ROCS

ROCS (Radiotherapy after Oesophageal Cancer Stenting) Study

Palliative radiotherapy in addition to self-expanding metal stent for improving dysphagia and survival in advanced oesophageal cancer: ROCS (Radiotherapy after Oesophageal Cancer Stenting) Study.

Clinical Trial Protocol

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Authorised by:			
Name:	Dr Douglas Adamson	Role:	Co-Chief Investigator
Signature:		Date:	30/04/15
Name:	Dr Anthony Byrne	Role:	Co-Chief Investigator
Signature:		Date:	28/4/15
Name:	Richard Adams	Role:	Interim Director, WCTU
Signature:		Date:	21/4/15

Developed on behalf of the NCRI Palliative Care and NCRI upper GI Clinical Studies Groups

General Information

This protocol describes the ROCS clinical trial, and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other patients. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial, but centres entering patients for the first time are advised to contact the Wales Cancer Trials Unit (WCTU) in Cardiff to confirm that they have the most up-to-date version of the protocol in their possession. Problems relating to the trial should be referred, in the first instance, to the Wales Cancer Trials Unit.

Compliance

This trial will adhere to the conditions and principles of Good Clinical Practice which apply to all clinical trials. It will be conducted in compliance with the protocol, the Research Governance Framework for Health and Social Care (Welsh Assembly Government November 2001, 2nd edition September 2009 and Department of Health 2nd July 2005), the Data Protection Act 1998, the Ionising Radiation (Medical Exposure) Regulations, 2000 (IRMER) and other regulatory requirements as appropriate.

Funding

The ROCS trial is being funded by National Institute for Health Research (NIHR), Heath Technology Assessment (HTA) programme and is thus part of the NIHR/NCRI portfolio of clinical trials.

WCTU Randomisation line:
029 2064 5500
(Open Monday – Friday, 9am – 5pm)

N.B. This telephone number is strictly for randomisation and should not be used for general queries.

Serious Adverse Event (SAE) Fax Number:

029 2064 4488

Trial Co-ordination

The ROCS trial is being coordinated by the Cancer Research UK and Marie Curie core funded WCTU, a NCRI accredited, and United Kingdom Clinical Research Collaboration (UKCRC) registered trials unit.

This protocol has been developed by the ROCS Trial Management Group (TMG).

Wales Cancer Trials Unit
School of Medicine
Cardiff University
6th Floor, Neuadd Meirionnydd
Heath Park
Cardiff
CF14 4YS

Tel: +44 (0) 29 2068 7500
Fax: +44 (0) 29 2068 7501
Email: ROCS@cardiff.ac.uk
Website: www.wctu.org.uk

ROCS trial staff

For all queries please contact the ROCS Trial Manager. Any clinical queries will be directed through the Trial Manager to either the Chief Investigator or one of the clinical Co-Investigators.

Senior Trial Manager:	Lisette Nixon	Tel: +44 (0) 29 2068 7458 Email: nixonls@cardiff.ac.uk
Interim Director:	Richard Adams	Tel: +44 (0) 29 2068 7456 Email: Richard.Adams@wales.nhs.uk
Senior Statistician	Chris Hurt	Tel: +44(0) 29 2068 7471 Email: hurtcn@cardiff.ac.uk
Safety Officer	Loys Richards	Tel: +44 (0) 29 2068 7474 Email: WCTU-safety@cardiff.ac.uk

Trial Management Group

Chief Investigators

Dr Douglas Adamson
Consultant Clinical Oncologist
Tayside Cancer Centre
Ward 32, Ninewells Hospital
Dundee
DD1 9SY

Dr Anthony Byrne
Director
Marie Curie Palliative Care Research Centre
Wales Cancer Trials Unit
6th Floor, Neuadd Meirionnydd
Heath Park
Cardiff
CF14 4YS

Co-investigators

Prof. Jane Blazeby
Professor of Surgery and Honorary Consultant Surgeon
School of Social & Community Medicine
University of Bristol
Canynge Hall
39 Whatley Road
Bristol
BS8 2PS

Prof. Gareth Griffiths
Professor of Clinical Trials
Director of the University of Southampton Clinical Trials Unit University of Southampton
Clinical Trials Unit, Mailpoint 131,
Southampton General Hospital, Tremona Road, Southampton. SO16 6YD

Dr Annmarie Nelson
Deputy Director
Marie Curie Palliative Care Research Centre
Wales Cancer Trials Unit
6th Floor, Neuadd Meirionnydd
Heath Park
Cardiff
CF14 4YS

Dr. Fasihul Alam
Senior Research Fellow
Swansea Centre for Health Economics (SCHE)
College of Human and Health Sciences
Swansea University Singleton Park
Swansea
SA2 8PP

Dr Tom Crosby
Consultant Clinical Oncologist
Velindre Cancer Centre
Velindre Hospital
Whitchurch
Cardiff
CF14 2TL

Dr John Staffurth
Consultant Clinical Oncologist and Senior Lecturer
NCRI Cardiff RTTQA Centre
Velindre Hospital
Whitchurch
Cardiff
CF14 2TL

Dr Jim Fitzgibbon (Research Partner)
c/o Marie Curie Palliative Care Research Centre
Wales Cancer Trials Unit
6th Floor, Neuadd Meirionnydd
Heath Park
Cardiff, CF14 4YS

Advisors

Mrs Mim Evans
WCRN Network Team Lead
Clinical Trials Unit (Portacabin)
Velindre Hospital
Cardiff
CF14 2TL

Stephen F Thomas (Research Partner)
c/o Wales Cancer Trials Unit
6th Floor, Neuadd Meirionnydd
Heath Park
Cardiff
CF14 4YS

Tony Millin
Medical Physicist
Medical Physics
Velindre Cancer Centre
Cardiff
CF14 2TL

Table of contents

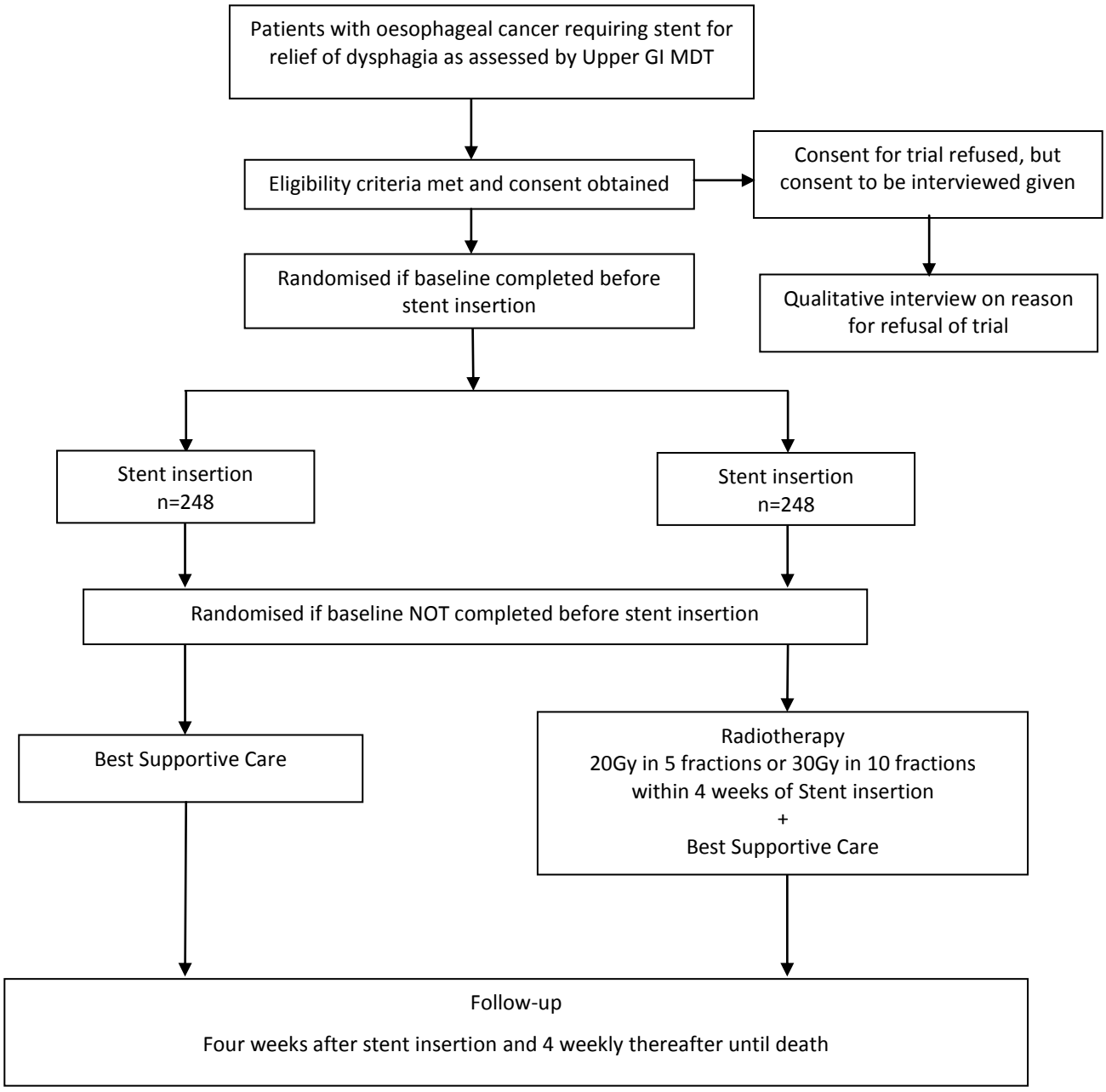
Abbreviations and glossary

AE	Adverse event
CI	Chief Investigator
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DICOM	Digital Imaging and Communications in Medicine
EBRT	External beam radiotherapy
EORTC	European Organisation for Research and Treatment of Cancer
FSDs	Focus to skin distances
GCP	Good Clinical Practice
GP	General Practitioner
GI	Gastrointestinal
Gy	Gray (SI Unit of absorbed radiation dose)
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
ICH	International Conference on Harmonisation
ICH-GCP	International Conference on Harmonisation – Good Clinical Practice
ICRU	International Commission or Radiation Units and Measurements
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IPA	Interpretative Phenomenological Analysis
IPEM	Institute of Physics and Engineering in Medicine
IR(ME)R	The Ionising Radiation (Medical Exposure) Regulations
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
MDM	Multi-disciplinary Meeting
MDT	Multi-disciplinary Team
MREC	Multi-centre Research Ethics Committee

MV	Megavolts
NCRI	National Cancer Research Institute
NCRN	National Cancer Research Network
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NHS	National Health Service
NHS-IC	NHS Information Centre
Patient	A patient under care who may be eligible for the trial but has not yet consented to participate in any trial related activities.
Participant	An individual who has given written informed consent and is participating in trial related activities
PI	Principal Investigator
PIS	Participant Information Sheet
QoL	Quality of Life
QALY	Quality Adjusted Life Years
R&D	Research and Development
REC	Research Ethics Committee
ROCS	ROCS (Radiotherapy after Oesophageal Cancer Stenting) Study
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
RTTQA	Radiotherapy Trials Quality Assurance Group
SAE	Serious Adverse Event
SAE(RT)	Serious Adverse Event to Radiotherapy
SAE(SEMS)	Serious Adverse Event to stent insertion
SEMS	Self-expanding metal stent
SOP	Standard Operating Procedure
SSA	Site-Specific Assessment
SUSAE(RT)	Suspected Unexpected Serious Adverse Event to Radiotherapy
SUSAE(SEMS)	Suspected Unexpected Serious Adverse Event to stent insertion
TMF	Trial Master File
TMG	Trial Management Group

TSC	Trial Steering Committee
TSF	Trial Site File
UKCRC	United Kingdom Clinical Research Collaboration
WCTU	Wales Cancer Trials Unit

1.0 Trial schema



2.0 Trial synopsis

Study title:	Palliative radiotherapy in addition to self-expanding metal stent for improving outcomes of dysphagia and survival in advanced oesophageal cancer					
Study acronym:	ROCS					
Short title:	ROCS (Radiotherapy after Oesophageal Cancer Stenting) Study					
Funder:	NIHR HTA	**Funder's No:**	10/50/49			
Chief Investigators:	Dr Douglas Adamson, Dr Anthony Byrne					
Sponsor:	Velindre NHS Trust	Sponsor No:	2012/VCC/0027			
Study period:	6 years	Phase:	III	Number of arms:	2	
Number of participants:	496					

Objectives

Primary:

Assess the impact of radiotherapy in addition to stent placement on time to progression of patient-reported dysphagia in a patient population unable to undergo surgery.

Secondary:

1. Assess the impact of combination treatment on core components of health related quality of life
2. Assess the impact of radiotherapy in addition to stent placement on overall survival
3. Measure morbidity associated with the interventions
4. Measure re-intervention rates
5. Assess the cost effectiveness of the addition of radiotherapy to stent placement

Inclusion criteria:

1. Histological confirmation of oesophageal carcinoma excluding small cell carcinoma
2. Not suitable for radical treatment (oesophagectomy or radical chemoradiotherapy) either because of patient choice or medical reasons
3. Dysphagia clinically assessed as needing stent as primary treatment of the dysphagia
4. Age 16 years or over
5. Discussion and treatment decision for stent placement made by an Upper GI multi-disciplinary team
6. Deemed suitable for radiotherapy
7. Expected survival of at least 12 weeks
8. Written informed consent

9. Patient has completed baseline Quality of Life Questionnaires (please note, as a minimum patients must have completed OG25)

Main exclusion criteria:

1. Small cell carcinoma
2. Tumour length of greater than 12 cm
3. Tumour growth within 2 cm of the upper oesophageal sphincter
4. Endoscopic treatment of the tumour, other than dilatation, planned in the peri-stent period
5. Presence of a tracheo-oesophageal fistula
6. Presence of a pacemaker in proposed radiotherapy field
7. Previous radiotherapy to the area of the proposed radiotherapy field
8. Female patient who is pregnant

Treatments:

Arm A: Stent alone (Control Arm)

Stent insertion will be undertaken in accordance with standard local protocols. Covered or partially covered metal stents will be used and the length type and mode of stent placement will be selected by the clinician.

Arm B: Stent plus external beam radiotherapy (Intervention Arm)

External beam radiotherapy (EBRT)),is routinely available at regional cancer centres across the UK. For palliation of dysphagia in oesophageal cancer, a radiotherapy course delivering a tumour absorbed dose of 20Gy in 5 fractions or 30Gy in 10 fractions within 4 weeks of stent insertion.

NOTE - Timing of randomisation: Ideally, the patient will give consent for the study and will complete the baseline questionnaires in the week prior to the stent insertion. When this is not possible, patients can be randomised into the study and complete the baseline questionnaires after the stent has been inserted. This should be done within two weeks of stent insertion, but preferably within one week of stent insertion.

Trial assessments:

Assessments will be undertaken by dedicated research staff who will visit patients at their home or at a place of their choice.

Baseline assessments (within 1 week prior to randomisation). For those patients consented prior to stent insertion(this is the preferred point of consent), baseline assessments will occur prior to the stenting procedure. For those patients consented following stent insertion, ideally baseline assessments will occur within one week, but not more than two weeks, following the procedure.

- WHO performance status
- Toxicity Assessment (CTCAE V4.03)
- Questionnaires (EORTC QLQ-C30, EORTC QLQ-OG25, EQ-5D)

- Stent morbidity data (if consented after stent)
- Qualitative interview (in subset of patients if consented after stent).

A post-stent assessment is an additional requirement if the patient is randomised before the stent is inserted. This visit should be done within one week after stent insertion.

Note: if patient does not give consent prior to stent insertion then miss this visit as the baseline assessment will be one week post stent insertion.

- WHO performance status
- Toxicity Assessment (CTCAE V4.03)
- Questionnaires (EORTC QLQ-C30, EORTC QLQ-OG25, EQ-5D)
- Stent morbidity data
- Qualitative interview (sub-set of patients)

Four weeks after stent insertion and 4-weekly thereafter until death:

- WHO performance status
- Toxicity Assessment (CTCAE V4.03)
- Stent morbidity data
- Questionnaires (EORTC QLQ-C30, EORTC QLQ-OG25, EQ-5D)
- Qualitative interview (sub-set of patients) (week 4 and week 8 only)

The qualitative component of the trial will have two aims: i) to explore the feasibility of patients' recruitment to the trial and ii) to explore participants' experience of the trial interventions. It will examine their experience of consent and recruitment including reasons for declining, and examine patients' motivation to accept randomisation to an intervention which may include extra radiotherapy. This is an optional component and will require separate consent. Patients who do not consent to the trial, but who do consent to the qualitative component, will be interviewed about their reasons for not-consenting as soon as possible after the approach to participate.

Trial participants who consent to the qualitative component will be interviewed three times: at weeks one and four to capture initial decision-making thoughts and then after the interventions (week 8) to explore patients' experience of interventions and perceptions of benefit or detriment.

2.1 Lay summary

Palliative radiotherapy in addition to self-expanding metal stent for improving outcomes of dysphagia and survival in advanced oesophageal cancer: ROCS (Radiotherapy after Oesophageal Cancer Stenting) Study.

The single most distressing symptom for more than 70% of patients with oesophageal cancer is difficulty in swallowing (dysphagia) caused by blockage of the gullet by a tumour. This causes severe restrictions on food intake, physical activity, social functioning and overall quality of life. Amongst the more effective treatments for improving swallowing, is the insertion of a metal stent across the blocked part, which then self-expands to open up the gullet (Self Expanding Metal Stent). The addition of radiotherapy may help to improve the problems caused by dysphagia and provide an additional survival benefit.

The purpose of this study is to test the impact of adding radiotherapy to a stent on:

- the length of time swallow remains improved for
- quality of life
- survival

Patients will be eligible to take part in the trial if they have oesophageal cancer, are in need of a stent because of dysphagia, are aged 16 years or older, have been clinically assessed to be able to receive radiotherapy, have an expected survival of at least 12 weeks and are able to give written informed consent.

496 patients will be randomised to receive either a stent alone or a stent with radiotherapy. Patients can be randomised before or after their stent has been inserted, but randomisation before stent insertion will provide more useful data and is encouraged. The radiotherapy will be given as an outpatient either as five treatments (one per day) over one week, or ten treatments over two weeks. Questionnaires will be completed before treatment, one week post stent and four weekly for up to one year to assess quality of life and cost effectiveness. Interviews will be held with trial participants at three time points to explore their experiences while on the trial. Interviews will also be held with patients who do not consent to take part in the trial to explore their reasons for non-consent.

3.0 Background, rationale and objectives

Oesophageal cancer resulted in 7,606 deaths in the UK in 2008, reflecting a 70% increase in male age-standardised mortality rates compared to 1971. It is the 6th most common cause of cancer deaths (4th in men) and incidence rates are increasing by 4.2% per annum[1]. Prognosis is poor, with 5-year survival rates of 10-15%[2]. It is also a disease of the elderly, with prevalence highest in the seventh and eighth decades of life. Most present with incurable disease, and for advanced disease, mean survival is 3-5 months[3].

The emphasis of treatment for the majority of patients is therefore on effective palliative interventions, with 70%-90% requiring intervention for dysphagia[4, 5]. This single symptom has profound impact on social and physical functioning and other aspects of quality of life. Interventions to improve swallowing must therefore aim to produce prompt and lasting palliation of dysphagia whilst minimizing the need for late re-interventions and hospitalisation. Interventions must produce these benefits without causing significant impairment of other aspects of quality of life.

The most recent Cochrane systematic review[6] of interventions for dysphagia in oesophageal cancer confirms the efficacy of self-expanding metal stents (SEMS) in providing rapid initial relief of dysphagia, with fewer adverse effects and lower re-intervention rates than endoscopic ablative therapies.

An HTA assessment[7] also highlights the efficacy of stent placement. However delayed complications are common and result in later re-interventions. A pragmatic study as part of that assessment found that 35% of stent patients required re-interventions[8]. Homs *et al*[9] in a comparative study of brachytherapy described a haemorrhage rate of 13% in stent patients within a median of 123 days post insertion. Conio[10] in a randomised comparison of two stent types described tumour overgrowth in 19% within a median of 97 days post stent insertion. It is such late re-interventions and complications which account for the major proportion of dysphagia treatment costs[8], requiring travel to hospital and inpatient stays which also impair quality of life. This is consistent with estimations that healthcare costs in general in the last year of life account for 20-30% of overall healthcare budgets[11]

Of the non-stent interventions, brachytherapy studies[9,12] suggest longer dysphagia-free survival and more stable quality of life compared to using a stent. However a recent survey by the Royal College of Radiologists showed that brachytherapy patients across tumour sites account for only 2.5% of all radiotherapy patients, with little access to or expertise in this type of radiotherapy for oesophageal cancer patients in the UK[13]. In contrast, external beam radiotherapy is readily accessible by patients at regional cancer centres across the UK, although its use in the immediate post-stent period has not been rigorously studied.

The evidence suggests that a stent is an appropriate intervention for rapid dysphagia relief in incurable oesophageal cancer. The efficacy of a stent alone however is limited by early problems with pain, decline in general aspects of quality of life and later complications such as haemorrhage and tumour overgrowth. Re-interventions not only impose significant burden on NHS resources but decrease the quality of life and functioning of an unwell, predominantly elderly, population. Combination with other treatments might reduce costs and patient burden; for example addition of radiotherapy may ameliorate these problems and provide additional survival benefit.

Given the sporadic and consistently limited availability of brachytherapy in the UK, the overarching aim of this study is to address uncertainties in the current evidence base by

assessing whether the addition of external beam radiotherapy prolongs improvement in dysphagia, improves quality of life and reduces health economic and personal burden in patients undergoing stent placement.

The specific aims of this study are:

Primary Aim:

To assess the impact of radiotherapy in addition to stent placement on time to progression of patient-reported dysphagia in a patient population unable to undergo surgery.

Secondary Aims:

- Assess the impact of combination treatment on core components of health related quality of life
- Assess the impact of radiotherapy in addition to stent placement on overall survival
- Measure morbidity associated with the interventions
- Measure re-intervention rates
- Assess the cost effectiveness of the addition of radiotherapy to stent placement

4.0 Study design

This will be a pragmatic, randomised controlled trial of external beam radiotherapy in addition to stent versus stent alone in patients clinically assessed as requiring stent insertion for relief of dysphagia caused by oesophageal cancer. Patients will be identified in secondary care including cancer centres and district general hospitals and will be identified in the local team meeting (MDM) or selected by members of the upper gastrointestinal (GI) multi-disciplinary team (MDT), for palliation of malignant dysphagia with an oesophageal stent.

Records of decisions made by Upper GI MDTs will be screened weekly for eligible patients recommended for stent insertion by the research nurse at site. Patients may be identified outside of the weekly MDT meeting. Before stent insertion full eligibility for the trial will be checked. All patients recommended for a stent will have details kept at each site in a trial screening log. This will record the details of patients who are or are not screened in full for trial entry, and the precise reasons for ineligibility. The screening log will record details of eligible participants who do not consent for randomisation (and reasons for this choice) as well as recording the treatment they finally received. The screening log will only contain anonymous data (except for trial number for patients who do consent to randomisation). The log will be used to understand barriers to trial recruitment and patient and surgeon preferences. Screening log anonymised data will be returned monthly to the WCTU for review. The Bristol Researcher will be part of the trial team, specifically trained in interpretation of MDT notes and will support research nurses at other sites. Following review centres may be contacted as appropriate if potentially eligible patients are not being fully screened, or if many patients are being classified as ineligible. Site visits by the lead nurse will consider these details and discuss with the site team as necessary to ensure that recruitment of all patients potentially eligible for the trial is maintained.

Qualitative assessments to understand patient experience of the recruitment process, focusing on non-consenting patients in the pilot phase, will further inform study conduct.

Planned Interventions

Self-expanding metal stents (SEMS) (control and intervention arms)

Stents, can be placed at a single endoscopic or radiological session. Stent insertion will be undertaken in accordance with standard local protocols. Covered or partially covered metal stents will be used and the length type and mode of stent placement will be selected by the clinician. Insertion will occur as soon as possible following randomisation and no more than two weeks after randomisation. Whether it is inserted under sedation or general anaesthetic, whether radiological imaging is used and whether dilatation is required before or after stent insertion will be recorded but be performed at the discretion of the clinician.

Experimental intervention: stent plus external beam radiotherapy

EBRT (will be referred to as RT in this protocol) is routinely available at regional cancer centres across the UK. For palliation of dysphagia in oesophageal cancer, a radiotherapy course delivering a tumour absorbed dose of 20Gy in 5 fractions or 30Gy in 10 fractions will be given.

Simulation of the radiotherapy fields needs to be timed to allow the treatment to commence four weeks after randomisation at the latest, preferably within two weeks to reflect national guidance on waiting times for palliative radiotherapy.

The treatment position will be that of the standard practice of the centre. Immobilisation devices, if routinely used, are permitted and the centre should specify its technique prior to recruitment. The use of portal imaging will be the centre's usual practice and is recommended.

Radiotherapy regimens for this trial are 20Gy in 5 daily fractions over one week or 30Gy in 10 daily fractions over two weeks, prescribed to the midplane or appropriate normalisation point. Centres will specify their preferred regimen prior to commencement of the study and will continue to use that regimen for participants in the trial for the duration of the study.

5.0 Participating centre selection

Patients will be identified in secondary care including cancer centres and district general hospitals. All study centres have been chosen on the basis of number of patients reviewed by the specialist upper GI MDT, or members thereof, and potential recruitment rates, as well as interest in the study. Geographical spread has also been an important consideration, in recognition of higher incidence rates of oesophageal cancer in particular parts of the UK including Scotland, North Wales and Northwest England.

All centres will be required to complete a registration form to confirm that they have adequate resources and experience to conduct the trial.

The following documentation must be completed and received by the WCTU in order for a centre to begin recruitment:

- Confirmation of local R&D approval
- Signed partnership agreement between the host care organisation and Sponsor
- Current Curriculum Vitae and GCP certificate of the PI
- A copy of the most recent version of the Participant Information Sheets and Consent Forms on host care organisation headed paper
- Completed Delegation Log (signature list and delegation of responsibilities)
- Full contact details for all host care organisation personnel, indicating preferred contact
- Submission of RT process document for RTQA (RT treatment centres only)

Once all the documentation has been received at the WCTU, confirmation of centre approval will be sent by the WCTU to the centre PI.

All documentation must be stored in the Investigator Site File (ISF) at the site and in the Trial Site File (TSF) at the WCTU. The WCTU must be notified of any changes to the trial personnel and their responsibilities during the running of the trial and the respective trial files must contain this up-to-date information.

Centre initiation will be by attendance at a national ROCS trial launch meeting or by teleconference if attendance of key personnel at the launch meeting is unfeasible. Due to the nature of the study and the study population, attendance by research nurse staff at these meetings will be mandatory to ensure appropriate training has been received.

6.0 Participant eligibility

Any queries about whether a patient is eligible to enter the trial should be discussed with the WCTU before randomisation. Any issues will then be raised with one of the Chief Investigators (CIs) or one of the clinical Co-Investigators in the absence of the CIs.

Eligible patients will have histologically confirmed oesophageal carcinoma, not suitable for radical treatment, who have dysphagia severe enough to require prompt insertion of an oesophageal stent to palliate the dysphagia. Patients are eligible for the trial if all the inclusion criteria (Section 6.2) are met and none of the exclusion criteria (Section 6.3) apply.

6.1 Screening procedures

Before any trial related procedures are undertaken, the patient's written informed consent must be obtained. The patient should be given adequate time after the initial invitation to participate before being asked to sign the consent form.

6.2 Inclusion criteria

Patients meeting the following criteria may be included in the trial:

1. Histological confirmation of oesophageal carcinoma excluding small cell carcinoma
2. Not suitable for radical treatment (oesophagectomy or radical chemoradiotherapy) either because of patient choice or medical reasons
3. Dysphagia clinically assessed as needing stent as primary treatment of the dysphagia
4. Age 16 years or over
5. Discussion and treatment decision for stent placement made by an upper GI multi-disciplinary team
6. Deemed suitable for radiotherapy
7. Expected survival of at least 12 weeks
8. Written informed consent
9. Patient has completed baseline Quality of Life Questionnaires (please note, as a minimum patients must have completed OG25)

The PI or nominated delegate must confirm the eligibility of a patient in the patient's medical notes prior to randomisation.

6.3 Exclusion criteria

If any of the following criteria apply, patients cannot be included in the trial:

1. Small cell carcinoma
2. Tumour length of greater than 12 cm
3. Tumour growth within 2 cm of the upper oesophageal sphincter

4. Endoscopic treatment of the tumour, other than dilatation, planned in the peri-stent period
5. Presence of a tracheo-oesophageal fistula
6. Presence of a pacemaker in proposed radiotherapy field
7. Previous radiotherapy to the area of the proposed radiotherapy field
8. Female patient who is pregnant

6.4 Informed consent

The patient's consent to participate in the trial will be obtained prior to any trial-related procedures which includes insertion of stent when consent is taken before stent insertion. Consent to take part will be requested after a full explanation has been given of the treatment options.

Consent may be taken before or after the stent insertion. When consent is obtained prior to stent insertion, a research practitioner will collect baseline data prior to stent insertion, 1 week post stent insertion, four weeks after stent insertion (which may be after radiotherapy in the RT arm) and four weekly thereafter. When consent is obtained after stent insertion the baseline assessment will take place at that time point (i.e. within 2 weeks of stent insertion) four weeks after stent insertion and then four weekly thereafter.

Consent will be taken by the appropriately trained research nurse or delegate. All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which they may be exposed. They will be informed of the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorised individuals other than their treating physician and care team. Patients will be given sufficient time after being given the trial Participant Information Sheet (PIS) to consider and discuss participation in the trial with friends and family. A contact number will be given to the patient should they wish to discuss any aspect of the trial. Following this, the recruiting investigator will ensure that the patient is fully informed of the trial and their participation, in accordance with the principles of GCP prior to signing the consent form. Patients who consent to randomisation will also be asked to consent to Health and Social Care Information Centre Flagging (England and Wales) or NHS Central Register (Scotland) so that the date and cause of death can be collected without longer term follow up. This will be optional and additional to the standard informed consent.

Patients who decline to participate in the main study, as well as participants who enter the main study, will be asked whether they consent to storage of their contact details so that a Qualitative Researcher may contact them to invite them to participate in a qualitative interview about the reasons behind their decision not to participate in the main trial, or of their experiences of the interventions, as appropriate.

Patients who agree to storage of their contact details will be asked to sign the appropriate section of the main consent form. At this time, they will also be given a separate Qualitative Interview PIS and consent form to take home and read. A sub-set of these patients will be contacted by a Qualitative Researcher to arrange a qualitative interview, as described in the qualitative section below. The Qualitative Researcher will collect consent for conducting the interview using the Qualitative Interview Consent Form, immediately prior to

commencement of the interview. The patient will remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment. Where a companion is present at an interview the researcher will explain that without formal consent, their contributions cannot be included in study. Companions who wish their contributions to be included will be given the Companions Patient Information Sheet 3 and consent will be taken. Their data will be treated in the same way as that of the patient participants.

Patients who do not consent to the main study or the qualitative study may benefit from time to reflect on their decision after the stent procedure has taken place. This group of patients will therefore be asked if the research nurse can contact them (up to two weeks) post stent insertion to ensure they do not wish to participate in the qualitative interview.

7.0 Randomisation

Participant randomisation will be performed centrally by the WCTU. Randomisation can only be performed once the participant has signed the consent form. The randomisation form should be completed and the WCTU contacted on the following telephone number:

WCTU Randomisation line:
029 2064 5500
(Open Monday – Friday, 9am – 5pm)

N.B. This telephone number is strictly for randomisation and should not be used for general queries.

Participants will be randomised to a trial arm using the method of minimisation with a random element. Minimisation will ensure balanced treatment allocation for a number of potential confounding factors. Randomisation will use a 1:1 allocation ratio.

At randomisation, the participant will be given a unique participant trial number and the treatment allocation. These details should be recorded on the participant randomisation form and the top copy returned to the WCTU within four weeks.

After randomisation, the WCTU will fax confirmation to the Research Nurse at the participating centre. Case report forms (CRFs) will also be sent to the Clinician, Data Manager or Research Nurse nominated as responsible for the participant. The participant's General Practitioner (GP) will be informed of the participant's enrolment, if the participant gives consent to do so.

It will usually be possible for participants to be recruited into other clinical trials, but this should be discussed with the CI via the WCTU before this is considered.

8.0 Trial treatments

8.1 Self-expanding metal stents (SEMS): both arms

8.1.1 Scheduling

A stent will be inserted, following the decision by the MDT, or members thereof, to proceed with stent as the primary treatment for the oesophageal cancer. Insertion will be in accordance with the standard procedures of the treating centre. The length and type will be determined by the responsible clinician. The following will be recorded: Whether the stent is inserted under sedation or GA, whether dilatation is required before or after stent insertion and whether radiological imaging is used. Where possible the length of stent will be chosen to ensure that at least 2cm of normal oesophagus is covered by the stent above and below the tumour stricture. Where necessary, more than one stent may be deployed. Ideally a post insertion oesophagogram will confirm stent position and exclude perforation.

8.1.2 Permitted procedures

Oesophageal dilatation that is used as part of the centre's normal procedure for stent insertion is permitted.

8.1.3 Non-permitted procedures

The trial should not be offered to patients who are deemed to need or are offered routine endoscopic treatment of the tumour (e.g. laser) in the immediate peri-stenting period, unless an emergency situation arises that requires such a procedure. Any exceptional use of such procedures should be recorded on the case report form. Brachytherapy or external beam radiotherapy should not be planned to be given routinely after stent insertion for those patients in the control arm.

8.2 External beam radiotherapy (EBRT) trial arm: intervention

8.2.1 Scheduling

Radiotherapy treatment should begin within 4 weeks of stent insertion (aiming for 2 weeks). Treatment dose will be either 20Gy in 5 fractions over one week or 30 Gy in 10 fractions over two weeks using daily fractionation and the centre's normal radiotherapy treatment procedures. The dose and fractionation schedule chosen will be at the discretion of the treating clinical oncologist.

8.2.2 Radiotherapy delays and modifications

If the patient misses more than 7 consecutive calendar days during radiotherapy treatment, then they should be withdrawn and further treatment given at the clinician's discretion. In the unlikely event of radiotherapy side effects severe enough to interfere with treatment delivery, the treating clinician may temporarily stop treatment and allow a break of no more than 7 calendar days prior to recommencement.

8.3 Procedures permitted with caution

The need for stent removal or piggy-back stents is per the institution's usual procedures.

8.4 Non-permitted procedures

The trial should not be offered to patients who are deemed to need or are offered routine endoscopic treatment of the tumour (e.g. laser) in the immediate peri-stenting period, unless an emergency situation arises that requires such a procedure. Any exceptional use of such procedures should be recorded on the case report form (CRF).

9.0 Radiotherapy

9.1 Introduction to radiotherapy

This section describes the process and procedures for Radiotherapy (RT) treatment planning. The aim is to aid the delivery of high quality radiotherapy of a consistent quality and to allow quality assurance procedures to be applied to ensure that this is achieved. However, some aspects of the process are not explicitly defined and will vary according to the characteristics of each centre and their local practice methods.

Patients should be planned and set up as per the institution's usual procedures. Planning should involve either simulation or CT planning. The set-up, use of contrast, and portal imaging will be as per the institution's usual practice in such cases, but will be detailed for each study centre prior to patient recruitment. The RT schedule will be either 20Gy in 5 daily fractions or 30Gy in 10 daily fractions, and treatment will be with 6-10MV X-rays.

9.2 Patient positioning and CT planning scan acquisition

The patient shall be planned as per the institution's usual procedures using a simulator or with a CT-Simulator/virtual simulation to acquire the target volumes. Determination of the isocentre position will be by using single or multiple reference marks and tattoos placed on stable areas of skin and bony anatomical landmarks or equivalent local practice during the planning process. Ideally this will involve two lateral and one anterior marker/tattoo.

9.3 Definition of treatment volumes

Treatment volumes will cover the gross primary tumour volume and any local nodal masses that the clinical oncologist feels are treatable and would benefit from treatment. A setup margin of approximately 2cm in the cephalad and caudal directions should be applied. (Usually, the fields would therefore cover the oesophageal stent in its entirety, but may not on rare occasions, such as when a piggy-back stent has been inserted, making the stented portion of the oesophagus much longer than the tumour. In this case, the aim would be to cover the tumour and nodes as above, leaving part of the stented portion of normal oesophagus or stomach uncovered by the radiotherapy fields.)

9.4 Dose calculation

Isocentric radiotherapy beams of 6-10MV should be used to deliver the required dose to the treatment volume. Monitor units should be obtained from a point dose calculation at the isocentre using either:

i. Tabular Based Calculation: Dose should be calculated at the isocentre using the centre's standard dose calculation method utilising percentage depth doses (PDDs) or tissue phantom ratios (TPRs) etc.

ii. Treatment Planning System Based Calculation: Dose should be calculated at the isocentre using a type-a or a type-b calculation algorithm. For consistency with table based calculations, the inhomogeneity correction should be turned OFF. Compensation for changes in patient separation may be made using superior – inferior wedges or 'filler' fields but is not mandatory.

9.5 Dose prescription

Radiotherapy dose will be prescribed to the midplane and will 20Gy in 5 daily fractions over one week or 30Gy in 10 daily fractions over two weeks. The prescription regimen will be at the discretion of the treating clinician but will be decided at the time of site opening and will remain for all patients in the ROCS study at that site.

9.6 On treatment verification

The position of the isocentre may be verified on treatment using the centres' standard protocol for such patients. However as a minimum a portal image taken on the first fraction should be compared with digitally reconstructed radiographs (DRRs) or simulator images and measurements of the FSDs during treatment on at least weekly intervals should made.

9.7 Compliance with IR(ME)R 2000 Regulations and other QA Requirements

All participating centres must comply with the requirement of the IR(ME)R 2000 regulations as amended and Medical and Dental Guidance Notes 2002.

In compliance with IR(ME)R 2000, participating centres must follow written protocols for radiotherapy treatment planning, prescription and delivery. In these protocols, there should be clear description of compliance with regard to the role of the employer, referrer and operator. The process for justification and authorisation of planning and treatment exposures must be clearly described.

Participating centres must participate in an external programme of dosimetry audit (such as performed by IPEM). There must be no unresolved dosimetry discrepancies.

9.8 Radiotherapy Quality Assurance

The Radiotherapy Quality Assurance (RTQA) will be carried out by the Cardiff NCRI Radiotherapy Trials Quality Assurance (RTTQA) Group. The ROCS Radiotherapy Quality Assurance (RTQA) Group, consisting of radiation oncologists and radiotherapy physicists from the Cardiff NCRI RTTQA Group, will give information and guidance regarding implementation of the protocol, monitor compliance with the protocol, and provide feedback on the RTQA accreditation (where necessary).

RTQA accreditation is required by all centres but due to the simple nature of the radiotherapy delivered in this trial will not be extensive and will consist of the following:

Pre-trial QA

A process document is to be completed by the RT site prior to being opened to recruitment. This should contain information on set up, verification and beam arrangement. This will be reviewed by the ROCS RTQA group.

National radiotherapy trials QA baseline questionnaire returned to the NCRI RTTQA Group, if not updated within the last two years.

On-trial QA

Following entry of the first patient into the trial at a RT treatment site, a set of CT images or simulator images, together with information concerning the treatment fields (DICOM-RT file or hard copy) and treated volumes should be forwarded to the ROCS RTQA group.

Details of the RTQA requirements and who to contact can be found on the NCRI RTTQA group website: http://www.rttrialsqa.org.uk and following the link to ROCS. Alternatively contact the ROCS Trial Manager.

10.0 Trial assessments

A research practitioner will collect baseline data around the time of stent insertion, depending on the timing of consent and randomisation (see below), then four weekly thereafter until death. For patients consented before stent insertion there will be a visit one week after stent insertion in addition to the baseline collection of data. Dedicated research staff will visit patients at home or a place of their choice. Dedicated face to face follow up is preferred to ensure optimum support for patients in completing assessments and to minimise disruption for them; however where patients specifically decline face to face follow up but express a preference to have telephone or postal follow up for questionnaire completion, research staff will undertake follow up assessments in this way.

10.1 Baseline assessments (within one week prior to randomisation).

This should be within one week of stent insertion which may be either before or after stent insertion. For patients consented after stent insertion there is a maximum of two weeks between stent insertion and consent/randomisation.

- WHO performance status
- Questionnaires (EORTC QLQ-C30, EORTC QLQ-OG25, EQ-5D) (Appendix 1, 2, 3)
- Toxicity Assessment (CTCAE V4.03) (Appendix 4)
- Stent morbidity data (patients in post stent consent group only).
- Qualitative interview (subset of patients in post stent consent group).

10.2 Post stent assessment

This is additional if consent and baseline assessment is carried out prior to stent insertion. This visit should be done one week after stent insertion.

- WHO performance status
- Questionnaires (EORTC QLQ-C30, EORTC QLQ-OG25, EQ-5D)
- Toxicity Assessment (CTCAE V4.03)
- Stent morbidity data
- Qualitative interview (sub-set of patients)

10.3 Four weeks after stent insertion and 4 weekly thereafter until death

- WHO performance status
- Questionnaires (EORTC QLQ-C30, EORTC QLQ-OG25, EQ-5D)
- Toxicity Assessment (CTCAE V4.03)
- Stent morbidity data
- Qualitative interview (sub-set of participants) (week 4 and week 8 only)

A detailed assessment schedule is given in section 10.5 overleaf.

10.4 Completion of CRFs

A full set of instructions for completing the CRFs are included on the inside cover of each CRF pack. CRFs will be printed on NCR (carbonless) paper and should therefore be completed in black ball point pen, with participant trial number, initials and data of birth recorded on the header of every page. Incorrectly entered information can only be amended on the top copy of the CRF and only if it has not been separated from the NCR copy underneath. Deletions should be made with a single line through the entry and the correct value should be written alongside the box, and all amendments should be initialled and dated. The top copy of completed CRFs should be torn out and sent in the post to the WCTU within four weeks of completion unless stated otherwise. The remaining copy is to be retained at the local site. The CRFs should not be altered after the top copy has been returned to WCTU. Refer to section 12.1.1 for handling of data queries.

It is the PIs responsibility to ensure completeness, legibility and timeliness of the data reported to WCTU.

CRF pages and data received by the WCTU from participating trial sites will be checked for missing, illegible or unusual values (range checks) and consistency over time. If missing or questionable data are identified, a data query will be raised on a data clarification form. The data clarification form will be sent to the relevant participating site. The site shall be requested to answer the data query or correct data on the data clarification form. The case report form pages should not be altered. All answered data queries and corrections should be signed off and dated by a delegated member of staff at the relevant participating site. The completed data clarification form should be returned to the WCTU and a copy retained at the site along with the participants' CRFs.

The WCTU will send reminders for any overdue data. It is the site's responsibility to submit complete and accurate data in timely manner.

10.5 Schedule of trial assessments

Procedure / Assessment	**Trial visit**				
	Baseline	1 week post stent insertion *	4 weeks post stent insertion	8 weeks post stent insertion	4 weekly thereafter until death
WHO Performance status	✓	✓*	✓	✓	✓
QLQ-OG25	✓	✓*	✓	✓	✓
EORTC QLQ-C30	✓	✓*	✓	✓	✓
EQ-5D	✓	✓*	✓	✓	✓
Stent morbidity	✓**	✓	✓	✓	✓
CTCAE toxicity assessment	✓	✓*	✓	✓	✓
Qualitative interview (sub-set of participants)	✓**	✓	✓	✓	
NHS resource use	✓	✓*	✓	✓	✓

* Only for patients who have consented and completed the baseline prior to stent insertion

** Only for patients who have had stent insertion before consent and randomisation

N.B. Serious Adverse Events (SAE) will be collected in real time via a designated SAE fax number.

11.0 Safety reporting

The following definitions are in accordance with ICH-GCP:

Adverse Event (AE): Any untoward medical occurrence in a clinical trial participant to whom an investigational medicinal product has been administered and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom, or disease.

Serious Adverse Event (SAE): Any adverse event that:

- Results in death
- Is life-threatening*
- Requires hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Other medically important condition ***

* Note: The term “life-threatening” in the definition of serious refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** Note: Hospitalisation is defined as an in-patient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure, for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened or elective procedures does not constitute an adverse event.

*** Note: other events that may not result in death, are not life-threatening, or do not require hospitalisation may be considered as a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Serious Adverse Event (SAE(SEMS)) or SAE(RT)): Any Serious Adverse Event occurring in a clinical trial participant for which there is a reasonable possibility that it is related to either the stent insertion or radiotherapy treatment respectively.

Suspected Unexpected Serious Adverse Reaction (SUSAE(SEMS))) or SUSAE(RT)): Any adverse event that was serious as defined above and is thought to be related to stent insertion or radiotherapy treatment but is not expected (listed in the expected adverse events tabulated overleaf).

11.1 Causality Assessments

The Principal Investigator (or another delegated medically qualified doctor from the trial team) and Chief Investigator (or another medically qualified doctor from the Trial Management Group) will assess each SAE to determine the causal relationship with the trial treatment, and will answer 'yes' or 'no' to the question "Do you consider that there is a reasonable possibility that the SAE may have been caused by the SEMS or RT?"

The causality assessment given by the Principal Investigator (or delegate) cannot be downgraded by the Chief Investigator (or delegate), and in the case of disagreement both opinions will be provided.

A guide to the interpretation of the causality question is found in Appendix 1 of this clinical trial protocol.

11.2 Expectedness Assessments

The Chief Investigator (or another delegated appropriately qualified individual) will assess each SAE to perform the assessment of expectedness.

The expectedness assessment should be made with reference to the table below of expected adverse events. The nature or severity of a radiotherapy toxicity should be considered when making the assessment of expectedness. If these factors are not consistent with the current information available on oesophageal radiotherapy the toxicity should be recorded as 'unexpected'. However, if the nature and severity are in accordance with previously documented events in relation to radiotherapy to this region, the event /toxicity should be recorded as 'expected'.

Other factors such as the participant population and participant history should not be taken into account. Expectedness is not related to what is an anticipated event within a particular disease.

SAEs which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected events.

Expected adverse events with stent and RT are tabulated below:

stent	**RT**
Aspiration	Anorexia
Cardiovascular (arrhythmia, acute coronary syndrome)	Fatigue
Dysphagia secondary to mechanical blockage	Fever
Fever	Gastrointestinal Fistula
Upper Gastrointestinal Fistula	Gastritis
Upper Gastrointestinal Bleed	Upper Gastrointestinal Haemorrhage
Haemorrhage requiring blood transfusion	Mucositis
	Nausea
	Vomiting

Bronchopulmonary infection Mucositis Oesophageal reflux Oesophagitis Perforation Pain Vomiting	Oesophageal reflux Oesophagitis Perforation Pneumonia Radiation dermatitis Skin hypo- or hyper- pigmentation

Please note that although this list was exhaustive at the time of authorisation of this protocol, practices may have changed and we encourage this to be taken into account when assessing the expectedness of an adverse event. PIs are expected to report any issue of concern.

11.3 When to report

Adverse events (AE) should be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

For all adverse events, stent and Radiotherapy toxicities occurring up to 60 days after the stent insertion:

- Grade 1-2 report only on the toxicity section of the relevant CRF
- Grade 3-4 report on the SAE form, only if the patient is admitted to hospital and it is not classed as an exception (as listed in section 11.2). Please also record on the toxicity section of the relevant CRF
- Deaths due to any cause except disease progression on an SAE form

A SAE form is not considered as complete unless the following details are provided:

- Full participant trial number
- An adverse event/reaction
- A completed assessment of the seriousness, causality and expectedness as performed by the Principal Investigator or another appropriately qualified clinician registered on the delegation log. N.B. It is a requirement of GCP that a clinician provides this clinical assessment. Research nurses and other local trial staff should NOT complete this section of the SAE CRF, or authorise SAE CRFs. If they do so, the SAE form will be immediately queried by WCTU trial staff and a clinician review must be gained as soon as possible and the SAE form resubmitted with this information.

If any of these details are missing, you will be contacted and the information must be provided as soon as it becomes available.

It is also required that centres respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the

resolution of the event. The WCTU shall send reminders for any overdue data on a regular basis.

Serious adverse events should be reported from time of signature of informed consent until 60 days after stent insertion except if they are not required to be reported as specified in section 11.5, Exceptions. Any toxicities or hospital admissions after this time should be recorded on the CRFs.

11.4 Pregnancy reporting whilst participating in the ROCS trial

Pregnancy occurring whilst participating in the ROCS trial, although not considered a SAE, must be notified to the WCTU within the same timelines as a SAE. In the event of a pregnancy in a trial participant, the WCTU must be contacted immediately to request a Pregnancy Report Form. The Pregnancy Report Form should be completed and returned to the WCTU to capture all the relevant information required for the expedited reporting of these events. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the foetus should be reported. This also applies to pregnancies following the administration of radiotherapy to the father prior to sexual intercourse.

11.5 Exceptions

For the purposes of this trial the following SAEs do not require immediate reporting:

- Death due to disease progression
- Hospitalisation for dysphagia caused by food bolus
- Hospitalisation for supportive and palliative therapies
- Hospitalisation to facilitate radiotherapy delivery
- Hospitalisation due to stent slippage (report on CRFs)

These should instead be reported on the relevant CRF page and forwarded to the WCTU in the normal timeframes for CRFs.

11.6 Participating centre responsibilities

All SAEs must be reported immediately and within 24 hours of knowledge of the event) by the PI at the participating centre to the WCTU unless the SAE is specified as not requiring immediate reporting (see above). All other AEs should be reported on the CRF as usual.

The PI (or delegated medically qualified doctor from the trial team) should sign and date the SAE CRF to acknowledge that he/she has performed the seriousness and causality assessments.

A completed SAE form for all events requiring immediate reporting should be faxed to the WCTU within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.

The participant will be identified only by trial number, date of birth and initials. The participant's name should not be used on any correspondence.

It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event.

Serious Adverse Event (SAE) Fax Number:

029 2064 4488

An SAE form is not considered as complete unless the following details are provided:

- Full participant trial number
- An Adverse Event / Adverse Reaction
- A completed assessment of the seriousness, and causality as performed by the PI (or another appropriately medically qualified doctor registered on the delegation log).

If any of these details are missing, the site will be contacted and the information must be provided by the site to the WCTU within 24 hours.
All other AEs should be reported on the CRF following the CRF procedure described in Section 10.4.

11.7 The Wales Cancer Trials Unit responsibilities

Following the initial report all SAEs should be followed up to resolution wherever possible and further information may be requested by the WCTU. The participant will be identified only by trial number, date of birth and initials. The participant's name should not be used on any correspondence.

Velindre NHS Trust is undertaking the duties of trial sponsor and has delegated to the WCTU the responsibility for reporting SUSAE(SEMS) and SUSAE(RT)s and other SAEs to the regulatory authorities as follows:

- SUSAE(SEMS) and SUSAE(RT)s to MREC within 15 days of the event coming to the attention of the WCTU.
- The WCTU will report a list of SAEs and any other safety recommendations to all Principal Investigators annually throughout the course of the trial. This frequency may be reviewed and amended as necessary.
- A list of all SAEs (expected and unexpected) will be reported annually to MREC and Velindre NHS Trust Research and Development Department.

The WCTU should continue reporting SAEs until 60 days after stent insertion of the last patient recruited.

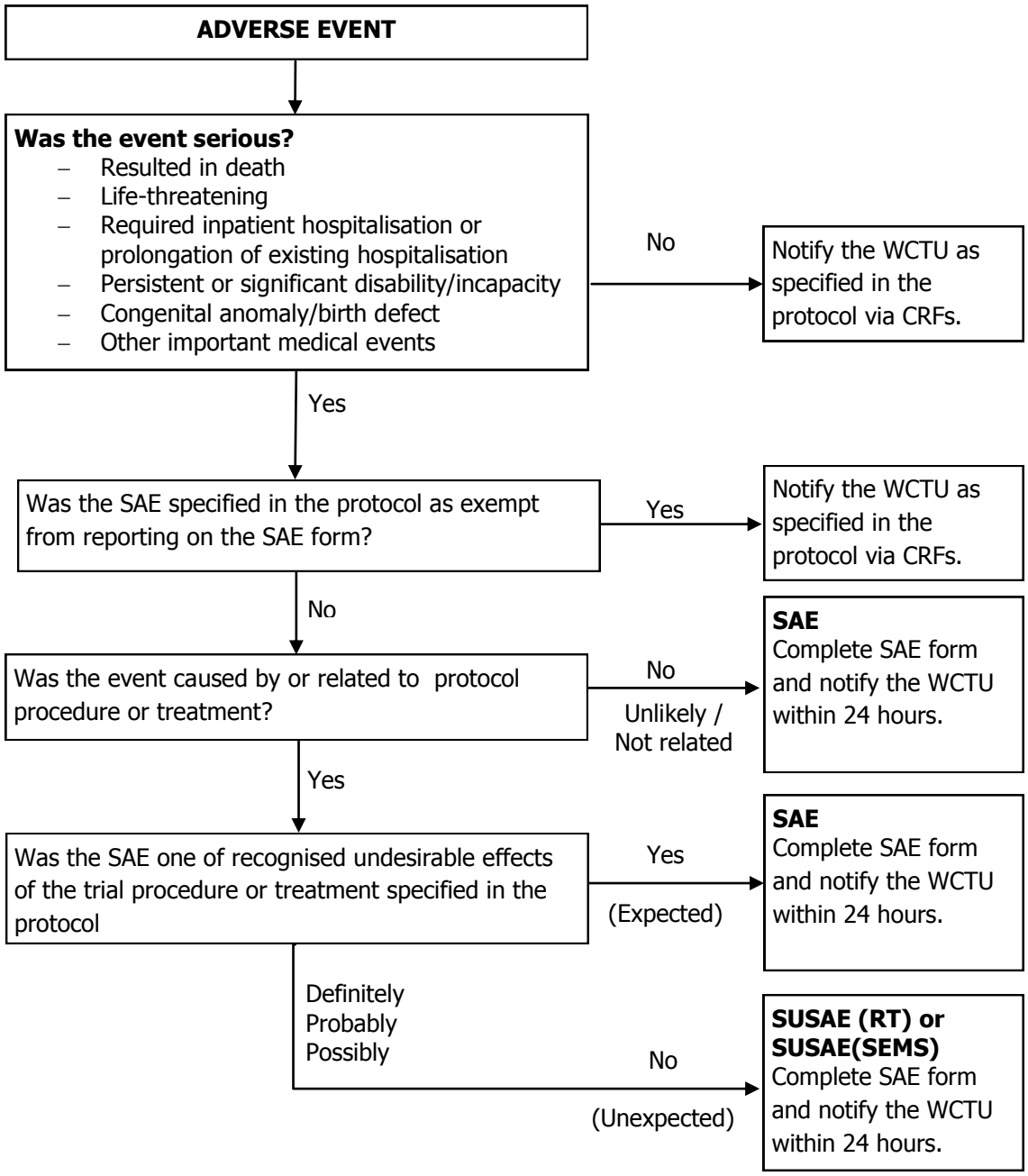
Once an SAE is received at the WCTU, it will be evaluated by staff at the WCTU and the Chief Investigator (or delegate) for seriousness, expectedness and causality. Investigator reports of suspected SUSAEs will be reviewed immediately and reported to the MREC within 15 days.

11.8 Safety Reports

A list of all SAEs (expected and unexpected) will be reported annually to the Main Ethics Committee and trial sponsor in an Annual Safety Report (ASR). This report should be submitted within 60 days of the anniversary of the Ethics approval date.

The WCTU will report a list of all SAEs (expected and unexpected) and any other safety recommendations to all PIs annually throughout the course of the trial. This frequency may be reviewed and amended as necessary. This reporting will be done via the Investigator safety report (ISR).

11.9 Flowchart for Serious Adverse Event reporting



CRF	Case Report Form
SAE	Serious Adverse Event
SAE(SEMS)	Serious Adverse Event to SEMS insertion
SAE(RT)	Serious Adverse Event to Radiotherapy
SUSAE(SEMS)	Suspected Unexpected Serious Adverse Event related to SEMS insertion
SUSAE(RT)	Suspected Unexpected Serious Adverse Event related to Radiotherapy
WCTU	Wales Cancer Trials Unit

12.0 Trial monitoring and management

12.1 Monitoring

12.1.1 Central monitoring and data queries

The top copy of each completed CRF should be returned to the WCTU for data entry within four weeks of the visit. The remaining copy is to be retained at the local centre.

CRF pages and data received by the WCTU from participating trial centres will be checked for missing, illegible or unusual values (range checks) and consistency over time.

If missing or questionable data are identified, a data query will be raised on a data clarification form. The data clarification form will be sent to the relevant participating site. The site shall be requested to answer the data query or correct data on the data clarification form. The case report form pages should not be altered.

All answered data queries and corrections should be signed off and dated by a delegated member of staff at the relevant participating site. The completed data clarification form should be returned to the WCTU and a copy retained at the site along with the participants' CRFs.

The WCTU shall send reminders for any overdue data. It is a centre's responsibility to submit complete and accurate data in timely manner

12.1.2 Site monitoring

Investigators should agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Patient consent for this will be obtained.

12.2 Trial committees and trial management

The conduct of the trial is being overseen by the following committees:

1. The data will be reviewed (approximately six monthly) by an Independent Data Monitoring Committee (IDMC), consisting of at least two Clinicians (not entering patients into the trial) and an independent Statistician. The IDMC will be asked to recommend whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients. A decision to discontinue recruitment, in all patients or in selected subgroups, will be made only if the result is likely to convince a broad range of Clinicians including PIs in the trial and the general clinical community. If a decision is made to continue, the IDMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDMC will make confidential recommendations to the Trial Steering Committee (TSC).

2. An independent Trial Steering Committee (TSC) which is a committee of independent members that provides overall supervision of the trial. The role of the TSC is to act on

behalf of the sponsor and funder, to provide overall supervision for the trial, to ensure that it is conducted in accordance with GCP, and to provide advice through its independent chairman. The TSC will review the recommendations from the IDMC and will decide on continuing or stopping the trial or modifying the protocol. It will meet at least annually when it will consider each report of the IDMC, as well as results of other trials and new information which has arisen, and recommend appropriate action.

3. The Trial Management Group (TMG) should meet at least once every six months to advise in the promotion and running of the trial. The TMG members should include active trial investigators, WCTU representatives, Chief Investigators and specialist advisors (e.g., Statistician, Consumer Representative). Minutes of the TMG meetings should be forwarded to the sponsor as the decisions based on these meetings may impact on the sponsorship arrangements.

4. Clinicians from all collaborating centres will be invited to investigator meetings during the trial to review progress.

12.3 Data handling

The top copy of each completed CRF should be returned to WCTU for data entry within 4 weeks of the visit. The remaining copy is to be retained at the local centre. The WCTU staff will be in regular contact with local centre personnel to check on progress and to help with any queries that may arise. Incoming forms will be checked for completeness, consistency, timeliness and compliance with the protocol. Centres may be withdrawn from further recruitment in the event of serious and persistent non-compliance. Data will be handled and stored in accordance with the Data Protection Act (1998).

12.4 Loss to follow-up

If a patient is lost to follow-up the WCTU will request the centre to contact the patient‘s GP to obtain information on the patient‘s status. If needed and the patient has given the necessary consent, they will be traced via the NHS IC or the NHS Central Register.

12.5 Quality assurance and quality control of data

There will be a formal risk review of the protocol prior to study commencement and a quality assurance programme will be in place to ensure adherence to the protocol. Major and minor deviations will be collected. A monitoring Standard Operating Procedure (SOP) will be developed for the trial. The Radiotherapy trials quality assurance will be conducted by the Cardiff NCRI RTTQA group.

12.6 End of trial

The end of the trial will be when the last patient has completed the last protocol assessment. This will include a follow-up period which will continue for up to one year after the last participant completes protocol treatment.

12.7 Archiving

The TMF containing essential documentation will be archived at an approved external storage facility for a minimum of 15 years. WCTU will archive the TMF on behalf of the sponsor. The PI is responsible for archival of the ISF at site. Essential documents pertaining to the trial (listed in ICH GCP Section 8) shall not be destroyed without permission from the Sponsor.

12.8 Participant withdrawal

In consenting to the trial, patients are consenting to radiotherapy (if allocated), trial follow up and data collection. Participants may withdraw from the trial at any time. Participants may:

Level 1: Does not have stent, radiotherapy, or stops radiotherapy early

Withdrawal from trial treatment; participant stops trial treatment but remains on follow-up. Participants should be followed up according to the ROCS protocol until week 52 and then as per routine follow-up.

Level 2: Stops home visits and questionnaires

Withdrawal from trial follow-up; participant is no longer visited by trial researchers. Available data is collected from hospital notes at the time points specified in the ROCS protocol and completed in the CRF and sent to the WCTU. CRFs will include missing data and no questionnaires will be completed.

Level 3: Stops all trial activity including any data collection

Complete withdrawal from trial; participant stops trial treatment and follow-up. Data collected up until the point of withdrawal should be completed in the CRF and sent to the WCTU. If a participant wishes to withdraw from trial treatment, participating sites should nevertheless explain the importance of remaining on trial follow up for the purposes of data capture only. Withdrawal for any reason requires a completed withdrawal CRF to be faxed to the WCTU with the hard copy to follow soon after. Participants do not have to give a reason for their withdrawal but sites should make a reasonable attempt to find out why.

A patient may withdraw, or be withdrawn, from trial treatment for the following reasons:

a. Intolerance to treatment (including SAEs and toxicities).
b. Participant choice.
c. Clinician's decision

d. Any participant whose stent treatment is delayed for longer than 1 week following randomisation or whose radiotherapy occurs more than 4 weeks post stent placement.

e. Participants who suffer perforation at the time of stent insertion and those who are deemed to require additional interventions such as laser therapy.

The reason should be recorded on the withdrawal form. Data collected prior to participant withdrawal at either of the levels indicated above will be collected and used for trial analysis by the WCTU.

Participants who initially consented to be registered with the National Health Service Information Centre (NHSIC) or equivalent will remain on the system so that important research information on date and cause of death can be requested from NHSIC by the WCTU.

12.9 Lost to follow up

If a participant is lost to follow up, the WCTU will contact the participant's GP to obtain information on the participant's status. Patients who consent to randomisation will also be asked to consent to NHS IC Flagging so that the date and cause of death can be collected without longer term follow-up. This will be optional and added to the standard informed consent. The participants NHS number (or equivalent, e.g. CHI number in Scotland), name and address, will be requested for those who consent to NHS IC Flagging.

12.10 Protocol/GCP non-compliance

The Principal Investigator should report any non-compliance to the trial protocol or the conditions and principles of Good Clinical Practice to the WCTU as soon as they become aware of it.

13.0 Statistical considerations

13.1 Randomisation

Randomisation will take place after confirmation of eligibility by a telephone call to the WCTU. Patients will be randomised using the method of minimisation with a random element. Minimisation will ensure balanced treatment allocation by number of potential confounding factors. Randomisation will use a 1:1 allocation ratio.

13.2 Outcome measures

In order to minimise participant disruption and optimise data capture, all assessments will occur in the home setting, unless the participant is in hospital or otherwise specified by the participant.

13.2.1 Primary outcome measure

Patient–reported dysphagia

This will be measured at the specified time points using the EORTC QLQ-OG25 questionnaire. The QLQ-OG25 is an updated and improved questionnaire[14] that amalgamates the widely used EORTC scales to assess health related quality of life in patients with oesophageal and gastric cancer[15,16].

In the earlier EORTC scales, problems with the validity of the dysphagia scale were noted with patients finding the response categories confusing. The EORTC QLQ-OG25 therefore further tested and revised the original dysphagia scales from both modules. In addition the QLQ-OG25 combined both oesophageal and gastric modules to ensure that the HRQOL issues are relevant to both groups of patients and patients with oesophago-gastric (junctional tumours) were included. The new questionnaire has six scales and the dysphagia scale is scored from 0 to 100 and a change of 10-15 points is considered clinically significant[17].

Relief of dysphagia is expected in the majority of participants following stent insertion. When consent is obtained prior to the insertion of the stent (this is encouraged), the baseline dysphagia score will be taken before stent insertion and then one week after stent insertion (prior to RT in the intervention arm). This second measurement will form the time zero measurement for the main endpoint of the study for these patients.

If patients enter the study following stent insertion, the first post-stent dysphagia score will form the time zero measurement for the main endpoint of the study. If that score is 89 or higher (on a 0 to 100 scale) then patients will remain in the study and will be documented as a failure at time zero, as a deterioration of more than 11 points will not be possible. They will undergo further interventions at the discretion of the treating physician. All patients will then be followed up at four-weekly intervals after stent insertion.

All patients will then be followed up at four weeks after stent insertion and then at four weekly intervals after that. The time point at which a 11 point deterioration is seen in the dysphagia scores compared to the time zero measurement will form the event for the

primary outcome. Following this time point (progression in dysphagia), patients will continue to be followed up four weekly until death. It is possible that patients undergoing radiotherapy may have a temporary worsening of dysphagia secondary to radiation-induced oesophagitis, and other temporary changes might occur. This will be important to capture. However to ensure that it does not bias the primary outcome, definitive deterioration in dysphagia will be defined as a 11 point change on two consecutive occasions with the first being taken as the event time point. If there is missing data at that subsequent assessment, deterioration will be assumed and timed at the previous assessment.

As a time to event outcome an event is defined as a progression in self reported dysphagia (see above). Participants will therefore fall into one of four categories:

i) an event due to a failure at time zero;

ii) an event due to a definite deterioration of 11 points or more;

iii) no event as the participant died without a definite deterioration of 11 points or more, these participants will be censored at the time of death and;

iv) no event as the participant is alive without definite deterioration of 11 points or more, these participants will be censored at the time last seen.

13.2.2 Secondary outcome measures

(i) Quality of life: will be measured using the EORTC QLQ-C30, EORTC QLQ-OG25 and EQ-5D at the time points described.

The EORTC QLQ –C30 has become a benchmark measure of quality of life (QoL) in cancer patients. It contains 5 functional scales: physical, role, cognitive, emotional and social; three symptom scales: pain, nausea/vomiting and fatigue, global health and quality of life scales and several other single items. This measure will be employed in addition to QLQ-OG25 as validation of the latter[14] demonstrated that they measure separate health-related quality of life (HRQoL) issues, and it is likely that dysphagia only accounts for a proportion of quality of life impact[18] The EQ-5D is a short QoL tool which is designed to complement other QoL measures and is recommended by National Institute for Health and Care Excellence (NICE) for use in providing an index of HRQoL for generation of economic analyses (see below).

In this trial the QoL outcomes are important and previous work shows how gaining self reported health data from patients with poor health and life expectancy is difficult[19]. Previous studies and Randomised Controlled Trials in this field therefore recommend that dedicated research staff collect the QoL data and home visits are undertaken if appropriate[9] . The research nurses will help patients complete the questionnaires and capture data on resource use in the home setting.

(ii) Patient experience of trial recruitment and interventions and perception of treatment effects:

An embedded qualitative component will explore the feasibility of patients' recruitment to the trial by examining their experience of consent and recruitment including reasons for non

consent, and to examine patients' motivation to accept randomisation to an intervention, which may include extra radiotherapy (see below).

(iii) Survival:

Notification of death will be collected and overall survival will be calculated from the date of randomisation to the date of death from any cause. Participants remaining alive will be censored at the date of last follow-up.

(iv) Morbidity:

Overall length of hospital stay, complication rates and re-intervention rates will be gathered from case notes and captured in the CRFs. Early complications will be defined as those occurring within 7 days of the intervention; late complications defined as those occurring more than 7 days after the intervention. Standard definitions of stent complications will be clearly described in the protocol.

Toxicity data will be scored using the NCI CTC V4.03 and RTOG acute/late questionnaire at baseline, during treatment and at the pre-specified time points on follow-up. Serious adverse events will be monitored "real-time" by the Chief Investigator and TMG.
Data will also be collected on symptom burden including pain, eating restrictions and physical functioning via the EORTC QLQ-C30 and QLQ-OG25 scales.

(v) Cost effectiveness:

The economic evaluation will be in the form of a cost utility analysis assessing total costs against differences in HRQoL. This is the form of economic evaluation preferred by the NICE[20]. In line with NICE guidance the analysis will be undertaken from an NHS and Personal Social Services perspective.

HRQoL will be assessed using EQ-5D which is a single index utility based measure[21]. Quality Adjusted Life Years (QALY) will be derived from between group differences in EQ-5D scores from baseline – after adjusting for baseline differences[22] - to death using the area under the curve method. EQ-5D has been used previously on patients with inoperable oesophageal cancer[8].

Costs associated with stent insertion are not relevant to the study question. The only direct cost of the intervention is that associated with delivery of radiotherapy which will be either 20Gy in 5 daily fractions over one week or 30Gy in 10 daily fractions over two weeks according to centre protocols. The primary source of unit costs for radiotherapy will be the relevant NHS tariffs[23].

Data on total NHS resource use will be collected prospectively by trial nurses at baseline and at all points specified above, via a combination of casenote review and patient recall. This will include inter alia contacts with health professionals in both primary and secondary care, prescribed drugs, outpatient visits, investigations, accident and emergency attendances and inpatient stays. Resources will be monitored prospectively and valued using relevant unit costs. Due to likely skewness, cost data will be bootstrapped[24]. Patient borne costs including travel by intervention patients to receive radiotherapy will be monitored but will not be included in the cost utility analysis.

Cost effectiveness will be reported in the form of an incremental cost effectiveness ratio. Uncertainty around individual parameter will be explored through a series of one way sensitivity analyses particularly with respect to the unit cost of radiotherapy which will be examined through alternative costing methodologies[25]. Joint uncertainty will be explored through a probabilistic sensitivity analysis which will produce a cost effectiveness acceptability curve showing the probability of the intervention being cost effective over a range of willingness to pay thresholds e.g. the £20,000 to £30,000 per additional QALY currently used by NICE. As no long terms costs or benefits are anticipated given the short life expectancy of study patients, discounting will not be applied.

13.3 Sample size calculation

In a population with a median survival of approximately four months, an increase in median time to deterioration in self reported dysphagia of four weeks is considered clinically meaningful. This is based on previous results (Homs),[9] and expert multidisciplinary and service user opinion. A survey of participating centres demonstrated clinician accord with this.

Progression of self reported dysphagia is defined in this study as a 11 point deterioration in the dysphagia scale of the EORTC QLQ-OG25 questionnaire. The dysphagia scale is scored from 0 to 100 and a change of 10-15 points is considered clinically significant in EORTC scales[17]. Time to event will be calculated from the time of stent insertion to the time of deterioration or death. Patients who do not achieve an improvement from baseline in self reported dysphagia of at least 11 points on the OG25 dysphagia subscale at the first two week assessment after stent insertion (time zero), will be included and followed up but assumed to have failed at time zero.

Those who are deterioration-free and alive will be censored at the time last seen.

Sample size is therefore calculated, based on a time to event analysis, to detect an increase in median time to deterioration in self reported dysphagia of 4 weeks: from 12 to 16 weeks (equivalent to a HR of 0.75 and a difference in 12 week event rate of 50% vs. 60%). Recruitment time will be 4 years with 6 months follow up after the final patient is recruited.

For 80% power with alpha=0.05 based on a two-sided log rank test:

198 patients per arm will be required: 396 in total, which is a total of 384 events.

Assuming 20% attrition, a total of 496 patients will be required. The degree of attrition is set at this higher level because of the vulnerability of the patient population.

13.4 Statistical analyses

The main analysis will be intention to treat and will compare the time until self reported dysphagia progression between the two groups using Kaplan-Meier curves and the log-rank test. Kaplan Meier curves and log-rank tests will also be used to compare the two groups for the secondary outcome of overall survival. The secondary outcomes of proportions of

morbidities and re-intervention rates will be compared using a chi-square test. The Area under the Curve (AUC) of health related quality of life scores will be compared using t-tests adjusted for follow-up interval and survival. The primary analysis will be carried out when the required number of events has been reached (see proposed sample size above).

The statistical package STATA will be used for all analysis and statistical analysis plan will be written before the data is analysed.

13.5 Subgroup analyses

No formal sub-group analyses are planned; however, exploratory analysis will be conducted to explore the association of different variables such as the radiotherapy schedule used by centres and cancer subtype (adenocarcinoma vs squamous cell carcinoma vs other). Interactions between these explanatory variables and the intervention will be assessed.

14.0 Qualitative research (patient experience of trial recruitment and interventions, and perception of treatment effects)

14.1 Background and Aims

The embedded qualitative component to the trial is designed to explore the feasibility of patients' recruitment to the trial by examining their experience of consent and recruitment, including reasons for non consent, and to examine patients' motivation to accept randomisation to an intervention, which may include extra radiotherapy.[26]

Existing qualitative studies have explored oesophageal patients' experiences in information giving and in relation to identity and social aspects of food and eating[27], and also fatigue and intrusion to daily living attributed to treatment of the disease[28]. There does not appear to be any available qualitative evidence in relation to stent placement or dysphagia. However, patient based reports of palliative radiotherapy for bone metastases indicate that practical aspects of extra treatment (travel, time, inconvenience) were of little importance when compared to symptom control[29]. The qualitative component of the trial will provide rich data in relation to patient motivation to participate in the trial, perceived benefits and burdens, and the acceptability of the interventions based on actual experience.

Aims:

- To explore patients' perceptions of participation in the trial;
- To explore reasons for non consent to the trial (sample accessed via initial PIS and permission to contact);
- To assess patient experience and perceptions of each trial arm ;
- To provide patient outcome data for use in assessing the feasibility of trial design and potential improvements to recruitment processes.

In terms of the acceptance of randomisation to an intervention for symptom palliation/survival benefit, patients' decision making is influenced by information delivery. For treatments aimed at palliation of symptoms, rather than curative intent, this may be difficult but is essential for full informed consent[30]. For the purposes of the trial, the PISs and delivery of information by research staff will be essential to the integrity and equipoise of the trial.

The pilot phase aimed to provide data on patients' experiences of information giving and recruitment.

The patients that refuse consent to the trial will be interviewed to explore their understanding of trial processes and reasons for non consent. Recruitment to palliative care trials is known to be difficult[31] and patient reported data at the pilot stage added to the

research teams' existing expertise in this area, and informed strategies for recruitment to further stages of the trial.

14.2 Sampling strategy

- 6-10 patients in control arm
- 12-20 patients in experimental arm (6-10 receiving 5 fractions of EBRT and 6-10 receiving 10 fractions)
- 6-10 non consenters

Sampling of participants is purposive and aims to engage homogeneous groups of participants in terms of trial experience, i.e. from non consenters, the experimental arm (incorporating differences in fractionation) and the control arm in order to explore recurring themes. For the purposes of this study, 6-10 patients will be recruited to each group, in line with the usual recommendations for sample sizes when applying Interpretative Phenomenological Analysis (IPA) methodology, where the intention is depth of analysis rather than quantity of analyses.

14.3 Timing of interviews

Non consenting patients (to the ROCS trial) will be interviewed as soon as possible after consenting to participate in the interview study.

Participants on trial arms will be interviewed three times; at weeks one and four to capture initial decision making thoughts, and then following the interventions (week 8) to explore their experiences of the interventions and perceptions of benefit (or not).

	Pre-Treatment		On Treatment		Post-Treatment
	Trial visit				
	Baseline	Week 1	Week 2	Week 4	Week 8
Qualitative interview		✓		✓	✓

14.4 Approaching patients

Eligible patients will be approached by a research nurse about participating in the qualitative study when they are invited to participate in the ROCS trial. They will be given the Patient Information Sheet requesting permission for the qualitative researcher to contact them about taking part in the ROCS interview study. Where consent is given, the qualitative researcher will contact the participant, and if appropriate, will arrange a convenient time and location for the interview. Patient details will be passed from the research nurse to the researcher verbally, via telephone to ensure adequate data protection.

All eligible patients will be approached until enough have been recruited to represent both trial arms and the non consenting group.

14.5 Taking consent

The research nurse or the Qualitative Researcher will collect consent for conducting the interviews using the Qualitative Interview Consent Form, either at clinic (by the research nurse) or immediately prior to commencement of the interview (by the interviewer). If there is a carer present at the time of the interview, they will also be invited to consent to the use of their data with respect to any comments that they may make in the interview. For the purposes of data management and presentation of results they will thereby be treated as a study participant, they will be given the Patient Information Sheet for Companions and asked to sign the companion consent form. Further details on consent procedures are provided in section 6.4.

14.6 The interviews

Participants will be interviewed at home or in a quiet clinic location, according to preference. If a face to face interview is not feasible, a telephone or a video-linked interview may be offered instead. Interviews will be 30 – 60 minutes in length and will be terminated earlier if the participant is thought to be fatigued or becomes unwell.

14.7 Data management

The interviews will be audio recorded and then transcribed in full and verbatim, at the WCTU, and following the WCTU transcription SOP to ensure data protection and confidentiality. It is WCTU policy not to outsource transcription work due to the sensitive nature of the data and the potential for distress to the transcriber, who will be monitored closely. The transcripts will be uploaded to the NVivo qualitative software programme for efficient data management. Participants will be asked to consent to the use of their anonymised extracts of talk in the study report and future publications. All voice data will be deleted at the end of the study and anonymised transcripts will be stored securely for 15 years.

14.8 Analytic framework

The analytic framework will be based on a thematic analysis. This allows for rich thematic descriptions of the entire data set in addition to more detailed accounts of one particular theme or group of themes. The transcript of each interview will be systematically analysed following Braun and Clarkes[32] five stage format of;

- Familiarization of the data
- Searching for themes
- Reviewing themes
- Defining and naming themes
- Producing report.

Ten percent of the data will be double coded by a supervising researcher to ensure rigour.

14.9 Presentation of results

The anonymised data will be represented by selected extracts in a narrative format with a thematic structure. The results will be discussed with data extracts used in support of claims made. The Trial Management Group (TMG) will review the results to assess potential alterations to trial design, and will include the qualitative analysis to complement the reporting of the full trial, where appropriate.

14.10 Dissemination

Potential publications resulting from the embedded qualitative study will not be reported before the completion of the main trial if any aspect of this will cause a negative affect or compromise the trial in any way. The decision whether or not to publish results arising from the qualitative study before the end of the main trial will be made by the TMG and the IDMC, and in consultation with HTA.

14.11 Interviews with research nurses responsible for recruiting patients to the trial

Research nurses have immediate experience of screening, providing trial information to, and consenting prospective participants to the ROCS trial. They will have experience based knowledge of why patients decline to accept randomisation to the trial, as well as views on the process of presenting and explaining the trial to participants and any difficulties that this may present. Semi- structured interviews with the research nurses involved in this trial will be used to explore their views and experiences with regards to recruitment and will provide insights into any problems and issues specific to this aspect of the trial.

14.12 Arranging interviews

We intend to interview the main research nurse responsible for recruitment to the trial at all sites which are participating in the qualitative sub-study and have been open to recruitment for at least two months. The research nurses will be sent an information sheet and consent form requesting that they return the signed consent form if they are willing to be interviewed. Once received, the researcher will then contact the nurse to arrange the interview, which will be conducted by telephone.

14.13 The interviews

The interview will be carried out by an experienced interviewer. The interview team will develop a master interview schedule with questions and prompts. The interviewer will digitally record the interview. The interview is likely to last between 20 minutes and one

hour and will be carried out either by telephone or in person at the nurse's place of work or another location convenient to them.

14.14 Data transfer and transcription

The interviewer will upload the digital media files onto a secure computer and files will be labelled with a study number. No identifiable data will be stored. Digital files will be stored at the WCTU. Digital recordings will be transcribed in full and verbatim by a transcription secretary at the MCPRC and following an SOP to ensure data protection and confidentiality. Transcripts will be anonymised and stored on secure servers. Transcripts will be uploaded onto QSR NVivo 10 qualitative software programme for efficient data management and analysed using a thematic analysis

Participants will be asked to consent to the use of their anonymised extracts of talk in the study report and future publications.

All digital recordings of voice data will be deleted at the end of the study (i.e. once the funders report has been accepted). However, anonymised transcripts and analysis data will be stored securely for 15 years, after which it will be destroyed according to the WCTU and Sponsor data protection and archiving SOPs.

15.0 Publication policy

Data from all centres will be analysed together and published as soon as possible. Individual participating PIs may not publish data concerning their participants that are directly relevant to questions posed by the trial until the TMG has published its report. The TMG will form the basis of the writing committee and advise on the nature of publications, subject to sponsor requirements.

All publications should include a list of participating PIs, and if there are named authors, these should include the CI, Co-Investigators, Trial Manager, and Statistician(s) involved in the trial. If there are no named authors then a writing committee will be identified.

16.0 Informed consent, ethical and regulatory considerations

16.1 Ethical and other issues

This clinical trial protocol will be submitted to a Multi-centre Research Ethics Committee (MREC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval. The approval of the MREC must be obtained before the start of a clinical trial or any trial procedures are conducted. The MREC will be informed of the location of all sites and the PI at each of these sites.

All substantial amendments to this trial protocol must be approved by the MREC responsible for the study, before the implementation of the amendments. Minor amendments will not require prior approval by the MREC.

The MREC will be notified within 90 days of trial completion. If the trial is terminated early, the MREC will be notified of this within 15 days.

A summary of the clinical trial report will be submitted to the MREC responsible for the study within one year of the completion of the last participant's final follow up procedure.

The patient's consent to participate in the trial should be obtained after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. All patients must be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which they may be exposed. They will be informed of the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorised individuals other than their treating physician.

Patient's consent will be sought to notify their GP of their involvement in the trial. Patients should be given sufficient time after being given the trial PIS to consider and discuss participation in the trial with friends and family, if desired. A contact number should be given to the patient should they wish to discuss any aspect of the trial. Following this, the randomising investigator should determine that the patient is fully informed of the trial and their participation, in accordance with the principles of GCP. Patients should always be asked to sign a consent form. One copy should be given to the participant but the original copy should be kept in the study site file and a further copy should be kept with participant's hospital notes.

The right of the participant to refuse to participate in the trial without giving reasons must be respected. After the patient has entered the trial, the investigator must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the participant. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow up and data analysis according to the treatment option to which he/she has been allocated. Similarly, the participant must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

This is a randomised controlled trial, therefore neither the participants nor their physicians will be able to choose the patient's treatment. Treatment will be allocated randomly using a computer-based algorithm. This is to ensure that the groups of participants receiving each of the different treatments are similar.

16.2 Regulatory status

The trial does not involve an Investigational Medicinal Product (IMP) or a device and therefore does not require Clinical Trial Authorisation (CTA) from the MHRA.

16.3 Research governance approval

This trial protocol will be submitted through the Research Governance process of the host care organisation for review and approval. The Research Governance approval of the host care organisation must be obtained before the start of the trial within that host care organisation.

16.4 Sponsorship

The ROCS trial is being sponsored by Velindre NHS Trust. Velindre NHS Trust shall be responsible for ensuring that the trial is performed in accordance with the following:

- The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031) and subsequent amendments
- Conditions and principles of Good Clinical Practice
- Declaration of Helsinki (1996)
- Research Governance Framework for Health and Social Care (Welsh Assembly Government 2009 and Department of Health 2nd July 2005)
- Data Protection Act 1998
- The Ionising Radiation Medical Exposure Regulations (2000) (SI No. 1059 (as amended)
- Other regulatory requirements as appropriate

The sponsor has/will be delegating certain responsibilities to Cardiff University (WCTU), the Chief Investigators, Principal Investigators, host sites and other stakeholder organisations as appropriate in accordance with the relevant agreement that is informed by regulation and study type.

16.5 Indemnity

Non-negligent harm: This trial is an academic, Investigator-led and designed trial sponsored by Velindre NHS Trust and coordinated by the WCTU. The Chief Investigator, local Investigators and WCTU do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any non-negligent harm indemnity. The Association of the British Pharmaceutical Industry (ABPI) guidelines will not apply.

Negligent harm: In accordance with Technical Note 12 Indemnity for Clinical Research for research Sponsored by a Welsh body, the Welsh Risk Pool Services provides indemnity cover against successful negligence claims arising from the management and conduct of the study.

Where NHS employees are responsible for the design of a study, indemnity cover will also be provided for negligent harm arising from the study design. Velindre NHS Trust does not accept liability for any breach in the other NHR Organisations duty of care, or any negligence on the part of employees of these NHS Organisations.

16.6 Data protection

The WCTU will act to preserve patient confidentiality and will not disclose or reproduce any information by which participants could be identified (except where participants are registered with the Health and Social Care Information Centre Flagging (England and Wales) or NHS Central Register (Scotland) (formerly the National Health Service Information Centre and previous to that the Office for National Statistics) or traced via the NHS Central Register, which requires separate consent). Data will be stored in a secure manner and our trials are registered in accordance with the Data Protection Act 1998. The data custodian for this trial is the Director of the WCTU.

16.7 Finance

This study is funded by the National Institute for Health Research, Health Technology Assessment Programme (Funder Ref: 10/50/49).

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APPENDIX 1:EORTC QLQ-C30

Quality of life questionnaire EORTC QLQ-C30

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ___ ___ ___
Your birthdate (Day, Month, Year): __ __ / __ __ / __ __ __ __
Today's date (Day, Month, Year): __ __ / __ __ / __ __ __ __

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4

Please go on to the next page

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
14.	Have you felt nauseated?	**1**	**2**	**3**	**4**
15.	Have you vomited?	**1**	**2**	**3**	**4**
16.	Have you been constipated?	**1**	**2**	**3**	**4**
17.	Have you had diarrhoea?	**1**	**2**	**3**	**4**
18.	Were you tired?	**1**	**2**	**3**	**4**
19.	Did pain interfere with your daily activities?	**1**	**2**	**3**	**4**
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	**1**	**2**	**3**	**4**
21.	Did you feel tense?	**1**	**2**	**3**	**4**
22.	Did you worry?	**1**	**2**	**3**	**4**
23.	Did you feel irritable?	**1**	**2**	**3**	**4**
24.	Did you feel depressed?	**1**	**2**	**3**	**4**
25.	Have you had difficulty remembering things?	**1**	**2**	**3**	**4**
26.	Has your physical condition or medical treatment interfered with your family life?	**1**	**2**	**3**	**4**
27.	Has your physical condition or medical treatment interfered with your social activities?	**1**	**2**	**3**	**4**
28.	Has your physical condition or medical treatment caused you financial difficulties?	**1**	**2**	**3**	**4**

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	**2**	**3**	**4**	**5**	**6**	**7**
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	**2**	**3**	**4**	**5**	**6**	**7**
Very poor						Excellent

APPENDIX 2:EORTC QLQ-OG25

EORTC QLQ – OG25

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
1. Have you had problems eating solid foods?	1	2	3	4
2. Have you had problems eating liquidized or soft foods?	1	2	3	4
3. Have you had problems drinking liquids?	1	2	3	4
4. Have you had trouble enjoying your meals?	1	2	3	4
5. Have you felt full up too quickly after beginning to eat?	1	2	3	4
6. Has it taken you a long time to complete your meals?	1	2	3	4
7. Have you had difficulty eating?	1	2	3	4
8. Have you had acid indigestion or heartburn?	1	2	3	4
9. Has acid or bile coming into your mouth been a problem?	1	2	3	4
10. Have you had discomfort when eating?	1	2	3	4
11. Have you had pain when you eat?	1	2	3	4
12. Have you had pain in your stomach area?	1	2	3	4
13. Have you had discomfort in your stomach area?	1	2	3	4
14. Have you been thinking about your illness?	1	2	3	4
15. Have you worried about your health in the future?	1	2	3	4
16. Have you had trouble with eating in front of other people?	1	2	3	4
17. Have you had a dry mouth?	1	2	3	4
18. Have you had problems with your sense of taste?	1	2	3	4
19. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
20. Have you had difficulty swallowing your saliva?	1	2	3	4
21. Have you choked when swallowing?	1	2	3	4
22. Have you coughed?	1	2	3	4
23. Have you had difficulty talking?	1	2	3	4
24. Have you worried about your weight being too low?	1	2	3	4
25. Answer this question only if you lost any hair: If so, were you upset by the loss of your hair?	1	2	3	4

APPENDIX 3: EQ-5D

Your Current State of Health

Please consider your state of health <u>today</u> and tick one box for each question.

Q.1: Your mobility….

- ❒ I have no problems in walking about.
- ❒ I have some problems in walking about.
- ❒ I am confined to bed.

Q.2: Your self-care…

- ❒ I have no problems with self-care.
- ❒ I have some problems with washing or dressing myself.
- ❒ I am unable to wash or dress myself.

Q.3: Your usual activities…(e.g. work, study, housework, family or leisure activities)

- ❒ I have no problems with performing my usual activities.
- ❒ I have some problems with performing my usual activities.
- ❒ I am unable to perform my usual activities.

Q.4: Pain / Discomfort…

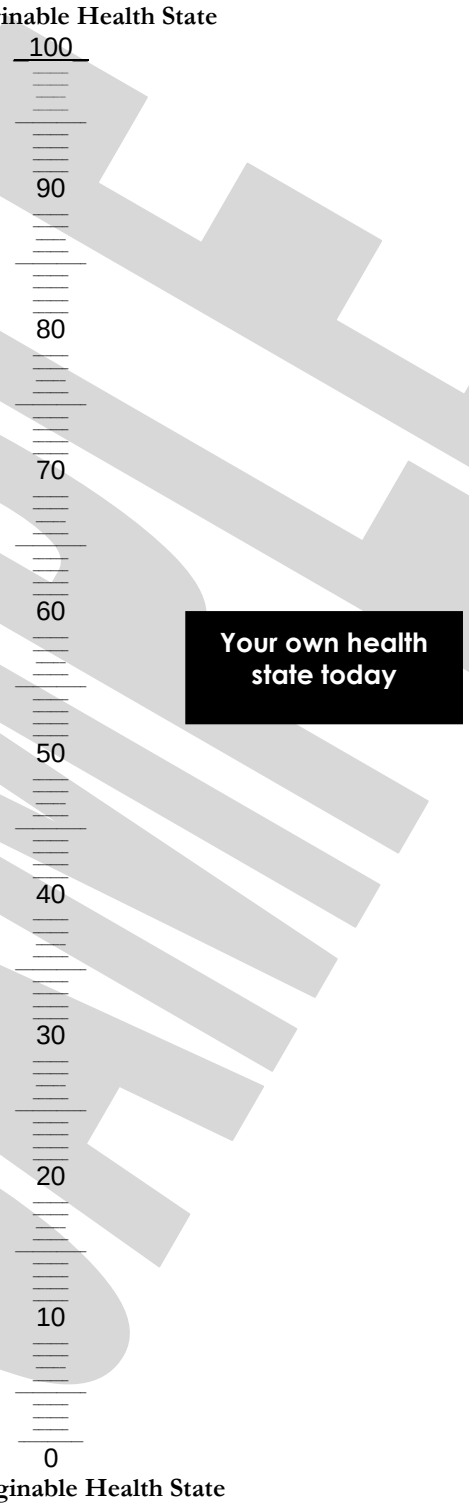
- ❒ I have no pain or discomfort.
- ❒ I have moderate pain or discomfort.
- ❒ I have extreme pain or discomfort.

Q.5: Anxiety / Depression…

- ❒ I am not anxious or depressed.
- ❒ I am moderately anxious or depressed.
- ❒ I am extremely anxious or depressed.

How good or bad is your health today?

To help people say how good or bad a health state is, we have drawn a scale (like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0. We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health is today.



APPENDIX 4: CTCAE (V4.03) – selected toxicities[33]

Adverse Event	1	2	3	4	5
Cardiac disorders					
Ventricular arrhythmia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Gastrointestinal disorders					
Esophagitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered eating/swallowing; oral supplements indicated	Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Esophageal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Gastrointestinal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Gastroesophageal reflux disease	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Upper gastrointestinal haemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Vomiting	1 – 2 episodes (separated by 5 minutes) in 24 hrs	3 – 5 episodes (separated by 5 minutes) in 24 hrs	≥6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
General disorders and administration site conditions					
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest limiting self care ADL	-	-
Fever	38.0 – 39.0 degrees C (100.4 – 102.2 degrees F)	>39.0 – 40.0 degrees C (102.3 – 104.0 degrees F)	>40.0 degrees C (>104.0 degrees F) for ≤24 hrs	>40.0 degrees C (>104.0 degrees F for > 24 hrs	Death

Injury, poisoning and procedural complications					
Dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate oedema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death
Metabolism and nutrition disorders					
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Respiratory , thoracic and Mediastinal disorders					
Aspiration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Altered eating habits; coughing or choking episodes after eating or swallowing; medical intervention indicated (e.g., suction or oxygen)	Dyspnoea and pneumonia symptoms (e.g., aspiration pneumonia); hospitalization indicated; unable to aliment orally	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death

Wales Cancer Trials Unit

Contact Details

6th Floor, Neuadd Meirionnydd,
Heath Park
Cardiff
CF14 4YS

General Telephone Number 029 2068 7500

Email: ROCS@cardiff.ac.uk

Visit our website – www.wctu.org.uk