
# A randomised trial of **CO**nventional care versus **R**adioablation (stereotactic body radiotherapy) for **E**xtracranial oligometastases

PROTOCOL

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| Sponsor: | Royal Marsden NHS Foundation Trust |
| Approval: | Cancer Research UK: Clinical Trials Awards & Advisory Committee (CTAAC) |
| Funders: | Cancer Research UK |
| Coordinating Trials Unit: | ICR Clinical Trials and Statistics Unit (ICR-CTSU)<br>The Institute of Cancer Research |

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The CORE trial has been approved
by Cancer Research UK's Clinical Trials Awards & Advisory Committee (CTAAC)
The CORE trial is part of the National Institute for
Health Research Clinical Research Network Trial Portfolio

ICR The Institute of Cancer Research
The ROYAL MARSDEN NHS Foundation Trust
CANCER RESEARCH UK

## ADMINISTRATION

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### Trial Coordination

ICR-CTSU (a UKCRC registered CTU and an NCRI cancer clinical trials unit) is responsible for the central coordination of the trial on behalf of the Sponsor.

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This protocol was developed in part at the ECCO-AACR-EORTC-ESMO Workshop on Methods in Clinical Cancer Research, Flims, Switzerland June 2013 by Katharine Aitken.

The Trial Management Group (TMG) will be constituted from members of the Protocol Development Group and will include the Chief Investigator, ICR-CTSU Scientific Lead, Co-investigators and identified collaborators, the Trial Statistician and Trial Manager. Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of sites and professional groups. Where possible, membership will include a lay/consumer representative. A copy of the current membership of the TMG can be obtained from the CORE Trial Manager at ICR-CTSU.

Protocol Authorised by:

| Name & Role | Signature | Date |
|---|---|---|
| Dr Vincent Khoo<br>(Chief Investigator) | | 14/12/2018 |

This protocol describes the CORE trial and provides information about procedures for entering participants into this trial. The protocol should not be used as a guide for the treatment of patients outside of this trial.

**Every care was taken in the preparation of this protocol, but corrections or amendments may be necessary. Protocol amendments will be circulated to participating sites as they occur, but sites entering patients for the first time are advised to contact ICR-CTSU to confirm they have the most recent version.**

## CONTENTS

CORE TRIAL SUMMARY

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| PROTOCOL TITLE | **CORE:** A randomised trial of COnventional care versus Radioablation (stereotactic body radiotherapy) for Extracranial metastases |
| TARGET DISEASE | Breast, prostate and non-small cell lung cancer |
| STUDY OBJECTIVES | **Primary:**<br>To evaluate if the addition of SBRT to standard therapy improves progression free survival outcomes in patients with a limited burden of oligometastatic disease.<br><br>**Secondary:**<br>1. To demonstrate feasibility of recruitment<br>2. To demonstrate deliverability of SBRT within dosimetric constraints<br>3. To evaluate if the addition of SBRT to standard therapy improves overall survival<br>4. To evaluate the lesion local control rates in those receiving SBRT<br>5. To evaluate the acute and late toxicity associated with the addition of SBRT to standard therapy<br>6. To compare the quality of life (QoL) in patients receiving SBRT compared to those receiving standard therapy alone.<br><br>**Exploratory:**<br>To evaluate if the addition of SBRT to standard therapy improves freedom from widespread metastatic disease (FFWMD). |
| STUDY DESIGN | Phase II/III, multi-centre, parallel group randomised controlled trial. |
| TRIAL POPULATION | Patients with breast, prostate or non-small cell lung primary cancer and ≤3 extracranial oligometastases suitable for SBRT. |
| RECRUITMENT TARGET | 230 patients |
| TRIAL DESIGN | Patients will be randomised (1:1) between:<br>1. Standard of care (SOC) therapy (Control)<br>2. Stereotactic Body Radiation Therapy (SBRT) + SOC.<br>SBRT dose and fractionation regimen will be dependent on metastatic site and proximity to normal tissues with SBRT delivery being non-platform specific. |
| PRIMARY ENDPOINT | Progression Free Survival (PFS) |
| SECONDARY ENDPOINTS | 1. Feasibility of recruitment<br>2. Feasibility of SBRT delivery<br>3. Overall survival (OS)<br>4. Local lesion control<br>5. Acute and late toxicity related to SBRT treatment.<br>6. Patient reported QoL |
| EXPLORATORY ENDPOINTS | Freedom from widespread metastatic disease (FFWMD). |
| ELIGIBILITY CRITERIA | **Inclusion criteria**<br>1. Age ≥ 18 years<br>2. WHO performance status 0-2<br>3. Histological confirmation of primary breast, non-small cell lung (NSCLC) or prostate cancer<br>4. Predicted life expectancy > 6 months |

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| | 5. ≤ 3 metastatic lesions (total). A maximum of 2 different organ systems (e.g. liver, lung, bone, nodal) may contain metastases but the total number of lesions must not exceed 3.<br>6. All metastases must be visible, imaging defined targets and be suitable for treatment with SBRT in accordance with the dose fractionation options specified in the protocol.<br>7. Patients who have received prior ablative therapy (e.g. surgery, RFA or SBRT) for metastatic disease are eligible, as long as this site is controlled on imaging at the point of trial entry and the total number of metastases over time since diagnosis of metastatic disease does not exceed 3. Patients with 2 or 3 metastases in which ablative therapy (e.g. surgery/RFA) to 1 site is deemed appropriate as part of standard therapy may be entered into the trial after ablative treatment, following successful delivery of clinical treatment. Ablative therapy (e.g. surgery, RFA, cryoablation, SBRT) is not permissible as a standard of care option following randomisation for patients as part of the trial.<br>8. Metachronous metastatic disease presentation only. Primary site must be controlled.<br>NSCLC patients with synchronous presentation of a single brain metastasis with the primary lung malignancy are eligible as long as both sites of disease have received radical treatment. Both primary lung site and solitary synchronous brain metastasis must be controlled at trial entry, and the total number of metastases over time including the brain metastasis must not exceed 3.<br>Disease-free interval:<br>*Breast*: ≥ 6 months from completion of radical treatment including any adjuvant therapy to diagnosis of metastases. Patients who have relapsed whilst on adjuvant endocrine therapy are eligible.<br>*NSCLC*: ≥ 4 months from completion of radical treatment (<u>not</u> including any adjuvant chemotherapy) to diagnosis of metastases.<br>*Prostate*: ≥ 6 months from completion of radical treatment including any adjuvant therapy to diagnosis of metastases. Patients who have relapsed whilst on adjuvant endocrine therapy are eligible.<br>9. Systemic therapy naïve in the metastatic setting. Prior systemic therapy in the adjuvant setting is permitted. Patients who have had a change in endocrine therapy due to diagnosis of oligometastatic disease can be entered into the CORE trial as long as entry is within 8 weeks of this change in therapy for prostate cancer patients and within 10 weeks of this change in therapy for breast cancer patients.<br>10. Adequate baseline organ function to allow SBRT to all relevant targets<br>11. Negative pregnancy test (for women of childbearing potential)<br>12. Written informed consent |

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| | **Exclusion criteria**<br>1. Intra-cranial metastases (not meeting above inclusion criterion 8)<br>2. Malignant pleural effusion<br>3. Malignant peritoneal disease<br>4. Any single metastasis >6cm,( >5cm for lung metastases)<br>5. Prior radiotherapy to a site that precludes safe delivery of SBRT.<br>6. Co-morbidities precluding staging or follow up imaging, or precluding procedures required to facilitate SBRT<br>7. Loco-regional nodal relapse where surgery is considered the standard of care and is technically feasible. Patients with internal mammary chain or supraclavicular fossa lymph node relapses of breast cancer are eligible if SBRT dose constraints can be met. Patients with axillary nodal relapse from breast cancer are excluded.<br>8. Spinal cord compression, or impingement of the cord or any other situation whereby the clinician feels that urgent radiotherapy to the spine is required (within 24 hours).<br>9. Any condition or significant clinical co-morbidities that precludes the safe delivery of SBRT (e.g. history of clinically significant diffuse interstitial lung disease if SBRT to lung metastases or lesions adjacent to lungs are considered or clinically significant colitis i.e. ulcerative colitis /Crohn's disease if SBRT to the pelvis or abdomen is considered).<br>10. Prostate cancer patients relapsing on Androgen Deprivation Therapy (ADT) which was started for biochemical relapse without staging investigations to define their relapse status, or who have relapsed on CAB which was started for biochemical relapse.<br>11. Prostate cancer patients receiving or have previously received abiraterone, enzalutamide or chemotherapy e.g. docetaxel.<br>12. Previous malignancy within the last 2 years (except basal cell carcinoma or squamous cell carcinoma of the skin), or if previous malignancy is expected to significantly compromise 5 year survival.<br>13. Patients whose entry to the trial will cause unacceptable clinical delays to their planned management.<br>14. Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule. |
| FOLLOW UP | All patients will be reviewed every 3 months with a clinical examination and tumour markers (where applicable) during years 1 and 2, and 6 monthly thereafter up to 5 years. Staging and follow up imaging protocols will be tumour type dependent:<br>• *Breast* = 3 monthly CT scans for years 1 & 2, and 6 monthly thereafter to 5 years.<br>• NSCLC = 3 monthly CT scans for years 1 & 2, 6 monthly to year 3 and then annually to year 5.<br>• *Prostate* = CT will be performed at 6, 12 and 24 months with imaging triggered by appropriate PSA rises. A rising PSA defined as 2 successive PSA rises from nadir, measured a minimum of 4 weeks apart. If the overall PSA rise has a doubling time of ≥ 3 months or |

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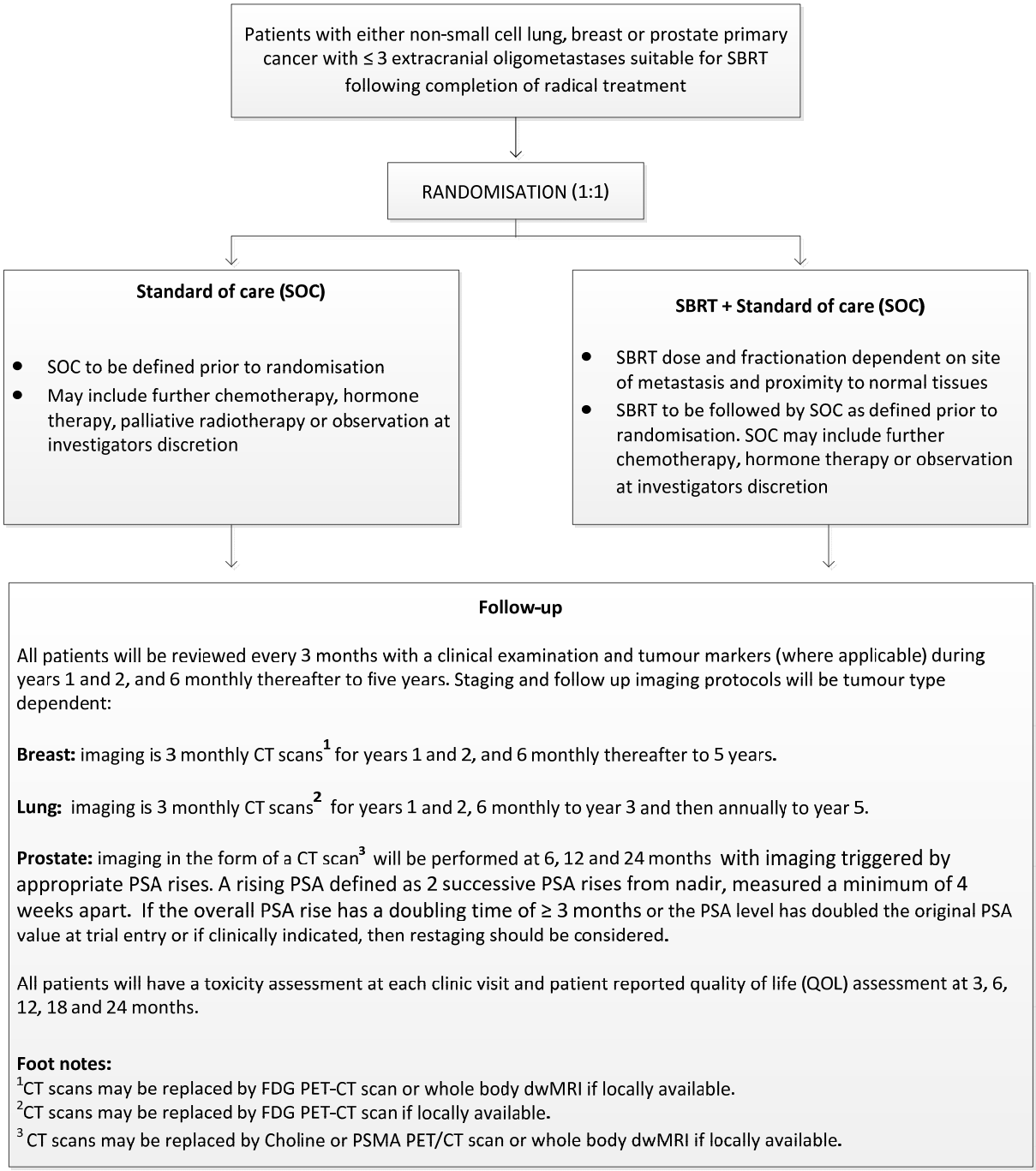
| | the PSA level has doubled the original PSA value at trial entry or if clinically indicated, then restaging should be considered.<br><br>All patients will have a toxicity assessment at each clinic visit and patient reported quality of life (QOL) assessment at 3, 6, 12, 18 & 24 months. |

TRIAL SCHEMA



# 1 INTRODUCTION

## 1.1 Background

The term oligometastases was first coined by Hellman and Weischelbaum in 1995 [1]. It describes the concept of an intermediary metastatic state, in which cancer exists as a limited number of metastases at first, before cells acquire the ability to metastasise more widely. It is hypothesized that successful eradication of disease at an oligometastatic stage may improve survival outcomes, and potentially may even result in cure for a select few [2, 3]. Whilst it is difficult to quantify the exact number of patients with true oligometastatic disease, an increase in the use of surveillance imaging, together with improved diagnostic sensitivity, has led to more patients being diagnosed with a limited metastatic disease burden at an asymptomatic stage.

Historically once a solid tumour has acquired the ability to spread to distant sites, treatment has focused on systemic therapy given with palliative intent. However it is now established that long term survival is possible following surgical resection of limited sites of metastatic disease. In a series of mixed primary sites, 26% of patients remained alive 10 years after pulmonary metastectomy [4]. Similarly, 5-year survival rates following chemotherapy and surgery for liver metastases in colorectal cancer have now improved to 40-50% [5-7]. This supports the concept that an oligometastatic disease state exists where radical treatment may result in long-term survival.

Stereotactic body radiation therapy (SBRT) is an advanced radiotherapy technique that may be used to deliver ablative doses of radiotherapy. It is non-invasive and can be used to treat a variety of oligometastatic disease sites. It may also be considered in patients when the option for surgery is not possible.

## 1.2 Known risks and benefits of SBRT

A number of retrospective and prospective cohort studies reporting outcomes for SBRT for the treatment of oligometastatic disease sites have been reported. These data have recently been succinctly reviewed [2, 3]. In general these studies demonstrate high rates of local control, together with acceptable rates of toxicity (generally <10% ≥ Grade 3). Anecdotally progression-free survival rates in these cohorts are better than would be expected in stage IV disease, with disease-free survival varying from 20-50% at 17-48 months follow up [3]. However survival data from historical cohort studies may be inherently biased as result of a highly selected patient population and other confounders. The lack of randomized data limits interpretation and a control group is required to evaluate the true benefit of adding local therapy to systemic treatment in this context.

Ascertaining which patients are most likely to benefit from such an approach is key. In this trial, only patients with ≤ 3 metastases will be included. This is based on the observations of Salama et al who reported outcomes of 61 patients with 1 to 5 metastases from miscellaneous primary sites treated with SBRT [12]. They found that patients with ≤ 3 metastases have better progression free and overall survival when compared to patients treated for 4 to 5 metastases, all of whom had experienced progression within 9 months of treatment. In addition 75% of patients with 4 or 5 metastases went on to develop widespread metastatic disease in comparison to 46% of patients with 1-3 metastases.

The potential therapeutic benefit of adding tumour ablation to standard therapy may vary between tumour sites, reflecting both different underlying tumour biology and natural disease courses. Milano et al reported a series of 121 patients with up to 5 sites of metastases from miscellaneous primary sites with a median follow up of 4.5 years. They found that patients with

breast cancer had significantly improved local control and overall survival rates at 6 years (LC 87%, OS 47%), in comparison to non-breast patients (LC 65%, OS 59%) [9]. Additionally, patients with breast cancer were less likely to develop widespread metastatic disease following SBRT compared to those with non-breast cancers (36% vs 13%). These results may simply reflect the better overall prognosis of patients with metastases from breast cancer. At present there is insufficient evidence to be able to predict which cancers may benefit most from such an approach. In this trial we will investigate the scientific hypothesis that the addition of SBRT to standard therapy improves survival outcomes, focusing on common primary tumour sites where oligometastatic disease is encountered.

### 1.3 Description of population

This study will be initiated in patients treated for primary breast, non-small cell lung or prostate cancer. At present there is insufficient clinical evidence and no strong biological rationale to suggest that SBRT would be effective, if at all, for some primary tumour sites and not others. Assessing efficacy overall in these prevalent tumour sites (rather than in individual primary tumour sites) at this stage will enable a positive "signal" to be identified more quickly. It is recognised that these three cancer types have different natural histories and time courses for progression. Inclusion of these three primary sites is a pragmatic decision aiming to provide a patient population that is large enough to permit adequate recruitment of patient cases and which is sufficiently homogenous to allow some conclusions with regards to the efficacy of SBRT in this context to be drawn.

### 1.4 Study rationale

SBRT has rapidly evolved as a radiotherapy technique over the past 5-10 years due to advances in radiation technology. In the UK, SBRT has been recently introduced into a number of specialist centres and nationally an SBRT service is being developed.

A randomised trial design is required for two reasons. Outcome data from historical cohort studies may be inherently biased as result of a highly selected patient population and other confounders. Additionally, it is important to establish prospectively the control group outcomes in contemporaneous oligometastatic patients treated with standard therapy. These are likely to represent a sub-set of patients with an improved prognosis compared to the general stage IV population and therefore extrapolation of outcome data as a comparator is unreliable.

## 2 TRIAL OBJECTIVES

### 2.1 Primary objective

To evaluate if the addition of SBRT to standard therapy improves progression free survival outcomes in patients with a limited burden of oligometastatic disease.

### 2.2 Secondary objectives

1. To demonstrate feasibility of recruitment to a randomised trial of SBRT plus standard therapy versus standard therapy alone.
2. To demonstrate deliverability of SBRT within dosimetric constraints.
3. To evaluate if the addition of SBRT to standard therapy improves overall survival.
4. To evaluate the acute and late toxicity associated with the addition of SBRT to standard therapy.

5. To evaluate the lesion local control rates in those receiving SBRT.
6. To compare the quality of life (QoL) in patients receiving SBRT compared to those receiving standard treatment alone.

### 2.3 Exploratory objectives

To evaluate if the addition of SBRT to standard therapy improves freedom from widespread metastatic disease (FFWMD).

## 3 TRIAL DESIGN

CORE is a phase II/III, multi-centre, non-blinded, parallel group randomised controlled trial in patients with breast, prostate or NSCLC primary cancer comparing standard of care (SOC) with or without SBRT for extra-cranial metastases. The aim of the phase II study is to demonstrate 1) feasibility of recruitment, 2) deliverability of the study in a multi-centre setting and 3) activity of SBRT, based on progression free survival, across the three tumour types. If all three aims are achieved the trial will be amended to roll into parallel tumour-site specific phase III trials.

Eligible patients are those with either primary breast, prostate or NSCLC who have presented with ≤3 extra-cranial, metachronous, oligometastases, all suitable for SBRT. Patients will be randomised in a 1:1 ratio to either SOC or SOC with the addition of SBRT. Choice of SOC treatment is at the discretion of the local oncologist and defined per patient prior to randomisation (see Section 9 Trial Treatment). Patients randomised to SBRT+SOC will receive a dose and fractionation regimen dependent on the metastatic site and proximity to dose limiting organs and normal tissues. Treatment will take place within 6 weeks of randomisation. The average scheme would be 3 treatments over 5 days but the maximum period of SBRT duration could be 8 treatments over 19 days.

All patients will be reviewed every 3 months with a clinical examination and tumour markers (where applicable) during years 1 and 2, and 6 monthly thereafter to 5 years. Staging and follow up imaging protocols will be tumour type dependent:

- **Breast:** 3 monthly CT scans for years 1 and 2, and 6 monthly thereafter to 5 years.
- **NSCLC:** 3 monthly CT scans for years 1 and 2, 6 monthly to year 3, then annually to 5 years.
- **Prostate:** CT scans will be performed at 6, 12 and 24 months with imaging triggered by appropriate PSA rises. A rising PSA defined as 2 successive PSA rises from nadir, measured a minimum of 4 weeks apart, will be used to trigger additional imaging (CT) between these time points.

All patients will have a toxicity assessment at each clinic visit and patient reported quality of life (QOL) assessment at 3, 6, 12, 18 and 24 months.

# 4 STUDY ENDPOINTS

## 4.1 Primary endpoint

Progression free survival.

## 4.2 Secondary endpoints

1. Recruitment rate and proportion of patients receiving SBRT (if allocated) in the absence of new developing widespread disease.
2. Recruitment of patients receiving SBRT within the dosimetric constraints.
3. Overall survival (OS).
4. Local lesion control.
5. Clinician reported acute and late radiation related toxicity (CTCAE version 4 and RTOG).
6. Patient reported QoL (EORTC QLQ C30 and EQ-5D questionnaire).

## 4.3 Exploratory endpoint

Freedom from widespread metastatic disease (FFWMD) i.e. freedom from disease not amenable to further ablative therapy (surgery, radiofrequency ablation (RFA), SBRT).

# 5 PATIENT SELECTION & ELIGIBILITY

## 5.1 Number of participants

The aim is to recruit 230 participants; 115 to SOC and 115 to SBRT + SOC. To ensure maximum feasibility information is obtained for each cohort, recruitment beyond 230 is permissible, to a maximum of 270. The decision to continue recruitment will be dependent on observed rates of accrual within each cohort and existing timelines for recruitment. Any decision to continue past 230 will be agreed in advance with the Trial Steering Committee.

## 5.2 Source of participants

Participants will be recruited from participating sites in the UK. Participation of sites from other countries will be dependent on adequate quality assurance and governance arrangements and on local funding. Most potential participants are likely to be identified in oncology clinics and discussed at Multi-Disciplinary Team (MDT) meetings.

## 5.3 Inclusion criteria

1. Age ≥ 18 years
2. WHO performance status 0-2
3. Histological confirmation of primary malignancy (histological confirmation of metastasis is not mandatory but should be performed in any situation where there is diagnostic uncertainty). Patients with breast, NSCLC or prostate primary malignancies are eligible.
4. Predicted life expectancy > 6 months
5. ≤ 3 metastatic lesions (total). A maximum of 2 different organ systems (e.g. liver, lung, bone, nodal) may contain metastases but the total number of lesions must not exceed 3. For example, a patient with 3 liver metastases or 1 liver metastasis and 2 lung metastases would

be eligible. A patient with 1 lung metastasis, 1 liver metastasis and an adrenal metastasis is ineligible.

6. All metastases must be visible, imaging defined targets and be suitable for treatment with SBRT in accordance with the dose fractionation options specified in the protocol. (See the associated CORE trial radiotherapy delivery guidelines for detailed SBRT guidance by metastatic site)
7. Patients who have received prior ablative therapy (e.g. surgery, RFA or SBRT) for metastatic disease are eligible, as long as this site is controlled on imaging at the point of trial entry and the total number of metastases over time since diagnosis of metastatic disease does not exceed 3. Patients with 2 or 3 metastases in which ablative therapy (e.g. surgery/RFA) to 1 site is deemed appropriate as part of standard therapy may be entered into the trial following successful delivery of the ablative treatment. Ablative therapy (e.g. surgery, RFA, cryoablation, SBRT) is not permissible as a standard of care option following randomisation for patients as part of the trial.
8. Only patients with metachronous metastatic disease presentation are eligible. Primary site must be controlled.

   NSCLC patients with synchronous presentation of a single brain metastasis with the primary lung malignancy are eligible as long as both sites of disease have received radical treatment. Both primary lung site and solitary synchronous brain metastasis must be controlled at trial entry, and the total number of metastases over time including the brain metastasis must not exceed 3.

   Permissible disease-free intervals are:

   **Breast**: ≥ 6 months from completion of radical treatment including any adjuvant therapy to diagnosis of metastases. Patients who have relapsed whilst on adjuvant endocrine therapy are eligible.

   **NSCLC**: ≥ 4 months from completion of radical treatment (<u>not</u> including any adjuvant chemotherapy) to diagnosis of metastases.

   **Prostate**: ≥ 6 months from completion of radical treatment including any adjuvant therapy to diagnosis of metastases. Patients who have relapsed whilst on adjuvant endocrine therapy are eligible.
9. Only patients who are systemic therapy naïve in the metastatic setting are eligible. Prior systemic therapy in the adjuvant setting is permitted. Patients who have had a change in endocrine therapy due to the diagnosis of oligometastatic disease can be entered into the CORE trial as long as entry is within 8 weeks of this change in therapy for prostate cancer patients and within 10 weeks of this change in therapy for breast cancer patients.
10. Adequate baseline organ function to allow SBRT to all relevant targets dependent on location of metastatic subsite
11. Negative pregnancy test (for women of childbearing potential)
12. Written informed consent.

### 5.4 Exclusion criteria

1. Intra-cranial metastases (not meeting above inclusion criterion 8).
2. Malignant pleural effusion
3. Malignant peritoneal disease
4. Any single metastasis >6cm,( >5cm for lung metastases)

5. Prior radiotherapy to a site that precludes safe delivery of SBRT
6. Co-morbidities precluding staging or follow up imaging, or precluding procedures required to facilitate SBRT
7. Loco-regional nodal relapse where surgery is considered the standard of care and is technically feasible. Patients with internal mammary chain or supraclavicular fossa lymph node relapses of breast cancer are eligible if SBRT dose constraints can be met. Patients with axillary nodal relapse from breast cancer are excluded
8. Spinal cord compression, or impingement of the cord or any other situation whereby the clinician feels that urgent radiotherapy to the spine is required (within 24 hours)
9. Any condition or significant clinical co-morbidities that preclude the safe delivery of SBRT (e.g. history of clinically significant diffuse interstitial lung disease if SBRT to lung metastases or lesions adjacent to lungs are considered or clinically significant colitis i.e. ulcerative colitis /Crohn's disease if SBRT to the pelvis or abdomen is considered).
10. Prostate cancer patients who have relapsed on Androgen Deprivation Therapy (ADT) which was started for biochemical relapse without staging investigations to define their relapse status, or who have relapsed on CAB which was started for biochemical relapse.
11. Prostate cancer patients receiving or have previously received abiraterone, enzalutamide or chemotherapy e.g. docetaxel.
12. Previous malignancy within the last 2 years (except basal cell carcinoma or squamous cell carcinoma of the skin), or if previous malignancy is expected to significantly compromise 5 year survival.
13. Patients whose entry to the trial will cause unacceptable clinical delays to their planned management.
14. Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

### 5.5 Life style guidelines

All female participants (including SOC patients as SOC may also involve non-high dose RT) must be surgically sterile or be post-menopausal, or must agree to use effective contraception during the period of therapy only.

All male participants (including SOC patients as SOC may also involve non-high dose RT) must be surgically sterile or must agree to use effective contraception during the period of therapy only.

Effective contraception is defined as double barrier contraception (e.g. condom plus spermicide in combination with a diaphragm, cervical cap or intrauterine device).

## 6 SCREENING

### 6.1 Screening log

All participating sites will be required to keep a log of all participants with either primary breast, prostate or NSCLC who have presented with oligo-metastatic disease (≤3 metastases or sites) that are potentially eligible for this study. The information collected on the log will include:

- Date patient identified
- Screening outcome (patient approached/accepted participation/declined participation)

- Reasons for not approaching / declining participation (if available)
- Trial ID (if applicable)
- Basic primary tumour characteristics (ER and HER2 status for breast, EGFR status for NSCLC and castrate status for prostate cancer patients).

This information will be used by the TMG to monitor recruitment activity and will inform phase III study planning. No patient identifiable data will be sent to ICR-CTSU at this stage.

### 6.2 Procedure for obtaining informed consent

The Principal Investigator (or designated individual) must ensure that each trial patient is fully informed about the nature and objectives of the trial and possible risks associated with participation. Participants should be given the current ethics approved CORE patient information sheet for their consideration. Patients should only be asked to consent to the study after they have had sufficient time to consider the trial, and the opportunity to ask any further questions.

No protocol specified assessments should be conducted until the CORE consent form has been signed and dated by both the patient and the Investigator, unless they are performed routinely as part of standard patient care.

Molecular biomarker and imaging translational sub-studies are planned subject to confirmation of funding and subsequent ethics approval. Patients will be made aware that participation in such sub-studies is entirely voluntary and refusal to participate will not result in ineligibility to participate in the main clinical trial and will not impact the medical care received.

Confirmation of the patient's consent and the informed consent process (including the date of consent) must be documented in the patient's medical notes. A copy of the signed consent form should be provided to the patient and the original retained in the investigator site file, which must be available for verification by ICR-CTSU study staff at any time.

### 6.3 Participation in other clinical trials

Patients who fulfil the eligibility criteria will be given the opportunity to participate in CORE if they have participated in other clinical trials prior to recruitment.

Participation in other clinical trials post-randomisation into CORE will be considered on a case by case basis by the Trial Management Group.

## 7 RANDOMISATION

Patients must be randomised centrally by the trials unit (ICR-CTSU) before trial treatment can commence.

Patients should be randomised by telephoning ICR-CTSU on:
**+44 (0)20 8643 7150**
09.00-17.00 (UK time) Monday to Friday

For non UK patients, randomisation outside of UK office hours should be requested by faxing the ICR-CTSU on:

**+44 (0) 20 8770 7876**
09.00-17.00 (UK time) Monday to Friday

Further details of randomisation procedures for non-UK patients will be detailed in the relevant country specific group appendix.

Randomisation should take place as close to the planned start date of treatment as possible. Treatment allocation will be by minimisation (with a random component). An eligibility and randomisation checklist must be completed prior to randomisation.

The following information will be required at randomisation:

- Name of hospital, consultant, name of QA approved clinician to deliver SBRT to specific metastatic site and person registering patient
- Confirmation that patient has given written informed consent for trial and for any sub-studies
- Confirmation that patient is eligible for the trial by completion of the eligibility checklist
- Patient's full name, hospital number, date of birth, postcode and NHS/CHI number (or equivalent for international participants)
- Site of primary tumour (breast, NSCLC, prostate)
- Basic primary tumour characteristics including ER status for breast cancer; EGFR status for NSCLC if known; Endocrine therapy naïve (includes patients who have started endocrine therapy in the 8 weeks prior to randomisation) vs castrate resistant for prostate cancer patients
- Details of planned standard of care including type and duration
- Sites of metastatic disease

The caller will be given the patient's unique randomisation number (Trial ID) and treatment allocation.

ICR-CTSU will send written confirmation of randomisation via email to the relevant personnel at the recruiting site to confirm a patients' entry into the trial.

# 8 TRIAL ASSESSMENTS

All trial specific assessments must be completed after the patient has given informed consent.

## 8.1 Pre-randomisation

All assessments should be conducted within 42 days prior to randomisation.

### 8.1.1 All patients

- Histological confirmation of primary breast, prostate or NSCLC*
- Complete medical history
- Physical examination including WHO performance status, body weight, height, blood pressure
- Negative pregnancy test (for women of childbearing potential)
- Baseline tumour assessment.

* Will be before 42 days prior to randomisation

The following are required to evaluate if patients are suitable for SBRT to the relevant metastatic subsite:

### 8.1.2 Liver/ Spine/ Lung metastases/Bone metastases

| | |
|---|---|
| Liver metastases | • Clotting screen (INR), liver function (ALT/AST, bilirubin, albumin) to ascertain sufficient organ function to enable SBRT.<br>• A DimercaptoSuccinic Acid (DMSA) scan or equivalent may be required as per local guidelines if the renal radiation dose is likely to be significant. |
| Spine metastases | • MRI whole spine. |
| Lung metastases | • Pulmonary function tests to include FEV 1, FVC, and TLCO/KCO. Follow up pulmonary function tests if clinically indicated. |
| Bone metastases | • Bone lesions defined as non-measurable via RECIST v1.1 should still be assessed at baseline if the lesion(s) is a visible, image definable target suitable for SBRT planning and delivery. |

### 8.1.3 Breast primary site

- CT scans of the chest, abdomen and pelvis. Scans may be replaced by FDG PET-CT scan (as long as the CT scan is of diagnostic quality), or whole body dwMRI if locally available.
- Baseline measure of tumour marker Ca 15-3 (where locally available)

### 8.1.4 NSCLC primary site

- Patients in the SBRT + SOC group will need to stop tyrosine kinase inhibitor (TKI) treatment **at least one day and up to one week prior** to commencing SBRT. Patients can recommence TKI treatment one day after receiving their last fraction.
- CT scans of the chest, abdomen and pelvis. Scans may be replaced by FDG PET/CT scan (as long as the CT scan is of diagnostic quality).
- CT brain with contrast or MRI brain with contrast to exclude intracranial disease.

### 8.1.5 Prostate primary site:

- Bone scan and CT scans of the chest, abdomen and pelvis. These scans may be replaced by choline or PSMA PET/CT scan (as long as the CT scan is of diagnostic quality), or by whole body dwMRI if locally available
- PSA and testosterone.

## 8.2 Pre-Treatment assessments

The following assessments should be conducted once patient eligibility has been confirmed:

- Full blood count, urea and electrolytes, LFTs (and clotting screen (INR) for patients with liver metastases)
- Assessment of baseline symptoms using NCI CTCAE v.4.0 and RTOG and concomitant medications taken from 30 days prior to randomisation
- Baseline quality of life questionnaire (EORTC QLQ C30 and EQ5D) (should be before treatment allocation is known to the patient).

## 8.3 Follow-up assessments

### 8.3.1 End of Treatment – All patients

The following assessments should be conducted within +/- 7 days of the last fraction of SBRT visit or within 6 weeks after randomisation for patients randomised to SOC only.

- Directed physical examination including WHO performance status, weight and height.
- Assessment of acute toxicity using NCI CTCAE v.4.0 and concomitant medications
- Quality of life questionnaire (EORTC QLQ C30 and EQ5D).

### 8.3.2 Breast Primary Patients

The following assessments should be conducted for all breast primary patients at each follow up visit (Months 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54 and 60 months post randomisation):

- CT scan of chest, abdomen and pelvis. This may be replaced by FDG PET/CT scan as long as the CT scan is of diagnostic quality, or whole body dwMRI if locally available.
- Tumour assessment according to RECIST v.1.1 criteria, where possible. In instances where RECIST assessment is not possible assessment by other methods should be considered or a clinical assessment of widespread progression should be performed. Assessment of tumour marker Ca 15-3 (where locally available).
- Physical examination including WHO performance status, weight and height.
- Assessment of late toxicity using NCI CTCAE v.4.0 and RTOG (RTOG is excluded for the first 3 month post randomisation).

In addition the following assessments should be performed:

Month 6 post randomisation

- Full blood count, urea, electrolytes and LFTs (ALT/AST, bilirubin, albumin).

Months 3, 6, 12, 18 and 24 post randomisation

- Quality of life questionnaire (EORTC QLQ C30 and EQ5D)

### 8.3.3 NSCLC Primary patients

The following assessments should be conducted for all NSCLC primary patients at each follow up visit (Months 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54 and 60 months post randomisation):

- Physical examination including WHO performance status, weight and height.

- Assessment of late toxicity using NCI CTCAE v.4.0 and RTOG (RTOG is excluded for the first 3 month post randomisation).

In addition the following assessments should be performed:

Months 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 48 and 60 months post randomisation

- CT scan of chest, abdomen and pelvis. This may be replaced by FDG PET/CT scan as long as the CT scan is of diagnostic quality.
- Tumour assessment according to RECIST v.1.1 criteria, where possible. In instances where RECIST assessment is not possible assessment by other methods should be considered or a clinical assessment of widespread progression should be performed.

Month 6 post randomisation

- Full blood count, urea, electrolytes and LFTs (ALT/AST, bilirubin, albumin).

Months 3, 6, 12, 18 and 24 post randomisation

- Quality of life questionnaire (EORTC QLQ C30 and EQ5D)

### 8.3.4 Prostate Primary patients

The following assessments should be conducted for all prostate primary patients at each follow up visit (Months 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54 and 60 months post randomisation):

- Physical examination including WHO performance status, weight and height.
- Assessment of late toxicity using NCI CTCAE v.4.0 and RTOG (RTOG is excluded for 3 month post randomisation).
- Assessment of tumour marker PSA.

  *A rise in PSA levels may indicate the need for unscheduled bone and CT scan. Scans may be replaced by choline or PSMA PET/CT scan or whole body dwMRI if locally available. A rising PSA is defined as 2 successive PSA rises from nadir, measured a minimum of 4 weeks apart. If the overall PSA rise has a doubling time of ≥ 3 months or the PSA level has doubled the original PSA value at trial entry or if clinically indicated, then restaging should be considered.* Where scanning has been indicated tumour assessment according to RECIST v1.1 criteria should be carried out, where possible.

In addition the following assessments should be performed:

6, 12 and 24 months after randomisation

- Bone and CT scan of chest, abdomen and pelvis. These may be replaced by choline or PSMA PET/CT or wb-dwMRI if locally available.
- Tumour assessment according to RECIST v.1.1 criteria, where possible. In instances where RECIST assessment is not possible assessment by other methods should be considered or a clinical assessment of widespread progression should be performed.

Month 6 post randomisation

- Full blood count, urea, electrolytes and LFTs (ALT/AST, bilirubin, albumin).

Months 3, 6, 12, 18 and 24 post randomisation

- Quality of life questionnaire (EORTC QLQ C30 and EQ5D)

Months 12, 24, 36, 48 and 60 post randomisation

- Assessment of testosterone

### 8.3.5 Liver metastases:

In addition to the assessments outlined for the primary tumour patients the following assessments should be performed for patients with liver metastases as indicated:

| | |
|---|---|
| 3 months after randomisation | Clotting screen (INR) and liver function (ALT/AST, bilirubin, and albumin) to ascertain liver function status regarding radiation induced liver disease |
| 6 months after randomisation: | Clotting screen (INR). |
| 12 months after randomisation | Clotting screen (INR), liver function (ALT/AST, bilirubin and albumin) to ascertain liver function status regarding radiation induced liver disease |

## 8.4 Procedure at disease progression

Progression events should be imaging defined in all tumour types according to RECIST criteria. In addition, for prostate cancer patients progression by bone scan and PSA progression will be considered. On the rare occasions that progression cannot be measured by scan or biochemical failure (prostate only), clinical evidence of widespread progression will count as a PFS event.

Participants should be treated according to local clinical judgement at disease progression. Following progression, participants will continue to be followed-up for FFWMD and overall survival. Imaging and visits following progression can be according to local practice and do not need to follow the protocol specified visit time points, however information regarding FFWMD and survival status should be entered onto the eCRFs.

The FFWMD endpoint is defined as radiological evidence that the patient has 4 or more metastatic sites and/or the site(s) of disease progression are not suitable for radical salvage therapy (e.g. surgery, RFA or SBRT).

## 8.5 Discontinuation from treatment

Participants may discontinue from trial treatment at any time at their own request, or they may be discontinued at the discretion of the Principal Investigator. Reasons for discontinuation may include:

- Disease progression or recurrence
- Unacceptable toxicity
- Pregnancy.

Participants who discontinue treatment should continue to be followed up as per section 8.4.

## 8.6 Discontinuation from follow-up

If a patient withdraws from further follow-up the appropriate eCRF form should be submitted to ICR-CTSU stating whether the patient has withdrawn consent for information to be sent to the ICR-CTSU or whether they simply no longer wish to attend trial follow up visits. In the very rare event that a patient requests that their data is removed from the study entirely, the implications of this should be discussed with the patient first to ensure that this is their intent and, if confirmed, ICR-CTSU should be notified in writing.

## 8.7 Radiological evaluation of SBRT treated metastatic lesions

It is acknowledged that response assessment of lesions to SBRT may be difficult particularly at early imaging time points. This is particularly relevant in the interpretation of response with liver metastases. Caution must be used in interpretation as post-treatment changes may mimic tumour progression. Therefore if there is suspicion of local progression on follow up CT scans, consideration should be given to performing additional imaging in the form of MRI and/or PET/CT for diagnostic clarification. If no conclusion can be drawn, a second CT, MRI or PET/CT at least 8 weeks apart should be performed to confirm disease progression.

## 8.8 Schedule of assessments

| Visit/Assessments/ Procedures | Pre-randomisation | Pre-treatment | End of trial treatment for SBRT + SOC group or equivalent for SOC group | Time from randomisation | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Within 42 days | Following confirmation of eligibility | SBRT + SOC group: within +/- 7days of last SBRT treatment SOC only group: within 6 weeks after randomisation | 3 M | 6 M | 9 M | 12 M | 15 M | 18 M | 21 M | 24 M | 30 M | 36 M | 42 M | 48 M | 54 M | 60 M |
| Informed consent | X | | | | | | | | | | | | | | | | |
| Histological confirmation of primary breast, prostate or NSCLC | X* | | | | | | | | | | | | | | | | |
| Complete medical history | X | | | | | | | | | | | | | | | | |
| Physical examination including WHO performance status, body weight, height, blood pressure (BP at baseline only) | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Tumour primary assessment using RECIST v.1.1 criteria | X | | | $X^{B,L}$ | X | $X^{B,L}$ | X | $X^{B,L}$ | $X^{B,L}$ | $X^{B,L}$ | X | $X^{B,L}$ | $X^{B,L}$ | $X^{B}$ | $X^{B,L}$ | $X^{B}$ | $X^{B,L}$ |
| Concomitant therapy assessment | | X | X | | | | | | | | | | | | | | |
| Full blood count, urea and electrolytes, LFTs | | X | | | X | | | | | | | | | | | | |
| Pregnancy test (for women of childbearing potential) | X | | | | | | | | | | | | | | | | |
| Symptom assessment using NCI | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| Visit/Assessments/ Procedures | Pre-randomisation | Pre-treatment | End of trial treatment for SBRT + SOC group or equivalent for SOC group | Time from randomisation | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Within 42 days | Following confirmation of eligibility | SBRT + SOC group: within +/- 7days of last SBRT treatment SOC only group: within 6 weeks after randomisation | 3 M | 6 M | 9 M | 12 M | 15 M | 18 M | 21 M | 24 M | 30 M | 36 M | 42 M | 48 M | 54 M | 60 M |
| CTCAE v.4.0 | | | | | | | | | | | | | | | | | |
| Symptom assessment using RTOG | | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Quality of life questionnaire (EORTC QLQ C30 and EQ-5D) | | X** | X | X | X | | X | | X | | X | | | | | | |
| Placement of fiducial markers (optional) | | X | | | | | | | | | | | | | | | |
| **NSCLC primary patients only:** CT scan of chest, abdomen and pelvis | X[2] | | | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | | X[2] | | X[2] |
| **NSCLC primary patients only:** CT brain with contrast or MRI brain with contrast | X | | | | | | | | | | | | | | | | |
| **Breast primary patients only:** Ca 15-3 (optional) | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Breast primary patients only:** CT scan of chest, abdomen and pelvis | X[2] | | | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] |
| **Prostate primary patients only:** PSA | X[1] | | | X[1] | X | X[1] | X | X[1] | X[1] | X[1] | X | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] |
| **Prostate primary patients only:** Testosterone | X | | | | | | X | | | | X | | X | | X | | X |

| Visit/Assessments/ Procedures | Pre-randomisation | Pre-treatment | End of trial treatment for SBRT + SOC group or equivalent for SOC group | Time from randomisation | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Within 42 days | Following confirmation of eligibility | SBRT + SOC group: within +/- 7days of last SBRT treatment SOC only group: within 6 weeks after randomisation | 3 M | 6 M | 9 M | 12 M | 15 M | 18 M | 21 M | 24 M | 30 M | 36 M | 42 M | 48 M | 54 M | 60 M |
| **Prostate primary patients only:** Bone and CT scan of chest, abdomen and pelvis | X[3] | | | | X[3] | | X[3] | | | | X[3] | | | | | | |
| **Liver metastases only:** Clotting screen (INR), LFTs and optional DMSA scan or equivalent as per local guidelines | X | | | | | | | | | | | | | | | | |
| **Liver metastases only :** Clotting screen (INR) and LFTs (ALT/AST, bilirubin and albumin) | | X | | X | X | | X | | | | | | | | | | |
| **Spinal metastases only:** MRI whole spine | X | | | | | | | | | | | | | | | | |
| **Lung metastases only:** Pulmonary function tests (FEV 1, FVC, and TLCO/KCO) (at baseline only and then as per symptoms)[L] | X | | | | | | | | | | | | | | | | |

Footnotes:

M = month

X[*] = will be before 42 days prior to randomisation

X** = within one week prior to randomisation or if this window is missed should be before treatment allocation is known to the patient (SOC or SBRT + SOC).

1. PSA levels may indicate the need for an unscheduled bone and CT scan. This may be replaced by choline or PSMA PET/CT scan or wb-dwMRI if locally available. Where scanning has been indicated tumour assessment according to RECIST v1.1 criteria should be carried out, where possible.

*2. NSCLC and breast patients:* CT scans of chest, abdomen and pelvis. Scans may be replaced by FDG PET-CT scan as long as the CT scan is of diagnostic quality, or whole body dwMRI if locally available.

3. Prostate patients: Bone and CT scans of chest, abdomen and pelvis. These may be replaced by choline or PSMA-PET or wb-dwMRI if locally available

*B* = breast

L= NSCLC

# 9 TRIAL TREATMENT

## 9.1 SBRT treatment

Patients randomised to receive SBRT+SOC will receive an SBRT dose and fractionation regimen dependent on the metastatic site and proximity to normal tissues.

### 9.1.1 Treatment timelines

To allow sufficient time for treatment planning, SBRT can commence up to 6 weeks after randomisation.

### 9.1.2 Radiotherapy planning

Radiotherapy planning and outlining should be carried out in accordance with the guidelines in the current version of the Radiotherapy Planning and Delivery Guidelines document, available on request from ICR-CTSU (CORE-icrctsu@icr.ac.uk) or via the Radiotherapy website (www.rttrialsqa.org.uk.). Fiducial marker insertion, where necessary, should be conducted according to local guidelines, ensuring SBRT treatment can commence within the 6 week timeframe from randomisation.

### 9.1.3 Treatment technique

Highly conformal treatment planning is a pre-requisite for SBRT. SBRT may be delivered using a specialist SBRT platform, such as CyberKnife, or with a linear accelerator with SBRT capabilities. Any SBRT delivery platform is acceptable as long as the individual centre has demonstrated they are able to comply with the radiotherapy standards laid out in this protocol and the Radiotherapy Planning and Delivery Guidelines document.

### 9.1.4 Dose prescription

Table 1 below summarises the recommended dose and fractionation options that can be used. Where a range of doses is provided, it is advised that the maximum dose that can be achieved whilst meeting the OAR planning constraints is prescribed.

| Metastasis site | Total Dose (Gy) | No. of Fractions | Dose/fraction (Gy) | Frequency | Maximum duration (days) |
|---|---|---|---|---|---|
| Lung | 54 | 3 | 18 | Alt daily | 14 |
| | 55-60 | 5 | 11-12 | Alt daily | 21 |
| | 60 | 8 | 7.5 | Alt daily | 21 |
| Adrenal | 30-36 | 3 | 10-12 | Daily or Alt days | 7 |
| Liver | 45-48 | 3 | 15-16 | Alt daily | 7 |
| | 50-60 | 5 | 10-12 | Daily or Alt days | 14 |
| Spine | 24-27 | 3 | 8-9 | Alt days | 7 |
| Bone | 30-40 | 3 | 10-13.3 | Alt days | 7 |
| Lymph node | 30-40 | 3 | 10-13.3 | Alt days | 7 |

### 9.1.5 Treatment scheduling and gaps

Treatment can start on any day of the week. Treatment is delivered as per table 1, above, for the maximum number of days the treatment should be delivered over dependent on the dose fractionation schedule being used.

### 9.1.6 Repeat SBRT

Only those patients allocated SBRT treatment at randomisation should be offered repeat SBRT treatment upon development of new extra-cranial lesions, where the total number of metastatic lesions over time since diagnosis of metastatic disease remains ≤ 3, and the primary site and other sites previously treated with SBRT are under control. Suitability of new lesions for further SBRT will be based on the same criteria as at trial entry (visible, imaging defined targets suitable for SBRT, ≤6cm (≤5cm for lung metastases)). Where multiple lesions are treated over the course of the trial, composite dose volume data must be assessed and all normal tissue dose constraints need to be met by the composite plan. Particular caution is required where isodose lines overlap serial organs. Any previous radiotherapy before trial entry should also be taken into account. 50% isodose lines for plans to individual lesions should not overlap. A period >3 months since the last SBRT treatment is required before commencing repeat SBRT.

**Re-irradiation**

Further SBRT treatment of lesions previously treated with SBRT either as part of the trial or prior to trial entry is not permitted in the CORE trial.

### 9.1.7 Radiotherapy Quality Assurance (QA)

The NCRI Radiotherapy Trials Quality Assurance (RTTQA) group will oversee the quality assurance of the SBRT within the trial to ensure the safety and consistency of radiotherapy delivery at participating sites. Prior to inclusion in the trial, individual centres will need to demonstrate they have robust procedures in place to ensure high quality plan RTTQA guidelines will be met. Thereafter case reviews will be in accordance with the RTTQA group guidelines (www.rttrialsqa.org.uk).

## 9.2 Standard of care treatment

Standard of care (SOC) is at the discretion of the local oncologist and will be defined for each patient at trial entry. The SOC treatment specified at randomisation should be administered irrespective of what arm the patient is randomised to (with the exception that palliative radiotherapy would not be administered if the patient was randomised to SBRT+SOC). It may include any standard therapy that is clinically appropriate: chemotherapy (including maintenance where appropriate), biological therapy, endocrine therapy, palliative radiotherapy (BED10≤40 i.e. equivalent to 30Gy in 10 fractions or less) or observation or any combination of these. As indicated in the eligibility criteria, patients for whom standard of care would be ablative therapy (e.g. surgery, RFA, cryoablation) are not eligible for CORE participation.

If allocated to SOC only group, SOC treatment may begin on the same day of randomisation or as soon as possible after randomisation. If allocated to SBRT+ SOC group, SBRT will precede SOC with the exception of endocrine therapy which may be initiated following randomisation and be given concurrently with the SBRT. All patients should commence SOC therapy within 4 weeks of SBRT finishing.

For patients where a change in endocrine therapy preceded trial entry (within 8 weeks of randomisation for prostate cancer patients and within 10 weeks of randomisation for breast cancer patients) it should be stated at trial entry whether endocrine therapy will be the only SOC treatment or whether palliative radiotherapy will also be offered (if known at this point).

### 9.2.1 Systemic therapy

#### Chemotherapy

For patients allocated to SBRT+SOC, a minimum period of 2 weeks after the final fraction of SBRT is suggested before chemotherapy is recommenced.

#### Radiosensitizers

Bevacizumab and any other potential radiosensitizers should be stopped 4 weeks prior to the start of SBRT treatment. Pre-treatment radiosensitizers information will be captured prior to the start of SBRT treatment. The management of potential radiosensitizers should be in accordance with local SBRT guidelines.

#### Tyrosine Kinase Inhibitors (TKIs) Therapy

The use of TKI for NSCLC patients is not permitted during SBRT. Patients in the SBRT + SOC group will need to stop TKI treatment at least one day and up to one week prior to commencing SBRT. TKI treatment can recommence one day after the patient receives their last fraction. The stop date of the last TKI treatment will be captured prior to the start of SBRT treatment. Where applicable, date of TKI treatment is recommenced post SBRT will also be captured.

#### Endocrine therapy

For patients allocated to SBRT+SOC where SOC is endocrine therapy, endocrine therapy may be initiated following randomisation and can be given concurrently with the SBRT.

### 9.2.2 Palliative radiotherapy

Patients in whom palliative radiotherapy to the target lesion would be indicated as SOC (examples may include symptomatic bone metastases or asymptomatic vertebral metastases where treatment to prevent spinal cord compression is felt to be indicated) should be entered into the trial before palliative RT. If the patient is allocated to SBRT + SOC group, the patient will receive SBRT alone.

The following fractionation schemes are permitted: 8Gy/1fr, 10Gy/1fr (lung metastases only), 20Gy/5fr and 30Gy/10fr.

The use of alternative palliative fractionation schedules should be discussed prior to trial entry with the CI. Those in whom a higher dose of radiation is felt to be indicated as part of standard therapy are not appropriate for trial entry.

## 9.3 Supportive care guidelines

All medication considered necessary for the patients' welfare and which is not expected to interfere with the evaluation of the treatment may be given at the discretion of the investigator. Toxicity should be managed as per local guidelines and RCR guidance where available (https://www.rcr.ac.uk/clinical-oncology/being-consultant/guidance-and-standards).

## 9.4 Concomitant therapy

All medication considered necessary for the patients' welfare and which is not expected to interfere with the evaluation of the treatment may be given at the discretion of the investigator. Prescription and over-the-

counter medications that the patient takes from 30 days prior to randomisation until the end of treatment visit (within +/- 7 days of the last fraction of SBRT or within 6 weeks after randomisation for patients randomised to SOC only) should be recorded on the eCRF.

### 9.5 Non-permissible medications/therapies

Ablative therapy (e.g. surgery, RFA, cryoablation, SBRT) is not permissible as a standard of care option following randomisation for patients as part of the trial.

## 10 SAFETY REPORTING

### 10.1 Definitions

**Adverse Event (AE)**

An AE is any untoward medical occurrence in a patient administered a study treatment; the event does not necessarily have a causal relationship with the treatment.

For the purpose of this trial, any detrimental change in the patient's condition subsequent to the start of the trial (i.e. randomisation) and during the follow-up period should be considered as an AE.

**Serious Adverse Event (SAE)**

An SAE is any untoward medical occurrence that occurs after randomisation and within the following 90 days and:

- results in death,
- is life-threatening
- requires hospitalisation or prolongation of existing inpatients´ hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect

**In addition, any radiotherapy related grade ≥4 events occurring between 90 days after randomisation and 5 years after randomisation should be reported according to serious adverse event reporting timelines.**

Important adverse events 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, may also be considered serious.

Progression of the indicated disease and death due to progression of the indicated disease are not considered SAEs.

Pregnancy or aid in the conception of a child whilst participating in a trial is not itself considered an SAE but should be followed up for congenital anomalies or birth defects.

**Serious Adverse Reaction (SAR)**

A serious adverse reaction is an SAE that is suspected as having a causal relationship to trial treatment, which for the purposes of this trial will be SBRT, as assessed by the investigator responsible for the care of the patient. A suspected causal relationship is defined as possibly, probably or definitely related (see definitions of causality table).

## 10.2 Definitions of causality

| Relationship | Description |
|---|---|
| Unrelated | There is no evidence of any causal relationship with the trial treatment (SBRT) |
| 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 treatment). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment) |
| 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 treatment). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments) |
| Probable | There is evidence to suggest a causal relationship, and the influence of other factors is unlikely |
| Definitely | There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out |
| Not assessable | There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship. |

**Related Unexpected Serious Adverse Event**

- An adverse event that meets the definition of serious and is assessed by the CI or nominative representative as: "Related" – that is, it resulted from administration of any of the research procedures, and
- "Unexpected" – that is, the type of event is not listed in the protocol as an expected occurrence (see Appendix A6) or, in the opinion of the Chief Investigator, is not expected.

## 10.3 Reporting Adverse Events to ICR-CTSU

For non-UK reporting requirements please see Appendix A7

Any toxicity, sign or symptom that occurs after trial randomisation which is not unequivocally due to progression of disease, should be considered an AE.

All AEs must be reported on the relevant toxicity, sign or symptom CRF.

- **Toxicity evaluation for patients randomised to SOC group**

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4 scoring system will be used for toxicity assessment for patients randomised to the SOC group.

- **Toxicity evaluation for patients randomised to SBRT+SOC group**

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4 and the Radiation Therapy Oncology Group (RTOG) Morbidity Scoring Criteria scoring system will be used for toxicity assessment for patients randomised to the SBRT+SOC group.

The severity of AEs should be graded according to the appropriate CTCAE/RTOG criteria. For each AE, the highest grade observed since the last visit should be reported.

Whenever one or more toxicity/sign/symptom corresponds to a disease or a well-defined syndrome only the main disease/syndrome should be reported.

### 10.4 Reporting of Serious Adverse Events to ICR-CTSU

Any SAE that occurs following randomisation and up to 90 days post randomisation must be reported. As detailed above, radiotherapy related SAEs occurring from 90 days post randomisation to 5 years post randomisation in patients receiving SBRT treatment should also be reported.

All SAEs should be reported to ICR-CTSU within 24 hours of the Principal Investigator (or designated representative) becoming aware of the event, by completing the CORE SAE form and faxing to:

The ICR-CTSU safety desk
Fax no: **+44 (0)208 722 4368**
For the attention of the CORE Trial team

As much information as possible, including the Principal Investigator's assessment of causality, must be reported to ICR-CTSU in the first instance. Additional follow up information should be reported as soon as it is available.

All SAE forms must be completed signed and dated by the Principal Investigator or designated representative.

The Site SAE log should be completed and the SAE form filed in the Site Investigator File.

### 10.5 Serious Adverse Events exempt from expedited reporting

The expected adverse events listed in Appendix A6 do not require reporting as SAEs to ICR-CTSU if grade ≤2 but should be reported using the appropriate CRF

### 10.6 Review of Serious Adverse Events

The Chief Investigator (or designated representative) will assess all SAEs reported as related to the study treatment, which for the purposes of this trial will be SBRT, for causality and expectedness (NB. The Chief Investigator cannot down-grade the Principal Investigator's assessment of causality).

SAEs assessed as having a causal relationship to study treatment (SBRT) and as being unexpected will undergo expedited reporting to the relevant authorities and all other interested parties by ICR-CTSU (see Figure 1).

Sites should respond as soon as possible to requests from the Chief Investigator or designated representative (via ICR-CTSU) for further information that may be required for final assessment of an SAE.

### 10.7 Expedited reporting of Related Unexpected SAEs

If an SAE is identified as being related and unexpected by the Chief Investigator it will be reported by ICR-CTSU to the main REC, the Sponsor and all other interested parties within 15 days of being notified of the event.

The Principal Investigators at all actively recruiting sites will be informed of any related unexpected SAEs occurring within the trial at appropriate intervals.

The collaborative group in each participating country will report related unexpected SAEs as per their local requirements to IECs and local investigators.

### 10.8 Follow up of Serious Adverse Events

SAEs should be followed up until clinical recovery is complete or until disease has stabilised. SAE outcomes should be reported to ICR-CTSU using the relevant section of the SAE form as soon as the Principal Investigator or designee becomes aware of the outcome.

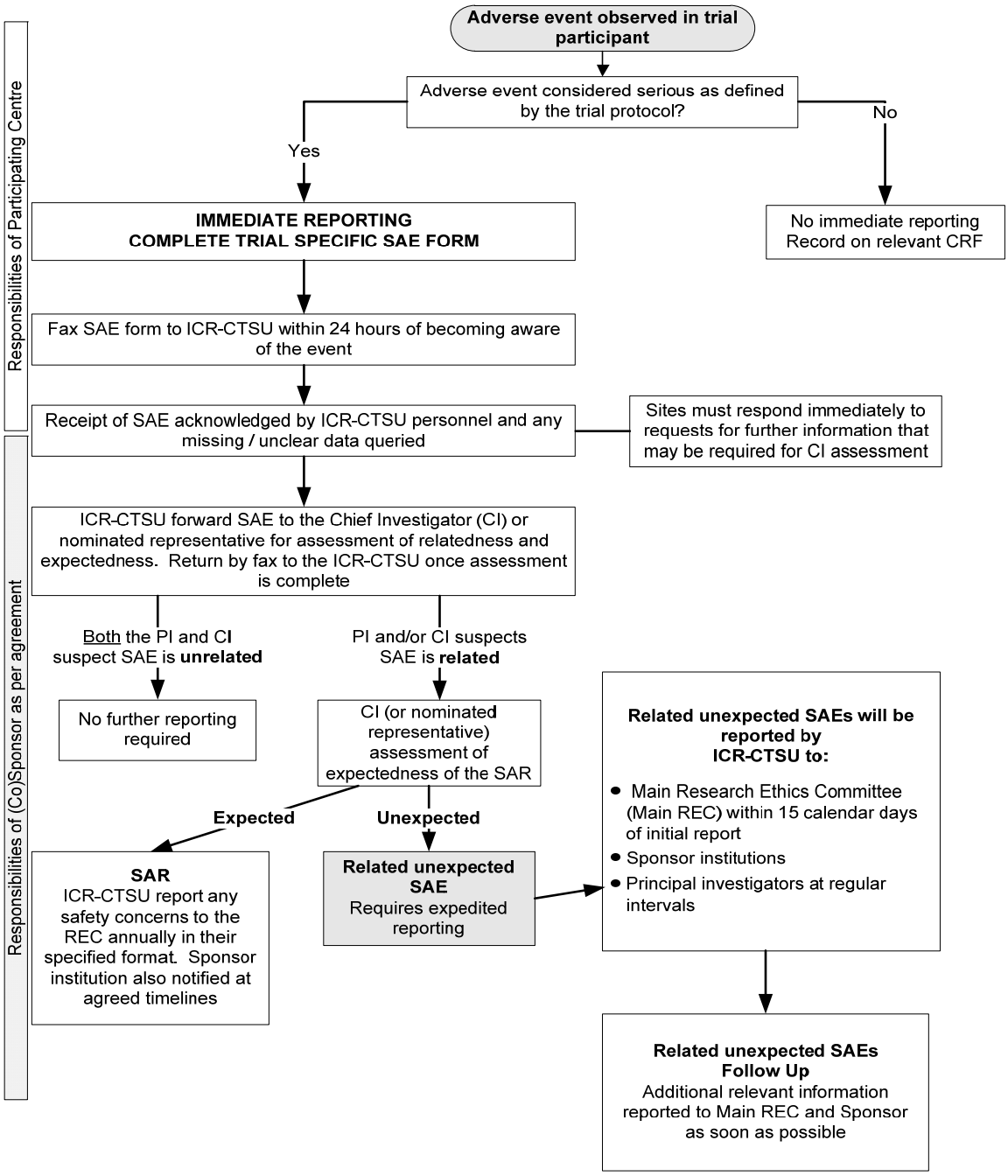
### 10.9 Annual safety reporting

An annual progress report will be provided to the main REC by ICR-CTSU and copied to the Sponsor and the collaborative group in each participating country at the end of the reporting year. This will include data about related unexpected SAEs and whether any safety concerns have arisen during the reporting period.

### 10.10 Reporting pregnancies

If any trial participant or a trial participants' partner becomes pregnant while receiving trial treatment (SBRT) or up to 90 days after receiving trial treatment, this should be reported to ICR-CTSU using the pregnancy reporting form. Participants who become pregnant should discontinue from trial treatment immediately. Pregnancies should be followed up until conclusion and all follow-up information should be reported to ICR-CTSU. If the outcome of the pregnancy meets the definition of serious (i.e. congenital abnormality) this should be reported to ICR-CTSU following the serious adverse event reporting procedures described above.

**Figure 1: Flow diagram for SAE reporting, and action following report**




NB. All SAEs should continue to be followed up as specified above

# 11 STATISTICAL CONSIDERATIONS

## 11.1 Statistical design and sample size justification

### 11.1.1 Statistical design

CORE is a phase II/III, multi-centre, non-blinded, parallel group randomised controlled trial in patients with breast, prostate or NSCLC primary cancer. A randomised trial is the most appropriate design to address the research question and minimise potential sources of bias. Three tumour types are included in the trial as there is currently insufficient evidence to choose a single tumour site to investigate. Whilst the increased heterogeneity with this approach is acknowledged it was felt that this is the most pragmatic design for phase II. The decision to include NSCLC, breast and prostate cancer was made following wide consultation with clinicians across the UK, including the relevant Clinical Studies Groups and CTRad.

Delivery of SBRT in this setting is novel across the UK and an early assessment of patient recruitment and feasibility of delivery in a multi-centre setting is essential. Assuming feasibility of recruitment and deliverability of SBRT are confirmed, an efficacy signal will be sought after across the three tumour sites. Assessing efficacy overall rather than in individual sites at this stage will enable a positive signal to be identified more quickly and at present there is no strong biological rationale why SBRT would be effective for some tumour sites and not others.

If a positive signal is seen in the phase II then the intention is for CORE to expand to parallel phase III trials. Unless there are data to suggest that a phase III trial will not be feasible in a particular tumour type, separate phase III trials are planned for breast, NSCLC and prostate cancer patients. The design and primary endpoint for the phase III trial has not been fixed in advance; this will allow better estimates of treatment effect and the experience gained in the phase II part of the trial in terms of the deliverability of SBRT nationally to be taken into account in phase III. In addition, data collected during phase II on the secondary endpoints will be used to inform the design of the phase III and support power calculations and therefore, in any revised design, patients from the phase II part will not be included in the analysis of phase III endpoints. This approach will also provide an opportunity to refine the intervention technique prior to initiation of phase III on the basis of experience gained in phase II if required.

### 11.1.2 Sample size

This phase II screening study has been designed with a primary endpoint of PFS, and relaxed one-sided alpha=0.20 and beta=0.20 (13). The control arm PFS is estimated based on the expected contribution of each primary tumour site to the overall final sample size. Based on observed recruitment in the first year this is estimated at 75% prostate, 14% breast and 11% lung. Assuming a median PFS of 5 months for NSCLC, 12 months for breast and 18 months for prostate patients (14-22), it is estimated that the median PFS in the control group after randomisation will be 16 months. The phase II SABR-COMET trial targets a hazard ratio (HR) for OS of 0.6 (23). For CORE, a more conservative effect size has been chosen reflecting clinical opinion of what would constitute a PFS signal worthy of a phase III OS trial. In order to detect a HR of 0.75 for improvement of PFS i.e. extending the median cohort PFS by 4 months in the experimental arm with 80% power, a total of 230 patients are required (138 events). Assuming a 5% rate of patients lost to follow up at the point of data analysis, a total of 242 patients will be required (121 per treatment group). Dependent on observed rates of accrual this total may increase to a maximum of 270 to allow for each cohort to achieve a minimum of 50 patients. The sample size calculations, made using the *artsurv* command in Stata version 13, assume 50% recruited in both years 1 and 2 and 12 months of additional follow up.

The decision rule to proceed to phase III will be based on a 3 outcome design. An overall result significant at the 10% level would support continuation to phase III; significance between 10% and 20% would require supportive evidence from secondary endpoints with a particular emphasis on local tumour control and FFWMD. If the significance is >20% then the study will not progress to phase III unless there is clear

heterogeneity of outcomes between the 3 tumour subgroups supporting a signal in selected tumour sites in which case consideration would be given to progressing to an extended phase 2 evaluation for that tumour site alone.

### 11.1.3 Treatment allocation

Patients will be randomised between SOC and SBRT + SOC in a 1:1 ratio. Patients will be randomised at different stages of their disease depending on the primary tumour site and in accordance with the inclusion and exclusion criteria. Treatment allocation will use minimisation with balancing factors of primary tumour site (breast, NSCLC, prostate) and centre. In tumour sites where there is felt to be a further important prognostic variable which may affect the primary PFS endpoint, a further stratification will be performed, as outlined below, to ensure the 2 treatment groups are balanced.

- **Breast**: patients will be stratified additionally into ER+ (relapsed post adjuvant therapy) vs all other subgroups, to reflect the difference in median PFS. It is acknowledged that breast cancer is a heterogeneous disease, essentially composed of several sub-groups with varying prognosis, dependent on receptor status, disease free interval (DFI) and prior adjuvant therapy. Whilst there is an argument in terms of homogeneity for limiting the eligible patient population to 1 sub-group only, such as ER+ disease, we feel it is more pragmatic at this stage to include all comers. The likely frequency of eligible patients within each sub-group is largely unknown and to ensure feasibility of recruitment, restricting trial entry to a particular sub-group from the outset is not warranted.

- **NSCLC:** stratified additionally into EGFR+ versus the remainder (with a similar rationale to the breast group).

- **Prostate**: patients will be stratified additionally into 2 groups:

    1) Patients who are endocrine therapy naïve
    2) Patients who are castrate resistant.

## 11.2 Endpoint definitions

### 11.2.1 Primary endpoint

Progression free survival is defined as time from randomisation to evidence of progression of cancer at any site or death from any cause.

Progression events should be imaging defined in all tumour types according to RECIST criteria. In addition, for prostate cancer patients progression by bone scan and PSA progression will be considered. On the rare occasions that progression cannot be measured by scan or biochemical failure (prostate only), clinical evidence of widespread progression will count as a PFS event.

Where SBRT specific consensus response assessment criteria exist for specific sites (e.g. spine), progression of SBRT treated lesions will be defined according to these guidelines.

### 11.2.2 Secondary endpoints

Recruitment rate is defined as the proportion of patients recruited to the trial. The denominator is the total number of patients required (i.e. 206 patients).

SBRT delivery is based on the proportion of patients allocated SBRT who received SBRT in the absence of new developing widespread disease and within the dosimetric constraints outlined in the SBRT protocol. The denominator is the number of patients allocated SBRT.

Overall survival is defined as time from randomisation until the time of death from any cause

Local lesion control is defined as time from randomisation until radiological evidence of progression at the treated site.
Clinician reported acute and late radiation related toxicity will be graded using NCI CTCAE v4.0/RTOG systems. Acute events are defined as those occurring up to 3 months follow up; late events are reported from 6 months post randomisation.

Patient reported quality of life will be measured using the EORTC QLQ C30 and EQ5D.

### 11.2.3 Exploratory endpoint

Freedom from widespread metastatic disease (FFWMD) will be measured from the time of randomisation until radiological evidence of disease progression, which is not suitable for radical salvage therapy (e.g. surgery, RFA or SBRT). Widespread metastatic disease is defined as greater than or equal to 4 metastatic sites, regional or distant, or a combination thereof. This will reflect the trial entry criteria, i.e. eligible patients must have ≤3 sites of metastatic disease relapse, all technically suitable for salvage therapy.

### 11.2.4 Statistical analysis plan

Analyses will be according to the intention-to-treat method. Time to event endpoints will be presented using Kaplan Meier methods with treatment effects presented as relative and absolute estimates. Hazard ratios will be derived from Cox proportional hazards models stratified by disease site. The time point of interest is 1 year from randomisation. The log rank test will be used to compare treatment groups stratified by disease site. For PFS, patients who are event free at time of analysis will be censored using the date of last disease assessment (imaging for breast, NSCLC and PSA assessment for prostate). An appropriate alternative method will be used if there is evidence of non-proportional hazards.

Acute and late toxicity will be summarised as frequencies and percentage at each time point. Non-haematological grade 2 or greater (G2+) toxicities related to SBRT treatment are of primary interest. The proportion experiencing G2+ will be presented by treatment group and comparisons made between treatments using Fishers exact tests, separate comparisons will be made of acute and late toxicity.

Quality of life data will be analysed using standard algorithms to derive scores and handle missing data according to the EORTC scoring manual. Descriptive statistics (median, IQR, range) will be presented by treatment group at each time-point. Statistical comparisons will be made at 12 and 18 months. Analyses to account for the longitudinal nature of the data may also be used.

A planned exploratory analysis will be performed to investigate the treatment effect in each primary site subgroup. This will be summarised with a hazard ratio and compared in each subgroup to look for consistency of effect (accepting that there will be little power for a formal test of heterogeneity). There will be very limited power and much uncertainty about these estimates, and therefore they will be interpreted with caution.

Further details of analysis methods will be specified in a Statistical Analysis Plan in accordance with ICR-CTSU Standard Operating Procedures.

### 11.2.5 Interim analyses and stopping rules

With the early assessment of feasibility there are will be opportunities to stop the trial early should accumulating data justify this based on recruitment, treatment deliverability or toxicity.

**Feasibility of recruitment:** The IDMC and TSC will monitor recruitment rates and may recommend on trial closure if these are significantly less than expected and continuation of the trial is felt futile. Recruitment feasibility will be assessed by the number of open centres, patient acceptance rates and the number of patients randomised. For example, target recruitment is 20% year 1, 30% year 2 and 50% year 3, if actual recruitment is not at least half of what is targeted (i.e. at least 10% in year 1) then consideration would be given for closing the study due to it not being feasible to complete within a timely manner. If the acceptance rate amongst eligible patients falls below 50% this will trigger review of the recruitment process at sites by the Trial Management Group; if acceptance rates fall below 33% this will trigger referral to the TSC.

**Deliverability of SBRT:** At least 85% of patients randomised to SBRT + SOC are anticipated to receive their allocated SBRT treatment in the absence of new developing widespread disease and within the dosimetric constraints outlined in the SBRT protocol.

**Safety:** The IDMC will monitor safety with a formal review after 10, 34 and 51 patients have been treated with SBRT and followed up for 6 months. Consideration would be given to stopping the trial if the late grade 4/5 toxicity rate exceeds 5% in the experimental arm.

There are no early stopping rules for efficacy planned during the phase II component of this trial.

## 12 TRIAL MANAGEMENT

### 12.1.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be set up and will include the Chief Investigator, ICR-CTSU Scientific Lead, Co-investigators and identified collaborators, the Trial Statistician and Trial Manager. Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of sites and professional groups. Where possible, membership will include a lay/consumer representative. The TMG will meet at regular intervals, and at least annually. Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG have operational responsibility for the conduct of the trial. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

### 12.1.2 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be set up and will comprise an independent Chairman and at least 2 further independent members with clinical or statistical expertise (at least 1 member must be a statistician). The TSC will meet at regular intervals, and at least annually. The TSC will provide expert independent oversight of the trial on behalf of the Sponsor and funder. The Committee's terms of reference, roles and responsibilities will be defined in charter issued by ICR-CTSU.

### 12.1.3 Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be set up to monitor the progress of the trial and will comprise a Chairman and at least 2 further members with clinical or statistical expertise (at least 1 member must be a statistician). Membership of the IDMC will be proposed by the TMG and approved by the TSC.

The IDMC will meet in confidence at regular intervals, and at least annually. In addition, the IDMC will monitor safety with a formal review after 10, 34 and 51 patients have been treated with SBRT and followed up for 6 months (see section 12.5). A summary of findings and any recommendations will be produced following each meeting. This summary will be submitted to the TMG and TSC, and if required, the main REC and the MHRA.

The IDMC will reserve the right to release any data on outcomes or side-effects through the TSC to the TMG (and if appropriate to participants) if it determines at any stage that the combined evidence from this and other studies justifies it.

The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

# 13 RESEARCH GOVERNANCE

## 13.1 Sponsor responsibilities

The Sponsor of this clinical trial is the Royal Marsden NHS Foundation Trust

A coordinating group in each participating (non-UK) country will be delegated responsibility for trial initiation and conduct in that country on behalf of the Sponsor, as defined in an agreement between the Sponsor and the coordinating group.

## 13.2 Participating site responsibilities

Responsibilities delegated to participating sites are defined in an agreement between the Sponsor and the individual site.

Responsibilities of participating sites are defined in an agreement between the individual participating site and the Sponsor (UK) or the coordinating group delegated that responsibility by the Sponsor (non-UK).

# 14 TRIAL ADMINISTRATION & LOGISTICS

## 14.1 Site activation

Before activating the trial, participating sites are required to sign an agreement accepting responsibility for all trial activity which takes place within their site.

Sites may commence recruitment once the site agreement has been signed by all required signatories, the required trial documentation is in place (as specified by ICR-CTSU) and a site initiation (visit or teleconference) has taken place. Site initiation visits will be conducted at sites where the Principal Investigator has requested one or where ICR-CTSU deems it is appropriate.

## 14.2 Investigator training

Each centre will complete the comprehensive pre-trial section of the quality assurance programme prior to commencing recruitment as detailed in the Radiotherapy Planning and Delivery Guidelines. The radiotherapy QA programme will continue throughout the trial, with investigator training as required.

## 14.3 Data acquisition

Electronic (e) Case Report Forms (CRF) will be used for the collection of trial data. Data from all collaborating groups will be held centrally by the ICR-CTSU.

CORE trial data should be reported to the ICR-CTSU in a timely manner. ICR-CTSU will provide guidance to sites to aid the completion of the eCRFs. The Trial Management Group reserves the right to amend or add to the eCRF template as appropriate. Such changes do not constitute a protocol amendment, and revised or additional forms should be used by sites in accordance with the guidelines provided by ICR-CTSU.

### 14.4 Central data monitoring

Once data has been entered on the eCRF by the site personnel, ICR-CTSU will review it for compliance with the protocol, and for inconsistent or missing data. Should any missing data or data anomalies be found, queries will be raised for resolution by the site.

Any systematic inconsistencies identified through central data monitoring may trigger an on-site monitoring visit.

### 14.5 On-site monitoring

If a monitoring visit is required, ICR-CTSU will contact the site to arrange the visit. Once a date has been confirmed, the site should ensure that full patient notes of participants selected for source data verification are available for monitoring.

ICR-CTSU staff conducting on-site monitoring will review essential documentation and carry out source data verification to confirm compliance with the protocol. If any problems are detected during the course of the monitoring visit, ICR-CTSU will work with the Principal Investigator or delegated individual to resolve issues and determine appropriate action.

### 14.6 Completion of the study and definition of study end date

The study end date is deemed to be the date of last data capture.

### 14.7 Archiving

Essential trial documents should be retained according to local policy and for a sufficient period for possible inspection by the regulatory authorities (at least 5 years after the date of last data capture). Documents should be securely stored and access restricted to authorised personnel.

## 15 PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

### 15.1 Trial approvals

This trial has been formally assessed for risk by ICR-CTSU.

In the UK, ICR-CTSU, on behalf of the Sponsor, will ensure that the trial has received ethics approval from a research ethics committee for multi-centre trials and HRA approval. Before entering patients, the Principal Investigator at each site is responsible for submitting Site Specific Information and gaining local Research and Development approval of this protocol.

The coordinating group in each country, on behalf of the Sponsor, will ensure that the trial has received all relevant ethical, regulatory and institutional approval prior to the recruitment of any patients.

### 15.1.1 Trial conduct

This trial will be conducted according to the approved protocol and its amendments, supplementary guidance and manuals supplied by the Sponsor and in accordance with the Research Governance Framework for Health and Social Care and the principles of GCP.

This trial will be conducted according to the approved protocol and its amendments, supplementary guidance and manuals supplied by the Sponsor and in accordance with relevant national guidelines.

### 15.1.2 Informed consent

Patients should be asked to sign the current ethics approved CORE consent form at trial entry after receiving both verbal and written information about the trial, having been given sufficient time to consider this information. All consent forms must be countersigned by the Principal Investigator or a designated individual. A signature log of delegated responsibilities, listing the designated individuals and the circumstances under which they may countersign consent forms, must be maintained at the participating site. This log, together with original copies of all signed patient consent forms, should be retained in the Site Investigator File and must be available for inspection. The current ethics approved CORE patient information sheets should be provided in addition to any standard patient information sheets that are provided by the site and used in routine practice. Confirmation of the patient's consent and the informed consent process (including the date of consent) must be documented in the patient's medical notes.

### 15.1.3 Patient confidentiality

Each investigator should keep a separate log of all participants' Trial IDs, names, addresses and hospital numbers. The investigator must retain trial documents (e.g. participants' written consent forms) in strict confidence. The investigator must ensure the participants' confidentiality is maintained at all times.

Representatives of ICR-CTSU and the regulatory authorities will require access to participants' hospital notes for quality assurance purposes. ICR-CTSU will maintain the confidentiality of participants at all times and will not reproduce or disclose any information by which participants could be identified.

### 15.1.4 Data protection

ICR-CTSU will comply with all applicable data protection laws.

## 16 LIABILITY

Indemnity to meet the potential legal liability of investigators participating in this trial is provided by the usual NHS indemnity arrangements.

The coordinating group in each country will ensure that appropriate indemnity arrangements are place to meet the potential legal liabilities of investigators conducting the trial.

## 17 FINANCIAL MATTERS

This trial is investigator designed and led and has been approved by the Clinical Trials Advisory & Awards Committee (CTAAC) of Cancer Research UK.

ICR has received funding from Cancer Research UK for the central coordination of the trial. In the UK, the trial meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England. The trial is part of the National Institute for Health Research Clinical Research Network

(NCRN) portfolio. NCRN resources should therefore be made available for the trial to cover UK specific research costs.

The coordinating group in each country will ensure that sufficient funding is available for the coordination and conduct of the trial.

## 18 PUBLICATION POLICY

The main trial results will be published in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group, consisting of members of the TMG. Participating clinicians may be selected to join the writing group on the basis of intellectual and time input. All participating clinicians will be acknowledged in the publication.

Any presentations and publications relating to the trial must be authorised by the TMG. Authorship of any secondary publications e.g. those relating to sub-studies, will reflect intellectual and time input into these studies.

No investigator may present or attempt to publish data relating to the CORE trial without prior permission from the TMG.

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## A1. RECIST

The primary endpoint of this trial is progression free survival (PFS) and for the purposes of this trial patients with non-measurable disease at baseline will be eligible provided lesions are considered visible and image definable sufficient to allow radiotherapy planning and treatment. Where possible Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1 criteria should be used for the assessment of treatment outcomes. A summary is given below but investigators should always refer to the published guidelines.

### A1.1 Evaluation of measurable and non-measurable lesions

- **Measurable lesions** – lesions that can be accurately measured in at least 1 dimension with the longest diameter ≥ 20 mm by chest X-ray, or ≥ 10 mm by CT/MRI scan or clinical exam.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- For the purposes of this study, bone lesions with no identifiable soft tissue component will be considered as non-target lesions if visible via CT scan and imaging definable sufficient to allow contouring and IGRT.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Malignant lymph nodes must be ≥15 mm in the short axis when assessed by CT scan to be considered measurable.
- Non-measurable lesions – all other lesions, including small lesions and malignant lymph nodes (longest diameter <10 mm, or pathological lymph nodes with ≥10 to <15 mm short axis) i.e., leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, blastic bone lesions and also abdominal masses that are not confirmed and followed by imaging techniques.
- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.
- The utilisation of endoscopy and laparoscopy for objective tumour evaluation is not advised. The utilisation of such techniques should be restricted to confirming complete pathological response when biopsies are obtained.

### A1.2 Baseline documentation of target and non-target lesions

- Only allowed 3 sites in total as part of eligibility. Measurable lesions up to a maximum of 2 lesions per organ and 3 lesions in total representative of all involved organs should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All screening evaluations should be performed as closely as possible to the beginning of treatment

and every effort should be made to ensure that assessments and procedures are completed within 4 weeks before the beginning of treatment.

- The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow up.
- A sum of the longest diameters (LD) for all target lesions will be calculated and reported as the baseline sum of LD. The baseline sum LD will be used as reference by which to characterise the objective tumour response.
- All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow up. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

## A1.3 Response criteria

### A1.3.1. Documentation of new lesions

- The presence of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions).
- A lesion identified at a follow-up visit in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

### A1.3.2. Lesions that become 'too small to measure'

- If lesions or lymph nodes recorded as target lesions at baseline become too faint on CT scan to assign an exact measure, a default value of 5mm should be assigned. This default value is derived from the 5mm CT slice thickness
- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm.

## A1.4 Evaluation of target lesions

| Response criteria | Evaluation of target lesions |
|---|---|
| Complete Response (CR) | Disappearance of all target lesions (lymph nodes must be <10mm short axis) |
| Partial Response (PR) | At least 30% decrease in the sum of LD of target lesions, taking as reference the baseline sum of LD. |
| Progressive Disease (PD) | At least 20% increase in the sum of LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started and at least 5mm absolute increase in this sum or the appearance of 1 or more new lesions. |
| Stable Disease (SD) | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started. |

### A1.5 **Evaluation of non-target lesions**

| Response criteria | Evaluation of non-target lesions |
|---|---|
| Complete Response (CR) | Disappearance of all non-target lesions |
| Incomplete response / Stable Disease (SD) | Persistence of one or more non-target lesions |
| Progressive Disease (PD) | Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions * |

** To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. Although a clear progression of a non-target lesion is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or Chief Investigator).*

### A1.6 **Evaluation of overall response**

The table below provides a summary of the overall response calculation at each time point.

| Target lesions | Non-Target lesions | New Lesions | Overall response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Incomplete response/SD | No | PR |
| CR | Not-evaluated* | No | PR |
| PR | Non-PD or not all evaluated | No | PR |
| SD | Non-PD or not all evaluated | No | SD |
| Not all evaluated | Non-PD | No | Not evaluable |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

** When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response.*

### A1.7 **Confirmation of disease progression**

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

### A1.8 **Duration of overall response**

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

### A1.9 **Duration of stable disease**

SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

### A1.10 **Evaluation of best overall response**

The best overall response is the best response recorded from the start of the study treatment until disease progression. The patient's best overall response assignment will depend on the findings of both target and non-target disease and the appearance of new lesions.
Best overall response is defined as the best response across all time points. For example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR.

### A1.11 **Central review**

For quality assurance purposes, some central review will be conducted.

### *A2.* WHO PERFORMANCE STATUS

| Grade | Performance Status |
|---|---|
| 0 | Able to carry out all normal activity without restriction. |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out light work. |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours. |
| 3 | Capable of only limited self-care; confined to bed or chair more than 50% of waking hours. |
| 4 | Completely disabled; cannot carry on any self-care; totally confined to bed or chair. |

## A3. RTOG/EORTC LATE RADIATION MORBIDITY SCORING SCHEMA

| ORGAN TISSUE | 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 | 5 |
|---|---|---|---|---|---|---|
| SKIN | None | Slight atrophy Pigmentation change Some hair loss | Patch atrophy; Moderate telangiectasia; Total hair loss | Marked atrophy; Gross telangiectasia | Ulceration | DEATH DIRECTLY RELATED TO RADIATION LATE EFFECTS |
| SUBCUTANEOUS TISSUE | None | Slight induration (fibrosia) and loss of subcutaneous fat | Moderate fibrosis but asymptomatic Slight field contracture <10% linear reduction | Severe induration and loss of subcutaneous tissue Field contracture >10% linear measurement | Necrosis | |
| MUCOUS MEMBRANE | None | Slight atrophy and dryness | Moderate atrophy and telangiectasia Little mucous | Marked atrophy with complete dryness Severe telangiectasia | Ulceration | |
| SALIVARY GLANDS | None | Slight dryness of mouth Good response on stimulation | Moderate dryness of mouth Poor response on stimulation | Complete dryness of mouth No response on stimulation | Fibrosis | |
| SPINAL CORD | None | Mild L'Hermitte's syndrome | Severe L'Hermitte's syndrome | Objective neurological findings at or below cord level treated | Mono, para quadraplegia | |
| BRAIN | None | Mild headache Slight lethargy | Moderate headache Great lethargy | Severe headaches Severe CNS dysfunction (partial loss of power or dyskinesia) | Seizures or paralysis Coma | |
| EYE | None | Asymptomatic cataract Minor corneal ulceration or keratitis | Symptomatic cataract Moderate corneal ulceration Minor retinopathy or glaucoma | Severe keratitis Severe retinopathy or detachment Severe glaucoma | Panopthalmitis/ Blindness | |
| LARYNX | None | Hoarseness, Slight arytenoid edema | Moderate arytenoid edema, Chondritis | Severe edema, Severe chondritis | Necrosis | |
| LUNG | None | Asymptomatic or mild symptoms (dry cough) Slight radiographic appearances | Moderate symptomatic fibrosis or pneumonitis (severe cough) Low grade fever Patchy radiographic appearances | Severe symptomatic fibrosis or pneumonitis | Severe respiratory insufficiency/ Continuous O2/ Assisted ventilation | |
| HEART | None | Asymptomatic or mild symptoms Transient T wave inversion & ST changes Sinus tachycardia >110 (at rest) | Moderate angina on effort Mild pericarditis Normal heart size Persistent abnormal T wave and ST changes Low ORS | Severe angina Pericardial effusion Constrictive pericarditis Moderate heart failure EKG abnormalities | Tamponade/ Severe heart failure/ Severe constrictive pericarditis | |

| ORGAN TISSUE | 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 | 5 |
|---|---|---|---|---|---|---|
| ESOPHAGUS | None | Mild fibrosis Slight difficulty in swallowing solids No pain on swallowing | Unable to take solid food normally Swallowing semi-solid food Dilatation may be indicated | Severe fibrosis Able to swallow only liquids May have pain on swallowing Dilation required | Necrosis/ Perforation Fistula | DEATH DIRECTLY RELATED TO RADIATION LATE EFFECTS |
| SMALL/LARGE INTESTINE | None | Mild diarrhoea Mild cramping Bowel movement 5 times daily Slight rectal discharge or bleeding | Moderate diarrhoea and colic | Obstruction or bleeding | Necrosis/ Perforation | |
| LIVER | None | Mild lassitude Nausea, dyspepsia Slightly abnormal liver function | Moderate symptoms Some abnormal liver function tests Serum albumin normal | Disabling hepatitic insufficiency Liver function tests grossly abnormal Low albumin Edema or ascites | Necrosis/ Hepatic coma or encephalopathy | |
| KIDNEY | None | Transient albuminuria No hypertension Mild impairment of renal function Urea 25-35 mg% Creatinine 1.5-2.0 mg% Creatinine clearance >75% | Persistent moderate albuminuria (2+) Mild hypertension No related anaemia Moderate impairment of renal function Urea >36-60 mg% Creatinine clearance (50-74%) | Severe albuminuria Severe hypertension Persistent anaemia (<10g %) Severe renal failure Urea >60mg% Creatinine >4.0 mg% Creatinine clearance <50% | Malignant hypertension Uremic coma/ Urea >100% | |
| BLADDER | None | Slight epithelial atrophy Minor telangiectasia (microscopic haematuria) | Moderate frequency Generalized telangiectasia Intermittent macroscopic haematuria | Severe frequency and dysuria Severe generalized telangiectasia (often with petechiae) Frequent haematuria Reduction in bladder capacity (<150 cc) | Necrosis/ Contracted bladder (capacity <100 cc) Severe haemorrhagic cystitis | |
| BONE | None | Asymptomatic No growth retardation Reduced bone density | Moderate pain or tenderness Growth retardation Irregular bone sclerosis | Severe pain or tenderness Complete arrest of bone growth Dense bone sclerosis | Necrosis/ Spontaneous fracture | |
| JOINT | None | Mild joint stiffness Slight limitation of movement | Moderate stiffness Intermittent or moderate joint pain Moderate limitation of movement | Severe joint stiffness Pain with severe limitation of movement | Necrosis/ Complete fixation | |

## A4. QUALITY OF LIFE STUDY

Patient reported outcomes (PRO) are a key secondary endpoint within CORE.

### A4.1 Quality of life measures

Patient reported outcomes will be measured using the EORTC QLQ C30 and the EQ-5D.Patients will complete the EORTC QLQ C30 general cancer questionnaire.
Participants will also be asked to complete the EQ-5D questionnaire, a brief standardised instrument which provides a simple descriptive profile of their health status.

### A4.2 Study design

Patients are eligible for the PRO study if they fulfil the CORE eligibility criteria. Participants will be asked in the patient information sheet to consent to regular completion of PRO questionnaires. Patients who decline to take part in the CORE PRO study will remain eligible for the main trial. PRO is a secondary endpoint in the main trial and the primary time point of interest is 12 and 18 months after completion of radiotherapy.

### A4.3 Timing of data collection

Participants will be asked to complete a questionnaire in clinic within one week prior to randomisation and if this window is missed should be before treatment allocation is known to the patient (SOC or SBRT+ SOC). Questionnaires will be completed in clinic at the end of SBRT delivery/6 weeks from randomisation. Further booklets will be sent to participants' homes by ICR-CTSU at 3, 6, 12, 18 and 24 months from randomisation.

### A4.4 Compliance

Missing data may hamper interpretation of PRO. Missing data may arise because participants do not complete the questionnaires at the appropriate time (unit non-response), or because patients may miss questions within the questionnaires (item non-response). During the study, compliance with PRO questionnaire completion will be monitored by the trial oversight committees.

### A4.5 Statistical considerations

Patient reported outcome analyses will be used to supplement results of clinician assessed treatment toxicity; therefore a formal sample size calculation has not been performed. An analysis plan will be developed in consultation with the TMG with key endpoints identified from each questionnaire. Standard algorithms will be used to derive scores and handle missing data in quality of life questionnaires. Quality of life data will be presented at individual time-points and analyses to account for the longitudinal nature of the data may be used.

## A5. EXPECTED SERIOUS ADVERSE EVENTS

Hospitalisation for any of the following adverse events does not need to follow SAE reporting procedures if the event is grade ≤2:

SBRT group

Thoracic and mediastinum

- Pericarditis
- Dysphagia
- GI haemorrhage
- Gastritis
- Cough
- Pneumonitis

L1-3, Liver, Adrenal, Kidney, Para-aortic

- Nausea
- Vomiting
- Spinal fracture
- Upper GI ulcer
- Duodenal/Gastric ulcer
- Liver enzymes: ALT
- Bilirubin

L4-5, Sacrum, pelvic bones, pelvic nodes/side wall

- Diarrhoea
- Proctitis
- Rectal Haemorrhage
- Haematuria
- Urinary frequency
- Urinary incontinence
- Urinary retention
- Urinary urgency

General

- Fever
- Fatigue
- Myelitis

Dermatology/Skin

- Dermatitis
- Hair loss (to treatment area)

Related to fiducial marker insertion

- Bleeding
- Sepsis (urinary and systemic)

## A6. NON-UK SAFETY REPORTING REQUIREMENTS

The site Principal Investigator or designee is responsible for reporting SAEs to their individual Institutional Review Board (IRB) and/or Institutional Ethics Committee (EC) as per local standards.

The collaborative group in each participating country should report related unexpected SAEs as per their local requirements to IECs and local investigators.

Further Sponsor safety reporting notification requirements will be agreed in the international site agreements.

## A7. LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| ALT | Alanine Aminotransferase |
| ANC | Absolute Neutrophil Count |
| AST | Aspartate Aminotransferase |
| CI | Chief Investigator |
| CIS | Carcinoma In Situ |
| CRF | Case Report Form |
| CT | Computed Tomography |
| DFI | Disease Free Interval |
| DFS | Disease Free Survival |
| DMSA | DimercaptoSuccinic Acid |
| EORTC | European Organisation for Research and Treatment of Cancer |
| FBC | Full Blood Count |
| FDG | Fluoro-DeoxyGlucose |
| FEV1 | Forced Expiratory Volume in 1 second |
| FFWMD | Freedom From Widespread Metastatic Disease |
| Fr | Fraction |
| FVC | Forced Vital Capacity |
| Gy | Gray |
| HR | Hazard Ratio |
| ICR | The Institute Of Cancer Research |
| IDMC | Independent Data Monitoring Committee |
| INR | International Normalised Ratio |
| LFT | Liver Function Test |
| M1 | Any visible disease |
| MDT | Multi-disciplinary team |
| MRI | Magnetic Resonance Imaging |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NCRI | National Cancer Research Institute |
| NSCLC | Non-Small Cell Lung Cancer |
| OS | Overall Survival |
| PET | Positron Emission Topography |
| PFS | Progression Free Survival |
| PI | Principal Investigator |
| PIS | Patient Information Sheet |
| PSA | Prostate Specific Antigen |
| QoL | Quality of Life |
| R&D | Research and Development |
| RCT | Randomised Controlled Trial |
| RFA | RadioFrequency Ablation |
| RT | RadioTherapy |
| RTOG | Radiation Therapy Oncology Group |
| RTTQA | RadioTherapy Quality Assurance |
| SAE | Serious Adverse Event |
| SAR | Serious Adverse Reaction |
| SBRT | Stereotactic Body Radiation Therapy |
| SOC | Standard of Care |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TROG | Trans Tasman Radiation Oncology Group |
| TMG | Trial Management Group |

| | |
|---|---|
| TSC | Trial Steering Committee |
| U+E | Urea & Electrolytes |
| ULN | Upper Limit of Normal |
| WBC | White Blood Cell |
| WHO | World Health Organisation |