SCORAD III

A randomised phase III trial of single fraction radiotherapy compared to multifraction radiotherapy in patients with metastatic spinal cord compression

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Please note:
This trial protocol must not be applied to patients treated outside the SCORAD III trial. UCL CTC can only ensure that approved trial investigators are provided with amendments to the protocol.

Acknowledgements:
The Protocol Writing Group is indebted to the late Venetia Franglen for her help in the development of this protocol in her capacity as Patient Representative.

In addition to the information in the SCORAD III protocol, sites in Australia and New Zealand should also refer to their Group Specific Appendix.
Sites in Australia and New Zealand should refer to BOTH the protocol and the Group Specific Appendix at all times.

Coordinating centre

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https://online.ctc.ucl.ac.uk

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ensuring 'SCORAD III randomisation' is included the subject title.

Telephone randomisation

During working hours (Monday to Friday, 09.00 - 17.00 hrs UK time) randomisations can be conducted with UCL CTC staff on
+44 (0) 20 7679 9880

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1.0 SCORAD III trial summary

SCORAD III: A randomised phase III trial of single fraction radiotherapy compared to multifraction radiotherapy in patients with metastatic spinal cord compression.

Sponsor:	University College London: UCL/09/0199	**ISRCTN:**	ISRCTN97108008
Funder:	Cancer Research UK: CRUK/06/034	**Design:**	A multicentre, randomised phase III trial.

Overall aim:

To show that ambulatory status using 8Gy in 1 fraction is no worse than with 20Gy in 5 fractions for patients with metastatic spinal cord compression (SCC).

Primary endpoint:

- Ambulatory status at 8 weeks from day 1 of treatment compared to randomisation

Secondary endpoints:

- Recovery of and time to ambulation
- Ambulatory status at 1, 4 and 12 weeks compared to randomisation (where available)
- Maintenance of ambulatory status
- Bladder and bowel function at 1, 4, 8 and 12 weeks from day 1 of treatment compared to randomisation
- Adverse events using RTOG and CTCAE v.4.02 at 1, 4, 8 and 12 weeks from day 1 of treatment
- Quality of life measured using the EORTC QLQ-C30 questionnaire at 1, 4, 8 and 12 weeks from day 1 of treatment compared to randomisation
- Further treatment and SCC retreatment up to 12 months after randomisation
- Duration of care in hospital, hospice, nursing home or home
- Preferred place of care
- Overall survival at 12 weeks and 12 months

Target accrual: 580 patients

Eligibilities:

Inclusion criteria:

- Decision to treat made no more than 48 hours prior to treatment of spinal cord or cauda equina (C1 to S2) compression, based on a full spinal MRI or CT scan confirming compression carried out no more than one week prior to treatment.
- Single site of compression or multiple sites that can be treated within a single radiation treatment field
- Histologically or cytologically confirmed malignant disease, or for prostate tumours a serum PSA >100 ng/ml at any point prior to randomisation (if biopsy done or planned but results not yet available patients may be entered provided all other inclusion and exclusion criteria are met. Biopsy results must be submitted on the relevant CRF page as soon as they are available)
- Life expectancy >8 weeks
- Age ≥18 years
- Able to give written informed consent
- Willing and able to complete assessment forms

Exclusion criteria:

- Patients for whom surgery or chemotherapy treatment is more appropriate
- Patients who are known to be pregnant
- Patients with multiple myeloma, lymphoma, leukaemia or glioma
- Patients undergoing purely prophylactic treatment in the absence of radiological spinal cord or cauda equina compression
- Patients whose spinal compression site has been treated previously with radiotherapy

Planned sites: ~50

Target Countries: United Kingdom, Australia and New Zealand

Treatment summary:

Arm 1: Multiple fraction radiotherapy 20Gy/5f

Arm 2: Single fraction radiotherapy 8Gy/1f

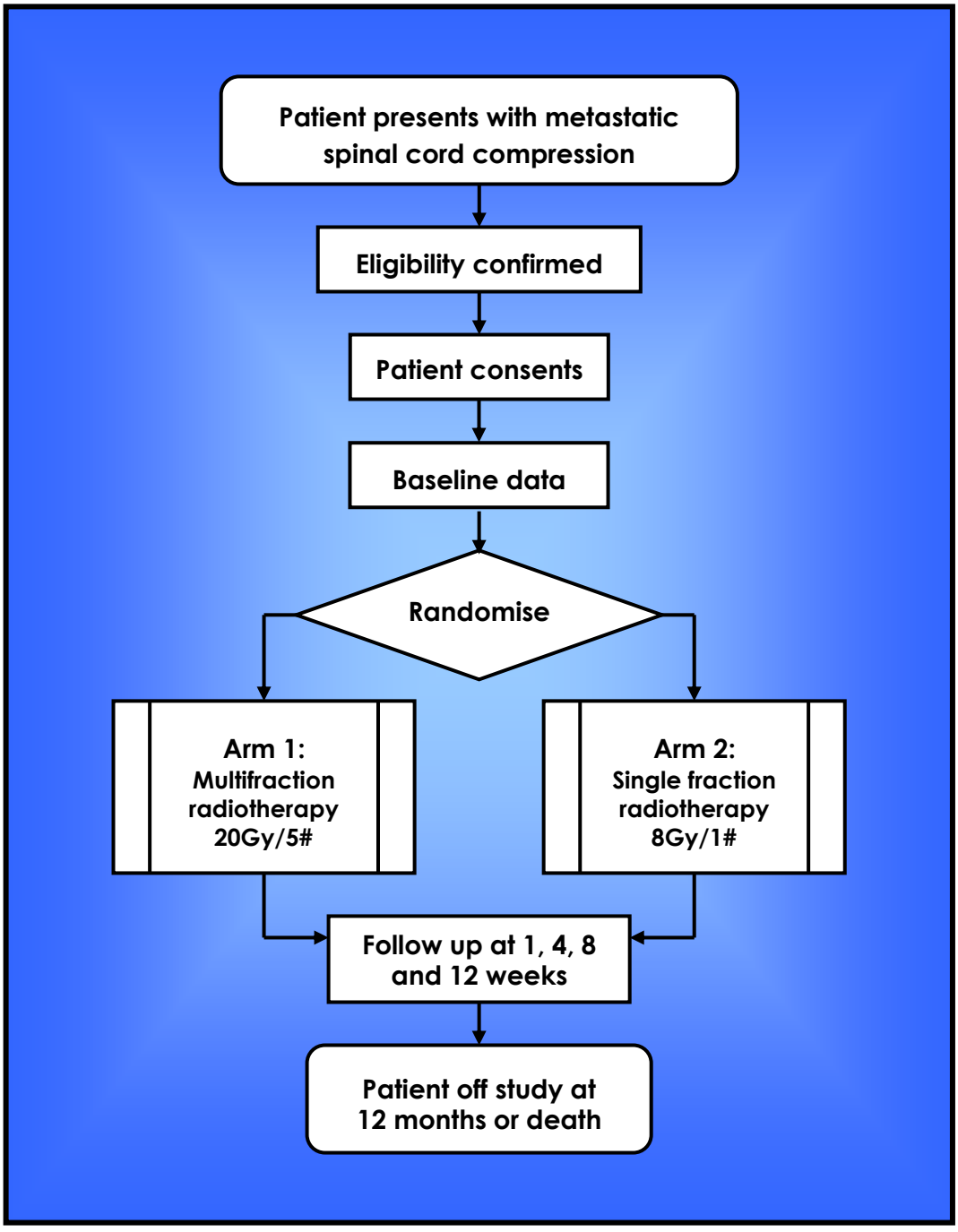
Anticipated duration of recruitment: 4 Years

Duration of patient follow up: 12 months

Definition of trial end:

12 months post randomisation of last patient or the death of the last surviving patient, whichever event occurs first

1.1 Trial schema



2.0 Introduction

2.1 Background

Spinal cord compression (SCC) is a common complication of metastatic cancer affecting around 4,000 patients in the UK annually, and is a major cause of morbidity resulting in pain, loss of mobility and of sphincter control. Whilst chemotherapy and surgery may be considered, for the vast majority of patients the treatment of choice is radiotherapy, the aim of which is to preserve or recover neurological function and prevent further progression of symptoms. Current common practice is to use between 20 and 30Gy in 5 to 10 fractions although many patients with poor performance status are treated with single doses of 8 to 10Gy. There is no standard fractionation schedule. Since the life expectancy of these patients is short (4 to 6 months), any prolonged treatment must be justified by randomised clinical trial based evidence. The aim of this trial is to determine whether single fraction radiotherapy is as effective as multifraction radiotherapy in terms of ambulatory status, function, quality of life, adverse events and survival in patients with SCC. Patients admitted to hospital for SCC and for whom radiotherapy is recommended will be randomised to either multifraction or single fraction radiotherapy. Patients will be assessed at 1, 4, 8 and 12 weeks after treatment.

The majority of SCC cases arise due to either extradural compression or invasion of the spinal cord by metastases from an adjacent vertebral body. The physiology of spinal cord and cauda equina damage is thought to relate initially to venous obstruction and oedema rather than direct physical pressure causing the initial symptoms[1] (direct pressure causing neuropraxia, axonal fracture or arterial occlusion causing infarction are generally thought to be irrecoverable). It is therefore entirely conceivable that minimal tumour shrinkage allowing restoration of venous drainage and a period of growth delay for a matter of months is adequate treatment for the majority of patients with metastatic spinal cord compression.

The standard treatment after histological and radiological confirmation of SCC is radiotherapy. Exceptions are patients with non-Hodgkin's lymphoma or germ cell tumours where primary chemotherapy may be appropriate, and those cases where there is gross spinal instability that requires surgery. New evidence suggests that those with a localised block and no metastatic disease elsewhere may also benefit from initial surgical decompression[2].

Nevertheless for the vast majority of patients the treatment of choice is radiotherapy, and standard radiotherapy techniques employ a direct posterior field and a treatment volume defined by the site of compression and a margin of one to two vertebral bodies above and below this. In the past myelography was used to define the site of block but magnetic resonance imaging (MRI) is now the investigation of choice giving optimum definition of the extent of spinal disease.

Studies comparing multiple fractions

Currently, there is no standard fractionation schedule for treating SCC. Common practice in the UK is to use between 20 and 30Gy in 5 to 10 fractions. Prolonged schedules delivering 45Gy in 4.5 weeks have been described but there is no evidence of an advantage to these higher dose schedules[3]. A retrospective nonrandomised comparison of 30Gy in 10 fractions with 37.5Gy in 15 fractions and 40Gy in 20 fractions revealed no difference in functional outcome between the three groups[4]. The only randomised trial compared 16Gy in 2 fractions with a split course treatment of 15Gy in 3 fractions followed after an interval by 15Gy in 5 fractions[5]. The results of this reported 72% of patients able to walk after treatment with no difference between the two radiation dose arms, however, neither of these radiotherapy doses would be considered standard.

Evidence for single fractions

A single fraction of 8 to 10Gy will achieve substantial tumour cell kill, which is illustrated by the very small proportion of cells remaining after only 2Gy (SF2). Typical values from human cell lines relevant to this population are 0.30 for breast

cancer and 0.18 for squamous lung cancer[6]. Such doses may therefore be entirely compatible with effective treatment.

In other palliative situations hypofractionation has proven to be as effective as the more traditional lengthy fractionated schedules: in particular for bone pain[7], palliation of non-small cell lung cancer[8] and cerebral metastases[9].

There are six published series in which single fractions of radiation have been used to treat spinal cord compression:

- Researchers from the Christie Hospital[10] reported a series of 100 consecutive patients treated with radiotherapy alone and 25 who received postoperative irradiation following laminectomy. Of these, 104 received single fractions of 12.5 to 15Gy, 10 received single fractions of 5 to 10Gy and 11 received a fractionated schedule. In the 100 patients treated with radiotherapy alone, 8 out of 9 ambulatory patients retained mobility, 14 out of 25 non-ambulatory patients were subsequently able to walk and 7 out of 66 paraplegic patients improved, 6 becoming ambulatory. As in other series the only significant factor predicting a good outcome in these patients was pretreatment neurological status.
- A smaller series of patients[11] treated with a single fraction of 10Gy reported an overall improvement in motor function in 15 out of 24 patients.
- A more recent series of 102 patients found no difference in outcome between the 32% who received single fraction radiotherapy compared to the remainder of the cohort who received fractionated treatment despite better performance status in this latter group[12]. Overall 71% were ambulant at 2 months after treatment. These figures compare with those published in a review of radiotherapy in spinal cord compression in which 79% of ambulant patients retained function, and 42% of those presenting with paraparesis became ambulant[13].
- A further series of 199 patients treated with 8Gy in a single fraction reported that mobility was regained in 26% of non-ambulatory patients, and only 17% deteriorated; results were compared to a multifraction series[14].

- A retrospective analysis of 204 patients treated with either a single dose of 8Gy or 30Gy in 10 fractions showed no significant differences between the schedules for motor function or ambulatory status[15].
- A pooled analysis from four European countries including one from the UK analysed data from 1,304 patients receiving one of five radiation schedules: 8Gy single dose, 20Gy in 5 fractions, 30Gy in 10 fractions, 37.5Gy in 15 fractions and 40Gy in 20 fractions. This concluded that all five schedules produced similar functional outcome[16].

An Italian group has also recently presented a further trial of 8Gy in a single fraction vs. 16Gy in 2 fractions in 96 patients with poor performance status reporting a 76% ambulation rate after radiotherapy with no difference between the two arms at a median follow up of 6 months[17], but this does not really address the question of whether single is as good as more standard multifractionated regimens.

The recently published UK NICE guidelines[18] highlighted the poor quality evidence currently available for radiotherapy schedules in SCC as follows: 'given the low quality of case series studies conclusions are limited about the effectiveness of different radiotherapy regimens'. It went on to conclude 'Radiotherapy may be delivered as a single treatment or a number of consecutive smaller treatments (fractionation). For patients with MSCC current clinical practice is to give fractionated radiotherapy, generally in five or ten fractions, especially for patients after surgery and for those with good prognostic factors, for whom the duration of tumour response may be important. The use of short fractionation regimens is the subject of continuing research'. In its summary conclusions it stated: 'Further research should investigate what are the most clinically and cost effective regimens of radiotherapy to treat patients with established MSCC'. These extracts highlight the recognition by NICE that research is urgently needed to define optimal radiotherapy fractionation in SCC. This will be addressed by SCORAD III.

Three systematic reviews have been carried out in this field more recently[19, 20, 21]. Loblaw concluded 'there are very few papers of high methodological quality in the literature. More studies are needed to satisfy the validity of many of the clinical decisions that are made today with regard to the management of malignant spinal cord compression'. At 2009, there are currently no RCTs listed on the International Cancer Research Portfolio (ICRP) website. The Cochrane Review, updated in 2008, again highlights the paucity of data available: only six RCTs addressing radiotherapy, surgery and steroid use were identified, none considering radiotherapy fractionation. The authors conclude: 'Limited evidence suggests that short courses of radiotherapy suffice in patients with unfavourable histologies or a predicted survival of less than six months. There are no RCTs to draw conclusions regarding the optimal radiotherapy dose in good prognostic patients.' and recommends that 'Adequately powered, multinational RCTs are needed'.

Risk of myelopathy

There is extensive literature on the use of single fractions of 8 or 10Gy for uncomplicated spinal metastases, none of which has identified a detectable risk of myelopathy. A retrospective analysis of 465 patients treated for spinal cord compression identified only one possible case of myelopathy in a patient receiving 16Gy in 2 fractions, becoming symptomatic 19 months after initial presentation[22]. In addition the estimated risk of radiation myelopathy from palliative radiotherapy for non small cell lung cancer was calculated using over 1,000 patients taking part in a series of MRC trials[23]. These patients will have had similar doses of radiotherapy to the spinal cord. Only five patients were reported as having radiation myelopathy, two who had received 17Gy/2f and three who had 39Gy/13f, but none in patients who received 10Gy/1f. The overall cumulative risk was estimated as 0.8% at year 1 and 1.5% at year 2. Thus the risk of radiation myelopathy appears negligible.

The life expectancy of these patients is short (4 to 6 months) and so any prolonged treatment must be clearly justified by randomised clinical trial based evidence. There is no evidence to suggest that single fraction radiotherapy for spinal cord

compression would be disadvantageous. If it is proven to be equivalent to multifraction radiotherapy, this would enable a major change in clinical practice with advantages both for the patient in terms of treatment duration and hospital stay, and with obvious socioeconomic advantages.

2.2 Proposed trial

The objectives are to evaluate multifraction radiotherapy against single fraction radiotherapy in terms of ambulatory status, bladder and bowel function, quality of life, further treatment, adverse events and survival. The trial will be a multicentre, randomised (1:1) phase III trial.

The patients will be randomised to receive either Arm 1: 20Gy over 5 fractions, or Arm 2: 8Gy in a single fraction.

2.2.1 Primary endpoint

- Ambulatory status at 8 weeks from day 1 of treatment compared to randomisation.

2.2.2 Secondary endpoints

- Recovery of and time to ambulation
- Ambulatory status at 1, 4 and 12 weeks compared to randomisation (where available)
- Maintenance of ambulatory status
- Bladder and bowel function at 1, 4, 8 and 12 weeks from day 1 of treatment compared to randomisation
- Adverse events using the Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring Criteria and Common Terminology Criteria for Adverse Events (CTCAE) v4.02 at 1, 4, 8 and 12 weeks from day 1 of treatment
- Quality of life measured using the EORTC QLQ-C30 questionnaire at 1, 4, 8 and 12 weeks from day 1 of treatment compared to randomisation
- Further treatment and SCC retreatment up to 12 months after randomisation
- Duration of care in hospital, hospice, nursing home or home
- Preferred place of care
- Overall survival to 12 weeks and 12 months

2.3 Trial activation

UCL CTC will ensure that all trial documentation has been reviewed and approved by all relevant bodies and that the following have been obtained prior to activating the trial:

- Research Ethics Committee approval
- Adoption into NIHR portfolio
- NHS permission
- Adequate funding for central coordination
- Confirmation of sponsorship
- Adequate insurance provision

3.0 Selection of sites and site investigators

3.1 Site selection

In this protocol, trial "site" refers to the hospital where trial related activities are conducted.

Sites must be able to comply with:

- Trial treatments, imaging, clinical care, follow up schedules and all requirements of the trial protocol

> NB: Sites can opt out of the multifraction schedule and use their own multifraction schedule in this trial but they must notify UCL CTC of this on the site registration form.

- UK sites: Requirements of the Research Governance Framework, 2nd Edition 2005
- Data collection requirements

Non-UK sites must be able to comply with:

- All local regulations governing clinical trials in radiotherapy.
  Where applicable a non-UK site should refer to their group specific appendix for additional details.

3.1.1 Selection of Principal Investigator and other investigators at sites

Sites must have an appropriate Principal Investigator (PI) i.e. a health care professional authorised by the site and ethics committee (if applicable) to lead and coordinate the work of the trial on behalf of the site. Other investigators at site wishing to participate in the trial must be trained and approved by the PI. All investigators must be appropriately qualified health professionals and have experience of treating SCC.

3.1.2 Training requirements for site staff

All site staff must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log.

CVs for all staff **must be kept up to date** and signed and dated copies held in the Investigator Site File (ISF). An up to date, signed copy of the CV for the PI must be forwarded to UCL CTC upon request.

GCP training is required for all staff responsible for trial activities at UK sites. The frequency of repeat training may be dictated by the requirements of their employing institution, or 2 yearly where the institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials.

For non-UK sites the frequency of GCP training will be dictated by that country's policy on repeat training.

GCP training will be provided by the Country Coordinating Centre (CCC) as part of site initiation for sites in countries where GCP training is not mandatory.

3.2 Site initiation and activation

3.2.1 Site initiation

Before a site is activated, the UCL CTC trial team will arrange a site initiation with the site, which the PI and site research team must attend. The site will be trained in the day to day management of the trial and essential documentation required for the trial will be checked.

Site initiation will be performed for each site, by either a visit to site or by teleconference. .

3.2.2 Required documentation

The following documentation must be submitted to UCL CTC prior to a site being activated by UCL CTC:

- Trial specific Site Registration Form (identifying relevant local staff)
- All relevant institutional approvals, including local Research and Development (R&D) approval, or equivalent for non-UK sites

- For UK sites: a signed Clinical Trial Site Agreement (CTSA) between the Sponsor and the relevant institution (usually an NHS Trust)
- A completed site delegation log, signed and dated by the PI
- A copy of the PI's CV that is signed and dated
- For non-UK sites:
    - A signed International Clinical Trials Site Agreement (ICTSA).
    - For countries with a Country Coordinating Centre (CCC) a signed International Country Coordinating Centre Agreement and a signed clinical trial agreement between the CCC and the relevant institution.

3.2.3 Site activation letter

Once the UCL CTC trial team has received all required documentation and the site has been initiated, a site activation letter will be issued to the PI, at which point the site may start to approach patients.

Once the site has been activated by UCL CTC, the PI is responsible for ensuring:

- Adherence to the most recent version of the protocol
- All relevant site staff are trained in the protocol requirements
- Appropriate recruitment and medical care of patients in the trial
- Timely completion and return of Case Report Forms (CRFs) (including assessment of all adverse events)
- Prompt notification and assessment of all serious adverse events
- That the site has facilities to provide **24 hour medical advice** for trial patients.

4.0 Informed consent

Sites are responsible for assessing a patient's capability to give informed consent. Sites must ensure that all patients have been given the current version of the patient information sheet, are fully informed about the trial and have confirmed their willingness to take part in the trial by signing a consent form.

All efforts should be made to enter all eligible patients into the trial, however the Site must assess a patient's ability to understand verbal explanations and written information in English. As patients for this trial are consented and randomised in an emergency setting, if local interpreters are not available in the time before approaching and treating a potential patient at the site, and whenever the patient is contacted, and fully informed consent is not deemed possible, the patient should not be considered for the trial.

The PI, or, where delegated by the PI, other appropriately trained site staff are required to provide a full explanation of the trial and all relevant treatment options to each patient prior to trial entry. During these discussions the current approved patient information sheet for the trial should be discussed with the patient.
A minimum of 30 minutes must be allowed for the patient to consider and discuss participation in the trial. Written informed consent on the current approved version of the consent form for the trial must be obtained before any trial specific procedures are performed. The discussion and consent process must be documented in the patient notes.
All Site staff are responsible for:

- checking that the correct (current approved) version of the patient information sheet and consent form are used
- checking that information on the consent form is complete and legible
- checking that the patient has completed and initialled all relevant sections and signed and dated the form
- checking that an appropriate member of staff has countersigned and dated the consent form to confirm that they provided information to the patient
- checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e. information given, consent signed etc.)

- giving the patient a copy of their signed consent form, patient information sheet and patient contact card
- following randomisation: adding the patient trial number to all copies of the consent form, which should be filed in the patient's medical notes and ISF and, for UK patients only, sending a copy to UCL CTC

The right of the patient to refuse to participate in the trial without giving reasons must be respected. All patients are free to withdraw at any time (also refer to section 13.0: Withdrawal of patients).

In addition, Non-UK Sites will need to consent patients to the trial according to local practice and regulatory and/or ethical requirements.

An Informed Consent Form Log will also be maintained and completed by site. A copy of the informed consent log must be returned to the CCC for forwarding to UCL CTC at the frequency detailed in the trial monitoring plan or when requested (see also section 12.1 Central monitoring).

5.0 Selection of patients

5.1 Pre-randomisation evaluation

The following assessments or procedures are required to evaluate the suitability of patients for the trial or to provide baseline data:

- A full spine MRI or CT scan to confirm spinal cord compression, no more than one week before treatment
- Assessment of ambulatory status (see appendix 2.1)
- Confirmation of bladder and bowel continence
- Patient completion of the Quality of Life questionnaire

In addition, all patients should have histological or cytological confirmation of malignant disease, or for prostate tumours a serum PSA of >100ng/ml **at any point prior to randomisation**. However, if these results are not yet available at the time of randomisation, but a biopsy has already been done or is planned, patients can be recruited as long as they meet all of the inclusion and exclusion criteria (see section 5.3 below). Sites must ensure that the biopsy results are submitted to UCL CTC on the relevant CRF page as soon as they are available.

Any non-routine procedures must not be performed prior to informed consent being taken.

5.2 Screening log

A screening log must be maintained by the site and kept in the ISF. This must record each patient screened for the trial and must include all patients identified with SCC together with the reasons why they were not randomised if this was the case.

The log must be sent to UCL CTC when requested, with patient identifiers removed prior to sending.

5.3 Patient eligibility

There will be no exception to the eligibility requirements at the time of randomisation. Queries in relation to the eligibility criteria must be addressed prior

to randomisation. Patients are eligible for the trial if the inclusion criteria are met and none of the exclusion criteria apply.

5.3.1 Inclusion criteria

- Decision to treat made no more than 48 hours prior to treatment of spinal cord or cauda equina (C1 to S2) compression, based on a full spinal MRI or CT scan confirming compression carried out no more than one week prior to treatment
- Single site of compression or multiple sites that can be treated within a single radiation treatment field
- Histologically or cytologically confirmed malignant disease, or for prostate tumours a serum PSA >100 ng/ml at any point prior to randomisation (if biopsy done or planned but results not yet available patients may be entered provided all other inclusion and exclusion criteria are met. Biopsy results must be submitted on the relevant CRF page as soon as they are available)
- Life expectancy >8 weeks
- Age ≥18 years
- Able to give written informed consent
- Willing and able to complete assessment forms

5.3.2 Exclusion criteria

- Patients for whom surgery or chemotherapy treatment is more appropriate
- Patients who are known to be pregnant
- Patients with multiple myeloma, lymphoma, leukaemia or glioma.
- Patients undergoing purely prophylactic treatment in the absence of radiological spinal cord or cauda equina compression
- Patients whose spinal compression site has been treated previously with radiotherapy

5.3.3 Pregnancy and birth control

Due to the risks of radiation damage to an unborn child, women who are known to be pregnant are excluded from the trial. Women who could become pregnant and men who could father a child should be advised of the risks involved, if this is deemed appropriate by the medical team.

A woman of childbearing potential is a sexually mature woman (i.e. any female who has experienced menstrual bleeding) who has not:

- undergone a hysterectomy or bilateral oophorectomy/salpingectomy
- been postmenopausal for 24 consecutive months (i.e. who has had menses at any time in the preceding 24 consecutive months without an alternative medical cause)

6.0 Randomisation procedure

This is a randomised phase III trial comparing single fraction radiotherapy versus multifraction radiotherapy for metastatic spinal cord compression.

Treatment allocation is by randomisation. Patients are stratified by:

1. radiotherapy centre
2. ambulatory status at randomisation
3. type of primary tumour
4. extent of disease (presence or absence of nonskeletal metastases)

Patient randomisation is performed using a 24 hour remote internet based randomisation programme and must be completed prior to commencement of any trial treatment. The programme is hosted and maintained by UCL CTC, and is accessed at:

https://online.ctc.ucl.ac.uk

Site staff responsible for the randomisation of patients must register for access to the programme. Details and instructions are provided by UCL CTC.

Following pre-treatment evaluations (as detailed in section 5.1), confirmation of eligibility and consent of a patient at a site, it is recommended that the paper randomisation form is completed fully prior to randomisation. Note that patient initials and date of birth are required for completion of the randomisation programme. Upon randomisation the trial number and treatment allocation are assigned for the patient and these details appear on the randomisation confirmation screen. The trial number and treatment allocation must be recorded in the patient notes. For UK patients, the site must fax the patient contact form (and if used, the randomisation form) to UCL CTC (020 7679 9871) within 48 hours of randomisation. For UK patients, the patient's address and NHS or CHI number must be supplied for the patient contact form. Other than for the purposes of flagging with the Health & Social Care Information Centre, patient name and address is not

stored electronically at UCL CTC. Confirmation of randomisation is sent to the randomiser by email automatically.

6.1 Alternative randomisation procedure for UK sites

During office hours UK sites may also randomise patients into the trial by telephone through UCL CTC on 020 7679 9880. Following pre-treatment evaluations (as detailed in section 5.1), confirmation of eligibility and consent of a patient at a site the randomisation form must be completed fully prior to telephoning UCL CTC. The eligibility criteria are reviewed during the randomisation telephone call using the same form at UCL CTC.

A trial number and treatment allocation are assigned to the patient during the call and must be recorded at site by the caller.

UCL CTC will fax confirmation of the patient's inclusion in the trial, their trial number and treatment allocation to the main site contact. In turn the site must ensure that the randomisation form and patient contact details form are faxed to UCL CTC within 48 hours of randomisation (020 7679 9871). CRFs are available for downloading from the UCL CTC website:

http://www.ctc.ucl.ac.uk/

6.2 Alternative randomisation procedure for non-UK sites

If non-UK sites are unable to access the internet randomisation programme they may fax a completed randomisation form to UCL CTC (on +44 (0)20 7769 9871), who will perform the randomisation on their behalf.

Following pre-treatment evaluations (as detailed in section 5.1), confirmation of eligibility and consent of a patient at a site the randomisation form must be fully completed and then faxed to UCL CTC. The faxed randomisation form will be used to confirm patient eligibility by UCL CTC.

A trial number and treatment allocation will be assigned for the patient and details added to the randomisation form, which will then be faxed back to the site.

Please note that if a fax is received outside UCL CTC working hours the randomisation may not be done until the following working day.

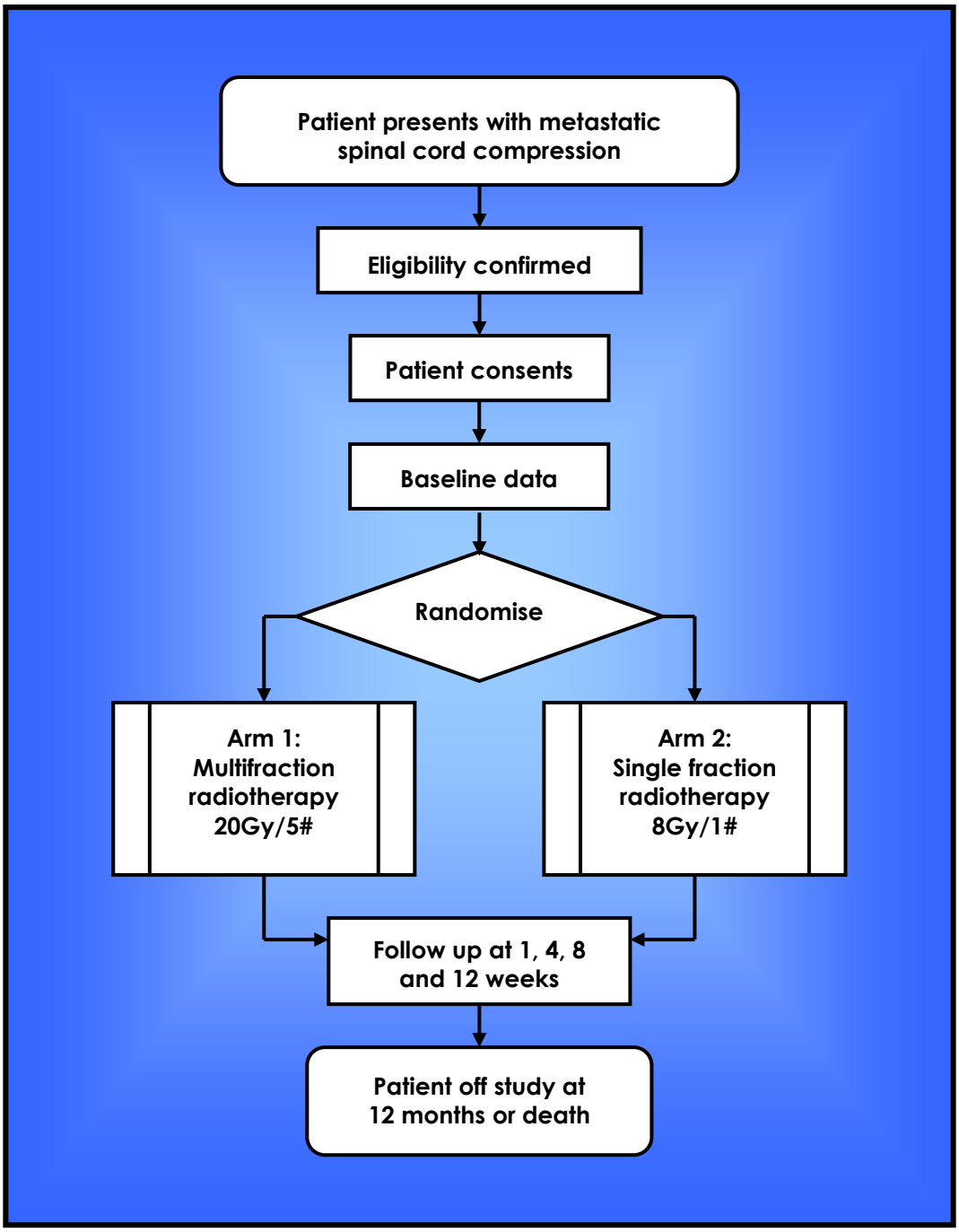
Randomisation telephone no.:	**+44 (0)20 7679 9880**
Randomisation fax no.:	**+44 (0)20 7679 9871**
Randomisation programme:	**https://online.ctc.ucl.ac.uk/Login.aspx**
Office hours:	**09:00 to 17:00 Monday to Friday (UK time)**

Once a patient has been randomised onto the trial they must be provided with the following:

- A copy of their signed consent form and patient information sheet
- A patient contact card. Site on call contact details for out of hours medical care must be added to this card and patients advised to carry this with them at all times while participating in the trial.

7.0 Trial treatment

Patients should be treated using MV photon therapy within 48 hours after the decision to treat is made. The decision to treat should be based on a full spinal MRI or CT scan that was performed no more than 7 days prior to treatment.



Arm 1: External beam multifraction radiotherapy: 20Gy/5f

Arm 2: External beam single fraction radiotherapy: 8Gy/1f

NB: Sites can opt out of the multifraction schedule and use their own multifraction schedule in this trial but they must notify UCL CTC of this on the site registration form.

7.1 Treatment planning

The radiotherapy field should be defined on a treatment simulator. Radiotherapy dose should be prescribed at cord depth as measured from the MRI scan or lateral radiograph when simulated.

7.2 Supportive care during treatment

Patients should receive appropriate supportive care as per local practice, which may include:

- Steroids, which should be reduced to the minimum as soon as possible
- Active physiotherapy and rehabilitation to optimise the chances of mobility
- Analgesics and anti-emetics as required

7.3 Management after treatment withdrawal

If the patient withdraws consent or treatment is stopped due to adverse events, subsequent treatment will be at the discretion of the treating clinician.

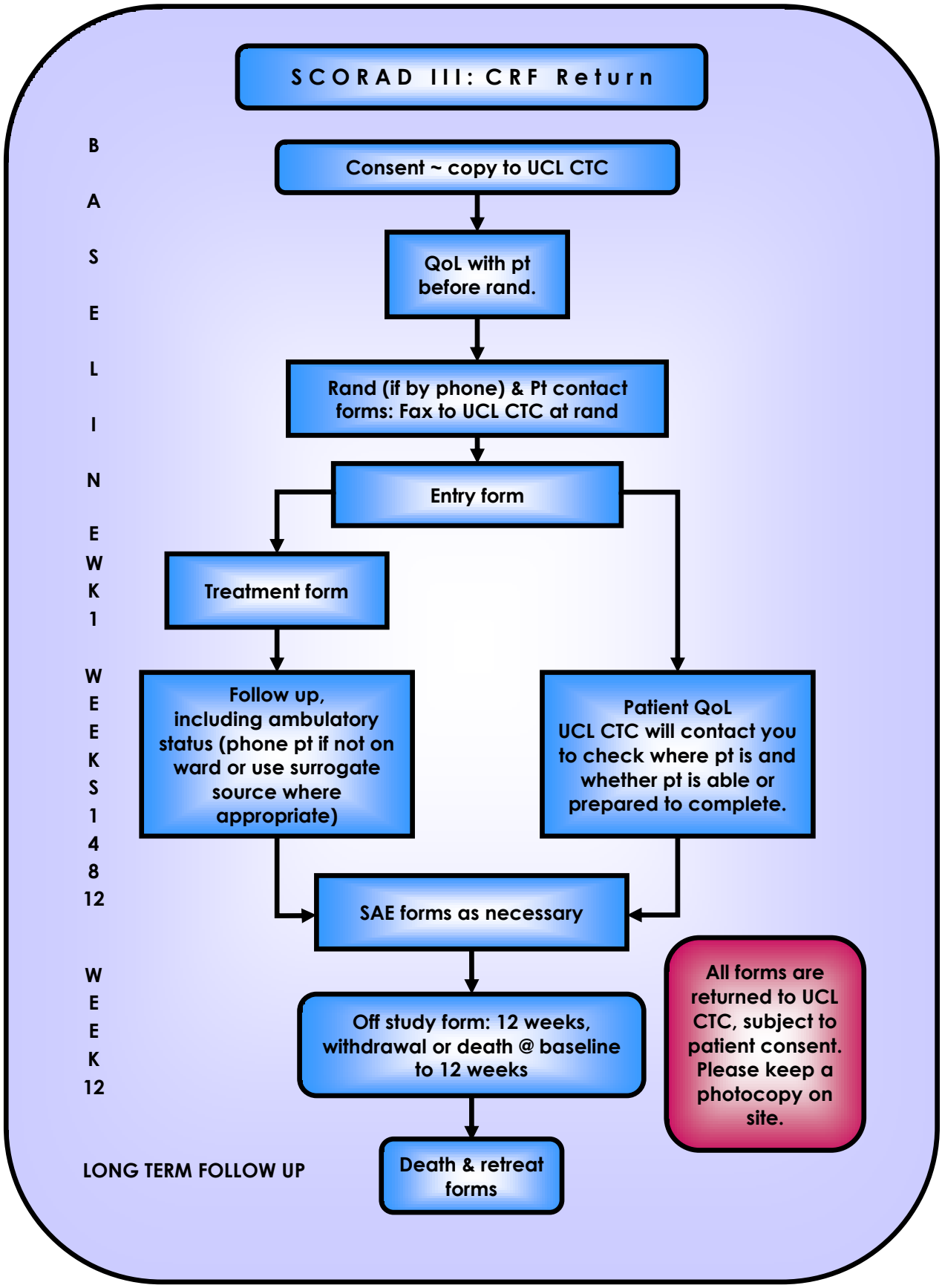
Refer also to section 13.0 (Withdrawal of patients) for further details regarding treatment discontinuation, patient withdrawal from trial treatment and withdrawal of consent to data collection.

7.4 Post protocol treatment

Post protocol treatment will be at the discretion of the treating clinician.

8.0 Assessments

8.1 Assessments for UK sites



Assessment will comprise:

- a simple 4 point ambulatory scale at weeks 1, 4, 8, and 12 from day 1 of treatment compared to randomisation (see appendix 2.1)
- bladder and bowel function at weeks 1, 4, 8 and 12 from day 1 of treatment compared to randomisation
- assessment of adverse events using the RTOG Acute Radiation Morbidity Scoring Criteria and/or CTCAE v4.02 at weeks 1, 4, 8 and 12 from day 1 of treatment
- Further treatment for primary or SCC
- Preferred and actual places of care
- WHO performance status
- EORTC QLQ-C30 at weeks 1, 4, 8, and 12 from day 1 of treatment compared to randomisation

At 1, 4, 8 and 12 weeks after day 1 of treatment, the site team will contact the patient and collect data on the following:

- ambulatory status
- bladder and bowel function
- adverse events
- WHO performance status
- Further treatment for primary or SCC
- Preferred and actual places of care

The EORTC QLQ-C30 will be posted to the patient, together with a prepaid envelope, for completion at home at 1, 4, 8 and 12 weeks from day 1 of their treatment. In the UK, this will be coordinated from UCL CTC.

If a patient fails to return the questionnaire, UCL CTC will contact the site team at the next follow up timepoint to confirm that there is no reason why the patient has not completed the questionnaire. If the patient agrees to continue completing the QoL questionnaire, this will be posted from UCL CTC.

If the patient is an inpatient at the time of follow up, the site team will be requested to ensure the patient completes the questionnaire.

If the patient is returning home, the site team will ensure that the questionnaire is passed on to the patient at discharge so that the questionnaire can be completed on time.
UCL CTC must be informed if the patient no longer wishes or is unable to complete the questionnaires.

Patients will continue to be followed as standard practice for survival data unless the patient specifically withdraws consent for this.

Where it is known, the patient's ambulatory status must be recorded at the follow up time points unless the patient specifically withdraws consent for this. The data may be collected from a surrogate source i.e. the carers where considered appropriate or the GP or hospital/hospice records if necessary.

8.2 Assessments after completion of first 12 weeks of trial

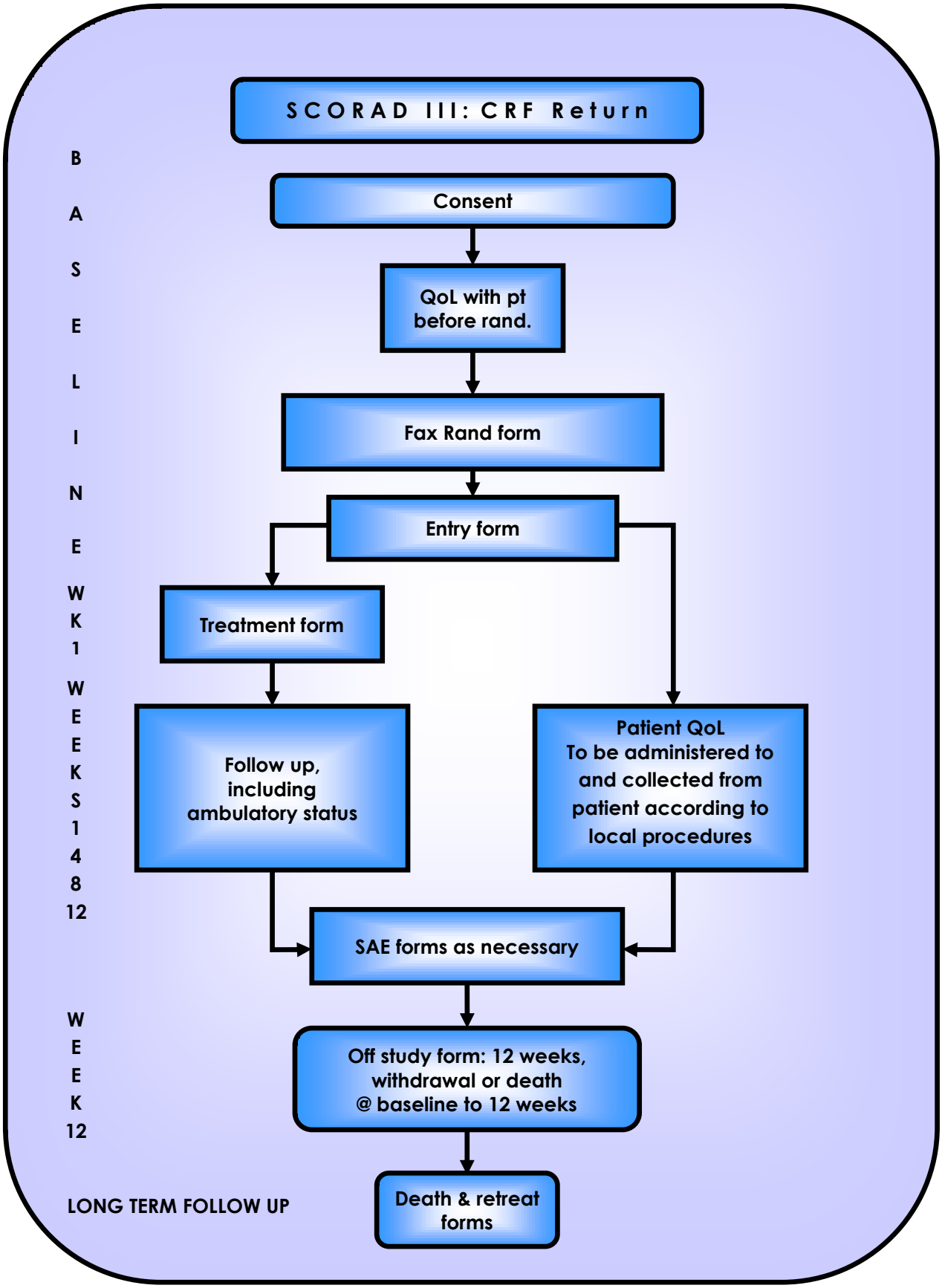
After the initial twelve weeks' follow up, all efforts must be made by the site to contact the patient's GP or use hospital patient notes to record the patient's ongoing treatments.

- The patient and the patient's carers must not be contacted after the 12 week assessment to gain this information.

At 12 months after first day of treatment, the site must submit details of retreatment (or absence of retreatment) of SCC, together with any further treatment (or absence thereof) to the primary cancer or other metastases on the appropriate form.

Sites must return the death form at 12 months as well, to record whether or not the patient remains alive at this timepoint.

8.3 Assessments for non-UK sites



Assessment will comprise:

- a simple 4 point ambulatory scale at weeks 1, 4, 8, and 12 from day 1 of treatment compared to randomisation (see appendix 2.1)
- bladder and bowel function at weeks 1, 4, 8 and 12 from day 1 of treatment compared to randomisation
- assessment of adverse events using the RTOG Acute Radiation Morbidity Scoring Criteria and/or CTCAE v4.02 at weeks 1, 4, 8 and 12 from day 1 of treatment
- Further treatment for primary or SCC
- Preferred and actual places of care
- WHO performance status
- EORTC QLQ-C30 at weeks 1, 4, 8, and 12 from day 1 of treatment compared to randomisation

For non-UK sites with a Country Coordinating Centre (CCC) it will be the responsibility of the CCC to coordinate the collection of trial data at each of the assessment timepoints.
Where there is no CCC in the country, sites must submit data to UCL CTC at each of the assessment timepoints.

At 1, 4, 8 and 12 weeks after day 1 of treatment, the site should contact the patient and collect data on the following:

- ambulatory status
- bladder and bowel function
- adverse events
- WHO performance status
- Further treatment for primary or SCC
- Preferred and actual places of care

Patients should also complete the EORTC QLQ-C30 quality of life questionnaire at each of these timepoints. The administration and collection of this should be performed according to local site procedures. Detailed instructions for assessments, administration of questionnaires and collection of data will be provided in the ISF.

9.0 Data management and data handling guidelines

Data will be collected from sites on version controlled case report forms (CRFs) designed for the trial and supplied by UCL CTC. Data entered on CRFs must be verifiable from source data at site. Source data are contained in source documents and must be accurately transcribed on to the CRF. Examples of source documents are hospital records which include clinical reports.

Where copies of supporting source documentation are being submitted to UCL CTC, the patient's trial number must be clearly indicated on all material and any patient identifiers removed or blacked out prior to sending to maintain confidentiality.

Please note that, for this trial, UK patients have consented to their names and addresses being supplied to UCL CTC. This is:

- for flagging with the Health & Social Care Information Centre
- in order to send QoL forms directly to patients

9.1 Completing case report forms

All CRFs must be completed and signed by staff who are listed on the site staff delegation log and authorised by the PI to perform this duty. The PI is responsible for the accuracy of all data reported in the CRF.

All entries must be clear, legible and written in ball point pen. Any corrections made to a CRF at site must be made by drawing a single line through the incorrect item ensuring that the previous entry is not obscured. Each correction must be dated and initialled. Correction fluid must not be used. The use of abbreviations and acronyms must be avoided. Once completed the original CRFs must be sent to UCL CTC (or via the CCC for non-UK sites) and a copy kept at site.

9.2 Missing data

To avoid the need for unnecessary data queries CRFs must be checked at site (and CCC if applicable) to ensure there are no blank fields before sending to UCL CTC.

- When data are unavailable because a measure has not been taken or test not performed, enter "ND" for not done.
- If an item was not required at the particular time the form relates to, enter "NA" for not applicable.
- When data are unknown enter the value "NK" (only use if every effort has been made to obtain the data).

9.3 Timelines for data return

For UK sites, the randomisation (if randomisation was via phone) and patient contact forms must be faxed to UCL CTC within 48 hours of a patient being randomised, to allow forwarding of the week 1 Quality of Life questionnaire to the patient in good time.

UK sites must complete and submit the entry and treatment forms within one week of the patient being seen.

For UK sites all other forms must be completed and submitted within two weeks of the patient being assessed.

Non-UK sites with a CCC must complete and submit the randomisation form within 48 hours of randomisation to their CCC. The entry and treatment forms must be submitted to their CCC within one week of the patient being seen. All other forms must be completed and submitted to the CCC within two weeks of the patient being assessed. CCCs must forward all CRFs to UCL CTC within five business days of receipt.

Non-UK sites without a CCC must complete and submit all CRFs to UCL CTC within two weeks of the patient being assessed.

9.3.1 Timelines for CRF submissions (UK sites):

Form	Submission time limit (from date of event)
Randomisation form	By fax, within 48 hours (phone based randomisations only)
Patient Contact form	By fax, within 48 hours
Entry form	1 week
Medical history form	1 week
Treatment form (both arms)	1 week
Follow up forms	2 weeks
Adverse event forms	2 weeks
Quality of life forms	2 weeks (if inpatient)
Off study form	2 weeks
Retreatment form	2 weeks of becoming aware of event and at 12 months after randomisation
Primary cancer therapy form	2 weeks of becoming aware of event and at 12 months after randomisation
Serious adverse event report form	24 hours of becoming aware of event
Death form	2 weeks of becoming aware of event or at 12 months after randomisation, if patient is still alive

Sites who persistently do not return data within the required timelines may be suspended from recruiting further patients into the trial by UCL CTC and subjected to a 'for cause' monitoring visit. See section 12.2 ('For cause' on site monitoring) for details.

9.4 Data queries

Data arriving at UCL CTC will be checked for legibility, completeness, accuracy and consistency, including checks for missing or unusual values. Query reports will be sent to the data contact at site (or CCC where applicable). Further guidance on how data contacts should respond to data queries can be found in the query reports.

10.0 Safety reporting

10.1 Definitions of Adverse Events

The following definitions have been adapted from Directive 2001/20/EC, ICH E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" and ICH GCP E6:

Adverse Event (AE)

Any untoward medical occurrence or effect in a patient treated on a trial protocol, which does not necessarily have a causal relationship with a trial treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a trial treatment, whether or not related to that trial treatment.

Adverse Reaction (AR)

All untoward and unintended responses to a trial treatment related to any dose administered. A causal relationship between the trial treatment and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

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

An adverse event or adverse reaction that at any dose:

- Results in death
- Is life threatening (the term "life threatening" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is otherwise medically significant (e.g. important medical events that may not be immediately life threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above)

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature or severity of which **is not consistent** with the applicable trial treatment information.

10.2 Reporting procedures

10.2.1 All Adverse Events (AEs)

All adverse events that occur between informed consent and 12 weeks post randomisation must be recorded in the patient notes and the trial CRFs. Those meeting the definition of a Serious Adverse Event (SAE) must also be reported to UCL CTC using the trial specific SAE Report. Also refer to section 10.2.2 (Serious Adverse Events (SAEs)).

Pre-existing conditions do not qualify as adverse events unless they worsen.

These however should be recorded on the Medical History Form in the CRFs.

Overdoses

All accidental or intentional overdoses, whether or not they result in adverse events, must be recorded in the patient notes and CRFs. Overdoses resulting in an adverse event are classified as SAEs and must be reported to UCL CTC according to SAE reporting procedures. The fact that an overdose has occurred must be clearly stated on the SAE Report. Also refer to section 10.2.2 (Serious Adverse Events (SAEs)).

Sites must inform UCL CTC immediately when an overdose has been identified. Also refer to section 11.0 (Incident reporting).

Adverse Event term

An adverse event term must be provided for each adverse event, preferably using the term listed in the RTOG Acute Radiation Morbidity Scoring Criteria or Common Terminology Criteria for Adverse Events (CTCAE) v4.02 available online at:

http://www.rtog.org/ResearchAssociates/AdverseEventReporting/AcuteRadiationMorbidityScoringCriteria.aspx

http://evs.nci.nih.gov/ftp1/CTCAE/Archive/CTCAE_4.02_2009-09-15_QuickReference_8.5x11.pdf

Severity

Severity of each adverse event must be determined by using the RTOG Acute Radiation Morbidity Scoring Criteria and CTCAE v4.02 as a guideline, wherever possible. These criteria are available online at:

http://www.rtog.org/ResearchAssociates/AdverseEventReporting/AcuteRadiationMorbidityScoringCriteria.aspx

http://evs.nci.nih.gov/ftp1/CTCAE/Archive/CTCAE_4.02_2009-09-15_QuickReference_8.5x11.pdf

In those cases where the RTOG Acute Radiation Morbidity Scoring Criteria or CTCAE v4.02 do not apply, severity should be coded according to the following criteria:

1 = Mild	(awareness of a sign or symptom, but easily tolerated)
2 = Moderate	(discomfort enough to cause interference with normal daily activities)
3 = Severe	(inability to perform normal daily activities)
4 = Life threatening	(immediate risk of death from the reaction as it occurred)
5 = Fatal	(the event resulted in death)

Causality

The PI, or other delegated site investigator, must perform an evaluation of causality for each adverse event.

Causal relationship to each trial treatment must be determined as follows:

- **None**
  There is no evidence of any causal relationship.
- **Unlikely**
  There is little evidence to suggest a causal relationship (e.g. because the event did not occur within a reasonable time after administration of a trial treatment). There is another reasonable explanation of the event (e.g. the patient's clinical condition, other concomitant treatments).
- **Possibly**
  There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of a trial treatment). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
- **Probably**
  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.

UCL CTC will consider events evaluated as possibly, probably or definitely related to be adverse reactions.

10.2.2 Serious Adverse Events (SAEs)

All SAEs that occur between informed consent and 12 weeks post randomisation (or after this date if the site investigator feels the event is related to the trial treatment) must be submitted to UCL CTC by fax within **24 hours** of observing or learning of the event, using the trial specific SAE Report. All sections on the SAE Report must be completed. If the event is **not being reported within 24 hours** to UCL CTC, the circumstances that led to this must be detailed in the SAE Report to avoid unnecessary queries.

Exemptions from SAE Report Submission

For this trial, the following events are exempt from requiring submission on an SAE Report, but must be recorded in the relevant section(s) of the trial CRFs:

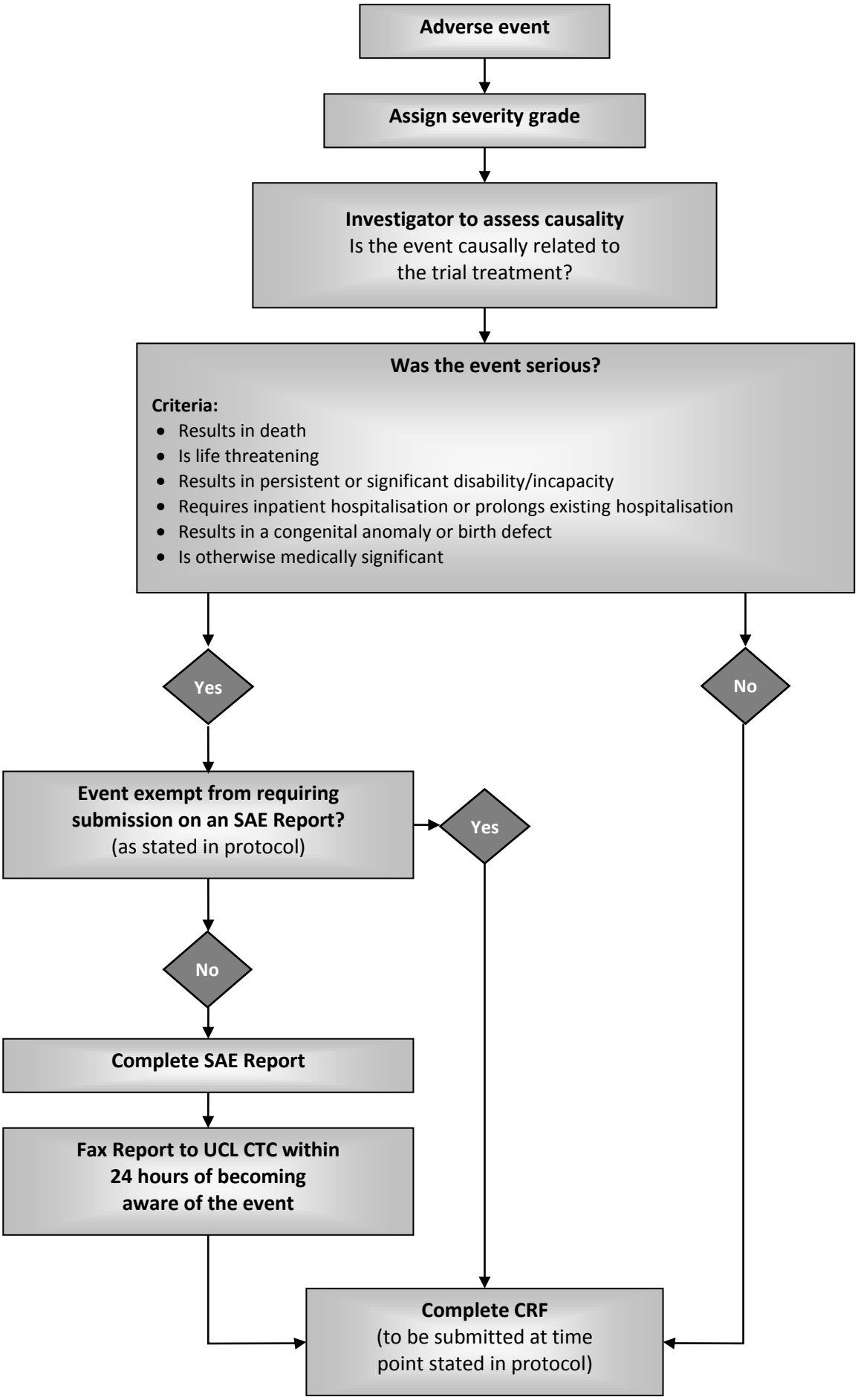
- events that occur after 12 weeks post randomisation that are not considered to be side effects of the trial treatment
- disease progression (including disease related deaths)

Please note that hospitalisation for elective treatment or palliative care does not qualify as an SAE.

Completed SAE Reports must be faxed within 24 hours of becoming aware of the event to UCL CTC

Fax: +44 (0)20 7679 9871

Adverse Event reporting flowchart



SAE follow up reports

All SAEs must be followed up until resolution and until there are no further queries. The PI, or other delegated site investigator, must provide follow up SAE Reports if the SAE had not resolved at the time the initial report was submitted.

SAE processing at UCL CTC

On receipt of the SAE Report, UCL CTC will check for legibility, completeness, accuracy and consistency. Expectedness will be evaluated, to determine whether or not the case qualifies for expedited reporting, using the list of expected adverse events for radiotherapy to the spine in protocol appendix 3.

The CI, or their delegate (e.g. a clinical member of the TMG), may be contacted to review the SAE and to perform an evaluation of causality on behalf of UCL CTC. If UCL CTC has considered expectedness difficult to determine, the CI, or their delegate, will be consulted for their opinion at this time.

10.3 SUSARs

If the event is evaluated as a Suspected Unexpected Serious Adverse Reaction (SUSAR), UCL CTC will submit a report to the UK REC within 15 calendar days and to CCCs/CLSs for forwarding to their ethics committee(s) within the timeframe required in that country. UCL CTC will ensure that consideration is given where the reporting deadline occurs at a weekend to allow reporting within the required timeframe. Where there are conflicting evaluations of causal relationship by the site and UCL CTC/CI, both opinions will be reported.

Informing sites of SUSARs

UCL CTC will inform all UK PIs of any SUSARs that occur on the trial. PIs will receive a quarterly line listing which must be processed according to local requirements.

For participating countries outside the UK, UCL CTC will submit reports to CCCs for forwarding to the PIs in their country within one business day. Where there is no CCC, UCL CTC will submit SUSAR reports directly to sites in that country.

10.4 Safety monitoring

UCL CTC will provide safety information to the TMG and the IDMC on a periodic basis for review.

Trial safety data will be monitored to identify:

- new adverse reactions to the trial treatment regimen or any trial treatment;
- trial related events that are not considered related to the trial treatment regimen.

Should UCL CTC identify or suspect any issues concerning patient safety at any point throughout the trial, the CI or TMG will be consulted for their opinion.

10.5 Pregnancy

If a female patient or the female partner of a male patient becomes pregnant at any point during the trial, a completed trial specific Pregnancy Report must be submitted to UCL CTC by fax within **24 hours** of learning of its occurrence. Consent to report information regarding the pregnancy must be obtained from the pregnant patient/partner. The trial specific pregnancy monitoring information sheets and informed consent forms for trial patients and the partners of trial patients must be used for this purpose.

All pregnancies must be reported by faxing a completed Pregnancy Report within **24 hours** of becoming aware of the pregnancy to UCL CTC
Fax: +44 (0) 20 7679 9871

Pregnancy follow up reports

All pregnancies must be followed up until an outcome is determined. Follow up Pregnancy Reports must be submitted to UCL CTC by fax within **24 hours** of learning of the outcome. Reports must include an evaluation of the possible relationship of the trial treatment to the pregnancy outcome.

SAEs during pregnancy

Any SAE occurring in a pregnant patient must be reported using the trial specific SAE Report, according to SAE reporting procedures. Refer to section 10.2.2 (Serious Adverse Events (SAEs)) for details.

Pregnancy Report processing at the UCL CTC

The UCL CTC will submit a Report to the UK REC, CCCs and CLSs should the pregnancy outcome meet the definition of a SUSAR. Refer to section 10.3 (SUSARs) for details.

11.0 Incident reporting

Organisations must notify UCL CTC of all deviations from the protocol or Good Clinical Practice (GCP) immediately. UCL CTC may require a report on the incident(s) and a form will be provided if the organisation does not have an appropriate document (e.g. Trust Incident Form for UK sites).

If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the UCL CTC trial team can be contacted immediately to discuss.

Where the incident has occurred in a site outside the UK, the CCC/CLS in that country must also notify the relevant ethics committee according to local requirements. Where UCL CTC identifies an incident at a site outside the UK, the CCC/CLS in the country where the incident occurred will be informed.

UCL CTC will use an organisation's history of non compliance to make decisions on future collaborations.

12.0 Trial monitoring and oversight

UK participating sites and PIs must agree to allow trial related on site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/documents as required. Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the consent form.

UCL CTC will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

In addition, monitoring of non UK sites will be performed in accordance with the regulatory requirements of each country.

12.1 Central monitoring

All Sites will be required to submit screening logs and staff delegation logs to the UCL CTC (or their CCC) at the frequency detailed in the trial monitoring plan or on request and these will be checked for consistency and completeness. Also refer to sections 3.2.2 (Required documentation) and 5.2 (Screening log).

In the UK a copy of the consent form for each patient must also be submitted to UCL CTC. These will be checked for completeness and accuracy i.e. the correct version of the form has been used, patient initials in every box, patient name and signature on the form, patient personally completed date of signing and the person taking consent has signed and dated and is listed on the delegation log as authorised to perform this duty. Also refer to section 4.0 (Informed consent).
Non-UK sites will be required to maintain a log of all patient informed consent forms that have been completed at site (regardless of whether the patient is subsequently randomised to the trial). This log will include details of the versions of informed consent form/patient information sheet used, patient completion of the consent form, date of consent, the name of the person taking consent, etc. A

copy of the ICF log must be submitted to UCL CTC at the frequency detailed in the trial monitoring plan or on request. Also refer to section 4.0 (Informed consent).

Sites will be requested to conduct quality control checks of documentation held within their Investigator Site Files at the frequency detailed in the trial monitoring plan. Checklists detailing the current version and date of version controlled documents will be provided for this purpose.

UK patients enrolled onto SCORAD III will be flagged with the Health & Social Care Information Centre.

Data received at UCL CTC will be subject to review in accordance with section 9.4 (Data queries).

Where central monitoring of data and/or documentation submitted by sites indicates that a patient may have been placed at risk, the matter will be raised urgently with site staff and escalated as appropriate (refer to sections 11.0 Incident reporting and 12.2 'For cause' on site monitoring for further details).

12.2 'For cause' on site monitoring

On site monitoring visits may be scheduled at a site where there is evidence or suspicion of non compliance with important aspect(s) of the trial protocol/GCP requirements. Sites will be sent a letter in advance outlining the reason(s) for the visit. The letter will include a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities, who will be performing the visit and when the visit is likely to occur.

Following a monitoring visit, the trial monitor/trial coordinator will provide a report to the site, which will summarise the documents reviewed and a statement of findings, deviations, deficiencies, conclusions, actions taken and actions required. The PI at each site will be responsible for ensuring that monitoring findings are addressed (this may be delegated to an appropriate member of staff).

UCL CTC will assess whether it is appropriate for the site to continue participation in the trial. Refer to section 11.0 (Incident reporting) for details.

12.3 Oversight Committees

12.3.1 Trial Management Group (TMG)

The Trial Management Group (TMG) will include the Chief Investigator, clinicians and experts from relevant specialities and SCORAD III trial staff from UCL CTC (see page 3). The TMG will be responsible for overseeing the trial. The group will meet regularly and will send updates to PIs (via newsletters) and to the meetings of the national working groups as requested.

The TMG will review substantial amendments to the protocol prior to submission to the REC. All PIs will be kept informed of substantial amendments through their nominated responsible individuals.

All members of the TMG must sign the SCORAD III TMG charter and supply this to the SCORAD III trial coordinator at, or prior to, their first meeting.

12.3.2 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial. The TSC will review the recommendations of the IDMC and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder and Sponsor.

A TSC charter will summarise the roles and responsibilities of the TSC and each member will be required to sign this prior to the first meeting.

12.3.3 Independent Data Monitoring Committee (IDMC)

The role of the IDMC is to provide independent advice on data and safety aspects of the trial. Meetings of the Committee will be held periodically, or as necessary to

address any issues. The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC.

An IDMC charter will summarise the roles and responsibilities of the IDMC and each member will be required to sign this prior to the first meeting.

12.4 Role of UCL CTC

UCL CTC will be responsible for the day to day coordination and management of the trial and will act as custodian of the data generated in the trial (on behalf of UCL). UCL CTC is responsible for all duties relating to safety reporting which are conducted in accordance with section 10.0 (Safety reporting).

13.0 Withdrawal of patients

In consenting to the trial, patients are consenting to trial treatment, assessments, follow up and data collection.

Discontinuation of trial treatment for clinical reasons

A patient may be withdrawn from trial treatment whenever continued participation is no longer in the patient's best interests, but the reasons for doing so must be recorded. Reasons for discontinuing treatment may include:

- Disease progression whilst on therapy
- Unacceptable toxicity
- Intercurrent illness which prevents further treatment
- Patients withdrawing from further trial treatment
- Any alteration in the patient's condition which justifies the discontinuation of treatment in the site investigator's opinion

In these cases patients remain within the trial for the purposes of follow up and data analysis according to the treatment option to which they have been allocated.

Patient withdrawal from trial treatment

If a patient expresses their wish to withdraw from trial treatment, sites should explain the importance of remaining on trial follow up, or failing this of allowing routine follow up data to be used for trial purposes and for allowing existing collected data to be used. If a patient gives a reason for their withdrawal, this must be recorded.

Withdrawal of consent to data collection

If a patient **explicitly** states they do not wish not to contribute further data to the trial, their decision must be respected and recorded on the Off study form in the CRF booklet. In this event details must be recorded in the patient's hospital records, no further CRFs must be completed and no further data sent to UCL CTC (or CCC for non-UK sites).

Losses to follow up

If a patient moves from the area, every effort must be made for the patient to be followed up at another participating trial site and for this new site to take over the responsibility for the patient, or for follow up via the GP. Details of participating trial sites can be obtained from the UCL CTC trial team who must be informed of the transfer of care and follow up arrangements.

If a patient is lost to follow up at a site every effort must be made to contact the patient's GP to obtain information on the patient's status.

UK patients who are lost to follow up will be tracked by UCL CTC via the Health & Social Care Information Centre.

14.0 Trial closure

14.1 End of trial

For regulatory purposes the end of the trial will be 12 months after randomisation of the last patient or the death of the last surviving patient, whichever event occurs first. At this point the 'declaration of end of trial' form will be submitted to the ethics committee, as required.
Following this, UCL CTC will advise sites on the procedure for closing the trial at the site.

14.2 Archiving of trial documentation

At the end of the trial, UCL CTC will archive securely all centrally held trial related documentation for a minimum of 5 years. Arrangements for confidential destruction will then be made. It is the responsibility of PIs to ensure data and all essential documents relating to the trial are held at site for a minimum of 5 years after the end of the trial, in accordance with national legislation and for the maximum period of time permitted by the site.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of GCP and all applicable regulatory requirements.

UCL CTC will notify sites when trial documentation held at sites may be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

14.3 Early discontinuation of trial

The trial may be stopped before completion as an Urgent Safety Measure on the recommendation of the TSC or IDMC (refer to sections 12.3.2 Trial Steering Committee (TSC) and 12.3.3 Independent Data Monitoring Committee (IDMC)). Sites will be informed in writing by UCL CTC of reasons for early closure and the actions to be taken with regard to the treatment and follow up of patients.

14.4 Withdrawal from trial participation by a site

Should a site choose to close to recruitment the PI must inform UCL CTC in writing. Follow up as per protocol must continue for all patients recruited into the trial at that site and other responsibilities continue as per the CTSA.

15.0 Statistics

This is a non-inferiority trial to show that ambulatory status using 8Gy in 1 fraction is no worse than 20Gy in 5 fractions.

15.1 Proposed sample size

Using the data from patients recruited to the feasibility stage of SCORAD, the percentage of patients with a response was about 75%. A maximum allowable difference of 11 percentage points is specified, i.e. using 8Gy in 1 fraction should not have a true response rate lower than 64% (or the true difference between the proportion of patients who respond should not exceed -11%). A non-inferiority trial would need 386 patients (193 per group), with 80% power and one-sided 5% level of statistical significance)[24]. About 33% of patients die before the 8 week assessment, so allowing for this increases **the target sample size to 580 patients**. This will be the minimum target.

To allow for the possibility of a lower response rate of 65% (instead of 75%) would require a sample size of 464 patients, or 700 allowing for the 33% death rate. The IDMC will monitor the response rate and make recommendations on continuing recruitment past N=580, considering other factors such as feasibility and funding.

15.2 Planned analyses

At 8 weeks the response rate (i.e. those with no change in ambulatory status 1 to 2 from randomisation, or improvement) will be compared using a chi-squared test. The risk difference (and 95% confidence interval) will be obtained.

Other categorical endpoints will be analysed in a similar way, e.g. ambulatory status at 1, 4 and 12 weeks (where available), and bladder and bowel function. Where endpoints have multiple timepoints, the p value could be inflated to allow for this.

Duration of care in home, hospital, hospice or nursing home will be compared using the Wilcoxon test, and the median days estimated in each trial group.

Survival will be examined using Kaplan-Meier plots, and compared between the two treatment groups using the hazard ratio and logrank test.

Quality of life will be examined using a repeated measures analysis (e.g. mixed model).

15.3 Subgroup analyses

The difference in response rate between the two groups will be examined according to

- age
- ambulatory status at randomisation
- primary tumour type
- extent of metastases (presence or absence of nonskeletal metastases)

A formal test for interaction will be used for each of these four factors.

15.4 Interim analyses of efficacy

No formal interim analyses of efficacy are planned. These will be carried out if the Independent Data Monitoring Committee request this as part of their assessment of the trial.

15.5 Quality of life assessments

Assuming that quality of life measures are Normally distributed (which they reasonably are, on either the original or logarithmic scale), a trial of 400 patients, after allowing for a 33% death rate by 8 weeks (see section 15.1), would be enough to detect a reasonably small/moderate maximum allowable difference of 0.28 standard deviation units (assuming non-inferiority, 80% power and one-sided 2.5% level of statistical significance).

16.0 Ethical approvals

In conducting the Trial the Sponsor, UCL CTC and sites shall comply with all laws and statutes, as amended from time to time, applicable to the performance of clinical trials including, but not limited to:

- the principles of ICH Harmonised Tripartite Guideline for Good Clinical Practice
- the Human Rights Act 1998
- the Data Protection Act 1998
- the Freedom of Information Act 2000
- the Mental Capacity Act 2005
- the Research Governance Framework for Health and Social Care, issued by the UK Department of Health (Second Edition 2005) or the Scottish Health Department Research Governance Framework for Health and Community Care (Second Edition 2006)

All non-UK sites must comply with all their local laws and statutes applicable to the performance of clinical trials.

16.1 Ethical approval

The trial will be conducted in accordance with the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (1996 version) and in accordance with the terms and conditions of the ethical approval given to the trial.

The trial has received a favourable opinion from the London – Camden & Islington Research Ethics Committee (formerly North West London REC 1 and Camden & Islington Community REC).

UCL CTC will submit Annual Progress Reports to the REC annually on the anniversary of the date of ethical approval for the trial.

16.2 Site approvals

Evidence of approval from the Trust R&D for a trial site must be provided to UCL CTC. Sites will only be activated when all necessary local approvals for the trial have been obtained.

All non-UK sites must provide confirmation of approval of their local institution(s).

16.3 Protocol amendments

UCL CTC will be responsible for gaining ethical approval for amendments made to the protocol and other trial related documents. Once approved, UCL CTC will ensure that all amended documents are distributed to sites, CLRNs and CCCs/CLSs as appropriate.

In the UK site staff will be responsible for acknowledging receipt of documents and for implementing all amendments.

Non-UK sites will be responsible for gaining approvals according to their local procedures, and for providing UCL CTC with evidence of this.

16.4 Patient confidentiality and data protection

For UK sites patient identifiable data, including full name, address, date of birth and NHS or CHI number will be required for the randomisation process and will be provided to UCL CTC. UCL CTC will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified, other than to the Health & Social Care Information Centre for flagging purposes. Data will be stored in a secure manner and UCL CTC trials are registered in accordance with the Data Protection Act 1998 with the Data Protection Officer at UCL.

CCCs will be responsible for registering the trial with their data protection agency if required for that country and for ensuring that each site complies with Local Data Protection Legislation and takes appropriate measures against unauthorised or unlawful processing of personal data and against accidental loss or destruction of, or damage to personal data.

Non-UK sites without a CCC will be responsible for ensuring that Local Data Protection Legislation is complied with and for taking appropriate measures against unauthorised or unlawful processing of personal data and against accidental loss or destruction of, or damage to personal data.

17.0 Sponsorship and Indemnity

Sponsor Name: University College London

Address: **Joint Research Office**
Gower Street
London
WC1E 6BT

Contact: Director of Research Support

Tel: +44 (0) 20 3447 9995/2178 (unit admin)

Fax: +44 (0) 20 3447 9937

17.1 Indemnity

University College London holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wishing to make a claim for compensation should do so in writing in the first instance to the Chief Investigator who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

18.0 Funding

Cancer Research UK is supporting the central coordination of the trial through UCL CTC.

19.0 Publication policy

All publications and presentations relating to the trial must be authorised by the TMG. The first publication of the trial results will be in the name of the TMG, if this does not conflict with the journal's policy. The TMG will form the basis of the writing committee and advise on the nature of publications. If there are named authors, these should include the Chief Investigator, Trial Coordinators and Statisticians involved in the trial. Contributing site investigators in this trial will also be acknowledged. Data from all sites will be analysed together and published as soon as possible. Participating sites must not publish trial results prior to the first publication by the TMG or without prior written consent from the TMG. The trial data is owned by UCL CTC. The ISRCTN number (ISRCTN97108008) allocated to this trial must be quoted in any publications resulting from this trial.

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Appendix 1: Abbreviations

#	Fraction (radiotherapy dosage)
AE	Adverse Event
AR	Adverse Reaction
CCC	Country Coordinating Centre
CI	Chief Investigator
CLS	Country Lead Site
CRF	Case Report Form
CT	Computerised Tomography
CTAAC	Clinical Trials Advisory & Awards Committee
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
CTRad	the NCRI Clinical and Translational Radiotherapy Research Working Group
DPA	Data Protection Act
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 – item core quality of life questionnaire
GCP	ICH Harmonised Tripartite Guideline for Good Clinical Practice
Gy	Gray, SI unit for radiation dosage, energy absorbed per unit mass (joules/kg).
Gy/f or Gy/#	Grays per fraction
f	Fraction (radiotherapy dosage)
ICH GCP	International Conference of Harmonisation-Good Clinical Practice
ICRP	International Cancer Research Portfolio
ICTSA	International Clinical Trials Site Agreement
IDMC	Independent Data Monitoring Committee
IRAS	Integrated Research Application System
ISF	Investigator site file
ISRCTN	International Standard Randomised Controlled Trial Number
MRC CTU	Medical Research Council Clinical Trials Unit
MRI	Magnetic resonance imaging
MSCC	Metastatic spinal cord compression
NCRI	National Cancer Research Institute
NCRN	National Cancer Research Network
NHS	UK National Health Service
NICE	National Institute for Clinical Excellence
NIHR	UK National Institute for Health Research
ng/mL	Nanogram per millilitre
NRES	National Research Ethics Service
OS	Overall Survival
PI	Principal Investigator
PSA	Prostate specific antigen
Pt	Patient
QoL	Quality of life
R&D	Research and development
RCT	Randomised controlled trial
REC	Research Ethics Committee
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event
SF2	Single fraction of 2Gy
SSI	Site Specific Information
SCC	Spinal Cord Compression
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UCL	University College London
UCL CTC	CR UK and UCL Cancer Trials Centre

Appendix 2: Definition of secondary endpoints

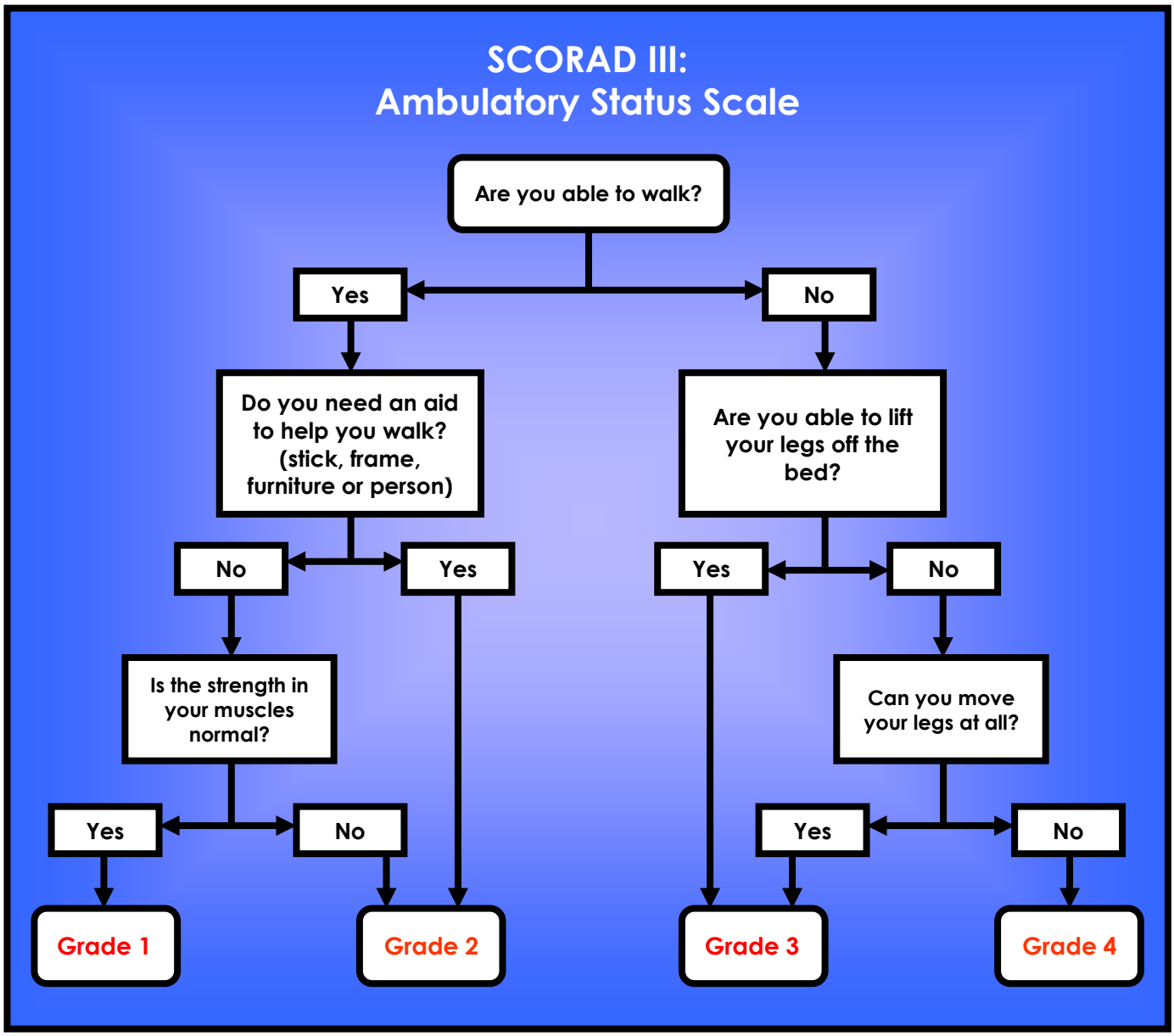
Ambulatory status definitions:

Neurologic assessment will be performed and categorised as:

Category	Definition
1	Ambulatory without the use of walking aids and grade 5/5 power in all muscle groups
2	Ambulatory with assistance of walking aids or grade 4/5 power in any muscle group
3	Unable to ambulate with no worse than grade 2/5 power in all muscle groups; or grade 2/5 power in any muscle group
4	Absence (0/5) or flicker (1/5) of motor power in any muscle group

1. **Ambulatory status:**
   - **Recovery of and time to ambulation:** Recovery of ambulation is defined as the movement from either Grade 3 or 4 at randomisation to either Grade 1 or Grade 2 at subsequent time points.
     - A change from Grade 2 to Grade 1 must also be reported.
   - **Maintenance of ambulatory status:** This is defined as the maintenance of an ambulatory score of Grade 1 or 2.
2. **Bladder function:**
   - Dichotomised into normal and abnormal (defined as significant urinary incontinence or urinary retention requiring catheterisation).
3. **Bowel function:**
   - Dichotomised into normal and abnormal (either constipation or diarrhoea/incontinence).
4. **Adverse events:**
   - Assessed using the RTOG Acute Radiation Morbidity Scoring Criteria and CTCAE v4.02.
5. **Quality of life:**
   - Measured using the EORTC QLQ-C30 questionnaire.
6. **Further treatment and retreatment:**
   - Surgery, radiotherapy, hormone and chemotherapy.
7. **Overall survival:**
   - Patient NHS numbers will be flagged with the Health & Social Care Information Centre for survival data. Where site becomes aware of event deaths are to be reported to CTC for the 12 months following randomisation.
8. **Total number of days spent in hospital/hospice/nursing home/home:**
   - Following admission with spinal cord compression.
9. **Preferred place of care:**
   - This will be an open question.

Appendix 2.1: Ambulatory status scale question sequence



Appendix 3: Expected adverse events

Certain AEs are expected for radiotherapy[25, 26]. The following AEs are commonly associated with the trial treatment regimen and will be considered expected.

General side effects of radiotherapy include:

- Fatigue
- Anorexia or reduced appetite
- Erythema in the irradiated field

Side effects following radiotherapy to the spine and pelvis include:

- mucositis in oesophagus, bladder, bowel or rectum, resulting in:
    - Transient sore throat
    - Dysphagia/oesophagitis/discomfort on swallowing from treatment to the cervical and dorsal spine
    - Diarrhoea from treatment to the dorsolumbar spine
    - Nausea from treatment to the dorsolumbar spine

Appendix 4: Protocol version history

Protocol:		Amendments:		
Version no.	**Date**	**Amendment number**	**Protocol section no**	**Summary of approval date and main changes from previous version**
1.0	18/09/09	n/a	n/a	Approved 3 November 2009 Initial submission to REC
1.1	24/11/09	1 (administrative)	n/a	Approved 3 December 2009 Administrative changes only
2.0	09/09/11	2		Approved 02/11/2011
				Advice on use of protocol
				MRC randomisation programme address
			Trial Summary:	Update of Secondary endpoints, eligibility criteria and end of trial definition and ff.
			Section 2:	Update of Trial activation
			Section 3:	Update of Selection of site investigators, training requirements for site staff, site initiation and activation
			Section 4:	Update of Informed consent
			Section 5:	Update of Selection of patients, screening log, pregnancy and randomisation sections
			Section 6:	Update of Randomisation procedure, Alternative procedures for UK sites, Alternative procedures for non UK sites
			Section 7:	Addition of Management after treatment withdrawal
			Section 8:	Update of Assessments, UK Assessment flowchart, Assessment for UK sites, Non UK Assessment flowchart
			Section 9:	Update of Data management guidelines, completing CRFs, Timelines for data return and submissions moved to 9.4 and data queries to 9.5
			Section 10:	Safety reporting moved from section 11, administrative changes, addition of overdose section, SAE processing at UCL CTC and to safety monitoring, update to pregnancy section. Deletion of Expectedness section.
			Section 11:	Addition of Incident reporting section
			Section 12:	Addition of monitoring sections, oversight committees moved to section 12 from section 10, update to Role of UCL CTC.
			Section 13:	Withdrawal of patients moved from section 12 to section 13, withdrawal of consent updated.
			Section 14:	Trial closure moved from section 13 to section 14, updated Early discontinuation and withdrawal from trial participation by site
			Section 15:	Statistical considerations moved from section 14 to section 15.
			Section 16:	Ethical and Regulatory approvals updated
			Section 17:	Sponsorship and indemnity moved from section 15 to section 17 and updated.
			Section 18:	Funding moved from section 17 to section 18.
			Section 19:	Publication policy moved from section 18 to section 19.
			Section 20:	References moved from section 19 to section 20 and updated.
			Appendix 1:	Updated
			Appendix 2:	Updated
			Appendix 3:	Updated

				And minor administrative changes.
3.0	08/08/12	3 (substantial)		
			Trial summary, Sections 1.1, 2.2.2, 7.0 and appendix 2.1	Update of secondary endpoints
				And minor administrative changes
4.0	01/01/13	4 (substantial)	Trial summary	Update of eligibility
			Sections 3.1.1,	Update of definition of Principal Investigator
			Section 4.0	Update of consent section
			Section 5.3.1	Update of eligibility
			8.1	Update of assessment of ambulatory status
			9.5	Update of data query procedures
			12.0	Update of Trial monitoring section
			13.0	Update of patient withdrawal and follow up procedures
			15.0	Update of statistical analysis
				And minor administrative changes.