FoRT

(Follicular Radiotherapy Trial)

A Phase III multi-centre randomised controlled trial of low dose radiotherapy for follicular lymphoma and marginal zone lymphoma

Developed by the NCRI Clinical Study Groups in Radiotherapy and Lymphoma

EUDRACT 2005-002416-19

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Signature		Date:	22 June 2009

GENERAL INFORMATION

This document describes the *FoRT* trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but sites entering patients for the first time are advised to contact the Cancer Research UK & UCL Cancer Trials Centre to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator.

- **Compliance**

  The FoRT Trial will be conducted in compliance with the protocol, GCP, Data protection Act (UCL Data Protection Registration, reference No Z6364106/2005/7/22), NHS research governance and other regulatory requirements, as appropriate.

- **Sponsor**

  University College London (Sponsor ref BRD/05/84)

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RANDOMISATIONS

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ABBREVIATIONS AND GLOSSARY

AE	Adverse event
AR	Adverse reaction
CF	Consent form
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trials Authorisation
CTC	Cancer Trials Centre
CTCAE	Common Terminology Criteria for Adverse Event Reporting
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
ERC	Endpoint Review Committee
EUDRACT	European Union Drug Regulatory Agency Clinical Trial
Gy	Gray – Unit of radiation
HE	Health Economics
IB	Investigator's Brochure
NHL	Non-Hodgkin's Lymphoma
IDMC	Independent Data Monitoring Committee
ISRCTN	International standard randomised controlled trial number
MHRA	Medicines and Healthcare Regulatory Authority
MRC	Medical Research Council
NHS	National Health Service
OAR	Organ at Risk
PI	Principal Investigator
PIS	Patient information Sheet
QA	Quality assurance
QL	Quality of life
RTOG	Radiation Therapy Oncology Group
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SAR	Serious adverse reaction
SOP	Standard operating procedures
SPC	Summary of product characteristics
SSA	Site specific assessment
SUSAR	Suspected unexpected serious adverse reaction
TLD	Thermoluminescent dosimeter
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected adverse reaction
UCL CTC	University College London Cancer Trials Centre

1. SUMMARY

1.1 Lay summary

Radiotherapy is the recommended therapy for palliative control of advanced follicular lymphoma, and for curative treatment of stage IA and IIA follicular lymphoma. Over recent years as a result of trials similar to this one we have defined a standard dose of radiotherapy for this condition that is known to be effective and safe. This standard dosage is 24 Gy (Gy is an abbreviation for Gray which is the unit of radiation dose) and is administered in 12 sessions each delivering 2Gy. Recently it has been shown that even lower doses of radiation that deliver a total of 4Gy in 2 sessions are very effective in follicular lymphoma and that similar results may be possible with such low doses as with the standard higher doses. This trial will enable a comparison of response and remission rates of treating indolent lymphoma with lower dose radiotherapy compared to that of the standard radiotherapy dosage. We aim to recruit 650 patients to this study.

The study is a randomised trial; this means that neither the patient nor doctor is able to chose which treatment is assigned. This is done by a random list of numbers generated by computer. Each radiotherapy treatment exposure will be the same (i.e. 2Gy will be administered per session); the difference will be in the number of treatment sessions received i.e. 12 sessions or only 2 sessions depending on which arm of the trial is allocated.

1.2 Abstract and summary of trial design

Type of design

This is a phase III multi-centre open randomised study comparing low dose radiotherapy (4Gy) with a control group receiving 24Gy for follicular lymphoma or marginal zone lymphoma. This is a UK multi-centre study co-ordinated under the auspices of Cancer Research UK and the NCRI Radiotherapy and Lymphoma Clinical Studies Group.

Disease / patients studied

Approximately 40% of all non-Hodgkin's Lymphoma diagnosed in the UK is follicular lymphoma. The study population will be patients diagnosed with histologically proven follicular non-Hodgkin's lymphoma or marginal zone lymphoma requiring radiotherapy for definitive treatment of stage IA or IIA disease or for palliation by virtue of tumour bulk or anatomical position.

For more details refer to section 2.

Trial interventions – research and control

Patients will be randomised to receive either 4Gy in 2 fractions (experimental arm) over the course of 2 consecutive days or 24Gy in 12 fractions (control) over 16 days, treating daily Monday to Friday. Involved field radiotherapy will be given based on the tumour mass rather than anatomical regions. Recently published data[2] has shown a high level of durable response with only 4Gy in 2 fractions.

For more details refer to section 3.

Outcome measures

Primary Outcome

- Local progression free interval

Secondary Outcomes

- Acute Toxicity
- Late Toxicity
- Tumour Response
- Overall survival
- Health economic assessment

Duration

Patients in the experimental arm (4Gy) will receive treatment over 2 consecutive days while those in the control arm (24 Gy) will be treated for 16 days on a Monday to Friday basis.

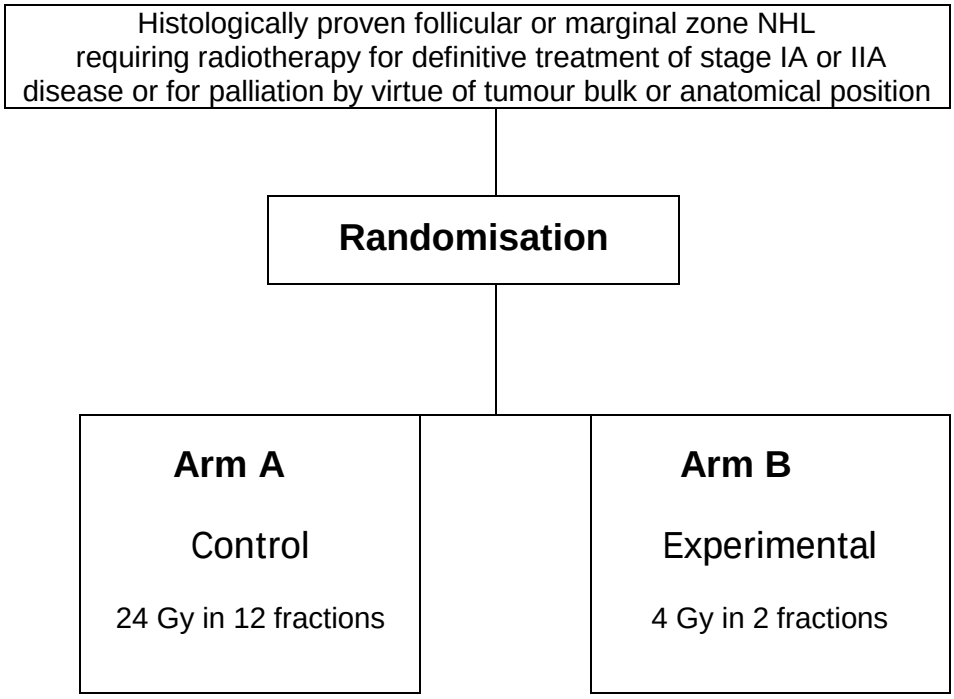
All patient follow up visits are calculated from the date of randomisation. Patients will be reviewed at 4 weeks, 12 weeks and 6 months post randomisation, then every 6 months until 2 years post randomisation. They will then be reviewed annually until they are 5 years post randomisation for assessment of late toxicity. Subsequently patients will be reviewed annually for monitoring of overall survival.

Data recorded directly on CRFs

Data will be recorded on the Case Report Forms, where the original wet ink copy should be sent to the CR UK and UCL Cancer Trials Centre and a copy should remain at site in a designated patient trial file. The type of data to be recorded is detailed in the Assessments and Procedures section (Section 3).

1.3 Flow diagram

Figure 1: Trial entry, randomisation and treatment



Assessment

		ARM A 24 Gy in 12#		ARM B 4Gy in 2#
Visit 1 Baseline		Registration & Randomisation forms		Registration & Randomisation forms
Week 1		Treatment		Treatment
Week 2		Treatment		
Week 3		Treatment		
Week 4		Acute toxicity		Acute toxicity
Week 12 Follow up		Post Treatment Assessment Tumour Assessment Tumour Response Evaluation Late toxicity		Post Treatment Assessment Tumour Assessment Tumour Response Evaluation Late toxicity
Follow up *		Tumour Assessment Late toxicity		Tumour Assessment Late toxicity

** After the week 12 follow up visit, patients will be assessed at 6 months, 12 months, 18 months, 24 months and annually thereafter until 5 years post randomisation using the above assessments.*

An EQ-5D Health Assessment questionnaire must be completed at every visit.

Patients will then be followed up yearly for life for monitoring of overall survival.

BACKGROUND

1.4 Introduction

Radiotherapy is a well-established treatment in the management of non-Hodgkin's lymphoma (NHL). In low-grade lymphoma it may be curative in Stage I disease and in more advanced disease it has a valuable palliative role for symptomatic lymph node masses or extra nodal disease. In high-grade lymphoma it may also be curative in Stage I disease and is frequently used to consolidate chemotherapy response in bulky sites of disease or extra nodal sites of disease. Again it also has a major palliative role for symptomatic lymphoma resistant to chemotherapy causing local symptoms.

1.4.1 Follicular lymphoma

Follicular lymphoma is the most common form of low grade non-Hodgkin's lymphoma (NHL) accounting for approximately 40% of all cases of this disease diagnosed; this equates to around 2,500 cases in the UK each year, of which only 10% will be stage I disease. Radiotherapy is the standard treatment for stage IA disease when it may be curative. In more advanced disease the mainstay of treatment is chemotherapy using oral alkylating agents such as Chlorambucil, intravenous schedules such as CVP or Fludarabine-based combination chemotherapy. Rituximab also has an increasing role in the management of follicular lymphoma. The role of radiotherapy in more advanced disease is palliation of localised nodal or extra-nodal tumour masses that have become symptomatic by virtue of bulk or proximity to critical organ structures.

Radiotherapy is a highly effective modality for local control of follicular lymphoma with response rates of over 90% reported in the literature[1]. Standard doses used in the UK range from 24Gy in 12 fractions to 40Gy in 20 fractions; these two fractionation schedules are the basis for the previous NCRN radiotherapy dose trial in low grade non Hodgkin's lymphoma with a total sample size of 1000 patients, which completed accrual in January 2005.

1.4.2 Marginal zone lymphoma

Marginal zone lymphomas are a much less common form of indolent lymphoma which may arise in extranodal sites (mucosa associated lymphoid tissue – MALT), or less frequently lymph nodes and spleen. The gastrointestinal tract is the most common extranodal site but others including the salivary gland, thyroid and lung are well recognised. Gastric MALT lymphoma is a recognised consequence of helicobacter pylori infection and may respond to eradication of the organism. There is however no consensus regarding optimal management of marginal zone lymphomas at

other sites or MALT gastric lymphomas which fail to respond or recur after H. pylori eradication. Chemotherapy, radiotherapy and even surgery for some extranodal sites have been reported.

For localised lesions local radiotherapy is effective but the optimal dose is not known. Published series have used doses ranging from 25Gy to 40Gy [6, 7]. In the previous BNLI radiation dose study a total of 39 patients with marginal zone lymphoma were treated of whom 14 received the low dose arm of 24Gy. No detrimental effect of the low dose treatment was identified. A recent series which included 10 patients with cutaneous marginal zone lymphoma treated at 4Gy in 2 fractions reports an overall response rate of 86% [8], similar to that seen in the larger series of patients with follicular lymphoma.

1.5 Relevant studies / trials

Recently published data[2] has shown a high level of durable response with only 4Gy in 2 fractions. In a total of 304 symptomatic sites treated in this way there was an overall response rate of 92% with 61% complete responses and a median time to local progression of 25 months; this was 42 months in those achieving complete responses. A smaller series of 11 patients had previously reported similar success with a 94% response rate of mean duration 7 months using this low dose schedule[3]. This raises the possibility that a dose of 4Gy, given in 2Gy fractions may be effective and potentially more efficient in the use of radiotherapy for indolent lymphoma. It would therefore seem that the next important question in the radiotherapeutic management of indolent lymphoma is the relative efficacy of such an ultra low dose 2 fraction schedules compared with a more conventional fractionated treatment over two to four weeks. Against this background it is therefore proposed that a prospective randomised trial of 4Gy in 2 fractions compared to a standard schedule of 24Gy in 12 fractions is undertaken.

1.6 Rationale and objectives

No systematic review has been identified in the Cochrane, Medline or Pub Med databases. No trials addressing this question are listed on the ICRP website or on the NCI PDQ trials database. A search of CancerLit, Medline and the Cochrane Database of randomised trials has not identified any other relevant trials other than those cited in this protocol. A recent audit[4] has demonstrated that despite increased investment and in number of linear accelerators, waiting times for radiotherapy have actually increased, thus highlighting the importance of critically evaluating fractionation schedules. The saving of 10 fractions per patients would for example

allow 6 patients with follicular NHL to receive palliative radiotherapy for the same linear accelerator resources as currently are required for one patient, or an additional 10 patients to be treated with palliative single doses for bone metastases in their place. Furthermore recent Ionising Radiation (Medical Exposure) Regulations 2000 (IRMER) have supported the need for all prescribers of radiation to critically appraise and justify each radiation exposure a patient receives.

1.7 Risks and benefits

The risks to the safety of participants are those associated with the treatment of radiotherapy, which is the standard palliative treatment for indolent lymphoma. There have been no reports of unexpected toxicity from the current NCRN radiotherapy dose trial[5] one arm of which will be the control arm of this trial. The 'experimental' arm will deliver a much lower dose of radiation using the same technique from which no additional risks could be identified.

SELECTION OF SITES/CLINICIANS

Before any patients can be randomised to the study, the Study Site and Principal Investigator must fulfil the following criteria:

Study Site/Clinician inclusion criteria

i. Registered with UCL Cancer Trials Centre
ii. Confirmation of local ethics approval (site-specific assessment)
iii. R&D approval has been obtained from the relevant NHS Trust
iv. Successfully completed the initial stage of the radiotherapy quality assurance (QA) exercise
v. Completed Principal Investigator Statement of Responsibilities signed by the institution Principal Investigator
vi. Completed Declaration of Participation

2. SELECTION OF PATIENTS

Population

The study population will consist of either males or females over the age of 18 years who are diagnosed with histologically proven follicular lymphoma or marginal zone lymphoma. It should be noted that histological review of the original biopsy material is required; if this material is not available patients will not be eligible for the study.

2.1 Patient inclusion criteria

i. Patients aged over 18 with no upper age limit
ii. Histologically proven follicular or marginal zone non-Hodgkin's lymphoma
iii. Biopsy material available for histological review
iv. Radiation indicated for definitive treatment of stage IA or IIA disease or for palliation by virtue of tumour bulk or anatomical position.
v. Written informed consent

2.2 Patient exclusion criteria

i. Histological sub-types other than follicular or marginal zone non-Hodgkin's lymphoma
ii. Predicted prognosis less than three months
iii. Chemotherapy within four weeks of planned radiotherapy

2.3 Number and source of patients

For patient numbers, and duration of recruitment refer to section 5.3.

2.4 Screening procedures and pre-randomisation investigations

Once informed consent has been obtained the Randomisation and Registration CRFs must be completed. Pre-randomisation investigations recommended are a CT scan (neck, chest, abdomen, pelvis) if required or indicated, and a mandatory full blood count. A biopsy is recommended if there is a clinical suspicion of a transformation to high-grade disease.

Patients' disease will be staged using the Ann Arbor system (Appendix 6) prior to randomisation. This information is to be recorded on the registration CRF. Investigators will be required to stipulate on the registration form whether treatment is to be given with curative or palliative intent.

RANDOMISATION & ENROLMENT PROCEDURE

Before entering a patient into the trial, written informed consent must be obtained from the patient. To enter a patient the Registration & Randomisation form should be completed and faxed to UCL CTC (Mon-Fri, 9:00-17:00) on 020 7679 9861. All eligibility criteria will be checked and patient will be allocated a trial number and a treatment immediately. Randomisation will be stratified by histology (follicular lymphoma vs. marginal zone lymphoma) and whether treatment is being given with curative or palliative intent. Written confirmation of a patient entering into the trial will be sent within one week.

Further details on the process of randomisation can be found in section 5.1.

RANDOMISATIONS

Tel: 020 7679 9860 (Mon - Fri, 09:00 – 17:00)

Fax: 020 7679 9861

3. TREATMENT OF PATIENTS

3.1 Introduction

Patients will be randomised to either Arm A (Control) or Arm B (Experimental).

All randomised patients must have samples of their original tumour biopsy sent to Dr. Andrew Jack at the Haematological Malignancy Diagnostic Service in Leeds. For further details about the histopathological review, please see Appendix 5: Pathology Review

Involved-field radiotherapy will be given based on the tumour mass rather than anatomical regions.

A margin of 3cm in all dimensions is recommended for the GTV to PTV expansion except where this would endanger normal tissues by exceeding radiation tolerance. Particular attention to

renal doses in treating abdominal masses and lung doses with large mediastinal masses is required. Normal tissue tolerance doses should conform to the following limits:

Table 1: Radiotherapy Dosage

OAR	**Limiting Dose / Volume**
Breast	Minimise volume inside PTV, particularly in young women
Heart	Maximum dose of 40Gy to any part of the volume
Kidney	V40 of 40%, if single kidney irradiated V15 of 65-70%, if both V15 of 20-25% for each kidney
Lens	Maximum dose of 10Gy to any part of the volume
Liver	V40 of 30-35%, D100 of 20Gy
Lung (whole)	V20 of 35%
Ovary	Maximum dose of 10Gy to any part of the volume outside PTV. If inside PTV discuss individual case with clinician
Parotid *	*Maximum dose of 32Gy to any part of the volume outside the PTV of the contra-lateral parotid*
*Spinal cord **	**Maximum dose of 40Gy to any part of the volume**
Testis	Maximum dose of 2Gy to any part of the volume

**Parotid and spinal cord doses are included for completeness and these doses should not be approached even in the 24Gy arm in this study.*

Treatment should be delivered with appropriate field arrangements using photons or electrons of appropriate energy to ensure dose homogeneity and taking into account possible hot spots in normal tissue outside the PTV. Brachytherapy or orthovoltage are not recommended.

Where appropriate CT localisation of nodes within the mediastinum, abdomen and pelvis is recommended.

All volumes should be formally simulated and check images taken prior to treatment.

The prescription point will be to an applied (100%) dose for direct photon beams, the 100% isodose for direct electron beams, and the intersection point dose for multi-beam plans including parallel-opposed beams. In the case of the latter dose homogeneity -5% and +7% should be achieved across the PTV.

3.2 Arm A (Control)

Radiotherapy - 24 Gy in 12 Fractions

The control arm of the study will involve the randomised patient receiving a dose of 24Gy in 12 fractions. This is one of the current standard doses used in the treatment of patients diagnosed with indolent non-Hodgkin's lymphoma.

Treatment schedule

Treatment will be given over 16 days, treating daily Monday to Friday.

3.3 Arm B

Radiotherapy – 4Gy in 2 Fractions

The experimental arm of the study will involve the randomised patient receiving a dose of 4Gy in 2 fractions.

Treatment schedule

Treatment will be given over 2 consecutive days.

3.4 Quality Assurance Programme

A Radiotherapy Quality Assurance programme is included in the trial and participating sites will be asked to complete a part of it before being able to recruit patients into the study.

Pre-Recruitment QA

Sites will be asked to complete one or more questionnaires, depending on whether they have already completed them for other trials. Please check with the Trial QA Physicist (contact details at front of protocol) which documents need completing. The questionnaires may be downloaded from the NCRI Clinical Trials Quality Assurance Group website: www.rttrialsqa.org.uk

(i) **Baseline Quality Assurance Questionnaire**: giving information on equipment and general radiotherapy techniques used at each site. This is downloadable from the front page of the rttrialsqa.org.uk website. To be completed once every two years. If already recently completed for any other national radiotherapy trial the site will not be required to do so again.

(ii) **Staff Questionnaire**: giving contact details for the specific trial and downloadable from the front page of the website. To be completed by all sites.

(iii) **FoRT Questionnaire**: giving trial-specific planning and treatment information and downloadable from the FoRT link on the front page of the website. This will not be necessary if already completed for the Stanford V vs ABVD Trial for Advanced Hodgkin's Disease.

Once these have been reviewed by the trial QA physicist the site will be approved to randomise patients into the trial.

On-going QA

This will involve *in-vivo* dosimetry. Sites are required to nominate a contact on the randomisation form to whom thermoluminescent dosimeters (TLDs) will be sent. Sites will be contacted by the trial QA physicist shortly after the patient is registered. Thermoluminescent dosimeters (TLDs) will be posted to the contact nominated by the site on the randomisation form to check the dose received by the patient during one fraction of their treatment. The trial QA physicist will require information on techniques used before the TLDs are sent: whether simulator or CT-based planning is used, if it is a fixed or isocentric treatment and the number of beams to be delivered. A form with instructions will be included with the TLDs. Once the TLDs are irradiated they will be posted back to the trial QA physicist together with treatment information, including a copy of the plan (for CT-planned treatments) and the linear accelerator daily output. Examples of these forms can be found on the www.rttrialsqa.org.uk website, under the FoRT section.

3.5 Randomisation codes

When a patient is randomised a unique study code will be assigned to the patient and can be used as an identifying factor.

3.6 Measures of compliance and adherence

Medications permitted

All anti-cancer therapies (including complementary treatments/therapies) are permitted. Chemotherapy is allowed providing it is administered 4 weeks after the completion of radiotherapy.

Data on concomitant medication

All details of any anti-cancer treatments or therapies received (except complementary medications) are to be recorded on the Anti-Cancer Treatment CRF.

ASSESSMENTS AND PROCEDURES

3.7 Follow up schedule

For details of follow up and visit schedule, please see Appendix 4.

3.8 Procedures for assessing efficacy

Data regarding efficacy will be recorded on the appropriate Case Report Forms at each visit made by the patient.

Tumour Assessment

There are several accepted methods of tumour assessment: clinical measurement/ examination, x-ray, and CT scan. If a method of assessment not listed is used, then the method used instead should be stated clearly.

Tumour assessment should be conducted at 12 weeks (3 months) post randomisation to determine response. Assessment of the tumour should be conducted using one of the accepted methods listed above. This information should be recorded on the Tumour Assessment CRF and dimensions with units should be included if available. If treatment is given with curative intent, a repeat CT scan should be performed at 12 weeks post randomisation and at relapse. For patients being treated with palliative intent, radiological imaging should be performed as clinically indicated. Patients should be monitored for localised disease progression at all follow up visits.

Tumour Response Evaluation

Will be measured at Week 12 (3 months post randomisation) using the Response Evaluation Criteria in Solid Tumours (RECIST) guidelines as recommended by the NCI (Appendix 3). Following this evaluation, the Tumour Response Evaluation CRF should be completed indicating the response status of the patient's disease **within the irradiated field**. If there is evidence of disease progression **within the irradiated field** then the Disease Progression Form should be completed. Distant progression does not need to be reported. However any subsequent treatment for lymphoma at any anatomical site should be recorded.

Overall Survival

Data will be collected until the time of death, upon which the Patient Death CRF should be completed.

3.9 Procedures for assessing safety

Acute toxicity will be determined at 4 weeks post randomisation using the RTOG Acute Radiation Morbidity Scoring Schema (Appendix 2). The late toxicity will then be assessed at every visit thereafter using the RTOG/EORTC Late Radiation Morbidity Scoring Schema (Appendix 2). See section 6 on Safety Reporting for more information.

3.10 Other assessments

EQ-5D – Health Economic Assessment

The EQ-5D questionnaires (Appendix 1) should be completed without conferring with friends or relatives and all questions should be answered even if the patient feels them to be irrelevant. The appointed person at the site should check each questionnaire for its completeness, ensuring that the correct date of completion and patient identifiers are present.

A questionnaire is to be completed at every scheduled visit (see Appendix 5). The Research Nurse or delegated member of the clinical team should approach patients at appropriate clinical visits to complete a questionnaire. The completed questionnaire and coversheet should then be sent to UCL CTC.

3.11 Loss to follow up

Patients will be followed up for five years in the first instance and then for survival until death. If a patient fails to attend a clinic or can not be followed up at site, efforts should be made to contact the patient's GP to assess their condition. Any patients "lost to follow up" and who subsequently die will be "flagged" by the Office for National Statistics. The trial will also be registered with a number of cancer registries to enable follow up. This will be mentioned on the Patient Information Sheet.

3.12 Trial closure

The trial will be considered closed 5 years after the last patient is recruited. However, further observational follow up of all patients enrolled in the trial will continue until all randomised patients have died. This will initially be via the hospital, but in the longer term may employ national registers.

4. WITHDRAWAL OF PATIENTS

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

4.1 Withdrawal from trial therapy

Patients may be withdrawn from treatment for any of the following reasons: -

i. Disease progression within the irradiated field whilst on therapy/treatment
ii. Patient withdraws consent
iii. Unacceptable toxicity
iv. Intercurrent illness, which prevents further treatment
v. Any change in the patient's condition which justifies the discontinuation of treatment in the clinicians opinion

Data regarding a patient withdrawal prior to or during radiotherapy should be recorded on the Withdrawal From Treatment CRF. This form is only applicable for patients who either do not start, or fail to complete their randomised radiotherapy treatment. Patients who withdraw from the trial for other reasons have previously consented to follow up in the trial. If a patient wishes to withdraw from trial treatment, sites should nevertheless explain the importance of remaining on trial follow up, or failing this of allowing routine follow up data to be used for trial purposes.

4.2 Withdrawal from trial

If the patient explicitly states their wish not to contribute further data to the study, UCL CTC should be informed in writing (and a Withdrawal of Consent CRF should be completed). Data up to the date when the patient withdraws consent must be submitted. Patients may need to reaffirm that they consent to follow up through usual NHS mechanisms e.g. ONS.

4.3 Patient transfers

For patients moving from the area, every effort should be made for the patient to be followed up at another participating trial site and for this new site to take over the responsibility for the patient. If it is not possible to transfer the patient's care to another participating site, the original recruiting site remains responsible for their follow up and should submit data based on copies of clinical correspondence from their new consultant or information obtained from the patient's GP (see section 3.11).

If a patient's follow up is transferred to another participating site, UCL CTC must be informed of the transfer in writing. The new site must be provided with a full copy of the patient's case

report form, and the original site must submit all data up to the time their care was transferred. The patient will have to sign a new consent form at the new site, and until this occurs, the patient remains the responsibility of the original site.

5. STATISTICAL CONSIDERATIONS

5.1 Method of Randomisation

Once written informed consent has been obtained, the completed registration and randomisation forms must be faxed to CR UK & UCL Cancer Trials Centre. Eligibility will be confirmed, and then the patient will be randomised. Randomisation will be at a 1:1 ratio and will be stratified by histology (follicular lymphoma vs. marginal zone lymphoma), and whether treatment is being given with curative or palliative intent.

5.2 Outcome Measures

Primary

Local progression free interval: time from randomisation to tumour progression **within the irradiated field** by clinical examination and imaging as appropriate for site of treatment and lymph nodes

Secondary

Acute toxicity: assessed at the week 4 visit using RTOG Acute Radiation Morbidity Scoring Criteria

Late toxicity: assessed using RTOG/EORTC Late Radiation Morbidity Scoring Criteria or, if the RTOG criteria are not applicable, using the Common Terminology Criteria for Adverse Events v3.0 (CTCAE), available online at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

Response: assessed at the 12 weeks from randomisation using RECIST criteria

Overall survival: time from randomisation to date of death of any cause

Health economic assessment: details of protocol treatments, other anti-cancer treatments (excluding complementary therapy), management of adverse events, hospital admission episodes, and EQ-5D questionnaire

5.3 Sample Size

The aim of the trial is to demonstrate that low dose radiotherapy is as effective as conventional dose radiotherapy in terms of time to tumour progression within the irradiated

field. Therefore it is designed as a non-inferiority trial with the sample size planned to reliably exclude a minimum of 10% reduction in 2-year local progression free interval within the irradiated field in the experimental arm. The following table shows the total number of patients required with 5% significance level (one-sided) and 90% power in a 4-year accrual and 1-year follow up. The 2-year local progression free interval in the control arm was reported to be about 50%[5]. The null hypothesis of non-inferiority will be rejected if the 10% difference specified in the table is excluded in the 95% upper confidence interval limit, calculated once the study is completed. We aim to accrual a total of 650 patients over 4 years.

Table 2: Calculation of Sample Size

2-year PFS in the control arm	Maximum of 10% reduction in 2-year PFS in the experiment	HR	No. of events	No. of patients
40%	30%	1.31	471	627
50%	40%	1.32	446	671
60%	50%	1.36	364	642

5.4 Analysis Plan

Analyses will be performed on an intention-to-treat basis. The standard log-rank approach will be applied for local progression-free interval and overall survival analysis. Comparisons of response and toxicity will be made by chi-squared tests or Mann-Whitney test wherever is appropriate.

No subgroup analyses are planned, although the size of node/lymphoma mass to be treated will be studied in an exploratory manner.

5.5 Interim Monitoring and Analyses

Formal interim analyses of the accumulating data will be performed at regular intervals (at least annually) for review by an Independent Data Monitoring Committee (IDMC) (see also section 9.3). The IDMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow up. 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 participants 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 recommendations to the Trial Steering Committee (TSC, see section 9.2) as to the continuation of the trial.

6. SAFETY REPORTING

Definitions of Adverse Events

The following definitions have been adapted from Directive 2001/20/EC and ICH GCP E6:

Adverse Event (AE)

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

Adverse Reaction

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

Serious Adverse Event (SAE) or Serious Adverse Reaction:

An adverse event or adverse reaction that at any dose:

- Results in death
- Is life threatening (The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires in-patient hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is otherwise medically significant (i.e. withdrawal reactions, all accidental or intentional overdoses whether they result in an adverse event or not, or any event which the investigator considers significant but which is not covered by the above.)

Suspected Unexpected Serious Adverse Reaction (SUSAR)

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

A serious event or reaction is not defined as a SUSAR when:

- it is serious but expected
- it does not fit the definition of an SAE, whether expected or not

Reporting Procedures

All Adverse Events (AEs)

All adverse events that occur between informed consent and the end of the trial must be recorded in the patient notes and the trial CRFs. Information regarding dates of event onset and resolution, outcome, severity and causality for the trial treatment must be recorded. Those meeting the definition of a Serious Adverse Event (SAE) must also be reported to the UCL CTC using the trial specific SAE Report (see Serious Adverse Events section for details).

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

Adverse Event Term

An adverse event term needs to be provided for each adverse event, preferably using the Short Name as listed in the Common Terminology Criteria for Adverse Events v3.0 (CTCAE), available online at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf.

Severity

Severity for each adverse event must be determined by using the RTOG Radiation Morbidity Scoring Criteria (Appendix 2), wherever possible. If the adverse event is not covered by the RTOG criteria, the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) can be used. The criteria are available online at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf.

In those cases where neither the RTOG nor the CTCAE criteria do not apply, severity should be coded according to the following criteria:

1 = Mild

2 = Moderate

3 = Severe

4 = Life threatening

5 = Fatal

Serious Adverse Events (SAEs)

All SAEs that occur between informed consent and 30 days post the last trial treatment administration (or after this date if the site investigator feels the event is related to the trial treatment) must be submitted to the UCL CTC by fax within 1 business day of observing or learning of the event, using the trial specific SAE Report. All sections on the SAE Report must be completed.

Causality

Site investigators must perform an evaluation of causality for each SAE. Causal relationship to the trial treatment must be determined as follows:

- **None**

  There is no evidence of any causal relationship.

- **Unlikely**

  There is little evidence to suggest a causal relationship (e.g. because the event did not occur within a reasonable time after administration of the trial treatment). There is another reasonable explanation of the event (e.g. the patient's clinical condition, other concomitant medications).

- **Possible**

  There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial treatment). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant medications).

- **Probable**

  There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

- **Definitely**

  There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Expectedness

Site investigators must perform an evaluation of expectedness for all SAEs regardless of causal relationship to the trial treatment. This evaluation must be performed using the list of expected adverse events in appendix 2 of the protocol. Expectedness of the event for the trial treatment must be determined as follows:

- **Expected**

  The event is listed as an expected adverse event in the protocol appendix.

- **Unexpected**

  The event is not listed as an expected adverse event in the protocol appendix or, the severity of the event is greater than that listed in the protocol appendix for example:

  - the event is life threatening or fatal (unless stated in the protocol appendix as expected).
  - the patient presents with an event which is considered to be moderate or severe, but only mild is listed as expected in the protocol appendix.

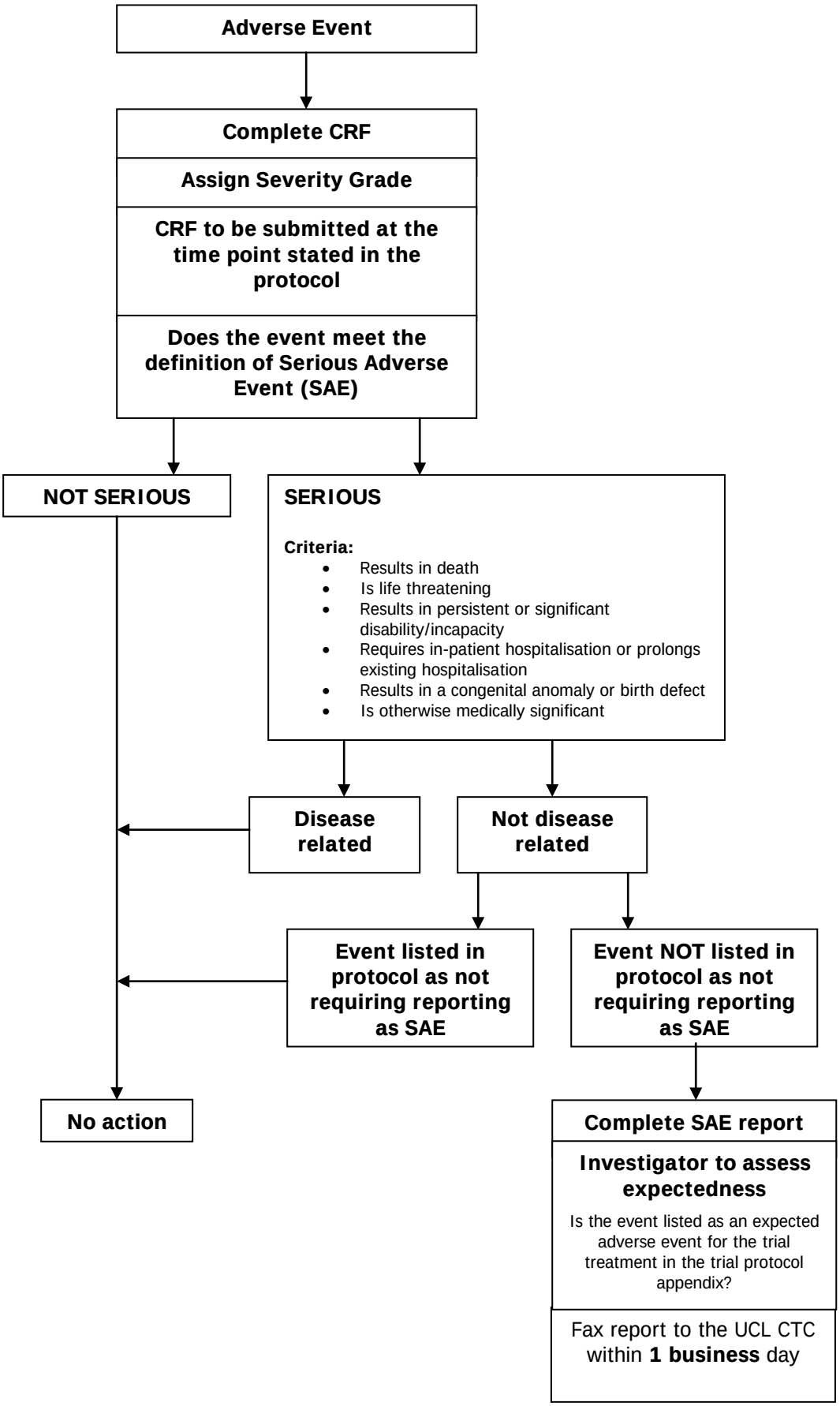
Events which do not Require Reporting as an SAE

The following events do not require reporting as an SAE, but must be recorded in the relevant section(s) of the CRF:

- disease progression
- disease related deaths
- admissions for palliative care

All SAEs must be reported by faxing a completed SAE Report within 1 business day of becoming aware of the event to the UCL CTC
Fax: 020 7679 9861

Adverse Event Reporting Flowchart



SAE Follow-Up Reports

All SAEs must be followed-up until resolution. Site investigators must provide follow-up SAE Reports if the SAE had not resolved at the time the initial report was submitted.

On receipt of the SAE Report, the UCL CTC will evaluate the event for seriousness and expectedness to determine whether or not the case qualifies for expedited reporting. If this is difficult to determine, the Chief Investigator and/or Trial Management Group will be consulted for their opinion. In the case of discrepant views, both opinions will be reported.

SUSARs

If the event is evaluated, by either the site or the UCL CTC, as a related and unexpected SAE, the UCL CTC will submit a report to MREC within 15 calendar days.

The UCL CTC will inform all Principal Investigators of any SUSARs which occur on the trial. Site investigators will receive expedited SUSAR reports that must be processed according to local requirements.

Additional Safety Monitoring at the UCL CTC

The UCL CTC will also monitor safety data for any trial related events that are not considered related to the trial treatment. In the event that any trial procedures appear to be resulting in adverse events, the Chief Investigator and/or Trial Management Group will be contacted for their opinion. If it is declared necessary to review the conduct of the trial, the UCL CTC will inform MREC, as appropriate.

Pregnancy

If a female patient or a female partner of a male patient becomes pregnant at any point during the trial, a completed trial specific Pregnancy Report must be submitted to the UCL CTC by fax within **1 business day** of learning of its occurrence.

All pregnancies must be reported by faxing a completed Pregnancy Report within 1 business day of becoming aware of the event to the UCL CTC

Fax: 020 7679 9861

Pregnancy Follow-Up Reports

All pregnancies must be followed-up until an outcome is determined. Follow-up Pregnancy Reports must be submitted to the UCL CTC by fax within **7 calendar days** of learning of the outcome. Reports must include an evaluation of the possible relationship of the trial treatment to the pregnancy outcome. Consent to report information regarding pregnancy outcomes must be obtained from the mother.

SAEs During Pregnancy

Any SAE occurring in a pregnant patient must be reported using the trial specific SAE Report, according to SAE reporting procedures.

Pregnancy Report Processing at the UCL CTC

The UCL CTC will submit Pregnancy Reports to MREC should the pregnancy outcome meet the definition of a SUSAR.

7. ETHICAL CONSIDERATIONS AND APPROVAL

7.1 Ethical considerations

FoRT is a randomised controlled trial. Therefore neither the patients nor their physicians will be able to choose the patient's treatment. Randomisation will be stratified by histology (follicular lymphoma vs. marginal zone lymphoma), and whether treatment is being given with curative or palliative intent. This is to ensure that the groups of patients receiving each of the different treatments are similar.

The study will abide by the principles of the Declaration of Helsinki.

7.2 Ethical approval

The protocol will be approved by the Cambridgeshire 4 Research Ethics Committee (formerly the Eastern MREC), and in addition Site Specific Approval must be obtained at each institution before patients are entered at that site.

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. Patients should be given sufficient time after being given the trial patient

information sheet to consider and discuss participation in the trial with friends and family. 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 ICH GCP guidelines. Patients should always be asked to sign a consent form. One copy should be given to the patient, one copy should be kept with patient's hospital notes and one copy should be kept in the local investigator's file.

The right of the patient 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 patient. However, the reason for doing so should be recorded and the patient 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 patient must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

8. INDEMNITY

Non-negligent harm: University College London, as Sponsor, holds insurance cover that will provide compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London. Participants who sustain injury and wishing to make a claim for compensation should do so in writing to the Chief Investigator in the first instance.

Negligent harm: Participants in this clinical trial are also able to seek compensation via a negligent harm route but this would involve proving negligence on the part of University College London. Insurance cover is held by University College London to cater for this but it is expected that any claim for compensation would be via the non-negligent harm route by virtue of compensation being paid without the need to prove negligence. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of the employees of hospitals. This applies whether the hospital is an NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

9. TRIAL COMMITTEES

9.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members with specific interest (e.g. nurses; radiographers). The TMG will be responsible for the day-to-day running and management of the trial and will meet approximately every six months but may convene more often by other means to advise the CI and UCL CTC in the promotion and running of the trial.

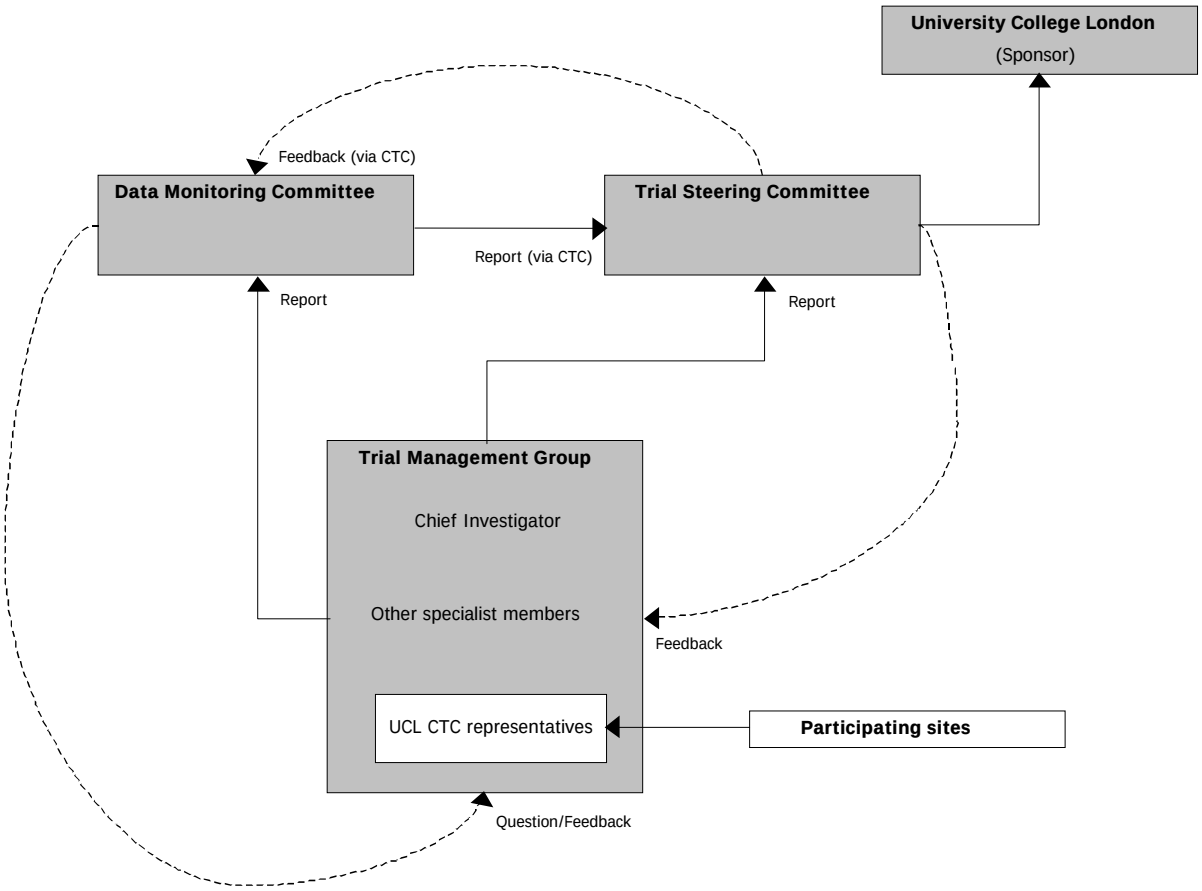
9.2 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC. Members of the TSC are currently being appointed. It will meet at least annually and will receive reports from UCL CTC, CI and IMDC.

9.3 Independent Data Monitoring Committee (IDMC)

The Independent Data Monitoring Committee will meet at least annually, with interim analysis reports from UCL CTC, to give advice on continuing recruitment. A recommendation 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 investigators including participants 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 recommendations to the TSC as to the continuation of the trial. Details of the interim analysis and monitoring are provided in the IDMC charter and in section 5.5.

Figure 2: Diagram of relationships between trial committees



10. PUBLICATION

Publication will follow the rules of the NCRI lymphoma CSG. Authorship will include the Chief Investigator, trial statistician, a representative of UCL CTC, a member of the central histopathology review team and one additional author from each site entering more than 5% of the total patients.

11. REFERENCES

1. Rohatiner A, Lister AT. Follicular lymphoma. *The Lymphomas* (eds) Canellos G, Lister AJ, Sklar A. WB Saunders Company, Philadelphia 1998. pp371-388
2. Haas RLM, Poortmans Ph, de Jong D et al. High response rates and lasting remissions after low dose involved field radiotherapy in indolent lymphomas. *J Clin Oncol*. 2003 **21**: 2474-2480
3. Sawyer EJ, Timothy AR. Low dose palliative radiotherapy in low grade non Hodgkins lymphoma. *Radiotherapy and Oncology* 1997; **42**: 49-51
4. Ash D, Barrett A, Hinks A, Squire C. Re-audit of radiotherapy waiting times 2003 *Clinical Oncology* 2004; **16**: 387-384
5. Hoskin et al. Abstract #59 *9th International Conference on Malignant Lymphoma* 8-11 June 2005, Palazzo Congressi, Lugano Switzerland
6. Yamashita H, Nakagawa K, Asari T, Murakami N, Igaki H, Ohtomo K. Radiotherapy for 41 patients with stage 1 and 2 MALT lymphoma: a retrospective study. *Radiotherapy and Oncology* 2008; **87**: 412-417
7. Tsang RW, Gospodarowicz MK, Pintilie M et al. Localised mucosa-associated lymphoid tissue lymphoma treated with radiation therapy has excellent clinical outcome. *Journal of Clinical Oncology* 2003; **21**:4157-4164
8. Neelis KJ, Schimmel EC, Vermeer MH, Senff NJ, Willemze R, Noorijk EM. Low dose palliative radiotherapy for cutaneous B and T cell lymphomas. *International Journal of Radiation Oncology Biology Physics* (epublication ahead of print: doi 10.1016/j.ijrobp.2008.06.1918)

12. APPENDICES

APPENDIX 1: HEALTH ECONOMIC QUESTIONNAIRE

The EQ-5D questionnaire is to be completed before each clinic visit from the point of registration and randomisation through to the final follow up visit.

EQ - 5D

Health Questionnaire

(English version for the UK)
(validated for use in Eire)

1

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

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

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	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

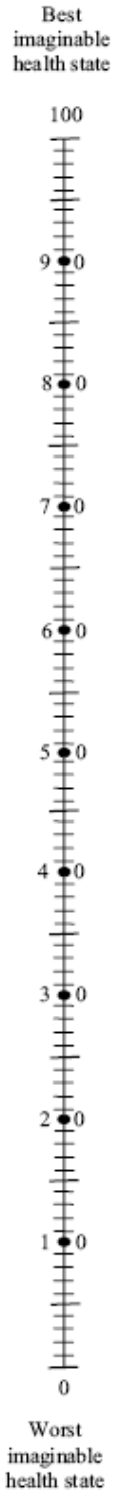
Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather 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 state is today.

Your own health state today



3

Because all replies are anonymous, it will help us to understand your answers better if we have a little background data from everyone, as covered in the following questions.

1.	Have you experienced serious illness?	Yes	No	
	in you yourself	❑	❑	PLEASE TICK APPROPRIATE BOXES
	in your family	❑	❑	
	in caring for others	❑	❑	
2.	What is your age in years ?			
3.	Are you:	Male	Female	PLEASE TICK APPROPRIATE BOX
		❑	❑	
4.	Are you:			
	a current smoker	❑		PLEASE TICK APPROPRIATE BOX
	an ex-smoker	❑		
	a never smoker	❑		
5.	Do you now, or did you ever, work in health or social services?	Yes	No	PLEASE TICK APPROPRIATE BOX
		❑	❑	
	If so, in what capacity?			
6.	Which of the following best describes your main activity?			
	in employment or self employment	❑		PLEASE TICK APPROPRIATE BOX
	retired	❑		
	housework	❑		
	student	❑		
	seeking work	❑		
	other (please specify)	❑		
7.	Did your education continue after the minimum school leaving age?	Yes	No	PLEASE TICK APPROPRIATE BOX
		❑	❑	
8.	Do you have a Degree or equivalent professional qualification?	Yes	No	PLEASE TICK APPROPRIATE BOX
		❑	❑	
9.	If you know your postcode, would you please write it here			

4

APPENDIX 2: RTOG RADIATION MORBIDITY SCORING CRITERIA

EXPECTED ADVERSE EVENTS DUE TO RADIOTHERAPY

The RTOG criteria for scoring acute and late radiation morbidity will be used to assess adverse events in the FoRT trial. As the FoRT trial involves comparatively low doses of radiotherapy, more severe reactions to radiotherapy will not be regarded as expected for the purposes of the study.

Because radiotherapy is a localised treatment, when assessing the relatedness of an adverse event to protocol treatment, the proximity of the affected area to the radiotherapy target field should be taken into consideration.

Grade 1 and 2 toxicity are regarded as expected for low dose radiotherapy (≤24Gy).

Grade 3, 4 and 5 toxicity are regarded as unexpected for the purposes of this trial.

Acute Radiation Morbidity Scoring Criteria

The RTOG acute radiation morbidity scoring criteria should be used to assess acute toxicity at visit 2 (4 weeks post randomisation)

	0	**1** (expected for FoRT)	**2** (expected for FoRT)	**3** (not expected for FoRT)	**4** (not expected for FoRT)
SKIN	No change over baseline	Follicular, faint or dull erythema/ epilation/ dry dequamation/ decreased sweating	Tender or bright erythema, patchy moist desquamation/ moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necosis
MUCOUS MEMBRANE	No change over baseline	Injection / may experience mild pain not requiring analgesic	Patchy mucositis which may produce an inflammatory serosanguinitis discharge/ may experience moderate pain requiring analgesia	Confluent fibrinous mucositis/ may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis
EYE	No change	Mild conjunctivitis with or without scleral injection. Increased tearing	Moderate conjunctivitis with or without keratitis requiring steroids &/or antibiotics/ dry eye requiring artificial tears/ iritis with photophobia	Severe keratitis with corneal ulceration/ objective decrease in visual acuity or in visual fields/ acute glaucoma/ panopthalmitis	Loss of vision (unilateral or bilateral)
EAR	No change over baseline	Mild external otitis with erythema, pruritis, secondary to dry desquamation not requiring medication. Audiogram unchanged from baseline	Moderate external otitis requiring topical medication/ serious otitis medius/ hypoacusis on testing only	Severe external otitis with discharge or moist desquamation/ symptomatic hypoacusis/ tinnitus, not drug related	Deafness

	0	1 (expected for FoRT)	2 (expected for FoRT)	3 (not expected for FoRT)	4 (not expected for FoRT)
SALIVARY GLAND	No change over baseline	Mild mouth dryness/ slightly thickened saliva/ may have slightly altered taste such as metallic taste/ these changes not reflected in alteration in baseline feeding behaviour, such as increased use of liquids with meals	Moderate to complete dryness/ thick, sticky saliva, markedly altered taste	----	Acute salivary gland necrosis
PHARYNX & OESOPHAGUS	No change over baseline	Mild dysphagia or odynophagia/ may require topical anaesthetic or non-narcotic analgesics. May require soft diet	Moderate dysphagia or odynophagia/ may require narcotic analgesics/ may require puree or liquid died	Severe dysphagia or odynophagia with dehydration or weight loss (>15% from pre-treatment baseline) requiring N-G feeding tube, IV fluids or hyperalimentation	Complete obstruction, ulceration, perforation, fistula
LARYNX	No change over baseline	Mild or intermittent hoarseness/ cough not requiring antitussive/ erythema of mucosa	Persistent hoarseness but able to vocalise/ referred ear pain, sore throat, patchy fibrinous exudate or mild arytenoid edema not requiring narcotic/ cough requiring antitussive	Whispered speech, throat pain or referred ear pain requiring narcotic/ confluent fibrinous exudate, marked arytenoid edema	Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary
UPPER G.I.	No change	Anorexia with <=5% weight loss from pretreatment baseline/ nausea not requiring antiemetics/ abdominal discomfort not requiring parasympatholytic drugs or analgesics	Anorexia with <=15% weight loss from pretreatment baseline/ nausea &/or vomiting requiring antiemetics/ andominal pain requiring analgesics	Anorexia with >15% weight loss from pretreatment baseline or requiring N-G tube or parenteral support. Nausea or vomiting requiring tube or parenteral support/ abdominal pain, severe despite medication/ hematemesis or melena/ abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Ileus, subacute or acute obstruction, perforation / GI bleeding requiring transfusion; abdominal pain requiring tube decompression or bowel diversion
LOWER GI INCLUDING PELVIS	No change	Increased frequency or change in quality of bowel habits not requiring medication/ rectal discomfort not requiring analgesics	Diarrhea requiring parasympatholytic drugs (e.g. Lotomil)/ mucous discharge not necessitating sanitary pads/ rectal or abdominal pain requiring analgesics	Diarrhea requiring parenteral support/ severe mucous or blood discharge necessitating sanitary pads/ abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; FI bkeeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression nor bowel diversion

	0	1 (expected for FoRT)	2 (expected for FoRT)	3 (not expected for FoRT)	4 (not expected for FoRT)
LUNG	No change	Mild symptoms of dry cough or dyspnea on exertion	Persistent cough requiring narcotic, antitussive agents/ dyspnea with minimal effort but not at rest	Severe cough unresponsive to narcotic antitussiveagent or dyspnea at rest/ clinical or radiologic evidence of acute pneumonitis/ intermittent oxygen or steroids may be required	Severe respiratory insufficiency/ continuous oxygen or assisted ventilation
GENITO-URINARY	No change	Frequency or urination or nocturia twice pretreatment habit/ dysuria, urgency not requiring medication	Frequency or urination or nocturia which is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anaesthetic (e.g. Pyridium)	Frequency with urgency and nocturia hourly or more frequently/ dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/ gross hematuria with/without clot passage	Hematuria requiring transfusion/ acute bladder obstruction not secondary o clot passage, ulceration or necrosis
HEART	No change over baseline	Asymptomatic but objective evidence of ECG changes or pericardial abnormalities without evidence of other heart disease	Symptomatic with ECG chabges abd radiologic findings of congestive heart failure or pericardial disease/ no specific treatment required	Congestive heart failure, angina pectoris, pericardial disease responding to therapy	Congestive heart failure, angina pectoris, pericardial disease, arrhythmias not responsive to non-surgical measures
CNS	No change	Fully functional status (i.e. able to work) with minor neurologic findings, no medication needed	Neurologic findings present sufficient to require home case/ nursing assistance may be required/ medications including steroids/ anti-seizure agents may be required	Neurologic findings requiring hospitalization for initial management	Serious neurologic impairment which includes paralysis, coma or seizures >3 per week despite medication/ hospitalization required
WBC	>/= 4.0	3.0 - < 4.0	2.0 - < 3.0	1.0 - < 2.0	< 1.0
PLATELETS	>/= 100	75 - < 100	50 - < 75	25 - < 50	<25 or spontaneous bleeding
NEUTROPHILS	>/= 1.9	1.5 - <1.9	1.0 - <1.5	0.5 - < 1.0	<0.5 or sepsis
HAEMOGLOBIN (GM%)	> 11	11 - 9.5	<9.5 - 7.5	<7.5 - 5.0	---
HAEMATOCRIT	>/= 32	28 - < 32	< 28	Packed red cell transfusion required	---

GUIDELINES: The acute morbidity criteria are used to score/grade toxicity from radiation therapy. The effects are criteria are relevant from day 1, the commencement of therapy, through day 90. Thereafter the EORTC/RTOG Criteria of Late Effects are to be utilized.

The evaluator must attempt to discriminate between disease- and treatment-related signs and symptoms.

An accurate baseline prior to commencement of therapy is necessary

All toxicity Grade 3, 4 or 5* must be verified by the Principal Investigator

* ANY TOXICITY WHICH CAUSED DEATH IS GRADED 5

http://www.rtog.org/members/toxicity/acute.html

RTOG/EORTC LATE RADIATION MORBIDITY SCORING SCHEMA

The RTOG/EORTC Late Radiation Morbidity Scoring Schema should be used to assess toxicity at visit 3 and all subsequent follow up visits.

	0	1 (Expected for FoRT)	2 (Expected for FoRT)	3	4	5
				Not expected for FoRT		
SKIN	None	Slight atrophy Pigmentation change Some hair loss	Patch atrophy; Moderate telangiectasia; Total hair loss	Marked atrophy; Gross telangiectasia	Ulceration	DEATH DIRECTLY RELATED TO RADIATION LATE EFFECTS
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosia) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; Slight field contracture <10% linear reduction	Severe induration and loss of subcutaneous tissue; Field contracture >10% linear measurement	Necrosis	
MUCOUS MEMBRANE	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia; Little mucous	Marked atrophy with complete dryness; Severe telangiectasia	Ulceration	
SALIVARY GLANDS	None	Slight dryness of mouth; Good response on stimulation	Moderate dryness of mouth; Poor response on stimulation	Complete dryness of mouth; No response on stimulation	Fibrosis	
SPINAL CORD	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono-, para-, quadraplegia	
BRAIN	None	Mild headache; Slight lethargy	Moderate headache; Great lethargy	Severe headaches; Severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis; Coma	
EYE	None	Asymptomatic cataract; Minor corneal ulceration or keratitis	Symptomatic cataract; Moderate corneal ulceration; Minor retinopathy or glaucoma	Severe keratitis; Severe retinopathy or detachment; Severe glaucoma	Panopthalmitis/ Blindness	
LARYNX	None	Hoarseness; Slight arytenoid edema	Moderate arytenoid edema, Chondritis	Severe edema; Severe chondritis	Necrosis	
LUNG	None	Asymptomatic or mild symptoms (dry cough); Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough); Low grade fever; Patchy radiographic appearances	Severe symptomatic fibrosis or Pneumonitis; Dense radiographic changes	Severe respiratory insufficiency/ Continuous O_2/ Assisted ventilation	
HEART	None	Asymptomatic or mild symptoms; Transient T wave inversion & ST changes; Sinus tachycardia >110 (at rest)	Moderate angina on effort; Mild pericarditis; Normal hear size; Persistent abnormal T wave and ST changes; Low ORS	Severe angina; Pericardial effusion; Constrictive pericarditis; Moderate heart failure; Cardiac enlargement; ECG abnormalities	Tamponade/ Severe heart failure/ Severe constrictive pericarditis	

	0	1 (Expected for FoRT)	2 (Expected for FoRT)	3	4	5
				Not expected for FoRT		
OESOPHAGUS	None	Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing	Unable to take solid food normally; Swallowing semi-solid food; Dilation may be indicated	Severe fibrosis; Able to swallow only liquids; May have pain on swallowing; Dilation required	Necrosis/ Perforation; Fistula	
SMALL/ LARGE INTESTINE	None	Mild diarrhoea; Mild cramping; Bowel movement 5 times daily; Slight rectal discharge or bleeding	Moderate diarrhoea and colic; Bowel movement >5 times daily; Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis/ Perforation; Fistula	
LIVER	None	Mild lassitude; Nausea, dyspepsia; Slightly abnormal liver function	Moderate symptoms; Some abnormal liver function tests; Serum albumin normal	Disabling hepatic insufficiency; Liver function tests grossly abnormal; Low albumin; Edema or ascites	Necrosis / Hepatic coma or encephalopathy	
KIDNEY	None	Tranient albuminuria; No hypertension; Mild impairment of renal function; Urea 25-35mg%, Creatinine 1.5-2.0mg%, Creatinine clearance >75%	Persistent moderate albuminuria (2+); Mild hypertension; No related anaemia; Moderate impairment of renal function; Urea >36-60mg%, Creatinine clearance 50-74%	Severe albuminuria; Severe hypertension; Persistent anaemia (<10g%); Severe renal failure; Urea >60mg%, Creatinine >4mg%, Creatinine clearance <50%	Malignant hypertension; Uremic coma/ Urea >100%	
BLADDER	None	Slight epithelial atrophy; Minor telangiectasia (microscopic hematuria)	Moderate frequency; Generalized telangiectasia; Intermittent macroscopic hematuria	Severe frequency and dysuria; Severe generalised telangiectasia (often with petechiae); Frequent hematuria; Reduction in bladder capacity (<150cc)	Necrosis/ Contracted bladder (capacity <100cc); Severe hemorrhagic cystitis	
BONE	None	Asymptomatic; No growth retardation; Reduced bone density	Moderate pain or tenderness; Growth retardation; Irregular bone sclerosis	Severe pain or tenderness; Complete arrest of bone growth; Dense bone sclerosis	Necrosis/ Spontaneous fracture	
JOINT	None	Mild joint stiffness; Slight limitation of movement	Moderate stiffness; Intermitten or moderate joint pain; Moderate limitation of movement	Severe joint stiffness; Pain with severe limitation of movement	Necrosis; Complete fixation	

http://www.rtog.org/members/toxicity/late.html

APPENDIX 3: RECIST CRITERIA

Response Evaluation Criteria in Solid Tumours (RECIST v1.0)

Quick Reference:

Eligibility

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.
    - **Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
    - **Measurable lesions** - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.
    - **Non-measurable lesions** - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.
- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Response Criteria

Evaluation of target lesions

* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

Although a clear progression of “non target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response

- The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

APPENDIX 4: FOLLOW UP SCHEDULE

Table 3 shows the visit schedule for the FoRT trial

Table 3: FoRT trial visit schedule

Visit number	Timepoint
1	Baseline
2	4 weeks post randomisation
3	12 weeks post randomisation – response assessment
4	6 months post randomisation
5	1 year post randomisation
6	18 months post randomisation
7	2 years post randomisation
8	3 years post randomisation
9	4 years post randomisation
10	5 years post randomisation

Once the five years of scheduled follow up are completed, patients will be followed up for survival annually until death.

The forms due at each visit are summarised in table 4 below.

Table 4: Forms due at each clinic visit

Form	Details	Compulsory / as required
Registration form	4 pages to be completed at visit 1 and faxed to UCL CTC	Compulsory
Randomisation form	1 page to be completed at visit 1 and faxed to UCL CTC	Compulsory
4-week follow up form	1 page to be posted to UCL CTC within 8 weeks of visit 2	Compulsory
Acute toxicity form	1 page to be posted to UCL CTC to be completed at visit 2 as required and posted to the UCL CTC within 8 weeks of visit 2 along with 4-week follow up form	Only required if patient experienced acute toxicity from radiotherapy
12-week follow up form	4 pages to be posted to UCL CTC within 8 weeks of visit 3	Compulsory
Follow up form	1 page to be completed at visits 4 – 10 and posted to UCL CTC within 8 weeks of visit	Compulsory up to the point of local progression
Late toxicity form	1 page to be completed at visit 3 – 10 as required and posted to UCL CTC within 8 weeks of the relevant visit along with the follow up form	Only required if patient experienced late toxicity from radiotherapy
Disease progression form	1 page to be completed at first progression **within the irradiated field**	Only required at local progression
Disease progression follow up form	1 page to be completed at all scheduled visits after local progression instead of the follow up form	Compulsory after local progression
Anti-cancer treatment form	1 page to be completed at visits 2-10 as required and posted to UCL CTC within 8 weeks of the relevant visit along with the follow up form	Only required if patient received cancer treatment other than their trial radiotherapy
Hospital admission form	1 page to be completed at visits 2-10 as required and posted to UCL CTC within 8 weeks of the relevant visit along with the follow up form	Only required if patient is admitted to hospital
Withdrawal from treatment	1 page to be completed at visit 2 if required and posted to UCL CTC within 8 weeks of visit 2 along with the 4-week follow up form	Only required if patient fails to complete their randomised radiotherapy
Withdrawal of consent	1 page to be completed at any visit if the patient withdraws consent to the trial. To be posted to UCL CTC immediately	Only required if patient withdraws consent to the trial
Patient death	1 page to be completed as soon as the site is aware of a patient dying. To be posted to UCL CTC immediately	Only required if patient dies
EQ-5D Health Questionnaire	Patient to complete this questionnaire at every trial visit. To be posted to UCL CTC with a coversheet indicating the patient's details and visit number within 8 weeks of the relevant visit.	Compulsory

APPENDIX 5: PATHOLOGY REVIEW

A central review of the diagnosis is organised for each case by a panel under the direction of Dr. Andrew Jack at the Haematological Malignancy Diagnostic Service in Leeds.

The review analysis will be done without the knowledge of patient outcome. It will comprise:

a) A confirmation of the diagnosis of follicular lymphoma or marginal zone lymphoma as defined in the WHO classification
b) A definition of the grade according to the WHO subgroups
c) A confirmation of the diagnosis of B cell proliferation with an anti-CD20 antibody and an anti-CD79a antibody.
d) Confirmation of a germinal centre phenotype using CD10 and bcl-6 for follicular lymphoma and absence of CD5, BCL6 and CD10 expression in the case of marginal zone lymphoma.
e) Bcl-2 protein expression will be determined by immunohistochemistry

Following randomisation a letter will be sent to the local pathologist requesting material be provided for central review.

All histological material is to be sent to:

CR UK and UCL Cancer Trials Centre
90 Tottenham Court Road
London W1T 4TJ

The material will then be forwarded to Dr. Jack in Leeds.

APPENDIX 6: ANN ARBOR STAGING SYSTEM

Ann Arbor staging for NHL*

Stage	Area of involvement
I	One lymph node region
I_E	One extralymphatic (E) organ or site
II	Two or more lymph node regions on the same side of the diaphragm
II_E	One extralymphatic organ or site (localised) in addition to criteria for stage II
III	Lymph node regions on both sides of the diaphragm
III_E	One extralymphatic organ or site (localised) in addition to criteria for stage III
III_S	Spleen (S) in addition to criteria for stage III
III_{SE}	Spleen and one extralymphatic organ or site (localised) in addition to criteria for stage III
IV	One or more extralymphatic organs with or without associated lymph node involvement (diffuse or disseminated); involved organs should be designated by subscript letters (P, lung; H, liver; M, bone marrow)

*A = asymptomatic; B = symptomatic (unexplained fever of ≥ 38.6°C [101.5°F]; unexplained, drenching night sweats; or loss of > 10% body weight within the previous 6 months).