This project has received funding from the European Union’s Seventh Framework Programme for research, technological development and demonstration under grant agreement no "602856."
# TRIAL MANAGEMENT GROUP

## Chief Investigator

<table>
<thead>
<tr>
<th>Name</th>
<th>Position and Contact Information</th>
</tr>
</thead>
</table>
| Dr Martin McCabe   | Consultant Paediatric Oncologist, The Christie Hospital, Manchester, UK  
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<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof Keith Wheatley</td>
<td>Professor of Medical Statistics, Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham, UK</td>
</tr>
<tr>
<td>Prof Jeremy Whelan</td>
<td>Consultant Medical Oncologist, University College Hospital, London, UK</td>
</tr>
</tbody>
</table>

## Clinical Coordinators

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof Uta Dirksen</td>
<td>Senior Consultant in Paediatric Haematology and Oncology, University of Munster, Munster, Germany</td>
</tr>
<tr>
<td>Prof Jeremy Whelan</td>
<td>Consultant Medical Oncologist, University College Hospital, London, UK</td>
</tr>
<tr>
<td>Dr Bernadette Brennan</td>
<td>Consultant Medical Oncologist, Royal Manchester Children’s Hospital, UK</td>
</tr>
</tbody>
</table>

## National Coordinating Investigators

<table>
<thead>
<tr>
<th>Name</th>
<th>Organization and Location</th>
</tr>
</thead>
</table>
| Prof Uta Dirksen   | European Organisation for Research and Treatment of Cancer (EORTC)  
  Brussels, Belgium |
| Prof Uta Dirksen   | Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH)  
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## Trial Statistician

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ms Veronica Moroz</td>
<td>Biostatistician, CRCTU, University of Birmingham, Birmingham UK</td>
</tr>
</tbody>
</table>

## SPONSOR

University of Birmingham, Edgbaston, Birmingham. B15 2TT
## COORDINATING CENTRES

### United Kingdom (UK) Coordinating Centre

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Senior Trial Manager</td>
<td>Ms Nicola Fenwick</td>
</tr>
<tr>
<td>Senior Trial Coordinator</td>
<td>Dr Joshua Savage</td>
</tr>
<tr>
<td>Trial Coordinator</td>
<td>Ms Jennifer Anderton</td>
</tr>
<tr>
<td>Pharmacy Advisor</td>
<td>Mr Nigel Ballantine</td>
</tr>
</tbody>
</table>

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- [https://www.cancertrials.bham.ac.uk/rEECurLive/](https://www.cancertrials.bham.ac.uk/rEECurLive/)
- In case of any problems with online randomisation, randomisation details can be phoned through to the CRCTU on: +44 (0)121 414 3366 or 0800 371 969

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  - Email: k.s.hall@klinmed.uio.no
  - Fax: +46 46 188 143
<table>
<thead>
<tr>
<th>Biological Studies Coordinators</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prof Sue Burchill</strong></td>
</tr>
<tr>
<td><strong>Prof Uta Dirksen</strong></td>
</tr>
</tbody>
</table>
This protocol describes the rEECur trial and provides information about procedures for patients taking part in the rEECur trial. The protocol should not be used as a guide for treatment of patients not taking part in the rEECur trial.

This protocol is based on CRCTU-PRT-QCD-001, version 1.0.
## AMENDMENTS

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version:

<table>
<thead>
<tr>
<th>Amendment Number</th>
<th>Date of Amendment</th>
<th>Protocol Version Number</th>
<th>Type of Amendment</th>
<th>Summary of Amendment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9th September 2014</td>
<td>3.0</td>
<td>Substantial amendment</td>
<td>Update from co-sponsorship model to a National Coordinating Centre model</td>
</tr>
</tbody>
</table>
| 2                | 29th February 2016  | 4.0                     | Substantial amendment   | - Updated trial management group (TMG) details  
- Schedule of events updated to reflect protocol updates  
- Clarification of eligibility criteria  
  - First and subsequent recurrences are eligible  
  - Addition of ‘Patients and investigators may now decline randomisation to one or more trial regimens but will be eligible for trial entry as long as they can be randomised between a minimum of two study arms’.  
- Addition of ‘Female patients must not breastfeed during chemotherapy’  
- Clarification of haematological criteria for patients with bone marrow infiltration  
- Details added regarding temozolomide administration, where a patient cannot swallow the capsules  
- IT arm: weekly monitoring of blood counts is recommended  
- IT arm: addition of new adverse events reported with the use of irinotecan (interstitial pulmonary disease, cardiac disorders and thromboembolic events) and temozolomide (cytomegalovirus and hepatitis B reactivation). Patients with known risk factors should be closely monitored during treatment  
- Clarification of the use of cefixime during IT administration  
- Further guidance added regarding the management of day 8 haematological toxicity for patients receiving GD |
<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<tr>
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</tr>
</tbody>
</table>

- Clarification that the use of Dexamethasone during GD administration is mandatory
- GD arm: if posterior reversible encephalopathy syndrome (PRES) develops during therapy - Institute supportive measures including blood pressure control and anti-seizure medication and permanently discontinue gemcitabine
- Duration of IFOS treatment clarified (4 cycles)
- IFOS adjustments to renal function updated
- Haematuria detected during IFOS and TC treatment should be confirmed using urine microscopy
- Clarification of the use of PET CT for staging of distance metastases: the quality of the CT component must be sufficient to allow disease assessment according to RECIST 1.1 criteria
- Bisphosphonates should not be given during trial directed therapy
- Clarification of Quality of Life sub-study eligibility
- Changes to pharmacovigilance reporting requirements: SUSAR reporting by EORTC and reporting of post study SARs
- Addition of optional Biological Studies
- Update to references in Section 16: Ethical Considerations
- Removal of Appendix 7: Declaration of Helsinki
TRIAL SYNOPSIS

rEECur: An international randomised controlled trial of chemotherapy for the treatment of recurrent and primary refractory Ewing sarcoma.

Trial Design
A seamless Multi-Arm, Multi-Stage (MAMS) randomised phase II/phase III, open-label, International trial

Objectives
The objective of rEECur is to identify the optimum chemotherapy regimen for recurrent and refractory Ewing sarcoma based on the balance between efficacy and toxicity.

Patient Population
Patients with recurrent and primary refractory Ewing sarcoma of the bone or soft tissues

- A minimum of 275 patients for the phase II part
- A target of at least 400 patients for the phase III part

Patients who take part in the phase II part may contribute data to the phase III part.

Main Eligibility Criteria

Principal inclusion criteria
- Histologically proven, recurrent or primary refractory Ewing sarcoma of the bone or soft tissues.
- Disease progression (during or after completion of first line treatment) or any subsequent recurrence
- Measurable disease by cross-sectional imaging (RECIST). Patients with bone lesions without a soft tissue component or with bone marrow disease only will be eligible but will not contribute to the phase II primary outcome measure
- Medically fit for cytotoxic chemotherapy
  Age ≥4 years and <50 years

Principal exclusion criteria
- Radiotherapy to target lesion within previous six weeks
- Cytotoxic chemotherapy or other investigational medicinal product within previous two weeks
- Myeloablative therapy within previous eight weeks
- No previous randomisation into the rEECur trial

Trial Duration
Anticipated time to complete accrual:

- Phase II – 2.2 years
- Phase III – 4 years

Follow-up will be for a minimum of 5 years, or until death if sooner.

Treatment Summary
Patients will be randomised to one of four chemotherapy regimens:

- Topotecan and Cyclophosphamide (TC): 6 cycles, of 21 days, additional cycles at clinician’s discretion
- Irinotecan and Temozolomide (IT) 6 cycles, of 21 days, additional cycles at clinician’s discretion
- Gemcitabine and Docetaxel (GD) 6 cycles, of 21 days, additional cycles at clinician’s discretion
- High dose Ifosfamide (IFOS), 4 cycles, of 21 days.

Local disease control measures are encouraged where possible but must be delayed until after 4 cycles of chemotherapy.

Stem cell harvesting may be carried out in patients for whom high dose therapy is planned but the first 4 chemotherapy cycles must be given according to the randomised regimen.

Myeloablative therapy may be given at the discretion of the treating physician after 6 cycles of TC, IT or GD, or after 4 cycles of IFOS.
**Trial Schema**

**RANDOMISATION**

2-3-4-way randomisation based on eligibility criteria

TC
IT
GD
IFOS

1st INTERIM ASSESSMENT

Drop one arm

2nd INTERIM ASSESSMENT

Drop one arm

Phase III evaluation

**CHEMOTHERAPY SCHEDULE AND RESPONSE ASSESSMENTS**

TC
IT
GD

IFOS

C1 C2 C3 C4 C5 C6

Local control and stem cell harvesting at investigator’s discretion, to be delayed until after cycle 4

Decision to stop treatment, give myeloablative therapy or continue randomised regimen at investigator’s discretion

**RESPONSE ASSESSMENTS**

Local control +/- myeloablative therapy at investigator’s discretion
## Schedule of Events

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Within 2 weeks prior to trial entry and randomisation</th>
<th>Prior to the start of each chemotherapy cycle</th>
<th>Following cycle 2 of randomised regimen</th>
<th>Following cycle 4 of randomised regimen</th>
<th>Following cycle 6 of randomised regimen</th>
<th>At the end of treatment</th>
<th>At each follow up visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent ( ^{b} )</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height, weight and surface area ( ^{c} )</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment of performance status by Lansky score (age &lt;16) or WHO Performance Status (age ≥16)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td></td>
</tr>
<tr>
<td>Menstrual history and pregnancy test (if indicated)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td></td>
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<tr>
<td>Tumour biopsy (not mandatory) ( ^{d} )</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Full blood count and biochemistry</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>GFR (calculated creatinine clearance (Ccrea) or isotopic)</td>
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<td>Tubular function</td>
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<td>X</td>
<td>X</td>
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<td>MRI or CT scan of symptomatic sites and target lesions</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>CT scan of chest if not done for imaging of disease site</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staging of non-pulmonary/pleural metastases</td>
<td>X(^{a})</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET CT (not mandatory, see Appendix 6)(^{i})</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staging of bone marrow disease (not mandatory)</td>
<td>X(^{i})</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment of treatment toxicity</td>
<td>X(^{i})</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Quality of Life assessment</td>
<td>X(^{a})</td>
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<td>X</td>
<td>X</td>
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<td></td>
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<tr>
<td>Assessment of disease status</td>
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<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<td>Samples for Biological Studies – see Section 9)</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( ^{a} \) for people who complete 6 cycles  
\( ^{b} \) may be performed more than 2 weeks prior to trial entry  
\( ^{c} \) according to institutional policy.  
\( ^{d} \) tumour biopsy is not mandatory and may be performed more than 2 weeks prior to trial entry  
\( ^{e} \) after trial entry and randomisation, GFR and tubular function need only be reassessed prior to each chemotherapy cycle for patients receiving IFOS, see section 7.2.4  
\( ^{f} \) for patients who receive IT, TC and GD  
\( ^{g} \) see section 7.5.7  
\( ^{h} \) PET CT response is a secondary outcome measure in rEECur; see section 7.5.7.  
\( ^{i} \) see section 7.5.7  
\( ^{j} \) not applicable to the first cycle  
\( ^{k} \) before first cycle of chemotherapy  
\( ^{l} \) at disease progression and/or relapse
# ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ALP</td>
<td>Alkaline phosphatase</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine transaminase</td>
</tr>
<tr>
<td>ANC</td>
<td>Absolute neutrophil count</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate transaminase</td>
</tr>
<tr>
<td>Ccrea</td>
<td>Creatinine clearance</td>
</tr>
<tr>
<td>COG</td>
<td>Children's Oncology Group</td>
</tr>
<tr>
<td>CR</td>
<td>Complete response</td>
</tr>
<tr>
<td>CRCTU</td>
<td>Cancer Research UK Clinical Trials Unit, Birmingham</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>DMC</td>
<td>Data Monitoring Committee</td>
</tr>
<tr>
<td>DSUR</td>
<td>Development Safety Update Report</td>
</tr>
<tr>
<td>EEC</td>
<td>Euro Ewing Consortium</td>
</tr>
<tr>
<td>EFS</td>
<td>Event-free survival</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>eRDC</td>
<td>Electronic Remote Data Capture</td>
</tr>
<tr>
<td>ES</td>
<td>Ewing sarcoma</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>G-CSF</td>
<td>Granulocyte-colony stimulating factor</td>
</tr>
<tr>
<td>GEIS</td>
<td>Spanish Group for Sarcoma Research</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular Filtration Rate</td>
</tr>
<tr>
<td>GPOH</td>
<td>German Society for Paediatric Haematology and Oncology</td>
</tr>
<tr>
<td>HCO</td>
<td>Bicarbonate</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>IMP</td>
<td>Investigational medicinal product</td>
</tr>
<tr>
<td>ISF</td>
<td>Investigator Site File</td>
</tr>
<tr>
<td>ISG</td>
<td>Italian Sarcoma Group</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention to treat</td>
</tr>
<tr>
<td>MAMS</td>
<td>Multi-arm, multi-stage</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>OR</td>
<td>Objective response</td>
</tr>
<tr>
<td>OS</td>
<td>Overall survival</td>
</tr>
<tr>
<td>PD</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression-free survival</td>
</tr>
<tr>
<td>POG</td>
<td>Pediatric Oncology Group</td>
</tr>
<tr>
<td>PR</td>
<td>Partial response</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
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<tr>
<td>SAE</td>
<td>Serious adverse event</td>
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<tr>
<td>SAR</td>
<td>Serious adverse reaction</td>
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<td>SFCE</td>
<td>Societe Francaise des Cancers d'Enfants</td>
</tr>
<tr>
<td>SSG</td>
<td>Scandinavian Sarcoma Group</td>
</tr>
<tr>
<td>TMG</td>
<td>Trial Management Group</td>
</tr>
<tr>
<td>TMZ</td>
<td>Temozolomide</td>
</tr>
<tr>
<td>TSC</td>
<td>Trial Steering Committee</td>
</tr>
<tr>
<td>TTP</td>
<td>Time to progression</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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1. BACKGROUND AND RATIONALE

1.1 Background

1.1.1 Characterisation of Ewing sarcoma

Ewing sarcomas (ES) are malignant, small round blue cell tumours of bone and soft tissue with variable neuroectodermal differentiation that preferentially affect children and young people [1]. In over 98% of cases the malignant phenotype derives from chromosomal translocations that result in gene fusions between EWS and an ETS transcription factor, the most common being FLI1. Multimodal treatment with chemotherapy, surgery and radiotherapy results in long-term survival in up to 60% of cases [2-4]. However, approximately 15% of patients with high-risk disease are refractory to initial therapy and up to 50% of patients recur after initial therapy [5, 6]. There has been no improvement in the proportion of long-term survivors for 25 years.

1.1.2 Treatment results in recurrent and primary refractory disease

Survival following relapse is poor [5-10]. The Rizzoli Institute reported a retrospective review of 195 patients treated for recurrent disease over an 18-year period to 1997 [9] and subsequently an updated review of 290 patients treated between 1972 and 1999 with median follow up of 13.6 years following recurrence [10]. In the more recent report of 378 recurrences in 290 patients, median time to first recurrence was 27 months after initial therapy. The majority had metastatic (75%) or combined local and metastatic (14%) recurrences. Following treatment with chemotherapy (36%), surgery (22%), radiotherapy (9%) or palliative treatment only (39%), 31% entered remission. Of those who entered remission, 87% recurred again at a median of 17.5 months. Reported 5-year overall survival (OS) was 14% for the first report and 8% for the updated series.

University College Hospital, London (UCLH) reported 144 patients including 37 with primary refractory ES and 77 with recurrences between 1992 and 2002. Median time to treatment failure was 13 months [7]. Most had metastatic (57%) or combined (17.5%) disease recurrence or progression. Chemotherapy according to several regimens was given to 89 patients (78%), of whom 29 subsequently had myeloablative therapy. A minority had surgery (14%) or definitive radiotherapy (6%). At a median follow up of 67 months, 2- and 5- year overall survival was 24% and 15% respectively.

A single centre review of 55 patients treated at The Washington Children’s Hospital for recurrence between 1985 and 2002 who recurred at a median of 17 months from initial diagnosis reported 5-year progression-free survival (PFS) of 20% and OS of 23%. Most patients had metastatic (71%) or combined (10%) recurrences. Chemotherapy with or without additional local therapy was given to 43 of 55 patients at recurrence, of whom 13 patients received high dose therapy. The remainder were given local therapy or palliative care only.

The Children’s Oncology Group (COG) group reported 262 patients prospectively enrolled onto the INT0091 trial, who recurred at a median of 1 year (metastatic disease at diagnosis) or 1.4 years (localised disease at diagnosis) [5]. Most had metastatic (63%) or combined (11%) recurrences. Median survival following recurrence was 9 months and 5-year OS was 12%. Treatment details were not reported.

The largest series reported to date is from the prospective German Society for Paediatric Haematology and Oncology (GPOH) database of patients recruited to the CESS81, CESS86 or EICESS92 trials [6], of whom 714 developed recurrences. Most had metastatic (73%) or combined metastatic and local (12%) recurrences. Median time to recurrence was 1.4 years from initial diagnosis and correlated with initial disease stage, patients with primary metastatic disease recurring a median of 129 days earlier than those with localised disease. Treatment details were not reported for the series. Combined 5-year OS of patients with disease recurrence was 13%.

1.1.3 Prognostic factors at recurrence

Although survival is poor following recurrence of ES, clinical and imaging prognostic factors have been associated with outcome. The most consistently reported is the interval from initial diagnosis to recurrence, all series to date reporting either an 18-month or 2-year threshold to be significant for OS.
or Event-free survival (EFS). The German and COG series report 5-year OS of 29 and 30% respectively for recurrences over 2 years from diagnosis, compared to 7% for recurrences within 2 years (p<0.001 both series). Corresponding 5-year EFS from the Rizzoli series are 11.5% versus 2.3% (p<0.001), from the Washington series 49 versus 8% (p=0.02) and from the UCLH series 32% versus 7% (p<0.001), the latter series using an 18-month threshold.

Disease sites at recurrence were also significantly correlated with outcome in the GPOH, COG, UCLH and Rizzoli series. In the GPOH series, recurrences in the lung and bone, multystem recurrences and combined local and systemic recurrences were associated with 30%, 70%, 108% and 162% increased risks of death compared to isolated local recurrences. In the COG and UCLH series combined local and distant recurrence was associated with worse outcome than local recurrence only, outcome gradually worsening in the UCLH series for local disease only, pulmonary metastases and extrapulmonary metastases. The Italian series [9] also reported progressively worse outcome for patients with lung metastases, bone metastases and combined lung and bone metastases.

The three series to have reported treatment at recurrence [7] found a correlation between therapy and outcome. In the Italian series the modality of treatment was related both to achieving disease remission (p<0.001) and to 5-year EFS (p<0.001) and OS (p=0.002), the groups with the highest EFS being the minority of patients who had surgery alone (n=12, 6%) or the combination of systemic chemotherapy and local therapy (n=20, 10%), who achieved 5-year EFS of 45% and 33% respectively. High dose chemotherapy (n=39) was also significantly associated with achieving a second remission, 5-year EFS and OS (all p<0.001). Because the Italian series did not report multivariate survival analyses it was not possible to assess the value of treatment modality independently of the other prognostic factors reported. The smaller Washington series also reported significant correlations between achieving a partial response (PR) or complete response (CR) following therapy (n=40/55) and 5-year PFS and OS. Despite the small number of patients in the series, the association remained significant on multivariate analysis (PFS p = 0.02, OS p<0.001). Those who had high dose therapy (n=13) also had improved PFS and OS (p = 0.01 and 0.03 respectively). Finally, in the UCLH series there were significant benefits in multivariate analysis for those patients treated with surgery and/or definitive radiotherapy and for those given high dose therapy (Hazard Ratio (HR) 0.5 (0.2-0.9) and 0.3 (0.2-0.6) respectively). In a separate publication the UCLH group reported 33 patients with recurrent ES treated with high dose therapy [11]. In this pre-selected group of patients with disease responsive to second line treatment, at a median of 5 years from high dose therapy, 5-year survival was 38% (21-55%).

Although gender was also associated with outcome on univariate analysis, it was not an independent risk factor on multivariate analysis. There is however a dearth of biological prognostic factors in the relapse refractory setting, although high levels of lactate dehydrogenase at initial diagnosis were associated with poor outcomes (>250 IU/l relative risk (RR) 1.4, p = 0.02).

1.2 Trial Rationale

1.2.1 Rationale for an international study

Numerous chemotherapy regimens have been reported in recurrent ES, incorporating alkylating agents [12, 13], camptothecin derivatives [14, 15] and platinum agents [16-18]. Four regimens have emerged to be in most widespread use across Europe in the setting of refractory or recurrent ES and have thus been chosen for inclusion in the rEECur trial. Published evidence of the activity of each regimen comprises a mixture of single institution retrospective reviews and early phase trials, each including small numbers of evaluable patients with ES. There have been no randomised trials comparing these regimens for efficacy or toxicity. The evidence base in support of specific regimens at relapse is therefore weak, resulting in widespread variation in chemotherapy delivery across Europe and inequitable access to drugs between European Union (EU) member states.

Evaluating the relative efficacy of chemotherapy agents and regimens in the relapse setting is essential (i) to improve outcomes after recurrence, (ii) to improve patient counselling prior to treatment, (iii) to identify the agents most appropriate for future evaluation in first line therapy and (iv) to develop consensus on the most appropriate backbone for the evaluation of novel therapies as they emerge. Recurrent ES is a rare disease; approximately 250 ES patients are estimated per year across the EU. Developing a robust evidence base in support of one or more chemotherapy regimens therefore requires cooperation across multiple centres and countries.
Cooperative sarcoma groups across Europe, recognising the need to identify the most effective agents at relapse, and building on the successful collaborations that have resulted in the first line phase III studies EuroE.W.I.N.G.99, Ewing2008 and EE2012, have coalesced to develop rEECur, the first randomised phase III study in recurrent ES.

1.2.2 Reported activity and toxicity of the chemotherapy regimens

1.2.2.1 Topotecan and cyclophosphamide

Topotecan and cyclophosphamide are effective agents in ES given singly and in combination. Cyclophosphamide has been a core constituent of first-line chemotherapy regimens in ES for several decades [19-21]. Topotecan has been used principally at recurrence, given as a single agent as a continuous infusion [22, 23] and as a 3-weekly, short infusion schedule of 2.0 mg/m²/day for 5 days [24]. The latter schedule (Paediatric Oncology Group (POG) 9361) resulted in objective responses in 2 of 29 and stable disease (SD) in 11 and was used as the basis for a combination study with cyclophosphamide, based on a theoretical synergy resulting from the binding of topotecan to DNA undergoing topoisomerase I-catalysed repair following treatment with alkylating agents. The POG phase I combination study identified a recommended phase II schedule of cyclophosphamide 250 mg/m² followed by topotecan 0.75 mg/m² for 5 days. The subsequent POG phase II study used that schedule [13] and two other groups [25, 26] have reported their experience using the same schedule, albeit with additional cytotoxic agents in some patients. Objective responses were seen in 6/17 (POG phase II [13]), 16/45 (GPOH series [26]) and 3/13 (American University of Beirut [25]) evaluable patients, with SD in 6, 15 and 4 respectively, giving an Objective Response (OR) of 33% and SD in 33%. Median time to progression, PFS and OS were not reported for any series, so although the 5-day regimen is in widespread use, only 80 patients’ outcomes have been reported, and the regimen’s efficacy, as judged by the standard survival metrics PFS and OS, is unknown. Moreover, the patients reported varied in the occurrence and timing of local therapies, in subsequent use of myeloablative therapies and in the timing of response assessments. The POG phase II study and Beirut study reported best observed response, documented after between 1 and 10 cycles [13, 25], while the GPOH study reported first evaluable response, which in approximately half of patients was after 2 cycles of chemotherapy [26].

Up to 2 cycles of the same schedule were used in a first line window study in 37 evaluable ES patients with primary metastatic disease recruited to the POG 9457 trial. Objective responses were seen in 21/37 patients, and SD in 15 patients [27].

An alternative continuous infusion schedule of cyclophosphamide 4200mg/m² over 48 hours and topotecan 6 mg/m² over 72 hours was investigated in a phase II study by Memorial Sloan Kettering [28]. Of 3 ES patients treated, there was 1 PR and 1 SD. More recently, Istanbul University Oncology Institute has reported a combination schedule of single dose vincristine 1.5 mg/m² with topotecan 1mg/m² for 3 days and cyclophosphamide 600 mg/m² for 2 days in 13 recurrent ES patients [29]. There were 7 objective responses and 2 with SD. Median survival after relapse was 15 months.

Reported grade 3 and 4 toxicities following the common, 5-day schedule are generally limited to myelosuppression, with neutropenia after 48-90% of cycles [30], thrombocytopenia after 31-44% and anaemia after 10-36%. Neutropenic fevers were relatively uncommon despite profound myelosuppression when Granulocyte-colony stimulating factor (G-CSF) support was given. In the COG phase I combination study, 86% of cycles at the phase II recommended dose level without filgrastim support were complicated by neutropenic fever. With filgrastim, there was a reduction to 20% of cycles [30]. The phase II combination study reported grade 3 and 4 infections after 11% of cycles [13]; the retrospective series reported infections after 4% [26] and 6% [25] of cycles. Haemorrhagic cystitis was uncommon, not dose-limiting and confined to those with pre-existing haematuria, pelvic irradiation or a history of previous chemotherapy-induced haematuria [13, 25, 30].

Two toxic deaths were reported, both from the GPOH cohort: one from fungal pneumonia, the other from pulmonary failure following a pneumonectomy for parenchymal lung metastases [26].

1.2.2.2 Irinotecan and temozolomide

Several groups have investigated the topoisomerase I inhibitor irinotecan and the alkylating agent temozolomide (TMZ) alone and in combination using different dosing schedules, and with additional cytotoxics or targeted agents. There is little evidence that either drug given alone is effective at recurrence in ES. Experience with temozolomides a single agent in recurrent ES is limited to a single
report: One hundred and eighty or 215 mg/m²/day given orally for 5 days to 7 children with recurrent ES in a compassionate use study resulted in disease progression after 1 or 2 cycles [12]. Single agent studies of irinotecan are almost exclusively based on protracted, low-dose schedules, reported to be as effective but less toxic than higher dose, short-course schedules in pre-clinical studies [31]. Memorial Sloan Kettering reported 3 ES patients given 20 mg/m² for 5 days on 2 consecutive weeks (20 mg/m² x 5 x 2) of a 3-weekly cycle [15]. All had progressive disease; the timing of response assessments was not given. St Jude’s reported a phase I dose escalation study of up to 45 mg/m² x 5 x 2 that included 2 ES patients [32]. One had a partial response maintained to 6 cycles. Another St Jude’s study of irinotecan 15-20 mg/m² x 5 x 2 with oral Gefitinib reported 3 patients with recurrent ES, of whom one patient had a partial response maintained for 4 cycles [33].

Single agent efficacy of irinotecan is more convincingly shown by a phase II window study in previously untreated primary metastatic ES recruited to the EuroEWING99 study who were given up to 2 cycles of a short-course regimen: 600 mg/m² as a single infusion 3-weekly [34]. From 22 patients there were 5 PRs, 1 minimal response and 9 with SD.

Combination studies have been based on pre-clinical data of increased cytotoxicity of irinotecan when given after the administration of temozolomide, the magnitude of effect being schedule-dependent [35]. Four combination studies of irinotecan and temozolomide in recurrent ES have been published, summarised in Table 1. All have used protracted, low-dose schedules of irinotecan, with up to a fourfold difference in total irinotecan dose per cycle, and include 65 evaluable ES patients in total. The combination was first reported from a mixed report of phase I and non-trial patients with advanced ES [14]. Best responses in 14 evaluable patients were 1 CR, 3 PR and 4 SD. MD Anderson reported a retrospective analysis of 25 evaluable patients [36]. The best responses were 7 CR, 9 PR and 6 stable disease (SD). Memorial Sloan Kettering reported 19 evaluable patients with best responses of 5 CR and 7 PR [37]. The Hospital Infantil Universitario Nino Jesus, Madrid reported 7 patients, with best responses of 3 PR and 2 SD [38]. Combining all four reports, the 65 patients had an OR of 54% and median time to progression (TTP) was 4.6 to 8.3 months. PFS and OS were not reported. The nature of the reports prevented more detailed analysis of the outcomes of specific dosing schedules.

Three groups have reported a total of 31 patients who had vincristine in addition to TMZ and irinotecan according to four different schedules, including 7 patients who had oral irinotecan (summarised in Table 1). The largest was a retrospective review of 22 Polish patients [39]. At reassessment following 1 to 3 cycles there were 5 CRs, 7 PRs and 3 SDs (OR 55%). One additional patient from a phase I study [40] had a PR after 4 cycles. Combination regimens using oral irinotecan have been reported by Cincinnati Children’s Hospital. In the first report, of 5 ES patients recruited to a phase I study there were 1 unconfirmed CR, 1 PR and 1 SD [41]. A second report with the addition of bevacizumab 15 mg/kg on day 1 included 2 ES patients [42]. There was 1 CR after 6 cycles and 1 PR after 3 cycles.

<table>
<thead>
<tr>
<th>Author</th>
<th>Ref</th>
<th>TMZ (mg/m²)</th>
<th>Irinotecan (mg/m²)</th>
<th>Other agents</th>
<th>N</th>
<th>Objective responses</th>
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<td>IV 10-20 x 5 x 2</td>
<td></td>
<td>14</td>
<td>4</td>
</tr>
<tr>
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<td>Vincristine x 1</td>
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<td>Vincristine x 1 Bevacizumab</td>
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Table 1: Summary of published irinotecan and temozolomide regimens
The toxicities associated with irinotecan and temozolomide were largely limited to myelosuppression and gastrointestinal side effects. Despite a heavily pre-treated population, grade 3 and 4 neutropenia and thrombocytopenia have been uncommon in ES patients, reported after up to 12% of cycles [14, 37, 38]. Myelosuppression may be more frequent when vincristine is added to the combination, although there was wide variation between reports, grade 3-4 neutropenia occurring after 0-45% of cycles [39, 40, 43]. Despite profound myelosuppression in some series, neutropenic infections were uncommon and there were no toxic deaths.

Although grade 1 and 2 diarrhoea is common, occurring after up to 50% of cycles [38, 44], most series report grade 3 or 4 diarrhoea after up to 10% of cycles and it has rarely led to cessation of treatment. There is a suggestion from the Cincinnati series that grade ≥3 diarrhoea was more common when irinotecan doses >10 mg/m²/day were used [14], although that is not borne out by all series. Of note, reports have been inconsistent in the use of prophylactic cephalosporins. Clinically significant dehydration and hypokalaemia have been reported rarely.

Additional toxicities reported with the irinotecan and temozolomide combination in ES and other malignancies are nausea and vomiting in up to 15% and rare cases of pneumonitis (1 case after whole lung irradiation [37]), grade 3-4 liver toxicity in 2 cases [38] and recurrent pancreatitis in a patient who had previously developed pancreatitis following oxaliplatin [40].

With such variation in reported dosing schedules, a single, preferred regimen in recurrent ES is not immediately obvious. Although the regimens reported in ES have incorporated 10, 15 or 20 mg/m²/day irinotecan, there is evidence from rhabdomyosarcoma and ES that higher dose, five-day regimens are as active, as well tolerated, and incur less time spent in hospital than low-dose, two-week regimens [39, 43]. Moreover, a survey (unpublished) of European clinicians has revealed wide variation in the schedules in current use in the setting of recurrent ES, including several regimens incorporating irinotecan doses of 40-50 mg/m²/day. Irinotecan 50 mg/m²/day x 5 is also the preferred regimen in two ongoing phase II combination studies with temozolomide in recurrent rhabdomyosarcoma (VIT-0910, http://www.controlled-trials.com/ISRCTN66172474) and neuroblastoma (BEACON, http://www.controlled-trials.com/ISRCTN40708286). For this trial, a pragmatic choice has been made to use a 5-day 50 mg/m²/day irinotecan regimen since this regimen, in addition to reflecting some current practice, will be more comparable to the other regimens under study than a protracted 10-day regimen.

1.2.2.3 Gemcitabine and docetaxel

Gemcitabine is a difluorinated analogue of deoxycytidine with poor single agent activity in recurrent ES (n=5 patients, no objective responses [45, 46]). Docetaxel is a semi-synthetic taxane with similarly poor activity in the combination in sarcomas from a series of adult leiomyosarcomas treated with gemcitabine 900 mg/m² by 30- or 90-minute intravenous (IV) infusion on days 1 and 8, and docetaxel 100 mg/m² on day 8 [49]. The 90-minute infusion resulted in a 50% increase in the time during which the plasma gemcitabine concentration was above the threshold value deemed to be cytotoxic from pre-clinical studies. Following publication of that series, several combination schedules have been reported in 31 ES patients, summarised in Table 2. The first two retrospective series reported a lower dose of gemcitabine than either the initial Hensley report or the recommended phase II gemcitabine dose, at 675 mg/m²/dose [50, 51]. Of 4 evaluable patients there were 1 PR and 2 SD. Since the recommended phase II dose for gemcitabine was 1000 mg/m² [52] and a higher dose combination had previously been tolerated [49] the Hospital Sant Joan de Deu, Barcelona reported a series of children and adolescents with recurrent bone sarcomas given gemcitabine at 1000 mg/m²/dose. With this higher dose combination, albeit in only 6 ES patients, there were 3 CR, 1 PR and 1 SD. Concerns over the tolerability of 3-weekly docetaxel in a predominantly older, carcinoma population, led to a subsequent phase II study in recurrent bone sarcoma of gemcitabine with docetaxel given on days 1 and 8 [53]. In 5 ES patients there was 1 PR and 2 SD. The two most recent reports, including a phase II study by the Sarcoma Alliance Through Research Collaboration (SARC) alliance, used lower doses of both agents [54, 55]. From 16 evaluable patients there were 2 PR and 6 SD.
Although the published data are very limited, there is a suggestion that higher doses of gemcitabine and docetaxel, if tolerable, may be associated with improved objective response rates, since there were 5 objective responses in 11 patients treated with gemcitabine 1000 mg/m²/dose, compared to 3 responses in 20 patients treated at the lower dose; and 5 responses in 10 patients treated with docetaxel 100 mg/m²/dose compared to 3 responses in 19 patients treated with lower doses.

Much of the published evidence base for toxicity of the gemcitabine/docetaxel combination comes from a highly pre-morbid, older population of patients with advanced or poor prognosis carcinomas, particularly metastatic or advanced non-small-cell lung cancer, pancreatic cancer and breast cancer. Toxicity data from adolescents and young adults, the population at highest risk of ES, are more limited and there is no evidence of greater toxicity with higher dose regimens in this age group either in ES or other sarcomas. On the contrary, low dose regimens deliver up to 33% less gemcitabine and 25% less docetaxel than the doses recommended by paediatric phase I studies. With G-CSF support, grade 3-4 neutropenia was reported in 0-47% given lower dose gemcitabine regimens (675 mg/m²/dose) [50, 51, 54, 55] and in 0-21% given higher dose regimens (900-1000 mg/m²/dose) [16, 18, 53, 56]; and in 0-60% given lower dose docetaxel [53-55] versus 0-35% with higher dose docetaxel [16, 18, 49-51, 56]. Despite profound myelosuppression neutropenic infections were uncommon. The reported incidences of thrombocytopenia and anaemia were similar to those of neutropenia, with no evidence of more profound or long-lasting cytopenias with higher doses of gemcitabine or docetaxel.

Although grade 3 to 4 dyspnoea was reported in 7 of 34 patients with leomyosarcomas in the Hensley study (median age 54 years) [49] it was a rare event in the population with ES and other bone sarcomas. A single child in the Barcelona series developed recall radiation pneumonitis after gemcitabine 1000 mg/m²/dose and docetaxel 100 mg/m²/dose and two patients from the adult SARC series developed grade 3 pneumonitis following gemcitabine 675 mg/m²/dose and docetaxel 75 mg/m²/dose. Skin and nail changes, neuropathy and fluid retention were relatively commonly reported but were mild in the majority of cases.

Two patients had presumed treatment-related deaths: one patient with chondrosarcoma had an unexplained death at home [51]; the other was thought to have non-neutropenic sepsis [53]. Other significant reported toxicities were grade 3 hypokalaemia (n=4, gemcitabine 675 mg/m², docetaxel 100 mg/m²), raised creatinine (n=3, gemcitabine 675 mg/m², docetaxel 75 mg/m²), allergic reaction (n=1), colitis (n=1), myositis and pericardial effusion (n=1), cardiac dysfunction (n=1) and hypercalcaemia (n=1). The latter three complications were all following low dose gemcitabine and docetaxel.

From published evidence alone there is no clear toxicity-based rationale for using low dose regimens in the relatively young population likely to be recruited to rEECur. However, widespread clinical experience with this regimen in young patients suggests that the highest dosing schedule is not well tolerated either by children or adults with recurrent ES or other diseases. A pragmatic solution for rEECur, based on a combination of reported data and clinical experience in this population is to evaluate the activity of a schedule already in widespread use across Europe but not specifically reported in this patient population: gemcitabine 900 mg/m²/dose and docetaxel 80 mg/m²/dose.
1.2.2.4 Ifosfamide

Ifosfamide has been a standard of first line treatment since it was shown to have activity in ES 3 decades ago [11]. More recently, single agent activity of ifosfamide has been reported at recurrence despite its use in first line treatment. Two continuous infusion schedules have been reported: 15 g/m² over 5 days [57] and 14 g/m² over 14 days [58].

The 5-day regimen has been more extensively reported. Of 35 evaluable patients there were 2 CR, 10 PR and 11 SD after 2 cycles. Following 2 cycles, in the absence of progressive disease patients who had previously received myeloablative therapy (n=12) received 2 further cycles. Those who had previously had only conventional dose chemotherapy were given high dose therapy (n=11). PFS was not given but 2-year OS for the series was 29%. Myelosuppression was the major toxicity reported. Ninety seven percent of 72 cycles were followed by grade 4 neutropenia and 22% by neutropenic fever despite mandatory G-CSF support. Grade 4 thrombocytopenia was reported after 54% of cycles. One patient had grade 3 neurotoxicity requiring cessation of treatment. Mild neurotoxicity occurred after 14% of cycles and did not interrupt treatment in any other patients. No renal dysfunction was reported.

Three paediatric ES patients have been reported after treatment with the 14-day schedule. After 3-4 cycles there were 2 PRs and 1 SD. One patient was still alive 6 months after the start of ifosfamide. Toxicity was less marked with this schedule. G-CSF was not given. Although grade 3 myelosuppression was reported in 20% of 66 cycles there was no grade 4 myelosuppression. There were 6 episodes of neutropenic fever (9% of cycles). There was no neurotoxicity.
2. OBJECTIVES AND OUTCOME MEASURES

2.1 Objectives
The objectives of the study are to compare four chemotherapy regimens in recurrent/refractory ES: cyclophosphamide & topotecan, irinotecan & temozolomide, gemcitabine & docetaxel, and high dose ifosfamide, in order to identify the best one for use as a backbone in future treatment with respect to efficacy (imaging response and survival), toxicity and acceptability to patients.

2.2 Outcome Measures

2.2.1 Primary outcome measure
- Phase II: Objective imaging response (OR) after 4 cycles of trial treatment, measured according to RECIST criteria (see Appendix 1)
- Phase III: Event-free survival (EFS)

2.2.2 Secondary outcome measures
- EFS (phase II)
- OR (phase III)
- PFS
- Overall survival (OS)
- Toxicity, defined by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (see Appendix 2)
- Imaging response after cycles 2 and 6 (for TC, IT and GD arms) and at the end of trial treatment (as per primary outcome for Phase II)
- PET-CT response will be analysed as per primary outcome for Phase II
- Quality of life (QoL)
- Days spent in hospital

3. TRIAL DESIGN
rEECur is a Multi-Arm, Multi-Stage (MAMS) randomised phase II / phase III, open-label, international trial. Patients will be randomised at trial entry to receive one of up to four regimens.

Some patients will not be eligible for randomisation to one or more chemotherapy regimens and will be randomised between the remaining regimens for which they are eligible.

The phase II part will comprise two stages. The first stage will include four chemotherapy arms. When 50 patients are recruited to each arm, one arm will be dropped based on activity and/or toxicity. The second stage will be a 3-way randomisation between the remaining arms. When 25 additional patients have been recruited to each arm, a second arm will be dropped based on activity and/or toxicity. The remaining two arms will progress to phase III evaluation. Patients in these two arms who took part in the phase II stage will contribute data to the phase III stage.

Using the rolling MAMS design will allow the introduction of novel agents or regimens as new arms, if appropriate. The introduction of new arms will take place pending approval of a substantial amendment by the relevant Competent Authority (the MHRA in the UK).
## 4. ELIGIBILITY

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

| Inclusion criteria | 1. Histologically confirmed ES.  
2. Disease progression (during or after completion of first line treatment) or any subsequent recurrence  
OR  
Refractory disease, defined by progression during first line treatment or within 12 weeks of its completion. Disease progression will be based on RECIST criteria (see Appendix 1). The appearance of new bone lesions on bone scan will require confirmation with cross-sectional imaging.  
3. Soft tissue disease component evaluable by cross-sectional imaging (RECIST). Patients with bone disease without a measurable soft tissue component or bone marrow disease only will be eligible for the study but will not contribute to the phase II primary outcome measure.  
4. Age ≥ 4 years and <50 years.  
5. Patient assessed as medically fit to receive cytotoxic chemotherapy.  
6. Documented negative pregnancy test for female patients of childbearing potential.  
7. Patient agrees to use effective contraception during therapy and for 12 months after last trial treatment, where applicable.  
8. Written informed consent from the patient and/or parent/legal guardian. |
|---|---|
| Exclusion criteria | 1. Bone marrow infiltration resulting in Absolute Neutrophil Count (ANC) <1.0 x 10^9/L or platelets <75 x 10^9/L.  
2. Cytotoxic chemotherapy or other investigational medicinal product (IMP) within previous two weeks.  
3. Myeloablative therapy within previous eight weeks.  
4. Radiotherapy to target lesion within previous six weeks.  
5. Pregnant or breastfeeding women.  
6. Follow-up not possible due to social, geographic or psychological reasons.  
7. Previous randomisation into the rEECur trial. |
| Additional criteria for specific arms | 1. Patients with a contraindication to any IMP may be entered into the study but may not be randomised to receive an arm that contains a contraindicated IMP. They will be eligible for trial entry as long as they can be randomised between a minimum of two study arms.  
2. Patients who are unable to receive one or more IMPs due to local or national funding arrangements will be eligible for trial entry as long as they can be randomised between a minimum of two study arms.  
3. Patients and investigators may decline randomisation to one or more trial regimens but will be eligible for trial entry as long as they can be randomised between a minimum of two study arms.  
4. Patients who have previously received one of the trial regimens off-trial may not be randomised to receive that chemotherapy regimen again. However, patients who have received cyclophosphamide during first line therapy may be randomised to receive the TC arm and patients who have had ifosfamide during first line therapy may receive the ifosfamide arm if they do not have pre-existing renal or other toxicity that would necessitate in rEECur a dose modification as described in section 7.2.4. There is no requirement for a minimum time between receiving first line ifosfamide and entry to rEECur. |

**Notes:**

Patients with bone marrow infiltration are eligible to enter the trial but they must meet all inclusion and no exclusion criteria, including ANC and platelet requirements.

Patients with reproductive potential must agree to use effective contraception during the period of therapy. Both men and women of childbearing potential should be advised to use effective...
contraception to avoid pregnancy up to 12 months after the last dose of study treatment. Effective contraceptive methods include latex condoms, diaphragms, cervical caps, etc.

Female patients must not breastfeed during chemotherapy. There is little evidence on which to base advice about breastfeeding after completion of chemotherapy. Centres are advised to seek local expert help in this situation.

5. SCREENING AND CONSENT

5.1 Screening

All patients who fit the clinical and imaging eligibility criteria in section 4 will be eligible for trial entry. No additional screening investigations are required.

A complete list of assessments at diagnosis is given in section 7.5.

5.2 Informed Consent

It is the responsibility of the investigator, or person to whom the investigator delegates the responsibility in compliance with national regulations, to obtain written informed consent for each patient prior to performing any trial related procedure. Where this responsibility has been delegated, this must be explicitly stated on a Site Signature and Delegation Log (or country specific equivalent). Country specific Participant Information Sheets (PIS) are provided along with summary information sheets, which may be handed out initially before the full PIS, to facilitate this process.

Investigators must ensure that they adequately explain the aims, trial treatments, anticipated benefits and potential hazards of taking part in the trial to the patient. The investigator should also stress that the patient is completely free to refuse to take part or withdraw from the trial at any time. The patient should be given ample time (e.g. 24 hours) to read the PIS and to discuss their participation with others outside of the site research team if they wish to do so. The patient must be given an opportunity to ask questions which should be answered to their satisfaction.

As the trial includes both child and adult patients, written consent/assent will be obtained from the patient wherever it is possible to do so (as appropriate according to age and national legislation). There is a section on the Parent Informed Consent Form where assent can be obtained. For those children who are not able to read, write or understand regarding assent, the clinician will explain the study and obtain verbal assent.

If the patient and/or parent/legal guardian agrees to participate in the trial they should be asked to sign and date the latest version of the applicable Informed Consent Form (ICF). The investigator or delegate where appropriate, must then sign and date the form. A copy of the ICF should be given to the patient and/or parent/legal guardian, a copy should be filed in the patient's medical records, and the original placed in the Investigator Site File (ISF) or country specific equivalent henceforth referred to as ISF. Once the patient is entered into the trial the patient's Trial Number should be entered on the ICF maintained in the ISF. If allowed by country specific legislation/guidance (as specified in the country specific quality and trial management plan, see Appendix 3) and if the patient has given explicit consent, a copy of the signed ICF should be sent to the applicable National Coordinating Centre (for the UK this will be the UK Coordinating Centre) for review. Where national guidelines do not permit transfer of ICFs outside of the treating organisation, consent will be monitored by the applicable National Coordinating Centre at site visits.

Details of the informed consent discussions should be recorded in the patient’s medical records. These should include date of, and information regarding, the initial discussion, the date consent was given, with the name of the trial and the version number of the PIS and ICF. Throughout the trial the patient and/or parent/legal guardian should have the opportunity to ask questions about the trial and any new information that may be relevant to the patient’s continued participation should be shared with them in a timely manner. On occasion it may be necessary to re-consent the patient in which case the process above should be followed and the patient’s right to withdraw from the trial be respected.

Electronic copies of the PIS and ICF are available from the applicable National Coordinating Centre and should be printed or photocopied onto headed paper of the local institution where required by country specific legislation/guidance.
Details of all patients approached about the trial should be recorded on a patient screening and enrolment log, and as specified in the country specific quality and trial management plan (see Appendix 3).

With the patient’s and/or parent/legal guardian’s prior consent, and if required by country specific legislation/guidance, the patient’s General Practitioner/Primary Physician will also be informed that they are taking part in the trial. A General Practitioner/Primary Physician Letter is provided electronically for this purpose but it is anticipated that this letter will be translated and adapted in accordance with national practices.

6. TRIAL ENTRY

Patients may be entered into the trial by a site once the applicable National Coordinating Centre has confirmed that all regulatory requirements have been met by the site and the site has been activated for randomisation by the UK Coordinating Centre.

Once informed consent has been obtained, patients can be randomised between chemotherapy regimens. Randomisation must be performed prior to the commencement of any trial treatment.

Pre-treatment evaluations should be carried out by sites as detailed in section 7.5.1.

6.1 Randomisation

At trial entry, patients will be randomised to one of the following treatment arms:

- TC 6 cycles of intravenous topotecan and cyclophosphamide  
- IT 6 cycles of intravenous irinotecan and oral temozolomide  
- GD 6 cycles of intravenous gemcitabine and docetaxel  
- IFOS 4 cycles of intravenous ifosfamide

Treatment according to the randomised regimen must begin within 2 weeks of randomisation.

6.2 Procedure for randomisation

It is expected that patients will be randomised 4-ways between all four available arms unless there are good clinical or logistical reasons not to do so. However, it is likely that certain treatments will not be available in some countries and that patients may only be eligible for a sub-set of the treatment arms, or may refuse certain arms, so it will not always be possible to randomise between all four treatment options. Patients must be eligible for at least two arms to be entered into the study. This flexibility will allow more patients to be recruited into the trial. Therefore, a randomisation that allows eligible patients to be randomised between two, three or four treatment arms will be employed. At trial entry, each patient will be assessed for suitability for each treatment and the appropriate randomisation options will be selected:

4-way option: TC or IT or GD or IFOS
3-way options:  
TC or IT or GD  
TC or GD or IFOS  
TC or IT or IFOS  
IT or GD or IFOS
2-way options:  
TC or IT  
TC or GD  
TC or IFOS  
IT or GD  
IT or IFOS  
GD or IFOS

Patients will be allocated in a 1:1:1:1, 1:1:1 or 1:1 ratio respectively.
Informed consent must be obtained prior to performing randomisation as described in section 5.2. Randomisation should be performed by sites using the rEECur online Remote Data Capture (eRDC) system which has been developed by the Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham (the UK Coordinating Centre). The randomisation program will allocate treatment via a computerised minimisation algorithm.

https://www.cancertrials.bham.ac.uk/rEECurLive/

In order to randomise a patient, an online Eligibility Checklist must be completed followed by a Randomisation Form. All of the requested information must be available at the time of randomisation. The randomisation will be minimised by:

- Disease type (primary refractory; 1st recurrence <2 years; 1st recurrence ≥2 years; 2nd or subsequent recurrences),
- Site(s) of disease recurrence or progression(local only; pleuropulmonary metastases only; other metastatic)
- Whether measurable or non-measurable disease

The patient’s treatment allocation and Trial Number will be confirmed at the end of the randomisation process.

A copy of the randomisation report should be printed and filed in the ISF and in the patient’s medical records.

In case of any problems with online randomisation, a paper Eligibility Checklist and Randomisation Form should be completed. These details can be phoned through to the UK Coordinating Centre using the numbers below:

RANDOMISATION
(09:00 to 17:00 GMT, Monday to Friday)
☎️ + 44 (0) 121 414 3366 or + 44 (0) 121 414 7844

General Enquiries:
☎️ +44 (0)121 415 1060 or reecur@trials.bham.ac.uk

The Trial Number will be used to identify the patient and should be recorded on any further correspondence with the applicable National Coordinating Centre. The Trial Number should also be documented on the original signed ICF filed in the ISF.

If allowed by country specific legislation (as specified in Appendix 3) and if consent has been given for this, a copy of the patient’s ICF must be sent to the applicable National Coordinating Centre.
7. TREATMENT DETAILS

7.1 Trial treatment

The following are regarded as IMPs for the purposes of this trial:

- Cyclophosphamide
- Docetaxel
- Gemcitabine
- Ifosfamide
- Irinotecan
- Temozolomide
- Topotecan

All IMPs will be provided from routine hospital stock at sites.

Full details of the IMPs, including preparation, labelling and accountability, are contained in the country specific Pharmacy Manual.

IMPs for parenteral administration should be diluted prior to infusion according to locally validated practice and/or procedures for the aseptic preparation of chemotherapy agents.

Such practice and/or procedures should also reflect the published data on the compatibility of IMP with the intended container, the chemical stability of IMP with the proposed diluent for infusion at the intended final concentrations of the prepared infusion and the appropriate storage conditions consequent on the choices made. A note should be made in the Pharmacy File which documents:

- The relevant practices/procedures with version control, updated as appropriate during the duration of the trial
- The method of preparation of the infusion with respect to the container, diluent, concentration and any other relevant information
- The storage conditions applied to the prepared infusion.

7.2 Treatment schedules and dose modifications

7.2.1 Topotecan and Cyclophosphamide (TC)

The first cycle of TC must begin within 2 weeks of randomisation.

7.2.1.1 Agents and dosage

Cycles of TC should be given at 21 day intervals or on haematological recovery to ANC \( \geq 1.0 \times 10^9/L \), platelets \( \geq 75 \times 10^9/L \), whichever is the later.

Body surface area should be calculated according to institutional practice.

No adjustments will be made to dose modification criteria for patients with bone marrow infiltration causing myelosuppression.
**TC**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Schedule</th>
<th>Total Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOPOTECAN</td>
<td>0.75 mg/m²</td>
<td>d1, d2, d3, d4, d5</td>
<td>3.75 mg/m²/cycle</td>
</tr>
<tr>
<td>(IV infusion, 30 min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYCLOPHOSPHAMIDE</td>
<td>250 mg/m²</td>
<td>d1, d2, d3, d4, d5</td>
<td>1.25 g/m²/cycle</td>
</tr>
<tr>
<td>(IV infusion, 1 h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G-CSF</td>
<td>Not mandatory</td>
<td></td>
<td>Section 7.10.5</td>
</tr>
</tbody>
</table>

The dose of cyclophosphamide used in this schedule will not normally require the use of hydration and/or MESNA urothelial protection. Use of these is at the discretion of the responsible physician based on patient experience and toxicity associated with first-line treatment.

7.2.1.2 Patient monitoring and assessments

Refer to sections 7.3 to 7.5.

7.2.1.3 Local control measures

Manoeuvres to achieve local control of all sites of disease are strongly encouraged where possible. The timing and modality of local therapies are at the discretion of the responsible clinician. However, local control measures for all target lesions must be delayed until after the response assessment following cycle 4.

Details of local control treatments will be captured on the Case Report Form (CRF).

7.2.1.4 Stem cell mobilisation and myeloablative therapy

Myeloablative therapy may be given at the discretion of the responsible clinician. However, where alternative chemotherapy regimens are to be used for stem cell mobilisation they must be delayed until after cycle 4.

Details of myeloablative therapy will be captured on the CRF.

7.2.1.5 Duration of treatment

In the absence of disease progression, a minimum of 6 cycles of TC will be given. For patients with stable disease or an objective response on imaging after 6 cycles, treatment may continue further at the discretion of the responsible clinician. Clinicians who choose to use myeloablative therapy after the sixth cycle may use their discretion regarding the number of additional TC cycles to give prior to myeloablative therapy. Minimal data on the additional cycles received will be collected on the CRF and patients will continue to be followed up for EFS and OS.

7.2.1.6 Toxicity

**Haematological toxicity**

Preference should be given to G-CSF support rather than dose reduction. If significant toxicity continues, despite G-CSF support, as defined by:

Day 21 Haematological recovery (ANC ≥1.0 x 10⁹/L, platelets ≥75 x 10⁹/L) delayed ≥14 days:

- Reduce topotecan dose by 20% for next TC cycle

For repeated episodes of febrile neutropenia grade 3 or 4 after ≥2 cycles:

- Reduce topotecan dose by 20% for next TC cycle

In the event of further episodes of toxicity, the topotecan dose should be reduced by an additional 20%. If toxicity recurs after a second dose reduction, discontinue study treatment.
Haematuria or haemorrhagic cystitis

Haematuria detected using a dipstick test should be confirmed via urine microscopy.

Treatment is at the discretion of the responsible clinician. The following suggestions may be followed or adapted as appropriate.

Microscopic haematuria during cyclophosphamide infusion:

- If hydration is not currently established, commence an infusion of the locally preferred fluid at a rate of at least $83 \text{ ml/m}^2/\text{hour}$ (2L/m²/24 hours). If hydration is established, double the rate of infusion.
- If MESNA is not currently being administered, consider whether it is necessary to do so. If MESNA is required treatment may be given as IV boluses or added to the infusion fluid at a dose equivalent to 100 mg/m² every eight hours (120% of cyclophosphamide dose in 24 hours).
- If MESNA is currently being given, consider the need to increase the dose and/or frequency of administration.

≥ Grade 2 haematuria:

- Discontinue cyclophosphamide. The advice provided for grade 1 haematuria above may be followed or adapted as clinically appropriate. Ensure that hydration and MESNA are prescribed for subsequent treatment cycles.

Other grade 3 or 4 non-haematological toxicities

Investigators may use their discretion with regards to dose reductions. In general, however, for other clinically significant grade 3 or 4 non-haematological toxicities attributed to study treatment:

- Withhold both agents until toxicity resolves to ≤ grade 2.
- If toxicity has resolved to ≤ grade 2 by day 35, both agents may be restarted with a 20% dose reduction of the responsible agent. If neither agent is clearly responsible for toxicity, both will be reduced by 20%.

Grade 3 or 4 non-haematological toxicity after one dose reduction:

- a second 20% dose reduction may be made.

Grade 3 or 4 non-haematological toxicity after two dose reductions:

- discontinue study treatment.

### 7.2.2 Irinotecan and Temozolomide (IT)

**Local control and stem cell harvesting at investigator’s discretion, to be delayed until after cycle 4**

Cycles of IT should be given at 21 day intervals or on haematological recovery to ANC ≥1.0 x 10⁹/L, platelets ≥75 x 10⁹/L, whichever is the later.
Body surface area should be calculated according to institutional practice.

<table>
<thead>
<tr>
<th>IT</th>
<th>Formula</th>
<th>Doses</th>
<th>Inj. Method</th>
<th>Total dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRINOTECAN</td>
<td>50 mg/m²</td>
<td>d1, d2, d3, d4, d5</td>
<td>IV infusion, 60 min</td>
<td>250 mg/m²/cycle</td>
<td>Refer to section 7.2.2.6</td>
</tr>
<tr>
<td>TEMOZOLOMIDE</td>
<td>100 mg/m²</td>
<td>d1, d2, d3, d4, d5</td>
<td>by mouth, 1 h before irinotecan</td>
<td>500 mg/m²/cycle</td>
<td>Refer to section 7.2.2.6</td>
</tr>
<tr>
<td>CEFIXIME</td>
<td>Not mandatory</td>
<td></td>
<td></td>
<td></td>
<td>Refer to section 7.10.5</td>
</tr>
<tr>
<td>G-CSF</td>
<td>Not mandatory</td>
<td></td>
<td></td>
<td></td>
<td>Refer to section 7.2.2.6</td>
</tr>
<tr>
<td>LOPERAMIDE</td>
<td>Refer to section 7.2.2.6</td>
<td></td>
<td></td>
<td></td>
<td>Refer to section 7.2.2.6</td>
</tr>
</tbody>
</table>

Please refer to the country specific Pharmacy Manual for suggestions regarding administration. Patients who have difficulty swallowing capsules may open the capsules required for each dose of temozolomide and mix the total contents with 5-10 ml. of fruit juice (not grapefruit) or apple sauce – use more if necessary to include the contents of several capsules - and administer from an oral syringe or spoon.

A suggested method for doing this is provided in the UK pharmacy manual.

**7.2.2.2 Patient monitoring and assessments**

Refer to sections 7.3 to 7.5

**7.2.2.3 Local control measures**

Manoeuvres to achieve local control of all sites of disease are strongly encouraged where possible. The timing and modality of local therapies are at the discretion of the responsible clinician. However, local control measures for all target lesions must be delayed until after the response assessment following cycle 4.

**7.2.2.4 Stem cell mobilisation and myeloablative therapy**

Myeloablative therapy may be given at the discretion of the responsible clinician. However, where alternative chemotherapy regimens are to be used for stem cell mobilisation they must be delayed until after cycle 4.

**7.2.2.5 Duration of treatment**

In the absence of disease progression, a minimum of 6 cycles of IT will be given. For patients with stable disease or an OR on imaging after 6 cycles, treatment may continue further at the discretion of the responsible clinician. Clinicians who choose to use myeloablative therapy after the sixth cycle may use their discretion regarding the number of additional IT cycles to give prior to myeloablative therapy. Minimal data on the additional cycles received will be collected on the CRF and patients will continue to be followed up for EFS and OS.

**7.2.2.6 Toxicity**

**Haematological toxicity**

Weekly monitoring of blood counts is recommended. Preference should be given to G-CSF support rather than dose reduction. If significant toxicity continues despite G-CSF support as defined by:

Haematological recovery (ANC ≥1.0 x 10⁹/L, platelets ≥75 x 10⁹/L) delayed ≥14 days:
- Reduce temozolomide dose by 20% for next IT cycle

Repeated episodes of neutropenic sepsis grade 3 or 4 after ≥2 cycles:
  - Reduce temozolomide dose by 20% for next IT cycle

In the event of further episodes of toxicity, the temozolomide dose should be reduced by an additional 20%. If toxicity recurs after a second dose reduction, discontinue study treatment.

**Diarrhoea**

Irinotecan-associated diarrhoea may be characterised as ‘early onset’ or ‘late onset’

‘Early onset’ diarrhoea occurring within 8 hours of the first irinotecan dose and possibly associated with other cholinergic symptoms (Cholinergic syndrome).
  - Give atropine according to institutional guidelines. Consider prophylactic atropine prior to subsequent irinotecan doses.

‘Late onset’ diarrhoea occurring 24 or more hours after irinotecan dose.
  - Loperamide should be given according to institutional guidelines. Patients and/or parents/carers should be counselled as to the need to start loperamide promptly once diarrhoea has started and seek further advice from their treatment centre if diarrhoea is uncontrolled with maximal Loperamide dosing.
  - Consider prophylactic cefixime 8 mg/kg (under 12 years) or 400 mg (over 12 years) daily by mouth from d-2 to d+7 if not already given.

Grade ≥3 diarrhoea for more than 3 days despite maximum loperamide therapy:
  - Consider use of octreotide, buscopan or oral budesonide
  - Reduce irinotecan dose by 20% for next IT cycle
  - If diarrhoea is ongoing on day 21, delay next cycle for up to 2 weeks until diarrhoea resolves to < grade 1
  - If grade 3 or 4 toxicity persists >2 weeks despite suitable symptomatic treatment, discontinue study treatment

If grade ≥3 diarrhoea occurs with a reduced dose of irinotecan:
  - Reduce irinotecan dose by 20% for next IT cycle
  - If diarrhoea is ongoing on day 21, delay next cycle for up to 2 weeks until diarrhoea resolves to < grade 1
  - If the same level of toxicity persists >2 weeks despite suitable symptomatic treatment, discontinue study treatment

**Liver toxicity**

Hepatic injury, including fatal hepatic failure, has been reported in some patients treated with temozolomide. Liver toxicity may occur several weeks or more after the last treatment with temozolomide. Liver function tests should be performed prior to each cycle of IT. If abnormal, clinicians should assess the benefit/risk prior to initiating temozolomide including the potential for fatal hepatic failure.

**Other grade 3 or 4 non-haematological toxicities**

Interstitial pulmonary disease, cardiac disorders and thromboembolic events have all been reported in patients receiving irinotecan. Cytomegalovirus and hepatitis B reactivation have been reported in patients receiving temozolomide. Patients with known risk factors for these complications should be closely monitored during treatment.

Investigators may use their discretion with regards to dose reductions. In general, however, for other grade 3 or 4 non-haematological toxicities attributed to study treatment:
  - Withhold both agents until toxicity resolves to ≤ grade 2
If toxicity has resolved to ≤ grade 2 by day 35, both agents may be restarted with a 20% dose reduction of the responsible agent. If neither agent is clearly responsible for toxicity, both will be reduced by 20%.

Grade 3 or 4 non-haematological toxicity after one dose reduction:
- a second 20% dose reduction may be made

Grade 3 or 4 non-haematological toxicity after two dose reductions:
- discontinue study treatment

### 7.2.3 Gemcitabine and Docetaxel (GD)

The first cycle of GD must begin within 2 weeks of randomisation.

No adjustments will be made to dose modification criteria for patients with bone marrow infiltration causing myelosuppression.

#### 7.2.3.1 Agents and dosage

Cycles of GD should be given at 21 day intervals or on haematological recovery to ANC $\geq 1.0 \times 10^9$/L, platelets $\geq 75 \times 10^9$/L, whichever is later.

Body surface area should be calculated according to institutional practice.

<table>
<thead>
<tr>
<th>GD</th>
<th><strong>GEMCITABINE</strong></th>
<th>900 mg/m² (IV infusion, 90 min)</th>
<th>d1, d8</th>
<th>(Total dose: 1.8 g/m²/cycle)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>DOCETAXEL</strong></td>
<td>80 mg/m² (IV infusion, 1 h)</td>
<td>d8</td>
<td>(Total dose: 80 mg/m²/cycle)</td>
</tr>
<tr>
<td></td>
<td><strong>DEXAMETHASONE</strong></td>
<td>Mandatory</td>
<td>3 mg/m² (under 16 years) or 8 mg (over 16 years)</td>
<td>d7, d8, d9</td>
</tr>
<tr>
<td></td>
<td><strong>G-CSF</strong></td>
<td>Mandatory - refer to section 7.10.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please refer to the country specific Pharmacy Manual for suggestions regarding administration.
7.2.3.2 Patient monitoring and assessments

Refer to sections 7.3 to 7.5

7.2.3.3 Local control measures

Manoeuvres to achieve local control of all sites of disease are strongly encouraged where possible. The timing and modality of local therapies are at the discretion of the responsible clinician. However, local control measures for all target lesions must be delayed until after the response assessment following cycle 4.

7.2.3.4 Stem cell mobilisation and myeloablative therapy

Myeloablative therapy may be given at the discretion of the responsible clinician. However, where alternative chemotherapy regimens are to be used for stem cell mobilisation they must be delayed until after cycle 4.

7.2.3.5 Duration of treatment

A minimum of 6 cycles of GD will be given. For patients with stable disease or an OR on imaging after 6 cycles, treatment may continue further at the discretion of the responsible clinician. Clinicians who choose to use myeloablative therapy after the sixth cycle may use their discretion regarding the number of additional GD cycles to give prior to myeloablative therapy. Minimal data on the additional cycles received will be collected on the CRF and patients will continue to be followed up for EFS and OS.

7.2.3.6 Toxicity

Haematological toxicity at day 1

G-CSF support is mandatory for GD cycles. If significant toxicity continues despite G-CSF support as defined by:

Haematological recovery (ANC ≥1.0 x 10^9/L, platelets ≥75 x 10^9/L) delayed ≥14 days:
- Reduce doses of both agents by 20% for next GD cycle

Repeated episodes of neutropenic sepsis grade 3 or 4 after ≥ two cycles:
- Reduce doses of both agents by 20% for next GD cycle

In the event of further episodes of toxicity, the doses of gemcitabine and docetaxel should be reduced by an additional 20%. If toxicity recurs after a second dose reduction, discontinue study treatment.

Haematological toxicity at day 8

ANC <0.5 x 10^9/L and/or platelets <50 x 10^9/L:
- omit day 8 gemcitabine and docetaxel, reduce doses of both agents by 20% for next and all subsequent GD cycles

0.5 ≤ ANC < 1.0 and/or 50 ≤ platelets < 100 x 10^9/L:
- Institutional guidance varies in this situation. For patients recruited to rEECur, investigators are given discretion to use one of three possible approaches:
  - give 100% dose according to the protocol. Investigators are encouraged to use this approach unless their standard institutional practice is to reduce or delay the doses of one or both agents.
  - reduce doses of both agents by 20% for this and subsequent cycles; give both agents on day 8
  - delay treatment for up to 1 week to allow ANC and platelet count to recover. If ANC and/or platelet count has not recovered by day 15, omit both agents for this cycle and reduce doses of both agents for subsequent cycles by 20%
Repeated haematological toxicity at day 8 despite dose reduction:
  - One further dose reduction of 20% may be applied for both agents.
Repeated haematological toxicity at day 8 despite two dose reductions:
  Discontinue study treatment

**Hypersensitivity**
Grade 1 and 2 hypersensitivity attributed to docetaxel:
  - Decrease rate of infusion, administer chlorphenamine
  - Use prophylactic chlorphenamine with future doses
≥ grade 3 hypersensitivity:
  - Omit docetaxel from future cycles

**Weight gain/fluid retention**
≥ grade 3 fluid retention attributed to docetaxel:
  - Omit docetaxel from future cycles

**Posterior reversible encephalopathy syndrome (PRES)**
If PRES develops during therapy
  - Institute supportive measures including blood pressure control and anti-seizure medication
  - Permanently discontinue gemcitabine

**Other grade 3 or 4 non-haematological toxicities**
Investigators may use their discretion with regards to dose reductions. In general, however, for other grade 3 or 4 non-haematological toxicities attributed to study treatment:
  - Withhold both agents until toxicity resolves to ≤ grade 2
  - If toxicity has resolved to ≤ grade 2 by day 35, both agents may be restarted with a 20% dose reduction of the responsible agent. If neither agent is clearly responsible for toxicity, both will be reduced by 20%
Grade 3 or 4 non-haematological toxicity after one dose reduction:
  - a second 20% dose reduction may be made
Grade 3 or 4 non-haematological toxicity after two dose reductions:
  - discontinue study treatment

### 7.2.4 Ifosfamide (IFOS)

The first cycle of IFOS must begin within 2 weeks of randomisation.

No adjustments will be made to dose modification criteria for patients with bone marrow infiltration causing myelosuppression.
7.2.4.1 Agents and dosage

Cycles of IFOS should be given at 21 day intervals or on haematological recovery to ANC \( \geq 1.0 \times 10^9/L \), platelets \( \geq 75 \times 10^9/L \), whichever is later.

Body surface area should be calculated according to institutional practice.

<table>
<thead>
<tr>
<th>IFOS</th>
<th>3 g/m(^2) (IV infusion, 24 h)</th>
<th>d1, d2, d3, d4, d5 (Total dose: 15 g/m(^2)/cycle)</th>
<th>plus MESNA and hydration*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFOSFAMIDE</td>
<td>d1, d2, d3, d4, d5</td>
<td>(Total dose: 15 g/m(^2)/cycle)</td>
<td>plus MESNA and hydration*</td>
</tr>
<tr>
<td>G-CSF</td>
<td>Mandatory starting 48 hours after final IFOS infusion - refer to section 7.10.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MESNA</td>
<td>400 mg/m(^2) IV bolus 1 hour before first ifosfamide dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 g/m(^2)/day IV infusion during days 1 to 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>800 mg/m(^2) IV or oral following final ifosfamide dose</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please refer to the country specific Pharmacy Manual for suggestions regarding administration.

7.2.4.2 Patient monitoring and assessments

Refer to sections 7.3 to 7.5

7.2.4.3 Local control measures

Manoeuvres to achieve local control of all sites of disease are strongly encouraged where possible. The modality of local therapy is at the discretion of the responsible clinician. However, local control measures for all target lesions must be delayed until after the response assessment following cycle 4.

7.2.4.4 Stem cell mobilisation and myeloablative therapy

Myeloablative therapy may be given at the discretion of the responsible clinician. However, where alternative chemotherapy regimens are to be used for stem cell mobilisation they must be delayed until after cycle 4.

7.2.4.5 Duration of treatment

In the absence of disease progression, a maximum of 4 cycles of IFOS will be given. No further cycles of IFOS should be administered.

7.2.4.6 Hydration

Sufficient hydration (2-3 L/m\(^2\)/day) with appropriate electrolyte supplementation must be provided during ifosfamide infusions. Routine clinical monitoring including heart rate, respiratory rate, blood pressure, body weight and urine output is essential as part of routine clinical care in this setting; the application of diuretics may become necessary in case of oedema or hypertension.

7.2.4.7 Toxicity

Haematological toxicity

Preference should be given to G-CSF support rather than dose reduction. If significant toxicity continues despite G-CSF support as defined by:

Haematological recovery (ANC \( \geq 1.0 \times 10^9/L \), platelets \( \geq 75 \times 10^9/L \)) delayed \( \geq 14 \) days or

Repeated episodes of neutropenic sepsis grade 3 or 4 after \( \geq 2 \) cycles:

- Discontinue study treatment.
Nephrotoxicity / Renal function monitoring

Glomerular Filtration Rate (GFR)

Serum creatinine and GFR should be monitored prior to each cycle of ifosfamide. GFR should be assessed according to routine practice at the trial site using either isotope clearance, or calculated creatinine clearance using one of the formulae below.

Schwartz’s Formula (1-18 years)[59]

According to Schwartz's formula, creatinine clearance (Ccrea) can be calculated from single serum samples:

\[
C_{\text{crea}} = \frac{F \times \text{Height [cm]}}{\text{Crea serum [mg/dl]}} \times \text{ml/min/1.73m}^2
\]

Where \( F \) is proportional to body muscle mass, hence depending on age and gender:

- **Infants (<1 year of age)**: \( F = 0.45 \)
- **Males, 1-16 years**: \( F = 0.55 \)
- **Females, 1-21 years**: \( F = 0.55 \)
- **Males, 16-21 years**: \( F = 0.70 \)

Normal range 90-120 ml/min/1.73 m²

Cockcroft- Gault Formula (>18 years) [60]

\[
\begin{align*}
\text{Females} & \quad \frac{1.05 \times (140 - \text{age (yrs)}) \times \text{wt(kg)}}{\text{Crea serum [\mu mol/L]}} \\
\text{Males} & \quad \frac{0.85 \times (140 - \text{age (yrs)}) \times \text{wt(kg)}}{72 \times \text{Crea serum [mg/dl]}}
\end{align*}
\]

PLEASE NOTE: These formulas have not been confirmed in patients receiving repeated cycles of intensive chemotherapy OR in adolescents. Renal function may be overestimated by these methods.

Tubular function (Tp/Ccrea or Tmp/GFR) [61, 62]

Tubular function should be monitored prior to each cycle. For tubular function, serum electrolyte and bicarbonate (HCO₃) levels, and the calculation of fractionated phosphate reabsorption, relative amino acid reabsorption and/or fractionated sodium excretion from single urine samples may be calculated according to Rossi et al.:

Fractionated phosphate reabsorption:

\[
T_p/C_{\text{crea}} = \text{Phosphate}_{\text{serum}} \times \text{Creatinine}_{\text{urine}} [\mu mol/\text{ml}]
\]

Reference value for all ages >1 year: mean = 1.5, lower limit = 1.07

Ifosfamide adjustment to renal function

Classify toxicity as grade 0/1, 2, or 3/4 and adjust ifosfamide treatment as indicated.
<table>
<thead>
<tr>
<th>Toxicity grade*</th>
<th>GFR (ml/min/1.73 m²)</th>
<th>HCO₃** (mmol/l)</th>
<th>Action (apply worst grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0/1</td>
<td>≥60</td>
<td>≥17.0</td>
<td>Continue ifosfamide dose 100%</td>
</tr>
<tr>
<td>Grade 2-4</td>
<td>&lt;60</td>
<td>&lt;17</td>
<td>Delay treatment and recheck renal function after one week. If grade 2-4 toxicity persists after one week, discontinue study treatment.</td>
</tr>
</tbody>
</table>

*  Toxicity is scored from 0 to 4, analogous to the CTCAE system, but for the purpose of modifying treatment grades 0 and 1 and grades 2, 3 and 4 are considered together.

**  Low values of HCO₃ should be re-checked when the patient is clinically stable (to rule out infection as a cause, etc.) before modifying ifosfamide dose / treatment.

<table>
<thead>
<tr>
<th>Toxicity grade*</th>
<th>Tp/Ccrea (Tm/P/GFR) (mmol/l)</th>
<th>Action (apply worst grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0/1</td>
<td>≥1.00</td>
<td>Continue ifosfamide dose 100%</td>
</tr>
<tr>
<td>Grade 2-4</td>
<td>&lt;1.00</td>
<td>In the absence of clinically significant electrolyte loss, continue ifosfamide dose 100%. If electrolyte loss is present, consider discontinuing study treatment.</td>
</tr>
</tbody>
</table>

**Haematuria or haemorrhagic cystitis**

Haematuria detected using a dipstick test should be confirmed via urine microscopy

Grade 1 microscopic haematuria during ifosfamide infusion: treatment is at the discretion of the responsible clinician. The following suggestions may be followed or adapted as appropriate:

- Give an additional bolus dose of MESNA 600 mg/m² and continue the 24 hour infusion of MESNA at double the current dose (6 g/m²/day).
- If there is scope to do so, increase the rate of the hydration infusion.

≥ Grade 2 haematuria:
- discontinue study treatment

**Central neurotoxicity**

Any central neurotoxicity with previous ifosfamide treatment:

- not eligible for IFOS

Grade 1-2 central neurotoxicity:

- consider using methylthioninium chloride (methylene blue) as follows:
  - ≥18 years: 50 mg (5 ml ampoule of 1% solution) 4 hourly, IV slow bolus
  - <18 years: 1 mg/kg/dose 4 hourly, IV slow bolus
- Patients who have had an episode of grade 1-2 ifosfamide-induced neurotoxicity in a previous cycle should receive one dose of methylthioninium chloride (methylene blue) 24 hours prior to ifosfamide. On the day of ifosfamide treatment the following dose schedule is recommended:
  - ≥18 years: 50 mg (5 ml ampoule of 1% solution) 6 hourly, IV slow bolus
  - <18 years: 1-2 mg/kg/dose 6 hourly, IV slow bolus
Grade 3 or 4 central neurotoxicity
  - discontinue study treatment

Other grade 2, 3 or 4 non-haematological toxicities
Investigators may use their discretion with regards to dose reductions. In general, however, for other grade 3 or 4 non-haematological toxicities attributed to study treatment:
  - Withhold ifosfamide until toxicity resolves to ≤ grade 2
  - If toxicity has resolved to ≤ grade 2 by day 35, ifosfamide may be restarted

Further Grade 3 or 4 non-haematological toxicity:
  - discontinue study treatment

7.3 Continued treatment following discontinuation of a trial arm
If a treatment arm is dropped from the trial patients who have stable disease or a treatment response at the time the arm is dropped may continue to be treated according to that regimen at the discretion of the individual investigator.

7.4 Schedule of assessments
The assessments included in the Schedule of Events in the Trial Synopsis (page vi) should be performed before and during treatment. Further monitoring can be performed according to institutional practice. Such further monitoring may be carried out at a hospital other than the trial site as all investigations would normally be part of routine care.

7.5 Assessments at diagnosis
Data on the assessments performed at diagnosis (including patient's initial diagnosis, histology, and staging) will be collected on the CRF.

7.5.1 Diagnosis of Ewing Sarcoma
Diagnosis of ES must be histologically confirmed in every patient. The diagnosis is based on the examination of routinely stained material supplemented by additional diagnostic methods as outlined below. Hematoxylin and eosin and Periodic-Acid-Schiff are necessary for preliminary classification, followed and supplemented by immuno-histochemistry and molecular biology.

CD99 immunohistochemistry is obligatory in the diagnostic work-up of Ewings Sarcoma Family of Tumours, as >95% of these show membraneous CD99 expression.

The definitive diagnosis may be based on examination of routinely stained material.

**plus** one of the following two investigations:
  - molecular/cytogenetic analysis (chromosome 22 rearrangement).
  - CD 99 (Mic-2) positivity.

7.5.2 Histological confirmation of Ewing Sarcoma at recurrence
Biopsy of recurrent disease is strongly recommended, to confirm the diagnosis and to allow storage of tumour material for studies of the biology of recurrent ES.

Where applicable, blood, fresh frozen tumour tissue, and paraffin-embedded tumour tissue should be deposited in existing tumour collections such as local or national tissue banks. Patients will be asked to given optional consent for these samples to be used for future research projects. Tissue samples should be collected and stored in accordance with country specific legislation/guidance.

Patients will be eligible for study entry without biopsy of recurrent disease.

7.5.3 Patient information
  - Physical exam including height, weight and surface area (calculated in accordance with
institutional practice).

- Assessment of performance status by Lansky score (age <16) [63], or WHO Performance Status (age ≥16) (see Appendix 4).

- Menstrual history and pregnancy test if indicated.

### 7.5.4 Quality of Life assessment

Quality of life (QoL) will be assessed and compared between the four chemotherapy regimens using age-appropriate tools (see section 8). Patients over the age of 5 years (and if applicable their parent/guardian) should be asked to complete the relevant age group QoL Booklet prior to the first cycle of chemotherapy. Prior to completing the baseline questionnaire a member of the site research team should discuss the questionnaire with the patient and answer any questions they may have regarding completion of the booklet. Once the patient has completed the baseline QoL Booklet the data should be entered onto the eRDC system. In some countries this task may be undertaken by the National Coordinating Centre (see Appendix 3).

### 7.5.5 Blood chemistry

- Blood biochemistry will be tested prior to chemotherapy to assess fitness to receive cytotoxic chemotherapy in line with institutional guidelines.

- GFR (calculated creatinine clearance (Ccrea) or isotopic). See section 7.2.4.6.

- Tubular function. See section 7.2.4.6.

### 7.5.6 Haematology

- Blood count

### 7.5.7 Radiological and other staging assessments

The following radiological and staging assessments will be performed

- Magnetic resonance imaging (MRI) or Computed Tomography (CT) scan of any symptomatic site of disease and all target lesions.

- Staging of distant metastases by radionuclide whole body scan of skeleton, whole body MRI or Positron Emission Tomography (PET) CT. In the rEECur trial, PET CT is included as an experimental assessment to prospectively determine its validity in staging Ewing sarcoma and assessing disease response. However, it may be used for baseline and subsequent staging of distant metastatic disease as long as the quality of the CT component is sufficient to allow disease assessment according to RECIST 1.1 criteria. Centres should pay attention to whether intravenous contrast is given during PET CT in judging whether the CT component is adequate.

- Chest CT scan if not done for imaging of disease.

- Bone marrow assessment may be performed according to institutional practice if there is no other evidence of distant metastatic disease. Since most patients with bone marrow disease also have other metastatic disease evaluable by cross-sectional imaging, bone marrow assessment is not a mandatory investigation in rEECur, unless it is the only site of recurrent disease.

- PET CT if not done for staging of distant metastases (not mandatory, see Appendix 6). Centres that use PET alone or low resolution PET CT to evaluate metastatic disease must confirm the presence and size of metastases with appropriate cross-sectional imaging prior to study entry.

### 7.5.8 Definition of evaluable bone disease

Bone disease will only be evaluable for the OR outcome measure if there is a measurable soft tissue component in two dimensions. However, all eligible patients with bone disease irrespective of associated soft tissue will contribute to all other outcome measures.
7.5.9 Definition of pulmonary / pleural disease

One pulmonary / pleural nodule of >1 cm or more than one nodule of >0.5 cm, will be considered evidence of pulmonary / pleural metastases, as long as there is no other clear medical explanation for these lesions. In case of doubt, biopsies should be considered.

A solitary nodule of 0.5-1 cm or multiple nodules of 0.3-0.5 cm are questionable evidence of metastatic disease, and confirmation by biopsy is recommended.

One solitary nodule of <0.5 cm or several nodules of <0.3 cm are not regarded as clear evidence of lung disease. In such cases, individual decisions regarding biopsy have to be considered.

7.6 Assessments during treatment

Data on the assessments performed prior to chemotherapy, treatment received by the patient including any modifications and delays, supportive treatment, and toxicity will be collected on the CRF.

7.6.1 Prior to each cycle of chemotherapy

During treatment the patient should be clinically assessed in accordance with standard institutional policy. It is anticipated that the following assessments will be performed prior to the start of each cycle:

- Height, weight and surface area (calculated in accordance with institutional practice).
- Assessment of treatment toxicity (not applicable prior to first cycle).
- Full blood count
- Blood chemistry
- GFR (calculated creatinine clearance (Ccrea) or isotopic) and tubular function only for patients randomised to receive IFOS – see section 7.2.4.6. GFR and tubular function should also be assessed after the final cycle of IFOS.

7.6.2 Radiological assessments

- Target lesion re-evaluation: CT scan or MRI (with measurements) should be performed of all target lesions to assess response or progression at the following time points:
  - following chemotherapy cycle 2
  - following chemotherapy cycle 4
  - following chemotherapy cycle 6 (not applicable for patients randomised to IFOS)

Where possible the same imaging modality should be used at all time points to assess the size of target lesions.

Chest CT should be repeated after cycle 4 if it has not been performed for assessment of target lesions.

PET CT, if performed at baseline, should be repeated after cycle 4 (not mandatory). Increased FDG uptake alone on PET CT without an associated increase in the size or number of lesions must not be used to define disease progression. Additional radiological assessments will be at the investigator’s discretion.

7.6.3 Quality of Life assessments

Site Research Staff should ask patients over the age of 5 years (and if applicable their parent/guardian) to complete the relevant age group QoL Booklet at the following time points:

- On completion of chemotherapy cycle 2.
- On completion of chemotherapy cycle 4.

Once the patient has completed the QoL Booklet it the data should be entered onto the eRDC system. In some countries this task may be undertaken by the National Coordinating Centre (see Appendix 3).
7.7 Assessments at the end of treatment

Protocol defined treatment data will be collected on the CRF. Some patients will have additional non-protocol defined treatments such as local disease control, myeloablative treatment and additional chemotherapy. At the end of their total course of treatment the following assessments should be performed:

- Physical examination.
- All target lesions should be evaluated with CT or MRI (with measurements)
  
  Data will be collected on a Follow-up Form.

7.8 Follow-up assessments

Following completion of treatment, the frequency of follow-up assessments should be guided by local practice.

Disease related follow-up for the first 5 years should include as a minimum:

- History and physical examination at each visit. Any clinical findings suggestive of recurrence should be investigated with cross-sectional imaging, histological examination or bone-marrow examination as appropriate.
- Chest imaging: the imaging modality and frequency should follow institutional guidelines. As a guide, 3-4 monthly imaging for the first two to three years, then six-monthly imaging to five years would be appropriate.
- Sites of recurrent or refractory disease for which patients were recruited to the study: existing practice in this setting varies widely. Some centres image metastatic sites only on symptomatic disease progression. Others perform cross-sectional imaging of all metastatic sites at each follow up visit. For this study the frequency and modality of imaging will follow existing institutional guidelines.
- The primary tumour site should be followed up according to institutional guidelines. If the primary site was not involved at disease recurrence, routine follow up imaging will not be required for this study.

Patients will be followed up for progression, second malignancy and death until all trial objectives have been met.

A Follow-up Form should be completed every six months from the date of randomisation into the trial.

7.9 Treatment Compliance

Compliance for IMP treatment will be monitored by the applicable National Coordinating Centre and as specified in the country specific Pharmacy Manual and by the data received on the Treatment Forms.

All IMPs except for temozolomide are administered intravenously.

Patients and/or parents/legal guardians must be instructed to return any unused capsules of temozolomide if dispensed for home use, and a capsule count should be performed. Returns must be documented on the pharmacy drug accountability log. Sites should follow their local practice for destruction of unused capsules.

7.10 Supportive Treatment

7.10.1 Venous Access

A permanent indwelling venous access device is recommended. This is not a trial requirement.

7.10.2 Antiemetics

Patients should be treated with antiemetics appropriate to the anticipated emetogenicity of the allocated treatment schedule according to institutional practice.
7.10.3 Neutropenic fever
Neutropenic fever should be managed using broad spectrum agents according to institutional practice.

7.10.4 Pneumocystis jirovecii infection prophylaxis
Pneumocystis jirovecii prophylaxis may be given according to the recommendations of the national groups or institutional guidelines.

7.10.5 Granulocyte colony-stimulating factor
Treatment intensity is essential in the treatment of ES. G-CSF support is preferable to dose reduction for all regimens and its use is mandated for the GD and IFOS regimens. The dose and type of G-CSF to be used will be according to institutional guidelines. Daily G-CSF must be stopped 24 hours prior to chemotherapy commencing.

7.10.6 Blood products
Blood and platelet transfusions and the use of filtering and irradiating blood products should be according to institutional guidelines.

7.10.7 Diarrhoea
Management of irinotecan-associated diarrhoea is outlined in section 7.2.2 above and should be treated promptly and aggressively according to institutional guidelines.

7.10.8 Bisphosphonates
Bisphosphonates are given routinely as a supportive medication in some centres for patients with multifocal bone metastases. However, there is some evidence that they may have anti-tumour activity in Ewing sarcoma, and the role of zoledronic acid in Ewing sarcoma is currently being evaluated in the EE2012 trial (EudraCT 2012-002107-17). For participants in rEECur, bisphosphonates should NOT be given during trial-directed therapy (i.e. cycles 1 to 6 of TC, IT and GD or cycles 1 to 4 of IFOS).

7.11 Concomitant Medication
Since all treatment arms contain IMPs that have been used extensively in clinical practice, concomitant medications will be recorded in accordance with regulatory requirements for Serious Adverse Event (SAE) reporting only. Where concomitant medications are given in relation to standard clinical management, this information will not be reported for this trial.

7.12 Patient Withdrawal

7.12.1 Withdrawal from rEECur trial treatment
If a patient stops rEECur protocol treatment before the end of the prescribed minimum number of cycles, the reason should be recorded in the patient’s medical records and should be reported on the Treatment Discontinuation Form. Reasons for withdrawal from protocol treatment may include, but are not limited to:

- The patient withdraws consent to further data collection (see section 7.11.2)
- Unacceptable toxicity (see also section 7.2)
- Disease progression whilst on therapy
- If the patient becomes pregnant

rEECur will be analysed on an intention-to-treat (ITT) basis and any patients withdrawn from trial treatment will remain in the trial for follow-up unless the patient and/or parent/legal guardian explicitly withdraws consent for data collection (see section 7.12.2).
7.12.2 Withdrawal of consent to data collection

The patient and/or parent/legal guardian may withdraw consent at any time during the study. For the purposes of this trial, two types of withdrawal are defined:

- The patient would like to withdraw from trial medication, but is willing to be followed up according to the schedule of assessments (i.e. the patient has agreed that data can be collected and used in the trial analysis).
- The patient would like to withdraw from trial medication and is not willing to be followed up for the purposes of the trial at any further visits (i.e. only data collected prior to the withdrawal of consent can be used in the trial analysis).

The details of withdrawal (date, reason and type of withdrawal) should be clearly documented in the patient’s medical records. A Withdrawal of Consent Form should be completed.

A patient’s wishes with respect to their data must be respected.

7.12.3 Loss to follow-up

If a patient is lost to follow-up, every effort should be made to contact the patient’s General Practitioner/Primary Physician (if consented) to obtain information on the patient’s status. Similarly, if a patient’s care is transferred to another clinician, the patient should be followed up by that site and the applicable National Coordinating Centre should be informed.

8. QUALITY OF LIFE SUB-STUDY

The QoL Sub-study is designed to assess the patient’s well-being during chemotherapy, by use of a questionnaire collected at three specified time-points. This will provide insight into the impact treatment has on patients.

8.1 Questionnaires

The QoL Sub-study will utilise the following questionnaires:

- PedsQL™ 4.0 [64] is a validated QoL measure for children and adolescents. It includes 4 multidimensional scales including physical, emotional, social and school functioning. There are both age specific child self-report and parent-proxy versions available, the questionnaires are also available in a large number of different languages.
- European Organisation for Research and Treatment of Cancer (EORTC)-QLQ30 [65] (version 3), is a validated general cancer questionnaire developed to assess the QoL of cancer patients. It consists of 6 functional scales including physical, role, emotional, cognitive, and social functioning and global quality of life. The questionnaire has been translated into more than 40 different languages.

The questionnaires will be presented to patients and parents/guardians (if applicable) as a relevant age group QoL Booklet in the appropriate language of their country of residence. Some questionnaires are not available in all languages. If one or more questionnaires are not available in the appropriate language and age group the patient will not be able to take part in the QOL sub-study.

8.2 Quality of Life Booklets

QoL Booklets will be composed of the following questionnaires:

**Young Child QoL Booklet**
- PedsQL™ Generic Core Scales Child Self Report Age 5-7
- PedsQL™ Cancer Specific Module Child Self Report Age 5-7

**Child QoL Booklet**
- PedsQL™ Generic Core Scales Child Self Report Age 8-12
- PedsQL™ Cancer Specific Module Child Self Report Age 8-12
8.3 Eligibility for Quality of Life Study

All participating patients over 5 years of age who have no diagnosis of neurodevelopmental disorder will be eligible for participation in the QoL Sub-study.

Patients who are not able to understand the QoL questionnaires in any of the languages for which there are validated copies should not complete the QoL assessments.

8.4 Questionnaire administration

The relevant age group (see section 8.2) QoL Booklet will be given to the patient and their parent/guardian (if applicable) as detailed below:

- A Young Child QoL Booklet will be given to eligible patients ≥5 to ≤7 years of age.
- A Parent/Guardian QoL Booklet will be given to all parent/guardians of eligible patients aged ≥5 to ≤7 years of age.
- A Child QoL Booklet will be given to eligible patients ≥8 to ≤12 years of age.
- A Parent/Guardian QoL Booklet will be given to all parent/guardians of eligible patients aged ≥8 to ≤12 years of age.
- A Teen QoL Booklet will be given to eligible patients ≥13 to ≤18 years of age.
- A Parent/Guardian QoL Booklet will be given to all parent/guardians of eligible patients aged ≥13 to
≤18 years of age.

- A Young Adult Booklet will be given to eligible patients ≥18 to ≤25 years of age.
- An Adult QoL Booklet will be given to all patients >26 years of age.

**Please note:** Patients and/or parents/guardians will be given the same age booklet throughout the trial regardless of patient birthdays.

The patient and parent/guardian (as applicable) will be given the QoL Booklet to complete at the following time points:

- **Baseline:** Prior to starting chemotherapy.
- **After completion of chemotherapy cycle 2 and preferably immediately before cycle 3.** This allows a direct comparison of the chemotherapy regimens.
- **After completion of chemotherapy cycle 4 and preferably immediately before cycle 5.** This allows a direct comparison of the chemotherapy regimens.
- The appropriate QoL Booklets will be given by a member of the Site Research Team, based on patient age at the assessment time point. The patient Trial Number should be recorded on the front page of the booklet.

An explanation of how to complete the questionnaires should be given to patient/parent/guardian at the baseline assessment. Questions can be read to a child or teen who is unable to complete the QoL Booklet without assistance. The patient and parent/guardian should complete the booklets independently of one another and preferably before they see the treating clinician. The booklets should take around 10 minutes to complete. The Site Research Team should continue to give support to patients/parents/guardians throughout the course of the study.

Once the booklets have been completed by the patient/parent/guardian the Site Research Team should check to make sure that all of the questions have been completed and that in particular that the date the QoL Booklet was completed has been accurately recorded.
9. BIOLOGICAL STUDIES

Where consent has been given the following samples should be collected from all patients entered into rEECur to achieve the common collective trial objectives below (where country specific approvals allow). Further information on sample collection, processing and transport from each participating country can be found in the accompanying country specific Laboratory Manual.

Subject to patient consent and appropriate centre facilities samples will be collected from all patients for the following biological studies:

- Tumour and matched constitutional DNA sequencing. Whole genome/exome/targeted gene sequencing will be performed on the primary diagnostic sample and on matched samples at recurrence where that is available. Depending on the type (frozen or paraffin-embedded) and quantity of tissue available, sequencing of the whole genome, exome or targeted genes will be performed. Constitutionally normal DNA will be required in each case for comparison with the tumour profile. Where frozen tissue is available RNA profiling will be performed. TMAs will be prepared from paraffin embedded material.

- In bone marrow, blood and plasma, the prognostic and predictive value of circulating DNA, mRNA and miRNA profiles at diagnosis and throughout the disease course will be established.

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>At diagnosis / prior to cycle 1</th>
<th>After cycle 2/prior to cycle 3</th>
<th>After cycle 4/prior to cycle 5</th>
<th>After cycle 6 a</th>
<th>At disease progression or relapse b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frozen tumour – snap frozen. Ship on dry ice to reference centre</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Paraffin embedded tumour block Send at room temperature to pathology reference centre</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Bone marrow aspirate (0.5 ml x 2, right and left) into PAXgene™ Blood RNA Tubes – DO NOT POOL. Store at -80°C. Ship on dry ice to reference centre.</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Whole blood (2 ml x 1) into PAXgene™ Blood RNA Tube. Store at -80°C. Ship on dry ice to reference centre.</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Whole blood (5 ml) into EDTA tube; separated into plasma (0.5 ml aliquots) and cellular fraction. Store at -80°C. Ship on dry ice to reference centre.</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Whole blood (5ml into EDTA) for sequencing of constitutional DNA Store at -80°C. Ship on dry ice to reference centre.</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a In treatment arms TC, ID, GD only
b If appropriate
Remaining samples may be used for future ethically approved projects that have been ratified by the rEECur TMG, and/or at the end of the approved studies transferred to appropriate biobanking facilities.

Some patients recruited to rEECur will have previously been recruited to other cooperative first-line studies including EuroEWING99 and EuroEWING2012. The prospective biological studies described here are to be carried out as part of a wider European initiative. Data and samples arising from patients recruited to rEECur may be combined with those from the previous and ongoing first line studies in Ewing sarcoma under a collaborative agreement where that would enable the most efficient use of patient material.

10. ADVERSE EVENT REPORTING

The collection and reporting of Adverse Events (AEs) will be in accordance with the EU Directive for Clinical Trials 2001/20/EC and the Detailed Guidance on the Collection, Verification and Presentation of Adverse Events/Reaction Reports Arising From Clinical Trials of Medicinal Products For Human Use (‘CT-3’). Definitions of different types of AE are listed in Appendix 5.

The investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the patient’s medical records) with reference to the Summary of Product Characteristics for each IMP.

10.1 Reporting Requirements

10.1.1 Adverse Events and Adverse Reactions

AEs are commonly encountered in patients receiving chemotherapy. The safety profiles of the IMPs used in this trial are well characterised and therefore only specific Adverse Reactions (ARs), or toxicities, will be reported on the Chemotherapy Form. In addition SAEs will be captured as detailed below.

10.1.2 Serious Adverse Events

Investigators should report AEs that meet the definition of an SAE (see Appendix 5 for definition) and are not excluded from the reporting process as described below and in compliance with national and international regulations.

10.1.2.1 Events that do not require reporting on a Serious Adverse Event Form

The events listed below should not be reported on an SAE Form:

- Hospital admissions for the following causes have been excluded from the SAE reporting process as this is considered a low risk trial:
  - Admissions to control symptoms of vomiting unless the condition is life threatening or proves fatal
  - Uncomplicated admissions for transfusions of blood or platelets
  - Admissions for neutropenia and uncomplicated neutropenic fever, unless this proves fatal or requires admission to a high dependency or intensive care facility

Data on the incidence of these ARs will be captured on the Treatment Form but will not be included in the Development Safety Update Report (DSUR).

- In addition, the following admissions are also excluded from the SAE reporting process and will not be included on the DSUR:
  - Admissions for protocol defined treatment
  - Admissions for pre-planned elective procedures unless the condition worsens
  - Admissions for the treatment of progression of the patient’s cancer

- Progression or death as a result of the patient’s cancer, as this information is captured elsewhere on the CRF
10.1.2.2 Monitoring pregnancies for potential Serious Adverse Events

It is important to monitor the outcome of pregnancies of patients in order to provide SAE data on congenital anomalies or birth defects.

In the event that a patient or their partner becomes pregnant during the SAE reporting period please notify the UK Coordinating Centre as soon as possible using a Pregnancy Notification Form. If it is the patient’s partner that is pregnant the patient should be given a Release of Medical Information Form for their partner to complete. If the patient’s partner is happy to provide information on the outcome of their pregnancy they should sign the Release of Medical Information Form. Once consent has been obtained provide details of the outcome of the pregnancy and if necessary also complete an SAE Form.

10.1.3 Reporting period

Details of all AEs (ARs and SAE, except those listed in 10.1.2.1 above) will be documented and reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last protocol-defined treatment (6 cycles for patients receiving TC, IT, GD and 4 cycles for IFOS).

Sites should continue to report SAEs which the investigator feels meet the definition of a Serious Adverse Reaction (SUSAR) using the procedure described below after this date.

10.2 Reporting Procedure

10.2.1 Site

AEs defined as serious and which require reporting as an SAE (excluding events listed in section 10.1.2.1 above) should be reported on an SAE Form. When completing the form, the investigator will be asked to define the causality and the severity of the AE which should be documented using the CTCAE 4.0.

On becoming aware that a patient has experienced an SAE, the investigator (or delegate) must complete, date and sign an SAE Form. The SAE Form should be completed in English. The completed form should be faxed together with a SAE Fax Cover Sheet to the UK Coordinating Centre using one of the numbers listed below as soon as possible and no later than 24 hours after the Site Research Team first becoming aware of the event:

To report an SAE, fax the SAE Form with an SAE Fax Cover Sheet to:

UK National Coordinating Centre

☎️ +44 (0)121 414 9520 or +44 (0)121 414 7989

General Enquiries

☎️ +44 (0)121 415 1060 or reecur@trials.bham.ac.uk

On receipt the UK Coordinating Centre will allocate each SAE a unique reference number. This number will be transcribed onto the SAE Fax Cover Sheet, which will then be faxed back to the site as proof of receipt. If confirmation of receipt is not received within 1 working day please contact the UK Coordinating Centre. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE Fax Cover Sheet completed by the UK Coordinating Centre should be filed with the SAE Form in the ISF.

For SAE Forms completed by someone other than the investigator the investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. This must be done as soon as possible but can be done after the form has already been faxed to the UK Coordinating Centre so as not to delay initial reporting. A copy of the countersigned form should then be faxed to the UK Coordinating Centre and a copy kept in the ISF.
Investigators should also report SAEs to the relevant bodies in accordance with local/national guidance.

For more detailed instructions on SAE reporting refer to the SAE Form Completion Guidelines contained in the ISF.

10.2.1 Provision of follow-up information

Patients should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form (refer to the SAE Form Completion Guidelines for further information).

10.2.2 UK Coordinating Centre

On receipt of an SAE Form seriousness and causality will be determined independently by a Clinical Co-ordinator. An SAE judged by the investigator or Clinical Coordinator to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The Clinical Coordinator will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the Reference Safety Information) it will be classified as a SUSAR.

10.2.3 Reporting to the Competent Authority and Ethics Committee

10.2.3.1 Suspected Unexpected Serious Adverse Reactions

The UK Coordinating Centre will report a minimal data set of all individual events categorised as SUSARs to the EORTC Pharmacovigilance Unit. The EORTC will report SUSARs to the EudraVigilance Clinical Trial Module (EVCTM) and where required, to the Competent Authority in all countries in which the trial has received regulatory approval. Events will be reported in accordance within the regulatory specified time frame:

- Fatal or life threatening SUSARs within a maximum of 7 days with a detailed follow-up report within an additional 8 days
- All other SUSARs within a maximum of 15 days

The UK Coordinating Centre will provide SUSAR reports to the National Coordinating Centres who will report SUSARs to the relevant Ethics Committee, within the time frame specified above, and Principal Investigators within their country. The UK Coordinating Centre will assume responsibility for reporting to these parties in the UK.

10.2.3.2 Development Safety Update Report

The UK Coordinating Centre will include details of all SAEs, SARs (including SUSARs) in a Development Safety Update Report (DSUR) produced annually from the date of the first Clinical Trial Authorisation received for the trial to the submission of the End of Trial Declaration. National Coordinating Centres will be provided with a copy of this report and where contractually required to do so will forward this report to the relevant Competent Authority and Ethics Committee. The UK Coordinating Centre will assume responsibility for reporting in all other countries.

10.2.3.3 Adverse Events

Details of all AEs will be reported to the Competent Authorities on request.

10.2.3.4 Other safety issues identified during the course of the trial

The Competent Authorities and Ethics Committees will be notified immediately if a significant safety issue is identified during the course of the trial.
10.2.4 Investigators
Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators of all participating sites. A copy of any such correspondence should be filed in the ISF.

10.2.5 Data Monitoring Committee
An independent Data Monitoring Committee (DMC) will review all SAEs (see section 15.5).
11. DATA HANDLING AND RECORD KEEPING

11.1 Data Collection

This trial will use an eRDC system which will be used for completion of the CRF. Access to the eRDC system will be granted to individuals via the UK Coordinating Centre. The rEECur eRDC system can be accessed from:

https://www.cancertrials.bham.ac.uk/rEECurLive/

Please Note: SAE reporting will be paper-based (see section 10).

The CRF must be completed by an investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log (or country specific equivalent) within the timeframe specified above.

Data reported on each form (with the exception of the QoL Booklet) should be consistent with the patient’s medical records (source data) or the discrepancies should be explained. All questions on the form must be answered. If information is not known, this must be indicated on the form. All missing and ambiguous data will be queried.

In all cases it remains the responsibility of the investigator to ensure that the CRF has been completed correctly and that the data are accurate.

CRFs may be amended by the UK Coordinating Centre, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, sites will be notified of new versions of the form when they are available in the eRDC system, and in the case of the SAE form, new versions of the form must be implemented by participating sites immediately on receipt and acknowledgement of receipt and implementation should be sent to the applicable National Coordinating Centre.

11.2 Archiving

It is the responsibility of the Principal Investigator at each site to ensure all essential trial documentation and source records (e.g. signed ICF, ISF, Pharmacy Files, patients’ medical records, copies of CRFs etc.) at their site are securely retained for at least 25 years after the end of the trial. Do not destroy any documents without prior approval from the UK Coordinating Centre Document Storage Manager.

12. QUALITY MANAGEMENT

12.1 Site Set-up and Initiation

Sites will be set up and initiated in accordance with the applicable National Coordinating Centre quality and trial management plan (see Appendix 3). All sites will be required to sign a clinical study site agreement (or country specific equivalent) prior to participation. In addition, all participating investigators will be asked to supply a current CV. All members of the site research team will also be required to sign the site signature and delegation log (or country specific equivalent).

Prior to commencing recruitment all sites will undergo a process of initiation. It is anticipated that key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, AE reporting, collection and reporting of data and record keeping.

It is anticipated that sites will be provided with an ISF and a Pharmacy File containing the documentation and instructions required for the conduct of the trial by the National Coordinating Centre. The applicable National Coordinating Centre must be informed immediately of any change in the site research team.
12.2 On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the country specific quality and trial management plan (see Appendix 3).

Investigators will allow the rEECur trial staff access to source documents as requested.

12.3 Central Monitoring

If allowed by country specific legislation/guidance (as specified in the country specific quality and trial management plan, Appendix 3), and if the patient and/or parent/legal guardian has given explicit consent, sites are requested to send copies of signed ICFs to the applicable National Coordinating Centre for in-house review.

Trial research staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trial research staff will check incoming data for compliance with the protocol, data consistency, missing data and timing. Sites will be sent requests for missing data or clarification of inconsistencies or discrepancies.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group (TMG), Trial Steering Committee (TSC) and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol.

12.4 Audit and Inspection

The investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspections at their site, providing direct access to source data/documents.

Sites are also requested to notify the applicable National Coordinating Centre of any inspections by the relevant Competent Authority.

National Coordinating Centres will notify the UK Coordinating Centre of any significant audit findings.

12.5 Notification of Serious Breaches

Country specific legislation may require the National Coordinating Centre of the trial to notify the Competent Authority and Ethics Committee in writing, within 7 days of becoming aware, of any serious breach of:

- The conditions and principles of GCP in connection with that trial
- The protocol relating to the trial

A “serious breach” is a breach which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the patients in the trial
- The scientific value of the trial

Sites are therefore requested to notify the applicable National Coordinating Centre of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the applicable National Coordinating Centre is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the applicable National Coordinating Centre in providing sufficient information to report the breach to the relevant Competent Authority where required and in undertaking any corrective and/or preventive action.

Please note: persistent failure by sites to provide prompt and accurate information, particularly with regard to the reporting of SAEs, can be considered a serious breach.

See Appendix 1 for country specific requirements.

The National Coordinating Centre will notify the UK Coordinating Centre of any serious breaches.
13. END OF TRIAL DEFINITION

The trial will remain open until all trial objectives have been met. The end of trial will be 12 months after the last data capture. This will allow sufficient time for the completion of protocol procedures, data collection input and cleaning.

The applicable National Coordinating Centre will notify the relevant Competent Authority and Ethics Committee that the trial has ended at the appropriate time and will provide them with a summary of the clinical trial report within 12 months of the end of the declaration of the end of trial.
14. STATISTICAL CONSIDERATIONS

rEECur is a MAMS randomised phase II/phase III clinical trial. The trial will include a 4-way, 3-way and 2-way randomisation, with one arm to be dropped after the first stage, a second after the second stage, with the remaining two arms progressing to a phase III evaluation. Randomisation to all four arms will continue while awaiting response assessments of all patients with measurable disease and interim analysis of the data.

14.1 Definition of Outcome Measures

14.1.1 Primary outcome measures

Phase II: Imaging response by CT or MRI after 4 cycles of trial treatment. Response is measured using the RECIST 1.1 criteria (see Appendix 1). Patients who are not assessable for response – e.g. because of early stopping of treatment or death – will be assumed to be non-responders. Patients without measurable disease will not contribute to this endpoint. CR or PR will constitute an OR.

Phase III: EFS is defined as the time from randomisation until first event (progression, recurrence following response, second malignancy or death without progression or recurrence). For those patients who do not experience an event during the course of the trial, EFS times will be censored at the date of their last available trial assessment.

14.1.2 Secondary outcome measures

14.1.2.1 Phase II

EFS defined as above.

PFS is defined as the time from randomisation until first event (progression, recurrence following response or death without progression or recurrence). Second malignancy is not classified as an event for PFS. For those patients who do not experience an event during the course of the trial, PFS times will be censored at the date of their last available trial assessment.

OS is defined as the time from randomisation to death, irrespective of the cause. Surviving patients will be censored at their last follow-up date.

Toxicity, defined by CTCAE v4.0.

Imaging response by CT or MRI after cycle 2, cycle 6 (for TC, IT and GD arms) and at the end of trial treatment (defined as per primary outcome for phase II).

PET-CT response after course 4.

QoL will be assessed at baseline and after 2 and 4 cycles using age-appropriate tools:

≥18 years: EORTC QLQ-C30 and PedQL™ Generic Core Scales and Cancer Specific Module

<18 years: PedsQL™ Generic Core Scales and Cancer Specific Module

Days spent in hospital while on trial chemotherapy treatment.

14.1.2.2 Phase III

OS, PFS, toxicity, imaging response after cycle 2, 6 and at the end of trial treatment, QoL and days spent in hospital, as defined as above.

14.2 Sample Size Calculations

14.2.1 Phase II

First stage – minimum of 200 (at least 50 in each of the four arms)

Second stage – minimum of 75 (at least an additional 25 in each arm of the remaining three arms)

Since EFS has not been reported for these regimens the calculations for the sample size of the phase II part are based on OR measured by imaging, which will also be ascertainable in a shorter time frame.
than EFS. Assuming a true OR of 40% for the worst regimen and a 4-way randomisation, a range of scenarios with true response rates in the other arms ranging from 40% to 55% have been constructed. There are a large number of possible scenarios, all of which have been simulated. Space constraints mean that only a limited selection of scenarios can be provided as examples (based on 50 patients per arm at stage 1 and 75 patients per arm at stage 2); if there is a true 15% difference in OR between the best and worst regimens, there will only be a 2% to 15% chance of dropping the best arm (the probabilities vary depending on whether more than one arm has a true outcome of 40% or 55% and on the probabilities for the arms with intermediate OR); with a true 10% difference, there will be a 8% to 18% chance of dropping the best arm; with a true 5% difference, there will be a higher (up to 25%) chance of dropping the best arm (but, since there is only a small difference between best and worst arms, it will not be clinically important if a slightly suboptimal arm is taken forward). These probabilities do not change substantially if true ORs of 30% and 50% are assumed for the worst regimen. Since it is unknown whether OR correlates with EFS in this population, the decision as to which arm to drop – while based primarily on OR – will also take account of EFS and toxicity.

14.2.2 Phase III
Two-arm phase III evaluation – a target of at least 400 patients (i.e. 200 per arm).

A likelihood Bayesian approach has been adopted [66]. Pragmatically, the sample size for the phase III part of the trial will depend on: the actual outcomes observed (there is little reliable data on EFS in recurrent/refractory ES on which to base the sample size); the number of available patients – i.e. the number of countries participating; the availability of novel agents – e.g. if a novel agent needed to be introduced as a new arm, it may be better to select the better standard arm at that point (in order to increase the numbers in the novel agent arm – although an alternative would be to adjust the allocation ratio), whereas if the novel agent were to be added to chemotherapy, then the comparison between chemotherapy regimens could continue with the novel agent being introduced in a factorial design. Hence, it can be seen that there are currently unknown factors that will impact upon the progress of this trial but the design has the flexibility that will be needed to accommodate them. Hence, based on the observed EFS in the two arms, probabilities that the EFS with one treatment is greater than that with the other will be given for a range of differences. Some scenarios are provided in Table 5 (assuming 30% 1-year EFS with one treatment and 200 patients per arm):

<table>
<thead>
<tr>
<th>1-yr EFS Arm A</th>
<th>Improvement</th>
<th>1-yr EFS Arm B</th>
<th>Total Events</th>
<th>Hazard Ratio (HR)</th>
<th>InHR</th>
<th>P(HR &lt; 1.00) (%)</th>
<th>P(HR &lt; 0.87) (%)</th>
<th>P(HR &lt; 0.76) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.30</td>
<td>0.00</td>
<td>0.30</td>
<td>280</td>
<td>1.00</td>
<td>0.00</td>
<td>50</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>0.30</td>
<td>0.05</td>
<td>0.35</td>
<td>270</td>
<td>0.87</td>
<td>-0.14</td>
<td>87</td>
<td>50</td>
<td>13</td>
</tr>
<tr>
<td>0.30</td>
<td>0.10</td>
<td>0.40</td>
<td>260</td>
<td>0.76</td>
<td>-0.27</td>
<td>99</td>
<td>86</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 5. Observed HRs scenarios and associated probabilities

A HR <1.0 indicates an approximately higher EFS in the treatment B. Absolute differences in 1-year EFS of 0%, 5% and 10% correspond to HRs of 1.00, 0.87 and 0.76 respectively.

14.3 Analysis of Outcome Measures
All analyses will be ITT with all patients analysed in the arm to which allocated at randomisation. Full details of the analysis will be specified in a Statistical Analysis Plan.

14.3.1 Primary outcome measures
Phase II: The primary analysis will be descriptive in nature. The analysis populations will be all randomised patients with measurable disease i.e. intention to treat. For each treatment arm and overall, the number of responders (and proportion with confidence intervals) will be presented. The number (and proportion) of patients within each category of RECIST will be given. Posterior probability
plots for all pair-wise comparisons will be presented, based on the observed risk ratio. Analysis adjusting for the minimisation factors will also be presented.

Phase III: Probability based i.e. likelihood based Bayesian approach will be used to give the probabilities that, based on the posterior distribution for HR, one treatment is better than the other and better by varying amounts. The analysis will use non-informative priors. The ln(HR) is assumed to be normally distributed with variance 4/n, where n=total number of events in both arms [16]. The priors will be combined with the observed data (likelihood) using conjugate analysis to obtain posterior distributions. Although reliable estimates of EFS from relapse are not available, it is anticipated that, with 400 patients randomised, there will be a minimum of 250 events and possibly more than 300.

If, with 250 or 300 events, a HR of 0.8 were to be observed, there would be 4% and 3% probabilities respectively that the treatment that appears better was actually worse (i.e. HR>1, plots below); if a HR of 1.0 was observed there would be 7% and 6% probabilities that one arm was actually more than 20% worse (i.e. HR>1.2, plots Figure 1).

Figure 1. Example probability plots for observed Hazard Ratios

These probabilities are within clinically acceptable limits for decision making. A probability based approach has been adopted mainly because we are comparing one regimen with another, with there being no standard control arm, so it is not necessary to use conventional limit (e.g. if there were a 75% probability that one treatment were better than the other, with no excess toxicity, this is likely to provide sufficiently robust evidence for clinical decision making, and demonstrating that one regimen is better than the other at p=0.05 is neither necessary nor appropriate). The presentation of results as probabilities is also much easier for clinicians and patients to interpret, compared to p-values or HRs. Kaplan Meier life tables and plots will be produced. Survival estimates at 1-, 2-, and 5-year and median survival time will be presented with 95% confidence intervals for each treatment arm and overall. Cox regression analysis adjusted by the minimisation factors will be performed.

14.3.2 Secondary outcome measures
Analysis methods for PFS and OS will be as per EFS.
Safety data will be summarised by arm for all treated patients using appropriate tabulations and descriptive statistics. Exploratory standard statistical tests will be performed to compare the arms.

Imaging response after cycle 2, cycle 6 (for TC, IT and GD arms) and at the end of trial treatment and PET-CT response will be analysed as per primary outcome for Phase II.

Days spent in hospital: the number (range) and proportion (with confidence intervals) of days in hospital will be presented for each arm and overall. Standard statistical tests will be performed to compare the arms.

QoL: the scores will be calculated according to the EORTC QLQ-C30 manual and PedsQL guidelines and compared across treatment groups using repeated measures methods.

14.4 Planned Sub Group Analyses

Exploratory subgroup analyses will be undertaken by the minimisation parameters.

14.5 Planned Interim Analyses

14.5.1 Phase II

First interim analysis is planned after 50 patients per arm (i.e. greater than 200 in total) have been recruited and assessed for the phase II primary outcome. Randomisation to all four arms will continue while awaiting response assessments of all patients and interim analysis of the data. The analyses presented will be the same as per primary outcome measure for phase II of the trial (section 14.3.1) When at least 50 patients are enrolled and assessed for the primary outcome in each arm, the arm with the worst response rate, however inferior, will be dropped. The decision criteria will be considered as a guideline and other factors – such as toxicity and EFS – will be taken into account before making the clinical decision as which arm to drop. It can be anticipated that there may be a significant preference for or against a certain treatment for both clinicians and patients. If uptake for one arm is particularly poor the requirement for 50 patients per arm will be reviewed. The DMC will make recommendations on this basis. The 3 remaining arms will continue to recruit to a minimum of 75 patients per arm.

The second interim analysis is planned after there are 75 patients in each of the three arms (i.e. greater than 275 patients in total) are enrolled and assessed for the primary outcome. The most inferior of the three arms will be dropped based on the same criteria as above. If uptake for one of the remaining three arms is poor the requirement for 75 patients per arm will be reviewed. The DMC will make recommendations on this basis. The two remaining arms will then continue to the phase III comparison.

14.6 Planned Main Analyses

14.6.1 Phase III

The first main analysis is planned after at least 400 patients (i.e. 200 per arm) have been recruited and followed up for a minimum of one year.
15. TRIAL ORGANISATIONAL STRUCTURE

15.1 Sponsor

The University of Birmingham is the Sponsor for the rEECur trial. In addition, the University of Birmingham (UK Coordinating Centre) will undertake the responsibilities of National Coordinating Centre in the UK.

15.2 National Coordinating Centres

The Sponsor has delegated the set-up, management and analysis of the trial to the UK Coordinating Centre. The role of the UK Coordinating Centre is assumed by the CRCTU, University of Birmingham. The trial will be set-up, managed and analysed in the UK in accordance with CRCTU standard policy and procedures.

Each National Coordinating Centre (see the introductory pages for the list) will manage the trial in accordance with the trial protocol, and their standard policy and procedures.

15.3 Trial Management Group

The TMG is composed of the Chief Investigator, co-investigators, representatives from each National Coordinating Centre and the trial team at the CRCTU. The TMG is responsible for the day-to-day running and management of the trial and will meet by teleconference or in person every 3 months.

15.4 Trial Steering Committee

The TSC will provide overall supervision for the trial and provide advice through its independent chair. The TSC will include members of the Euro Ewing Consortium (EEC) External Advisory Board and be supported by CRCTU staff and the Chief Investigator. The TSC will assume responsibility for the oversight of the trial on behalf of the Sponsor. The TSC will meet or hold teleconferences at least once a year, or more often if required.

15.5 Data Monitoring Committee

Analyses will be supplied in confidence to an independent DMC. In the light of these analyses, and the results of any other relevant trials, the DMC will advise the TSC if, in their view, the randomised comparisons in the rEECur trial have provided both (i) “proof beyond reasonable doubt” that for all, or some specific types, of patient, any of the randomised treatments are clearly indicated or contraindicated in terms of a net difference in a major endpoint; and (ii) evidence that might be reasonably expected to influence materially the patient management of many clinicians who are already aware of the main results of any other trials. The DMC may also consider recommending stopping or modifying the trial, or part of the trial, if: any issues are identified which might compromise patient safety; or the recruitment rate or data quality are unacceptable. The TSC can then decide whether to modify the trial, or to seek additional data. Unless this happens, the TSC, the investigators, the study participants, and all trial staff (except those who provide the confidential analyses to the DMC) will remain blind to the interim trial results.

The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The DMC will meet annually during the recruitment and treatment phases of the trial. Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified.

The DMC will report to the TSC via the TMG. The TMG will also convey the findings of the DMC to the Sponsor and funders, where applicable.

15.6 Finance

This is an investigator-initiated and investigator-led trial funded by the European Commission FP7 funding stream. No individual per patient payment will be made to healthcare providers, investigators or patients.
16. ETHICAL CONSIDERATIONS

The accepted basis for the conduct of clinical trials in humans is founded on the protection of human rights and the dignity of human beings with regard to the application of biology and medicine, and requires compliance with the principles of GCP and detailed guidelines in line with those principles (Directive 2001/20/EC (2) and Directive 2005/28/EC (1)).

GCP is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with GCP provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible (Article 1 (2) of Directive 2001/20/EC).

The National Coordinating Centres and Investigators shall consider all relevant guidance with respect to commencing and conduct the study in accordance with the GCP Directive (2005/28/EC)

The conduct of the trial shall be based on the following international ethical and statutory sources:

- The **WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects**.

- If the region has adopted the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: **Convention on Human Rights and Biomedicine** (CETS No.: 164).


- **Directive 2005/28/EC** of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (Official Journal L 91, 09/04/2005 P. 0013 – 0019).


- Scientific guidelines relating to the quality, safety and efficacy of medicinal products for human use, as agreed upon by the CHMP and published by the Agency, as well as the other Community guidelines published by the Commission in the different volumes of the rules governing medicinal products in the European Community (Directive 2005/28/EC (9)).

This trial will be conducted under Clinical Trial Authorisation in each participating country. Appropriate country specific Ethics Committee approval must also be obtained prior to recruitment of patients within that country.

Before any patients are enrolled into the trial, the Principal Investigator at each site is required to obtain any necessary local approvals required within the country for the conduct of the trial at their site (see the country specific Trial and Quality Management Plan, Appendix 3). It is the responsibility of the Principal Investigator to ensure that all subsequent amendments also gain the necessary local site specific approval prior to implementation. This does not affect the individual clinicians’ responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.
17. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the relevant data protection legislation in the applicable country.

Patients will be identified using only their unique Trial Number in correspondence between the applicable National Coordinating Centre and participating sites. However, if local regulation/guidance permits patients are asked to give permission for the applicable National Coordinating Centre to be sent a copy of their signed ICF which will not be anonymised. This will be used to perform in-house monitoring of the consent process.

The investigator must maintain documents not for submission to the applicable National Coordinating Centre (e.g. patient identification logs) in strict confidence. In the case of specific issues and/or queries from the Competent Authority, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

The National Coordinating Centres will maintain the confidentiality of all patients’ data and will not disclose information by which patients may be identified to any third party other than those directly involved in the treatment of the patient and organisations for which the patient has given explicit consent for data transfer. Representatives of the rEECur trial team may be required to have access to patient’s notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

18. INSURANCE AND INDEMNITY

The National Coordinating Centres are responsible for obtaining insurance to set up and run the rEECur trial in their respective countries and for ensuring that sites in their country are adequately covered.

University of Birmingham employees are indemnified by the University insurers for negligent harm caused by the design or co-ordination of the clinical trials they undertake whilst in the University’s employment.

The University of Birmingham cannot offer indemnity for non-negligent harm. The University of Birmingham is independent of any pharmaceutical company and, as such, it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation.

19. PUBLICATION POLICY

Results of this trial will be submitted for publication in peer reviewed journals. Manuscripts will be prepared by the TMG and authorship will be determined by mutual agreement.

The first publication of the results of this study shall be made as a joint multi-centre publication under the Chief Investigator and the lead of the UK Coordinating Centre at the CRCTU. Any secondary publications and presentations prepared by investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of the University of Birmingham and where applicable other National Coordinating Centres. Intellectual property rights will be addressed in the agreements between the Sponsor and the National Coordinating Centres and the clinical study site agreement (or country specific equivalent) between the National Coordinating Centres and sites.

Individual countries will be allowed to publish their efficacy results, however the publication of efficacy results from the pooled analysis will take precedence over efficacy result publications of individual countries, unless the TMG decides otherwise.
20. REFERENCE LIST


APPENDIX 1 – RECIST CRITERIA

From the revised RECIST guideline (version 1.1)[18].

MEASURABILITY OF TUMOUR AT BASELINE

Only patients with measurable disease at baseline will be included in the objective response assessment. Measurable disease is defined by the presence of at least one measurable lesion.

Tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows:

**Measurable lesions:** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.

**Unmeasurable lesions:** All other lesions including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitic involvement of lung.

**Bone lesions:** Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions. Bone lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

**Tumour lesions situated in a previously irradiated area,** or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

**Method of assessment:** The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

BASELINE DOCUMENTATION OF ‘TARGET’ AND ‘NON-TARGET’ LESIONS

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

Pathological lymph nodes which are defined as measurable and identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’.

**Baseline sum diameters:** A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters.
RESPONSE CRITERIA

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10mm on study. This means that when lymph nodes are included as target lesions, the ‘sum’ of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become ‘too small to measure’. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being ‘too small to measure’. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned in this circumstance as well). This default value is derived from the 5mm CT slice thickness (but should not be changed with varying CT slice thickness).

Evaluation of non-target lesions: While some non-target lesions may be measurable, they should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s).

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression). The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will be extremely rare. In this setting, to achieve ‘unequivocal progression’ on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy.

New lesions: The appearance of new malignant lesions denotes disease progression. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions).
DURATION OF OVERALL RESPONSE
The duration of overall response is measured from the time measurement criteria are met for CR or PR until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded on study.
SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest sum on the study.

APPENDIX 2 - COMMON TOXICITY CRITERIA GRADINGS
Toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The full CTCAE document is available on the National Cancer Institute website, the following address was correct when this version of the protocol was approved:

APPENDIX 3 - UNITED KINGDOM SPECIFIC QUALITY AND TRIAL MANAGEMENT PLAN
Records of Screening/enrolment
Details of all patients approached about the trial should be recorded on the Patient Screening and Enrolment Log provided by the CRCTU which should be kept in the ISF and copies sent to the CRCTU for review when requested.

Informed Consent Form Review
Where a patient has given explicit consent sites are requested to send copies of signed ICF in the post to the CRCTU for in-house review.

Site Set-up and Initiation
Before any patients are enrolled into the trial, the Principal Investigator at each site is required to obtain local Research and Development (R&D) approval. Sites will not be permitted to enrol patients until written confirmation of R&D approval is received by the UK Coordinating Centre (CRCTU). It is the responsibility of the Principal Investigator to ensure that all subsequent protocol amendments gain the necessary local approval.

All sites will also be required to sign a Clinical Study Site Agreement prior to participation.

In addition, all participating investigators will be asked to complete and sign a Registration Form and supply a current CV and proof of GCP training to UK Coordinating Centre. Investigators will not be able to recruit patients until this information is received. Other members of the site research team will also be required to complete a Registration Form indicetg what tasks they will undertake for the trial. All members of the site research team will be required to sign the Site Signature and Delegation Log supplied in the ISF which should be returned to the UK Coordinating Centre. The UK Coordinating Centre must be informed immediately of any change in the site research team.

Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference covering all aspects of the trial. On completion of the process sites will be provided with a Site Initiation Report and formal notification that recruitment can commence. Sites will be provided with an ISF containing essential documentation, guidelines, instructions, and other documentation required for the conduct of the trial.
Pharmacy
Sites should elect a Pharmacist to assume the role of Responsible Pharmacist. The Responsible Pharmacist will be expected to attend the Site Initiation meeting and will be provided with a Pharmacy File containing the Pharmacy Manual, protocol, labels and accountability logs.
When patients are randomised into the trial the Responsible Pharmacist will be sent a Pharmacy Notification by fax.

Data Handling
If the eRDC system is unavailable for an extended period of time a paper based CRF should be completed and forms returned to the applicable UK Coordinating Centre (CRCTU) for data entry.
In the UK the CRCTU will also assume the responsibility for entering QoL data onto the eRDC database on behalf of participating sites.

On-site Monitoring
Monitoring will be carried out as required following a Risk Assessment and as documented in the rEECur UK Quality Management Plan. Additional on-site monitoring visits may be triggered for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of patient withdrawals or deviations. If a monitoring visit is required the UK Coordinating Centre will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the UK Coordinating Centre trial research staff access to source documents as requested.

Serious Breach Notification
In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments the UK Coordinating Centre will notifying the licensing authority in writing of any serious breach within 7 days of becoming aware of that breach.
Sites are therefore requested to notify the UK Coordinating Centre of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the UK Coordinating Centre is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the trials research staff in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action.

Archiving
With reference to section 11.2, do not destroy any documents without prior approval from the CRCTU Document Storage Manager.
# APPENDIX 4 – PERFORMANCE STATUS SCALES

## Lansky score

<table>
<thead>
<tr>
<th>Score</th>
<th>Descriptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Fully active, normal</td>
</tr>
<tr>
<td>90</td>
<td>Minor restrictions in strenuous physical activity</td>
</tr>
<tr>
<td>80</td>
<td>Active, but gets tired more quickly</td>
</tr>
<tr>
<td>70</td>
<td>Both greater restriction of play and less time spent in active play</td>
</tr>
<tr>
<td>60</td>
<td>Up and around, but minimal active play; keeps busy with quieter activities</td>
</tr>
<tr>
<td>50</td>
<td>Gets dressed but lying around much of the day but no active play; able to participate in all quiet play and activities</td>
</tr>
<tr>
<td>40</td>
<td>Mostly in bed; participates in quiet activities</td>
</tr>
<tr>
<td>30</td>
<td>In bed; needs assistance even for quiet play</td>
</tr>
<tr>
<td>20</td>
<td>Often sleeping; play entirely limited to very passive activities</td>
</tr>
<tr>
<td>10</td>
<td>No play; does not get out of bed</td>
</tr>
<tr>
<td>0</td>
<td>Unresponsive</td>
</tr>
</tbody>
</table>

*Table 6: Lansky score [63]*

## World Health Organisation (WHO) (ECOG/Zubrod) score

<table>
<thead>
<tr>
<th>Score</th>
<th>Descriptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Asymptomatic (Fully active, able to carry on all predisease activities without restriction)</td>
</tr>
<tr>
<td>1</td>
<td>Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)</td>
</tr>
<tr>
<td>2</td>
<td>Symptomatic, &lt;50% in bed during the day (Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours)</td>
</tr>
<tr>
<td>3</td>
<td>Symptomatic, &gt;50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)</td>
</tr>
<tr>
<td>4</td>
<td>Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>

*Table 7: WHO score [67]*
APPENDIX 5  - DEFINITION OF ADVERSE EVENTS

Adverse Event
Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Comment:
An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

Adverse Reaction
All untoward and unintended responses to an IMP related to any dose administered.

Comment:
An AE judged by either the reporting investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event
Any untoward medical occurrence or effect that at any dose:
- Results in death unrelated to the original cancer
- Is life-threatening*
- Requires hospitalisation** or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Or is otherwise considered medically significant by the investigator***

Comments:
The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.

* Life threatening in the definition of an SAE 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 that hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE.

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

Serious Adverse Reaction
An Adverse Reaction which also meets the definition of a Serious Adverse Event.
Suspected Unexpected Serious Adverse Reaction

A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the Reference Safety Information.

A SUSAR should meet the definition of an AR, unexpected adverse reason (UAR) and SAR.

Unexpected Adverse Reaction

An AR, the nature or severity of which is not consistent with the Reference Safety Information.

When the outcome of an AR is not consistent with the Reference Safety Information the AR should be considered unexpected.

APPENDIX 6 – FDG-PET-CT GUIDELINES

The following instructions on FDG-PET examination are based on the guideline of the European Association of Nuclear Medicine (EANM) concerning FDG PET and FDG PET/CT in paediatric patients [68] and the latest version of the paediatric dosage card of the EANM [69]. However, some modifications have been applied in order to adapt the examination technique to the requirements in Ewing sarcoma patients and to standardise the FDG PET/CT examinations within this trial.

Only FDG PET/CT images will be eligible for inclusion in the study. FDG-PET images alone will not be eligible.

Centres undertaking PET-CT should ideally be certified by EARL (EANM Research Ltd). Non-certification will not, however, be an exclusion criterion for undertaking PET-CT imaging as part of this study.

Patient preparation

A fasting period of 6-8 h before the FDG PET/CT examination is crucial to maintain low glucose and low insulin levels. In very young patients < 6 years, 4 h fasting is sufficient to improve compliance. The ban regarding soft drinks, sweets, and glucose containing infusions during the fasting phase should be addressed explicitly. However, the patient ought to take water or unsweetened tea during the fasting period to maintain good hydration. The blood glucose level must be measured before FDG application. If it is > 120 mg/dl, FDG injection has to be postponed for several hours or FDG PET/CT has to be scheduled for another day. A thorough explanation of the scan should be provided to the patient and/or his/her parents by the technologist or physician (including hydration, time/duration of scanning, and details of the procedure itself).

Ideally, IV access will have been established prior to scanning. This is particularly important for children to improve compliance.

Uptake of FDG in brown adipose tissue is noted on 15-20% of PET scans in children and adolescents, which limits the study's ability to detect or rule out disease in these regions. It has been observed that brown fat uptake is encountered less frequently if the room, where the child spends the injection uptake phase, is warm. A warm blanket may also help to reduce tracer uptake in brown fat.

FDG application

The amount of activity that needs to be administered to obtain sufficient image quality depends largely on the crystal of the PET camera and the acquisition parameters. Acquisition in 3D mode (image acquisition without septa), if available, will be preferable to 2D mode due to its higher sensitivity (in combination with detectors using fast scintillator materials). This assumption may not apply to very large patients (Body Mass Index >34). In general, the activity should be adjusted to the patient's weight and to the type of acquisition (2D or 3D) according to the latest version of the EANM dosage card (see Table 8). The recommended minimum activity (70 MBq) applies to commonly used positron emission tomographs. Lower activities could be administered when using systems with higher
counting efficiency. For adults and children of ≥70 kg, activity should be administered at 4 MBq/kg, up to a maximum dose of 400 MBq, equivalent to an absorbed dose of approximately 8 mSv (PET) and 13.5 mSv (PETCT). Please note that the maximum activity might be limited by national regulations.

**Interval between FDG Injection and Data Acquisition**

The patient should rest until the start of PET scanning. Standard imaging time commences at approximately 60 min post injection. It is important to use the same injection-to-scan interval +/- 10 min at the initial and subsequent scans to assess response to treatment. Before the start of image acquisition the child should be encouraged to void.

**Positioning of the Patient and Sedation**

To ensure an optimum position in the scanner and to avoid movement artefacts, all patients should be comfortably immobilised during study acquisition with straps, tape, or cushions. In small children, the need for sedation has to be assessed individually and if required should be performed by an experienced physician, ideally by a paediatrician or paediatric anaesthetist. An adapted environment, an adequate attitude toward the child, a well-trained technologist for paediatric procedures, and involved parents during the procedure all help to examine a co-operative child and may obviate the need for sedation in the majority of cases.

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Activity (MBq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
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<tr>
<td>6</td>
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<td>16</td>
<td>104</td>
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Table 8: Recommended dose based upon the EANM Dosage Card for FDG-PET Torso [69]
Data Acquisition
FDG-PET examinations have to be performed with a full ring, PET-CT scanner. In Ewing sarcoma patients, a whole-body PET examination should include the entire legs and arms as the primary tumour and metastases can occur even in the distal extremities. The body (vertex of the skull to the tip of the toes) and the primary tumour have to be scanned with transmission to allow attenuation corrected images and the calculation of standardised uptake values (SUV).

Acquisition parameters depend largely on the detector and the type of scanner. Transmission measured by low-dose CT, acquisition parameters such as tube voltage and tube current time product have to be adapted to body weight and axial diameter.

Reconstruction
Attenuation corrected PET images are reconstructed iteratively.

Local evaluation of FDG-PET/-CT
The role of FDG-PET/-CT in Ewing sarcoma is not established, although FDG-PET-CT is an indication for assessment of response in some national guidance (Ref: Evidence-based indications for the use of PET-CT in the UK 2013, joint royal college report). As the role of FDG-PET/-CT is a secondary outcome measure the FDG-PET-CT data should not be used to dictate treatment. Local nuclear medicine/radiology departments may report FDG-PET/-CT images for local use. However, for the purposes of the trial, tumour responses and/or disease progression will be based only on cross-sectional imaging changes according to RECIST 1.1 evaluation.
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https://www.cancertrials.bham.ac.uk/rEECurLive/
In case of any problems with online randomisation, randomisation details can be phoned through to the CRCTU on:
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