life-threateningconsequences; urgentintervention indicated | Death |
| Dry mouth | Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min | Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min | Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min | - | - |
| Glaucoma | Less than 8 mmHg of elevated intraocular pressure (EIOP); no visual field deficit | EIOP which can be reduced to 21 mmHg or under with topical medications and no visual field deficit | EIOP causing visual field deficits | Visual field deficit within the central 10 degrees of the visual field in the affected eye | - |
| Nausea | Loss of appetite without alteration in eating habits | Oral intake decreased withoutsignificant weight loss, dehydration or malnutrition | Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated | - | - |
| Palpitations | Mild symptoms; intervention not indicated | Intervention indicated | - | - | - |
| Intramuscular injection procedure | Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL | Life-threatening consequences; urgent intervention indicated | Death |
| Urinary retention | Urinary, suprapubic or intermittent catheter placement not indicated; able to void with some residual | Placement of urinary, suprapubic or intermittent catheter placement indicated; medication indicated | Elective invasive intervention indicated; substantial loss of affected kidney function or mass | Life-threatening consequences; organ failure; urgent operative intervention indicated | Death |
| Vomiting | Intervention not indicated | Outpatient IV hydration; medical intervention indicated | Tube feeding, TPN, or hospitalisation indicated | Life-threatening consequences | Death |

# Appendix C: End of treatment participant questionnaire



**HBB-SABR: A feasibility study investigating the effect of hyoscine butylbromide injections on cone beam CT quality when delivering abdomino-pelvic stereotactic ablative radiotherapy (SABR)**

**End of treatment questionnaire (version 1.0 06/11/2018)**

**IRAS Project ID: 252816**

**Participant initials:**

**Participant study number:**

**Trial site:**

For each of the following questions please tick the box to indicate your response.

1. How did you find having the hyoscine butylbromide injection before your radiotherapy treatment?

Fine, no problem for me [ ]

Somewhat difficult for me [ ]

Highly difficult for me [ ]

Not sure [ ]

1. If you had problems having the injection, what were they? (tick all that apply)

No problems with having injection [ ]

Injection was too painful [ ]

Too much of a delay in having treatment (as a result of the injection) [ ]

I had side effects from the injection that were difficult to cope with [ ]

If you noticed other problems, please write them in the box below:

1. If you were to have this treatment again in the future, would you be prepared to have an injection before every treatment?

Yes [ ]

No [ ]

Not sure [ ]

1. If you have any other comments, please write them in the box below:

# Appendix D: End of treatment staff questionnaire



**HBB-SABR: A feasibility study investigating the effect of hyoscine butylbromide injections on cone beam CT quality when delivering abdomino-pelvic stereotactic ablative radiotherapy (SABR)**

**End of treatment staff questionnaire (version 1.0 06/11/2018)**

**IRAS Project ID: 252816**

**Participant initials:**

**Participant study number:**

**Trial site:**

**Indicate staff role (e.g. therapy radiographer):**

For each of the following questions please tick the box to indicate your response.

1. How did you find patients having an injection of hyoscine butylbromide within the SABR workflow?

Fine, no problems [ ]

Somewhat problematic [ ]

Highly problematic [ ]

Not sure [ ]

1. If applicable, what reasons made it problematic having the injection within the SABR workflow? (Tick all that apply)

No problems [ ]

Caused delay to treatment of patients [ ]

Caused discomfort or side effects for patients [ ]

If you noticed other problems, please write them in this box:

1. Did you notice if the cone beam CT imaging appeared better when patients had hyoscine butylbromide injection? (e.g. less streak artefact, easier to see and match to target) (Tick all that apply)

Yes- less streak artefact [ ]

Yes- easier to see target [ ]

Yes- easier to match to target [ ]

No [ ]

1. Would you be happy for hyoscine butylbromide to be incorporated within routine SABR treatments?

Yes [ ]

No [ ]

Not sure [ ]

1. Please enter any other comments you have in the box below.

# Appendix E: End of treatment toxicity assessment form



**HBB-SABR: A feasibility study investigating the effect of hyoscine butylbromide injections on cone beam CT quality when delivering abdomino-pelvic stereotactic ablative radiotherapy (SABR)**

**Participant toxicity assessment (version 1.0 06/11/2018)**

**(To be completed by study co-investigator)**

**IRAS Project ID: 252816**

**Participant initials:**

**Participant study number:**

**Trial site:**

Score any toxicity judged to be related to hyoscine butylbromide injection using CTCAE version 5 criteria listed below. Insert score of 1 to 5 in box, or 0 if no toxicity elicited.

**Gastrointestinal toxicity:**

Abdominal distension 🗆

Abdominal pain 🗆

Bloating 🗆

Constipation 🗆

Diarrhoea 🗆

Nausea 🗆

Vomiting 🗆

**Genitourinary toxicity:**

Urinary retention 🗆

**Cardiovascular toxicity:**

Cardiac arrest 🗆

Chest pain- cardiac 🗆

Dizziness 🗆

Palpitations 🗆

**Ocular toxicity:**

Blurred vision 🗆

Acute glaucoma 🗆

**General toxicity:**

Allergic reaction 🗆

Anaphylaxis 🗆

Bruising (intramuscular injection site) 🗆

Dry mouth 🗆

Intramuscular injection procedure 🗆

|  |  |
| --- | --- |
| **Adverse Event** | **Grade** |
|  | 1 | 2 | 3 | 4 | 5 |
| Abdominal distension | Asymptomatic; clinical or diagnostic observations only; intervention not indicated | Symptomatic; limiting instrumental ADL | Severe discomfort; limiting self care ADL | - | - |
| Allergic reaction | Systemic intervention not indicated | Oral intervention indicated | Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated | Life-threatening consequences; urgent intervention indicated | Death |
| Abdominal pain | Mild pain | Moderate pain; limitinginstrumental ADL | Severe pain; limiting self care ADL | - | - |
| Anaphylaxis | - | - | Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related oedema/angioedema; hypotension | Life-threatening consequences; urgent intervention indicated | Death |
| Bloating | No change in bowel function or oral intake | Symptomatic, decreased oral intake; change in bowel function | - | - | - |
| Blurred vision | Intervention not indicated | Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL | Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL | Best corrected visual acuity of 20/200 or worse in the affected eye | - |
| Bruising (intramuscular injection site) | Localized or in a dependent area | Generalized | - | - | - |
| Cardiac arrest | - | - | - | Life-threatening consequences; urgent intervention indicated | Death |
| Cardiac disorders - Other, specify: Dizziness | Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated | Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL | Life-threatening consequences; urgent intervention indicated | Death |
| Chest pain- cardiac | Mild pain | Moderate pain; pain on exertion; limiting instrumental ADL; haemodynamically stable | Pain at rest; limiting self care ADL; cardiac catheterization; new onset cardiac chest pain; unstable angina | - | - |
| Constipation | Occasional or intermittentsymptoms; occasional use of stool softeners, laxatives, dietary modification, or enema | Persistent symptoms withregular use of laxatives orenemas; limiting instrumental ADL | Constipation with manual evacuation indicated; limiting self care ADL | Life-threateningconsequences; urgentintervention indicated | Death |
| Diarrhoea | Increase of <4 stools per day over baseline; mild increase in stoma output compared to baseline | Increase of 4 - 6 stools perday over baseline; moderate increase in stoma output compared to baseline | Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated;severe increase in stomaoutput compared to baseline; limiting self care ADL | Life-threateningconsequences; urgentintervention indicated | Death |
| Dry mouth | Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min | Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min | Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min | - | - |
| Glaucoma | Less than 8 mmHg of elevated intraocular pressure (EIOP); no visual field deficit | EIOP which can be reduced to 21 mmHg or under with topical medications and no visual field deficit | EIOP causing visual field deficits | Visual field deficit within the central 10 degrees of the visual field in the affected eye | - |
| Nausea | Loss of appetite without alteration in eating habits | Oral intake decreased withoutsignificant weight loss, dehydration or malnutrition | Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated | - | - |
| Palpitations | Mild symptoms; intervention not indicated | Intervention indicated | - | - | - |
| Intramuscular injection procedure | Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated | Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL | Life-threatening consequences; urgent intervention indicated | Death |
| Urinary retention | Urinary, suprapubic or intermittent catheter placement not indicated; able to void with some residual | Placement of urinary, suprapubic or intermittent catheter placement indicated; medication indicated | Elective invasive intervention indicated; substantial loss of affected kidney function or mass | Life-threatening consequences; organ failure; urgent operative intervention indicated | Death |
| Vomiting | Intervention not indicated | Outpatient IV hydration; medical intervention indicated | Tube feeding, TPN, or hospitalisation indicated | Life-threatening consequences | Death |

# Appendix F: Patient information sheet



**PATIENT INFORMATION SHEET: *A research study using hyoscine butylbromide to improve quality of images used to guide stereotactic radiotherapy in the lower abdomen and pelvis***

**IRAS Project ID: 252816**

**LTHT R+D Number:**

**REC Number:**

**Version 1.0 06/11/2018**

You are invited to take part in a research study. Before you decide whether or not you wish to take part it is important for you to understand why the study is being done and what it will involve if you agree to take part. Please read the following information carefully and discuss it with friends, relatives or your GP if you wish. Take time to decide whether or not you wish to take part. Please ask us if there is anything that is not clear, or if you would like more information.

***Summary of the study***

Accuracy of stereotactic radiotherapy is checked by using CT (computed tomography) scans. In the abdomen (tummy) and pelvis these scans are affected by motion of the bowel. In x-ray departments a drug called hyoscine butylbromide is used to reduce this motion and produce better images. It is not used in radiotherapy at present. We wish to perform a study to test if hyoscine butylbromide improves the image quality of the radiotherapy CT scans. Patients in the study will be given hyoscine butylbromide before some of their radiotherapy treatments and the images will be checked to see if they appear better when the drug is given.

***What is the purpose of the study?***

Radiotherapy has been advised for treatment of your cancer in the lower abdomen or pelvis. Radiotherapy is high-energy x-ray treatment. Stereotactic radiotherapy delivers a large amount of radiotherapy very accurately to the cancer and a small area around it. Each radiotherapy treatment is called a fraction and usually patients with your type of cancer have radiotherapy given in three or five fractions over one to two weeks. A type of scan called a CT (computed tomography) scan is performed before and after each fraction of radiotherapy. The images are used to check that the cancer is being accurately treated by the radiotherapy. However, movement of the bowel affects the quality of the images. Sometimes this makes it more difficult to see the cancer on the cone beam CT scan.

This trial will test a new way of improving the quality of the cone beam CT scans using a drug called hyoscine butylbromide. The main aim is to assess if this reduces the movement of the bowel and leads to better quality cone beam CT images. Hyoscine butylbromide is used routinely in the x-ray department for other types of scan such as MRI (magnetic resonance imaging). You may well have had it before if you have had an MRI scan. However, it is not used routinely in the radiotherapy department.

All patients in this trial would receive thehyoscine butylbromide. The drug would be administered as a single injection into the muscle of the buttocks just before your radiotherapy treatment. It would be given on alternate fractions of radiotherapy, which is before the first, third and fifth treatments if you are having five radiotherapy fractions (or the first and third treatments if you are having three radiotherapy fractions). This is so the trial can test whether the hyoscine butylbromide is having the predicted effect of reducing movement of the bowel or not.

This trial does not change any aspect of your radiotherapy treatment apart from having the hyoscine butylbromide injection. The drug could cause some patients side effects. This is discussed in the section ‘**Potential ways this study could harm those who take part**’ along with how we try to overcome this potential problem.

***What will happen to me if I take part?***

Before the treatment starts you will be assessed to check that you are suitable to take part in the study and you will be asked to read this patient information sheet. If you are happy to take part in the study you will be asked to sign a consent form.

About 3 weeks before the start of radiotherapy you will be asked to come to the radiotherapy department for a planning CT scan. This is used to design the radiotherapy. You may also be asked to drink some water or cordial an hour beforehand. You lie on a hard bed and pass through the scanner (which looks a bit like a large Polo mint) while a series of x-rays is taken. These let us see your insides around the cancer as a series of ‘slices’. The planning scan shows us how to target the radiotherapy so that the cancer gets a high dose but the area around it does not get too much radiotherapy.

The radiotherapy treatment involves coming for three or five visits over one to two weeks. There will be a gap of at least 2 days between treatment visits. You may also be asked to drink some water or cordial an hour before each treatment. This helps keep most of the bowel out of the way from the radiotherapy.

On the day of the radiotherapy treatment the first thing that happens is that you will come to the radiotherapy department and be directed around to the radiotherapy machine. You will get changed into a gown, and drink some water if this is needed.

When it is time for the radiotherapy treatment you will be given the hyoscine butylbromide injection into the muscle of one of your buttocks. This is an additional part of this research study.

You will then lie on your back on a hard bed under the radiotherapy machine. The machine that delivers the radiotherapy is called a linear accelerator. This is always about 50cm away from you. Before the radiotherapy is given you have a cone beam CT scan taken to let us check that the cancer is lined up in the same as at the planning scan. This process is called image-guided radiotherapy (IGRT). We might have to move the bed to make sure it is lined up as closely as possible to the positions on the planning scan. Once everything is lined up the radiotherapy is started. The radiotherapy machine moves around you once or twice. Nothing touches you during the radiotherapy and you do not see, feel or hear it- a bit like when you have an x-ray. It is important that you lie as still as you can during scans and radiotherapy. After the radiotherapy has been given another cone beam CT scan is taken. This is to check that nothing has moved during the treatment. The total length of time you will be lying in the treatment room is about 10 to 20 minutes.

After your final radiotherapy treatment you will be asked questions about any side effects that you might have experienced and you will be asked to complete a short questionnaire about the treatment.

***What are the possible risks and side effects of taking part?***

You might get side effects from the hyoscine butylbromide but we do not think that these are likely to be serious because the drug is routinely used in the x-ray department and most patients do not have significant problems with it.

**Short term side effects**

Hyoscine butylbromide can cause some temporary side effects but these usually settle within 30-60 minutes. Some patients may notice blurring of vision. We will ask you not to drive for around 45 minutes after the hyoscine butylbromide injection, or until any blurred vision has settled (usually within 60 minutes).

Rarely some patients can have a condition called acute glaucoma that they do not know about and it might be brought on by hyoscine butylbromide. **If you notice painful blurred vision after having hyoscine butylbromide then you must go straight to the nearest A&E department.**

It is relatively common to experience a temporary dry mouth after having hyoscine butylbromide. Other side effects that might happen include dizziness and palpitations (a feeling of your heart racing). Very uncommon side effects from hyoscine butylbromide might include an allergic reaction, difficulty in passing urine, abdominal pain or vomiting.

There have been cases where a small number of patients died after having tests in hospital where hyoscine butylbromide was also given. It is not certain whether or not the hyoscine butylbromide contributed towards their death but these patients also had underlying heart problems. This risk from hyoscine butylbromide is thought to be very small but the recommendation is not to give hyoscine butylbromide to patients with heart problems. **It is very important that you inform your oncologist if you have ever had any heart problems now or in the past.**

**Long term side effects**

We do not think that there are long term side effects from hyoscine butylbromide because the effects of the drug wear off quickly.

***What happens after treatment?***

On the last day of your radiotherapy we will ask you to complete a questionnaire about any side effects that you might have experienced and how you found having the hyoscine butylbromide injections alongside your radiotherapy.

Once the radiotherapy has finished, your usual oncology doctor will follow you up.

***What are the potential benefits of taking part?***

Taking part is completely voluntary.

The study would not change the radiotherapy treatment for you but it could help improve the treatment for future patients.

The possible ways taking part in this study could help are:

We will gain a better understanding of whether hyoscine butylbromide helps give us better radiotherapy CT images. This could help us more accurately target radiotherapy for future patients.

***What if something goes wrong?***

We would not expect a significant risk of severe side effects in the short or long term following this treatment. If you are harmed while taking part in this research project there are no special compensation arrangements. If you are harmed due to someone’s negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms may be available to you.

***Loss of capacity during the trial***

In the very unlikely event that you became unwell during the research study and were no longer able to make decisions for yourself (this is called ‘loss of capacity’), you would be withdrawn from the research study. No further information about you would be collected after this point, although we would use any information obtained prior to the event. Should you recover sufficiently you could continue within the study.

***Will my taking part in this study be kept confidential?***

The information collected about you during the course of the research will be kept strictly confidential. Your information will be entered into a password-protected database and no one outside the research group and the hospital team treating you will be allowed access to this information. Any information about you that leaves the hospital will be anonymous so that you cannot be recognised from it. Any forms completed about you during the trial will be anonymised using a unique identifying number and your initials rather than your name or other personal details.

***What will happen to the results of the study?***

The results of the study may be presented at scientific meetings nationally and internationally and published in the oncology literature. You will not be identified in any report or publication. This study forms part of a PhD research degree and will be described within a thesis for this degree.

***Who is organising the study?***

A research team, made up of consultant oncologists, clinical research fellow, physicists and a research radiographer is responsible for this study.

***Who has reviewed the study?***

The study has been reviewed and approved by Leeds (Central) Health Authority Research Ethics Committee.

***Contact for further information or to participate in the study:***

If you require any further information please contact Dr Finbar Slevin at St James’s Hospital on 0113 206 7630 saying you are calling about the hyoscine butylbromide SABR study, and we will call you back at a time convenient to you to discuss the study.

***General Data Protection Regulation statement***

The University of Leeds is the sponsor for this study based in the United Kingdom. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Leeds Teaching Hospitals NHS Trust (or other NHS Trusts participating within this study) will keep identifiable information about you for at least 5 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information by contacting the University data protection officer via e-mail on DPO@leeds.ac.uk.

***Use of personal data in this research study***

Leeds Teaching Hospitals NHS Trust (or other NHS Trusts participating within this study) will collect information from you and/or your medical records for this research study in accordance with our instructions.

Leeds Teaching Hospitals NHS Trust (or other NHS Trusts participating within this study) will keep your name, address, NHS number, date of birth and contact details confidential and will not pass this information to the University of Leeds. Leeds Teaching Hospitals NHS Trust (or other NHS Trusts participating within this study) will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Certain individuals from the University of Leeds and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The University of Leeds will only receive information without any identifying information. The people who analyse the information will not be able to identify you and will not be able to find out your name, address, date of birth, NHS number or contact details.

Leeds Teaching Hospitals NHS Trust (or other NHS Trusts participating within this study) will keep identifiable information about you from this study for at least 5 years after the study has finished.

***Future research use of data***

Your information could be used for research in any aspect of health or care, and could be combined with information about you from other sources held by researchers, the NHS or government.

Where this information could identify you, the information will be held securely with strict arrangements about who can access the information. The information will only be used for the purpose of health and care research, or to contact you about future opportunities to participate in research. It will not be used to make decisions about future services available to you, such as insurance.

Where there is a risk that you can be identified your data will only be used in research that has been independently reviewed by an ethics committee.

Thank you for taking the time to read this information sheet.

# Appendix G: Patient consent form



IRAS Project ID: 252816

Participant Identification Number for this trial:

**CONSENT FORM (version 1.0 06/11/2018)**

Title of Project: HBB-SABR: A feasibility study investigating the effect of hyoscine butylbromide injections on cone beam CT quality when delivering abdomino-pelvic stereotactic ablative radiotherapy (SABR)

Name of Researcher:

Please initial box

1. I confirm that I have read the information sheet dated 24th September 20178 (version 1.0) for the
above study. I have had the opportunity to consider the information, ask questions and have
had these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time
without giving any reason, without my medical care or legal rights being affected.
3. I understand that relevant sections of my medical notes and data collected during
the study may be looked at by individuals from University of Leeds, from regulatory authorities or
from the NHS Trust, where it is relevant to my taking part in this research. I give permission for
these individuals to have access to my records.
4. I understand that the information collected about me will be used to support
other research in the future, and may be shared anonymously with other researchers.
5. I understand that the information held and maintained byLeeds Teaching Hospitals NHS Trust (or other participating NHS Trusts)

may be used to help contact me or provide information about my health status.

1. I agree to take part in the above study.

Name of Participant Date Signature

Name of Person Date Signature

taking consent

# Appendix H: Image quality assessment form



**HBB-SABR: A feasibility study investigating the effect of hyoscine butylbromide injections on cone beam CT quality when delivering abdomino-pelvic stereotactic ablative radiotherapy (SABR)**

**Cone beam CT image quality assessment form (version 1.0 06/11/2018)**

**IRAS Project ID: 252816**

**Participant initials:**

**Participant study number:**

**Trial site:**

**Cone beam CT reference number:**

**Likert-type scale score:**

1 impossible to match [ ]

2 poor quality imaging for matching [ ]

3 satisfactory quality imaging for matching [ ]

4 excellent quality imaging for matching [ ]

**Factors influencing score:**

Streak artefact close to target [ ]

Lack of soft tissue contrast [ ]

Small target size [ ]

Lack of surrogate for target matching [ ]

**Please use this comments box to explain your decision:**

**Patient separation (cm):**

**Severity of streak artefact:**

None [ ]

Mild [ ]

Moderate [ ]

Severe [ ]

**Type of bowel causing artefact:**

Small bowel [ ]

Colon [ ]

Sigmoid [ ]

Rectum [ ]

**Location of node:**

Pre-sacral [ ]

Right external iliac [ ]

Left external iliac [ ]

Right internal iliac [ ]

Left internal iliac [ ]

Right common iliac [ ]

Left common iliac [ ]

Para-aortic [ ]

# Appendix I: Healthcare staff participant information sheet



**HEALTHCARE STAFF INFORMATION SHEET: *A research study using hyoscine butylbromide to improve quality of images used to guide stereotactic radiotherapy in the lower abdomen and pelvis***

**IRAS Project ID: 252816**

**LTHT R+D Number:**

**REC Number:**

**Version 1.0 18/01/2019**

You are invited to take part in a research study. Before you decide whether or not you wish to take part it is important for you to understand why the study is being done and what it will involve if you agree to take part. Please read the following information carefully and discuss it with friends, relatives or your GP if you wish. Take time to decide whether or not you wish to take part. Please ask us if there is anything that is not clear, or if you would like more information.

***Summary of the study***

Accuracy of stereotactic radiotherapy is checked by using CT (computed tomography) scans. In the abdomen (tummy) and pelvis these scans are affected by motion of the bowel. In x-ray departments a drug called hyoscine butylbromide is used to reduce this motion and produce better images. It is not used in radiotherapy at present. We wish to perform a study to test if hyoscine butylbromide improves the image quality of the radiotherapy CT scans. Patients in the study will be given hyoscine butylbromide before some of their radiotherapy treatments and the images will be checked to see if they appear better when the drug is given. We also wish to see if routinely giving hyoscine butylbromide within a busy radiotherapy department for stereotactic radiotherapy treatments would be possible.

***What is the purpose of the study?***

Radiotherapy has been advised for treatment of your patient’s cancer in the lower abdomen or pelvis. Radiotherapy is high-energy x-ray treatment. Stereotactic radiotherapy delivers a large amount of radiotherapy very accurately to the cancer and a small area around it. Each radiotherapy treatment is called a fraction and usually patients with this type of cancer have radiotherapy given in three or five fractions over one to two weeks. A type of scan called a CT (computed tomography) scan is performed before and after each fraction of radiotherapy. The images are used to check that the cancer is being accurately treated by the radiotherapy. However, movement of the bowel affects the quality of the images. Sometimes this makes it more difficult to see the cancer on the cone beam CT scan.

This trial will test a new way of improving the quality of the cone beam CT scans using a drug called hyoscine butylbromide. The main aim is to assess if this reduces the movement of the bowel and leads to better quality cone beam CT images. Hyoscine butylbromide is used routinely in the x-ray department for other types of scan such as MRI (magnetic resonance imaging). It is often used when patients have an MRI scan. However, it is not used routinely in the radiotherapy department.

All patients in this trial would receive thehyoscine butylbromide. The drug would be administered as a single injection into the muscle of the buttocks just before the radiotherapy treatment. It would be given on alternate fractions of radiotherapy, which is before the first, third and fifth treatments if patients are having five radiotherapy fractions (or the first and third treatments if patients are having three radiotherapy fractions). This is so the trial can test whether the hyoscine butylbromide is having the predicted effect of reducing movement of the bowel or not.

This trial does not change any aspect of the radiotherapy treatment apart from having the hyoscine butylbromide injection.

We also wish to see whether hyoscine butylbromide injections could be routinely used for stereotactic radiotherapy treatments within a busy radiotherapy department (for example, whether it interfered with your work). We also wish to know whether it seemed to help improve the quality of the cone beam CT images used before and after each radiotherapy fraction.

***What will happen to me if I take part?***

You will be asked to read this participant information sheet. If you are happy to take part in the study you will be asked to sign a consent form.

When the patient attends for their final radiotherapy treatment you will be asked to complete a short questionnaire. This will ask questions about how you found patients having the injection, any impact on your work and whether their cone beam CT images seemed to be of better quality when hyoscine butylbromide was given.

***What are the possible risks and side effects of taking part?***

We do not anticipate any risks or side effects occurring as a result of completing the questionnaire. No sensitive, embarrassing or upsetting topics will be discussed.

***What are the potential benefits of taking part?***

Taking part is completely voluntary.

The study could help improve the treatment for future patients.

The possible ways taking part in this study could help are:

We will gain a better understanding of whether hyoscine butylbromide helps give us better radiotherapy CT images. This could help us more accurately target radiotherapy for future patients.

***What if something goes wrong?***

We would not expect any risks or side effects as a result of completing the questionnaire. If you are harmed while taking part in this research project there are no special compensation arrangements. If you are harmed due to someone’s negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms may be available to you.

***Loss of capacity during the trial***

In the very unlikely event that you became unwell during the research study and were no longer able to make decisions for yourself (this is called ‘loss of capacity’), you would be withdrawn from the research study. No further information about you would be collected after this point, although we would use any information obtained prior to the event. Should you recover sufficiently you could continue within the study.

***Will my taking part in this study be kept confidential?***

The information collected about you during the course of the research will be kept strictly confidential. Your information will be entered into a password-protected database and no one outside the research group and the hospital team treating you will be allowed access to this information. Any information about you that leaves the hospital will be anonymous so that you cannot be recognised from it. Any forms completed about you during the trial will be anonymised using a unique identifying number and your initials rather than your name or other personal details.

***What will happen to the results of the study?***

The results of the study may be presented at scientific meetings nationally and internationally and published in the oncology literature. You will not be identified in any report or publication. This study forms part of a PhD research degree and will be described within a thesis for this degree.

***Who is organising the study?***

A research team, made up of consultant oncologists, clinical research fellow, physicists and a research radiographer is responsible for this study.

***Who has reviewed the study?***

The study has been reviewed and approved by Leeds (Central) Health Authority Research Ethics Committee.

***Contact for further information or to participate in the study:***

If you require any further information please contact Dr Finbar Slevin at St James’s Hospital on 0113 206 7630 saying you are calling about the hyoscine butylbromide SABR study, and we will call you back at a time convenient to you to discuss the study.

***General Data Protection Regulation statement***

The University of Leeds is the sponsor for this study based in the United Kingdom. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Leeds Teaching Hospitals NHS Trust (or other NHS Trusts participating within this study) will keep identifiable information about you for at least 5 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information by contacting the University data protection officer via e-mail on DPO@leeds.ac.uk.

***Use of personal data in this research study***

Leeds Teaching Hospitals NHS Trust (or other NHS Trusts participating within this study) will collect information from you and/or your medical records for this research study in accordance with our instructions.

Leeds Teaching Hospitals NHS Trust (or other NHS Trusts participating within this study) will keep your name, address, NHS number, date of birth and contact details confidential and will not pass this information to the University of Leeds. Leeds Teaching Hospitals NHS Trust (or other NHS Trusts participating within this study) will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Certain individuals from the University of Leeds and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The University of Leeds will only receive information without any identifying information. The people who analyse the information will not be able to identify you and will not be able to find out your name, address, date of birth, NHS number or contact details.

Leeds Teaching Hospitals NHS Trust (or other NHS Trusts participating within this study) will keep identifiable information about you from this study for at least 5 years after the study has finished.

***Future research use of data***

Your information could be used for research in any aspect of health or care, and could be combined with information about you from other sources held by researchers, the NHS or government.

Where this information could identify you, the information will be held securely with strict arrangements about who can access the information. The information will only be used for the purpose of health and care research, or to contact you about future opportunities to participate in research. It will not be used to make decisions about future services available to you, such as insurance.

Where there is a risk that you can be identified your data will only be used in research that has been independently reviewed by an ethics committee.

Thank you for taking the time to read this information sheet.

# Appendix J: Healthcare staff consent form



IRAS Project ID: 252816

Participant Identification Number for this trial:

**CONSENT FORM (version 1.0 18/01/2019)**

Title of Project: HBB-SABR: A feasibility study investigating the effect of hyoscine butylbromide injections on cone beam CT quality when delivering abdomino-pelvic stereotactic ablative radiotherapy (SABR)

Name of Researcher:

Please initial box

1. I confirm that I have read the information sheet dated 18th January 2019 (version 1.0) for the
above study. I have had the opportunity to consider the information, ask questions and have
had these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time
without giving any reason, without my medical care or legal rights being affected.
3. I understand that the information collected about me will be used to support
other research in the future, and may be shared anonymously with other researchers.
4. I agree to take part in the above study.

Name of Participant Date Signature

Name of Person Date Signature

taking consent