**rEECur**

**International Randomised Controlled Trial of Chemotherapy for the Treatment of Recurrent and Primary Refractory Ewing Sarcoma**

Version 6.0

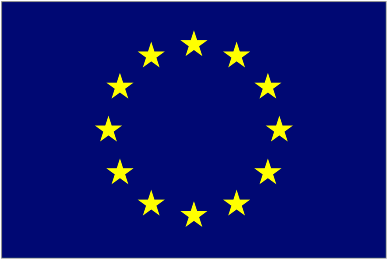
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Trial Management Group

|  |  |
| --- | --- |
| **Chief Investigator** | |
| **Dr Martin McCabe** | Consultant Paediatric Oncologist, The Christie Hospital, Manchester, UK  🕿 +44 (0)161 446 3954 or +44 (0)161 446 3000 |
| **Co-investigators** | |
| **Prof Keith Wheatley** | Professor of Clinical Trials, Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham, UK |
| **Prof Jeremy Whelan** | Consultant Medical Oncologist, University College Hospital, London, UK |
| **Dr Sandra Strauss** | Senior Clinical Lecturer and Consultant Medical Oncologist, University College Hospital, London, UK |
| **Clinical Coordinators** | |
| **Prof Uta Dirksen** | Senior Consultant in Paediatric Haematology and Oncology, University Hospital Essen, Essen, Germany |
| **Prof Jeremy Whelan** | Consultant Medical Oncologist, University College Hospital, London, UK |
| **Dr Bernadette Brennan** | Consultant Medical Oncologist, Royal Manchester Children’s Hospital, UK |
| **National Coordinating Investigators** | |
| **Prof Uta Dirksen** | European Organisation for Research and Treatment of Cancer (EORTC) Brussels, Belgium |
| **Prof Uta Dirksen** | Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH)  University Hospital Essen, Essen, Germany |
| **Dr Alessandra Longhi** | Italian Sarcoma Group (ISG) Bologna, Italy |
| **Dr Nathalie Gaspar** | Société Française de Lutte contre les Cancers et Leucémies de l'Enfant et de l'Adolescent (SFCE), Villejuif Cedex, France |
| **Dr Cristina Mata** | Spanish Society of Paediatric Haematology and Oncology (SEHOP)  Madrid, Spain |
| **Dr Akmal Safwat** | Scandinavian Sarcoma Group (SSG) Aarhus, Denmark |
| **Dr Claudia Valverde** | Grupo Español de Investigación en Sarcomas(GEIS), Madrid, Spain |
| **Assoc. Prof. Marianne Phillips/ Dr Susie Bae** | Australian and New Zealand Children’s Haematology/Oncology Group (ANZCHOG) Victoria, Australia |
| **Dr Mark Winstanley** | New Zealand: Australia and New Zealand Sarcoma Association c/o Australian and New Zealand Children’s Haematology/Oncology Group (ANZCHOG) Victoria, Australia |
| **Prof. Thomas Kühne** | Swiss Paediatric Oncology Group (SPOG) Bern, Switzerland  Pädiatrische Hämatologie und Onkologie, Universitäts-Kinderspital beider Basel (UKBB) |
| **Trial Statistician** | |
| **Ms Laura Kirton** | Biostatistician, CRCTU, University of Birmingham, Birmingham UK |

Sponsor

|  |
| --- |
| **University of Birmingham, Edgbaston, Birmingham. B15 2TT** |

Coordinating Centres

|  |  |  |
| --- | --- | --- |
| **United Kingdom (UK) Coordinating Centre** | | |
| **Senior Trial Manager** | Ms Nicola Fenwick | |
| **Senior Trial Coordinator** | TBA | |
| **Trial Coordinator** | Ms Maria Khan | |
| **Pharmacy Advisor** | Ms Cherelle Dayus | |
| **Contact Details** | Children’s Cancer Trials Team (CCTT)  Cancer Research UK Clinical Trials Unit (CRCTU),  University of Birmingham, Institute of Cancer and Genomic Sciences, Edgbaston, Birmingham. B15 2TT. UK  🕿 +44 (0)121 415 9877 or +44 (0)121 415 1060  🖂 [reecur@trials.bham.ac.uk](mailto:reecur@trials.bham.ac.uk)  🖶 +44 (0)121 414 9520 | |
| **Randomisation** | <https://www.cancertrials.bham.ac.uk/rEECur>Live/  In case of any problems with online randomisation, randomisation details can be phoned through to the CRCTU using the details above. | |
| **Serious Adverse Event (SAE) Reporting** | Email: [reg@trials.bham.ac.uk](mailto:reg@trials.bham.ac.uk) | |
| **National Coordinating Centres** | | |
| **EORTC** | European Organisation for Research and Treatment of Cancer, Avenue Emmanuel Mounier 83/11, 1200 Brussels, Belgium  🕿 +32 2 774 16 11  🖂 [sandrine.marreaud@eortc.org](mailto:sandrine.marreaud@eortc.org) | |
| **Germany** | Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH)  University Hospital Essen  Paediatrics III, Haematology/ Oncology International Ewing Sarcoma Study Group  West German Cancer Centre, Hufelandstr. 55  45147 Essen, Germany  🕿 +49 (0)201 723-8084  🖶 +49 (0)201 723-6298  🖂 [Reecur@uk-essen.de](mailto:Reecur@uk-essen.de) [uta.dirksen@uk-essen.de](mailto:uta.dirksen@uk-essen.de) | |
| **Italy** | Instituto Ortopedico Rizzoli (IOR)  Via Pupilli 1 40136 Bologna, Italy  🕿 +39 0516366400  🖂 [alessandra.longhi@ior.it](mailto:alessandra.longhi@ior.it)  Clinical Trials Unit: Italian Sarcoma Group (ISG)  Via Cà Ricchi 33, 40068 San Lazzaro di Savena (BO) Italy   +39 3335359192  🖂 emanuela.marchesi@italiansarcomagroup.org  🖶 +39 05 16366400 | |
| **Spain** | Grupo Espanol De Investigacion En Sarcomas  Velazquez 7, 3rd Floor 28001 Madrid, Spain  🕿 +34 648 414 261  🖂 secretaria@grupogeis.org  🖶 +34 971 570 222 | |
| **Sweden (Scandinavia)** | Scandinavian Sarcoma Group (SSG)  Lund University, Department of Oncology and Pathology, Barngatan 4,  S-22185 Lund, Sweden  🕿 +46 46 275 21 82  🖂 akmal.safwat@auh.rm.dk | |
| **Australia and New Zealand** | Australian and New Zealand Children’s Haematology/Oncology Group (ANZCHOG)  Hudson Institute of Medical Research  27-31 Wright Street, Clayton, Victoria, Australia 3168   +61 3 8572 2684   [robyn.strong@hudson.org.au](mailto:robyn.strong@hudson.org.au)   +61 3 9902 4810  Clinical Trials Unit:  Kids Oncology and Leukaemia Trials (KOALA)  Kids Cancer Centre, Sydney Children’s Hospital, Level 1, South Wing, High Street, Randwick, NSW, Australia 2031   +61 2 9382 3122 or +61 2 9382 3102   schn-reecur[@health.nsw.gov.au](mailto:SCHN-REECUR@health.nsw.gov.au) | |
| **Switzerland** | Swiss Paediatric Oncology Group (SPOG)  SPOG Coordinating Centre  Effingerstrasse 33  CH - 3008 Bern Switzerland   +41 31 389 91 89   [info@spog.ch](mailto:info@spog.ch) | |
| **Biological Studies Coordinators** | | |
| **Prof Sue Burchill** | | Institute of Medical Research, St James’s, University Hospital, Leeds, UK |
| **Prof Uta Dirksen** | | University Hospital Essen, Essen, Germany |

**SIGNATURE PAGE**

rEECur Trial Protocol version 6.0, 18th September 2020

## This protocol has been approved by:



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.

Trial sites in Germany will only recruit patients to the phase II part of the study. The results of the first interim analysis, at which a decision will be made about whether to continue or drop arms, or to bring in novel arms, will be shared with the PI for Germany. Further participation in the trial for German participants will depend on the results of the interim analysis and subsequent review of any planned protocol amendments by the appropriate regulatory authorities, i.e. ethics committee.

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:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Amendment Number | Date of Amendment | Protocol Version Number | Type of Amendment | Summary of Amendment |
| 1 | 9th September 2014 | 3.0 | Substantial amendment | Update from co-sponsorship model to a National Coordinating Centre model |
| 4. | 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 note: 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 * 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 * 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 sufficent to allow disease assessment accordign 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 |
| 6 | 11-Apr-2016 | 5.0 | Substantial amendment | * Updated GD Arm: Use of any corticosteroid as premedication for docetaxel |
|  | 01-Jun-2017 | 5.0a | Non-substantial amendment  Germany Only | * Statement on the signature page regarding German sites initially only recruiting patients in to the Phase II part of the study |
| 19 |  | 6.0 | Substantial amendment | * Addition of new carboplatin and etoposide arm * Closure of the GD and IT arms and summmary of results provided * Update to inclusion age ranges * Updated trial management group (TMG) details * Schedule of events updated to reflect protocol updates * Clarification of eligibility criteria and addition of new inclusion criteria:   + Date of planned randomisation within 4 weeks of baseline imaging * Addition of new exclusion criteria:   + Glomerular filtration rate that would preclude use of ifosfamide or carboplatin * Clarification of trial duration and design * Trial schema updated * Local control measures and Stem cell mobilisation and myeloablative therapy sections updated * IFOS arm: addition of new adverse event & warning; “there have been occasional reports of serotonin syndrome in patients treated with serotonin uptake inhibitor antidepressants who receive methylene blue. Investigators are advised to use caution in this setting.” * Clarification on MESNA and hydration delivery during IFOS administration * Duration of IFOS treatment clarified * IFOS adjustments to renal function updated * Quality of Life sub-study eligibility and age ranges updated * Updated pharmacovigilance reporting procedure * Change of Phase II primary outcome measure from OR after 4 cycles of trial treatment to EFS, including rationale. OR is now a secondary outcome * Section 14 Statistical considerations has been extensively updated, in relation to the above, sample size calculations and plans for future analyses |

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 systemic anticancer 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

Main Eligibility Criteria

**Principal inclusion criteria**

* Histologically proven, Ewing or Ewing-like sarcoma of the bone or soft tissues

Radiological evidence of disease progression during or after completion of first or any subsequent line of treatment.

* Medically fit to receive trial treatment
* Age ≥2years

**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
* Previous randomisation in the rEECur trial
* Glomerular filtration rate that would preclude use of ifosfamide or carboplatin

Trial Duration

Anticipated time to complete accrual:

* Phase II – with 3 arms, estimated 1.6 years to accrue 50 patients per arm, 2.4 years to accrue 75 patients per arm
* Phase III –to accrue 200 patients per arm, estimated 6.25 years with 3 arms, 4.2 years with 2 arms

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

Treatment Summary

Patients will be randomised to one of the available chemotherapy regimens:

* Topotecan and Cyclophosphamide (TC): 6 cycles, of 21 days, additional cycles at clinician’s discretion
* High dose Ifosfamide (IFOS), 4 cycles, of 21 days, additional cycles at clinician's discretion.
* Carboplatin and Etoposide (CE): 6 cycles of 21 days, additional cycles at clinician’s discretion

Local disease control measures are encouraged where possible. However, these should be delayed if possible until completion of protocol defined treatment (6 cycles of TC or CE, 4 cycles of IFOS).

Stem cell harvesting may be carried out in patients for whom high dose therapy is planned. However, if an alternative chemotherapy regimen is planned for stem cell mobilisation, it should be delayed if possible until completion of protocol defined treatment, (6 cycles of TC or CE, 4 cycles of IFOS) or as a minimum must be delayed until after the response assessment following cycle 4..

Myeloablative therapy may be given at the discretion of the treating physician after 6 cycles of TC or CE, or after 4 cycles of IFOS.

Trial Schema

A screenshot of a cell phone

Description automatically generated

Schedule of Events

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

1. for patients who complete 6 cycles
2. may be performed more than 2 weeks prior to trial entry
3. according to institutional policy.
4. tumour biopsy is not mandatory and may be performed more than 2 weeks prior to trial entry
5. after trial entry and randomisation, GFR and tubular function need only be reassessed prior to each chemotherapy cycle for patients receiving CE and IFOS, see section 7.2.2 and 7.2.3
6. for patients who receive TC and CE
7. see section 7.5.7
8. PET CT response is a secondary outcome measure in rEECur; see section 7.5.7.
9. see section 7.5.7
10. not applicable prior to the first cycle
11. before first cycle of chemotherapy
12. at disease progression and/or relapse

Abbreviations

AE Adverse event

ALP Alkaline phosphatase

ALT Alanine transaminase

ANC Absolute neutrophil count

AST Aspartate transaminase

Ccrea Creatinine clearance

CE Carboplatin and Etoposide

COG Children’s Oncology Group

CR Complete response

CRCTU Cancer Research UK Clinical Trials Unit, Birmingham

CRF Case Report Form

CT Computed tomography

CTCAE Common Terminology Criteria for Adverse Events

DMC Data Monitoring Committee

DSUR Development Safety Update Report

EEC Euro Ewing Consortium

EFS Event-free survival

EORTC European Organisation for Research and Treatment of Cancer

eRDC Electronic Remote Data Capture

ES Ewing sarcoma

EU European Union

GCP Good Clinical Practice

G-CSF Granulocyte-colony stimulating factor

GEIS Spanish Group for Sarcoma Research

GD Gemcitabine and Docetaxel

GFR Glomerular Filtration Rate

GPOH German Society for Paediatric Haematology and Oncology

HCO Bicarbonate

HR Hazard ratio

ICF Informed Consent Form

IFOS Ifosfamide

IMP Investigational medicinal product

ISF Investigator Site File

ISG Italian Sarcoma Group

IT Irinotecan and Temozolomide

ITT Intention to treat

MAMS Multi-arm, multi-stage

MRI Magnetic resonance imaging

OR Objective response

OS Overall survival

PD Progressive disease

PET Positron Emission Tomography

PFS Progression-free survival

POG Pediatric Oncology Group

PR Partial response

QoL Quality of life

RR Relative risk

SAE Serious adverse event

SAR Serious adverse reaction

SD Stable disease

SFCE Societe Francaise des Cancers d’Enfants

TC Topotecan and Cyclophosphamide

SSG Scandinavian Sarcoma Group

TMG Trial Management Group

TMZ Temozolomide

TSC Trial Steering Committee

TTP Time to progression

UK United Kingdom

WHO World Health Organisation

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   1. Background
      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](#_ENREF_1)]. In over 98% of cases the malignant phenotype derives from chromosomal translocations that result in gene fusions between *EWS* andanETS 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](#_ENREF_2)]. 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](#_ENREF_5), [6](#_ENREF_6)]. There has been no improvement in the proportion of long-term survivors for 25 years.

* + 1. Treatment results in recurrent and primary refractory disease

Survival following relapse is poor [[5-10](#_ENREF_5)]. The Rizzoli Institute reported a retrospective review of 195 patients treated for recurrent disease over an 18-year period to 1997 [[7](#_ENREF_7)] and subsequently an updated review of 290 patients treated between 1972 and 1999 with median follow up of 13.6 years following recurrence [[8](#_ENREF_8)]}. 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 [[11](#_ENREF_11)]. 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.

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](#_ENREF_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. Smaller single centre series of patients have been reported from The Washington Children’s Hospital (n=55) [[9](#_ENREF_9)], Istanbul University Oncology Institute (n=54) [[12](#_ENREF_12)], and the Mayo Clinic (n=49) [[13](#_ENREF_13)]}.

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](#_ENREF_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. 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, Rizzoli, Mayo and Istanbul series. In the GPOH series, recurrences in the lung and bone, multisystem 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 [[7](#_ENREF_7)] also reported progressively worse outcome for patients with lung metastases, bone metastases and combined lung and bone metastases.

Several series that reported treatment at recurrence 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 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). Survival was better in the Istanbul series in patients who had ifosfamide and etoposide +/- carboplatin (n=24) than those who did not (n=26, HR 2.38, multivariate p=0.003). 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 [[10](#_ENREF_10)]. 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. Trial Rationale
     1. Rationale for an international study

Numerous chemotherapy regimens have been reported in recurrent ES, incorporating alkylating agents [[14](#_ENREF_14), [15](#_ENREF_15)], camptothecin derivatives [[16](#_ENREF_16), [17](#_ENREF_17)] and platinum agents [[18-20](#_ENREF_18)]. Several regimens have emerged to be in most widespread use 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 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 internationally and inequitable access to drugs and regimens.

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 Europe. 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 study in recurrent ES.

* + 1. Reported activity and toxicity of the chemotherapy regimens
       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 [[17](#_ENREF_17), [21](#_ENREF_21), [22](#_ENREF_22)]. Topotecan has been used principally at recurrence, given as a single agent as a continuous infusion [[23](#_ENREF_23), [24](#_ENREF_24)] and as a 3-weekly, short infusion schedule of 2.0 mg/m2/day for 5 days [[25](#_ENREF_25)]. 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 [[15](#_ENREF_15)] and two other groups [[26](#_ENREF_26), [27](#_ENREF_27)] 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 [[15](#_ENREF_15)]), 16/45 (GPOH series [[27](#_ENREF_27)]) and 3/13 (American University of Beirut [[26](#_ENREF_26)]) evaluable patients, with SD in 6, 15 and 4 respectively, giving a combined 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 [[15](#_ENREF_15), [26](#_ENREF_26)], while the GPOH study reported first evaluable response, which in approximately half of patients was after 2 cycles of chemotherapy [[27](#_ENREF_27)].

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 [[28](#_ENREF_28)].

An alternative continuous infusion schedule of cyclophosphamide 4200mg/m2 over 48 hours and topotecan 6 /m2 over 72 hours was investigated in a phase II study by Memorial Sloan Kettering [[29](#_ENREF_29)]. 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 [[30](#_ENREF_30)]. 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 [[31](#_ENREF_31)], 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 [[31](#_ENREF_31)]. The phase II combination study reported grade 3 and 4 infections after 11% of cycles [[15](#_ENREF_15)]; the retrospective series reported infections after 4% [[27](#_ENREF_27)] and 6% [[26](#_ENREF_26)] 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 [[15](#_ENREF_15), [26](#_ENREF_26), [31](#_ENREF_31)].

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 [[27](#_ENREF_27)].

* + - 1. 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 [[14](#_ENREF_14)]. 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 [[32](#_ENREF_32)]. 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 [[16](#_ENREF_16)]. 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[[33](#_ENREF_33)]. 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 [[34](#_ENREF_34)].

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 [[35](#_ENREF_35)]. 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 [[36](#_ENREF_36)]. 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 four-fold 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 [[37](#_ENREF_37)]. Best responses in 14 evaluable patients were 1 CR, 3 PR and 4 SD. MD Anderson reported a retrospective analysis of 25 evaluable patients [[38](#_ENREF_38)]. 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 [[39](#_ENREF_39)]. The Hospital Infantil Universitario Nino Jesús, Madrid reported 7 patients, with best responses of 3 PR and 2 SD [[40](#_ENREF_40)]. 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 [[41](#_ENREF_41)]. 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 [[42](#_ENREF_42)] 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 [[43](#_ENREF_43)]. A second report with the addition of bevacizumab 15 mg/kg on day 1 included 2 ES patients [[44](#_ENREF_44)]. There was 1 CR after 6 cycles and 1 PR after 3 cycles.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Ref** | **TMZ  (mg/m2)** | **Irinotecan  (mg/m2)** | **Other agents** | **N** | **Objective responses** |
| Wagner | [[37](#_ENREF_37)] | 100 x 5 | IV 10-20 x 5 x 2 |  | 14 | 4 |
| Anderson | [[38](#_ENREF_38)] | 100 x 5 | IV 10 x 5  IV 10 x 5 x 2 |  | 25 | 16 |
| Casey | [[39](#_ENREF_39)] | 100 x 5 | IV 20 x 5 x 2 |  | 19 | 12 |
| Hernandez-Marques | [[40](#_ENREF_40)] | 80-100 x 5 | IV 10-20 x 5 x 2 |  | 7 | 3 |
| Raciborska | [[41](#_ENREF_41)] | 125 x 5 | IV 50 x 5 | Vincristine x 1 | 22 | 12 |
| McKnall-Knapp | [[42](#_ENREF_42)] | 100 x 5 | IV 20 x 5 x 2 | Vincristine x 1 | 1 | 1 |
| Wagner | [[43](#_ENREF_43)] | 100-150 x 5 | Oral 35-90 x 5  Oral 35-90 x 5 x 2 | Vincristine x 1 Vincristine x 2 | 5 | 2 |
| Wagner | [[44](#_ENREF_44)] | 150 x 5 | Oral 90 x 5 | Vincristine x 1  Bevacizumab | 2 | 2 |
| **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 [[37](#_ENREF_37), [39](#_ENREF_39), [40](#_ENREF_40)]. 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 [[41](#_ENREF_41), [42](#_ENREF_42), [45](#_ENREF_45)]. 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 [[40](#_ENREF_40), [46](#_ENREF_46)], 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 [[37](#_ENREF_37)], 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 [[39](#_ENREF_39)]), grade 3-4 liver toxicity in 2 cases [[40](#_ENREF_40)] and recurrent pancreatitis in a patient who had previously developed pancreatitis following oxaliplatin [[42](#_ENREF_42)].

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 [[41](#_ENREF_41), [45](#_ENREF_45)]. 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.

Following the second planned interim analysis; the IT randomisation closed to recruitment on 18 March 2020. The results are presented below and will be published when data from patients recruited to the IT arm are more mature.

* + - 1. Gemcitabine and docetaxel

Gemcitabine is a difluorinated analogue of deoxycytidine with poor single agent activity in recurrent ES (n=5 patients, no objective responses [[47](#_ENREF_47), [48](#_ENREF_48)]). Docetaxel is a semi-synthetic taxane with similarly poor activity in recurrent ES (n= 34, 0 CR, 4 PR [[49](#_ENREF_49), [50](#_ENREF_50)]). Hensley *et al.* reported the first series with activity of 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 [[51](#_ENREF_51)]. 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 [[52](#_ENREF_52), [53](#_ENREF_53)]. Of 4 evaluable patients there were 1 PR and 2 SD. Since the recommended phase II dose for gemcitabine was 1000 mg/m2 [[54](#_ENREF_54)] and a higher dose combination had previously been tolerated [[51](#_ENREF_51)] 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 [[55](#_ENREF_55)]. 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 [[56](#_ENREF_56), [57](#_ENREF_57)]. From 16 evaluable patients there were 2 PR and 6 SD.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author** | **Ref** | **Gemcitabine** | **Docetaxel** | **N** | **Objective responses** |
| Leu | [[52](#_ENREF_52)] | 675 mg/m2 days 1 & 8 | 100 mg/m2 day 8 | 2 | 1 |
| Navid | [[53](#_ENREF_53)] | 675 mg/m2 days 1 & 8 | 100 mg/m2 day 8 | 2 | 0 |
| More | [[58](#_ENREF_58)] | 1000 mg/m2 days 1 & 8 | 100 mg/m2 day 8 | 6 | 4 |
| Lee | [[55](#_ENREF_55)] | 1000 mg/m2 days 1 & 8 | 35 mg/m2 days 1 & 8 | 5 | 1 |
| Fox | [[56](#_ENREF_56)] | 675 mg/m2 days 1 & 8 | 75 mg/m2 day 8 | 14 | 2 |
| Rapkin | [[57](#_ENREF_57)] | 675 mg/m2 days 1 & 8 | 75 mg/m2 day 8 | 2 | 0 |
| **Table 2: Summary of published gemcitabine and docetaxel regimens** | | | | | |

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) [[52](#_ENREF_52), [53](#_ENREF_53), [56](#_ENREF_56), [57](#_ENREF_57)] and in 0-21% given higher dose regimens (900-1000 mg/m2/dose) [[18](#_ENREF_18), [19](#_ENREF_19), [55](#_ENREF_55), [58](#_ENREF_58)]; and in 0-60% given lower dose docetaxel [[55-57](#_ENREF_55)] versus 0-35% with higher dose docetaxel [[18](#_ENREF_18), [19](#_ENREF_19), [51-53](#_ENREF_51), [55](#_ENREF_55), [58](#_ENREF_58)]. 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) [[51](#_ENREF_51)] 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 [[53](#_ENREF_53)]; the other was thought to have non-neutropenic sepsis [[55](#_ENREF_55)]. 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.

Following the first planned interim analysis; the GD randomisation closed to recruitment on 16 November 2018. The results are described below and will be published when follow up data for all patients recruited to GD are more mature.

* + - 1. Ifosfamide

Ifosfamide has been a standard of first line treatment since it was shown to have activity in ES 3 decades ago [[11](#_ENREF_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 [[59](#_ENREF_59)] and 14 g/m2 over 14 days [[60](#_ENREF_60)].

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.

* + - 1. **Platinum adducts and etoposide**

The activity of cisplatin and carboplatin as single agents is limited, reported respectively in a first line window study by AEIOP [[63](#_ENREF_63)] and in relapsed disease by the Children’s Cancer Group [[64](#_ENREF_64)].

In combination, carboplatin has been used as a component of myeloablative therapy since the early 1990s [[65-68](#_ENREF_65)], and more recently in first line therapy at non-myeloablative doses by the Bambino Gesu Children’s Hospital [[69](#_ENREF_69)], the Brazilian collaborative Ewing sarcoma study group [[70](#_ENREF_70)], and as a window study with topotecan by the German cooperative soft tissue sarcoma study group CWS. Cisplatin has been used as a component of combination regimens in initial treatment by the Scandinavian sarcoma group [[71](#_ENREF_71)] and in a retrospective series reported by Leuven University Hospital [[72](#_ENREF_72)].

In relapsed disease, both cisplatin and carboplatin have been reported in combination with other drugs, most frequently with etoposide +/- ifosfamide. University College London Hospital reported 1 CR and 9 PR in 39 patients treated with carboplatin to an area under the carboplatin concentration-time curve (AUC) of 6 mg/ml in combination with etoposide and cyclophosphamide [[73](#_ENREF_73)]. Median time to progression was 10 weeks. In a series of trials the Children’s Cancer Group used an ICE regimen of carboplatin 800 mg/m2/cycle with ifosfamide and etoposide in children with relapsed sarcomas [[20](#_ENREF_20)], there were 6 CR and 4 PR in 21 children with Ewing sarcoma (OR 48%); 1- and 2-year OS were 49% and 28%. More recently, van Maldegem and colleagues reported an international retrospective series of 61 patients with relapsed and refractory ES treated with carboplatin and etoposide according to a variety of weekly and 3-weekly regimens [[74](#_ENREF_74)], in whom there were 10 CR and 7 PR (OR 28%) and median time to progression was 14.5 months.

Cisplatin given in combination with etoposide and ifosfamide resulted in 8 PR and 1 CR in 27 adult patients with relapsed/refractory disease in a retrospective single centre series from Riyadh [[75](#_ENREF_75)]. Median time to progression was 6.6 months. A prospective phase II study in France [[76](#_ENREF_76)] evaluated a regimen of weekly cisplatin in combination with oral etoposide in 40 evaluable patients with 7 PR and a median time to progression of 6 months. The van Maldegem report also included 46 patients given a variety of cisplatin and etoposide regimens, with 4 CR, 7 PR (OR 24%) and median time to progression of 6.3 months.

This evidence of activity of both cisplatin and carboplatin in combination with etoposide from several independent series is similar in scale to the activity of the other regimens currently evaluated in rEECur, and randomised data of activity are lacking. Moreover, the most recent international series reported by van Maldegem and colleagues, although uncontrolled, suggests that the carboplatin and etoposide combination has activity in excess of that reported for other chemotherapy regimens in this setting. We therefore plan to evaluate an outpatient carboplatin and etoposide combination in rEECur.

* + 1. Results presented to date from the rEECur trial

The results of the first interim analysis were presented at the annual meeting of the American Society of Clinical Oncology (ASCO) in June 2019 [[61](#_ENREF_61)], and from the second interim analysis at the annual meeting of ASCO in June 2020 [[62](#_ENREF_62)]. Respectively, the first 220 and 366 randomised patients were presented. The GD arm was closed to recruitment after the first interim analysis on the basis of worse observed imaging response, PFS and OS than the other three arms. Results were presented at ASCO 2019 for patients recruited to GD, and for the IT, TC and IFOS arms combined. The IT arm was closed to recruitment after the second interim analysis on the basis of worse observed imaging response, PFS and OS in patients recruited to IT than the other two open arms. Results were presented at ASCO 2020 for patients recruited to the GD and IT arms separately, and for the TC and IFOS arms combined.

At the time of the second interim analysis, the numbers recruited to each arm were 72 (GD), 119 (IT), 119 (TC) and 46 (IFOS). The observed response rates for patients recruited to the GD arm, IT arm and the TC and IFOS arms combined were 11%, 20% and 23% respectively. PFS at last follow up was 11%, 26% and 27% respectively and OS was 29%, 44% and 47%. With median follow up 24.2 months, PFS and OS for the whole trial cohort was 4.7 months and 13.7 months. Median PFS for the individual arms was 2.1 months (GD), 4.7 months (IT) and 5.3 months (TC and IFOS combined).

Patients were more likely to report ≥ grade 3 toxicity with IT, TC and IFOS than GD (32% GD, 41% IT, 42% TC and IFOS combined). Patients recruited to TC and IFOS had more episodes of febrile neutropenia and ≥ grade 3 infections than those recruited to IT or GD. Patients treated with IT had more ≥ grade 3 gastrointestinal toxicity.

* + 1. Change of Phase II primary outcome measure

EFS and OS are more relevant measures to patients and parents than short-term imaging response. When the rEECur trial was designed, insufficient information on EFS was published in relapsed/refractory ES to allow a Phase II sample size calculation. Response was therefore used as the primary outcome in Phase II. Imaging response is the most commonly reported metric in this disease setting from early phase trials and retrospective series, although there had not been data available to show whether response is a valid surrogate for survival in ES.

An analysis of the first 239 patients with imaging response and survival data recruited to rEECur demonstrated no difference in EFS/PFS or OS after two, four or six cycles of chemotherapy between patients with RECIST 1.1-defined objective imaging response or stable disease. Hazard ratios for progression and death at one year for patients with objective response after the 4th cycle of chemotherapy compared to those with stable disease at the same timepoint were 0.9 (0.6 - 1.4) and 1.5 (0.9-2.5). It is therefore illogical to count imaging response as a success and stable disease as a failure. Moreover, 13% of patients recruited to rEECur have RECIST-non-measurable disease and cannot therefore contribute to the primary outcome if it is response. Therefore, EFS will be the primary outcome measure for both phase II and phase III components of the rEECur trial.

1. Objectives and Outcome Measures
   1. Objectives

The objectives of the study are to compare chemotherapy regimens in recurrent/refractory ES in order to identify the best one with respect to efficacy (imaging response and survival), toxicity and acceptability to patients.

* 1. Outcome Measures
     1. Primary outcome measure

Event-free survival (EFS)

* + 1. Secondary outcome measures
* Objective imaging response (OR) according to RECIST 1.1 criteria after 2, 4, and 6 cycles for TC and CE, after 2 and 4 cycles for IFOS, and at the end of trial treatment
* Progression-free Survival (PFS)
* Overall survival (OS)
* Toxicity, defined by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (see Appendix 2)
* PET-CT response after 4 cycles
* Quality of life (QoL)
* Days spent in hospital

1. 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 the available 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.

For each arm, the phase II evaluation comprises two stages, with the number of patients needed being dependent on the design parameters. Because arms are introduced at different times, the evaluations will not occur simultaneously for all arms. At each assessment, the outcomes of contemporaneously randomised patients will be compared and one arm will be dropped based on activity and/or toxicity. The remaining arms will continue to recruit. Arms that remain in the study after the required number of phase II patients have been recruited will progress to phase III evaluation. Patients recruited in the phase II stage for each comparison will contribute data to the phase III stage for that comparison.

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).

1. 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 Ewing or Ewing-like sarcoma of the bone or soft tissues. Histological confirmation either at initial diagnosis or disease progression. 2. Radiological evidence of disease progression during or after completion of first or any subsequent line of treatment. 3. Age ≥ 2 years. 4. Eligible for randomisation between at least two open study arms. 5. Patient assessed as medically fit to receive trial treatment 6. Date of planned randomisation within 4 weeks of baseline imaging. 7. Documented negative pregnancy test for female patients of childbearing potential. 8. Patient agrees to use effective contraception during therapy and for 12 months after last trial treatment, where applicable. 9. Written informed consent from the patient and/or parent/legal guardian. |
| **Exclusion criteria** | 1. Absolute Neutrophil Count (ANC) <1.0 x 109/L or platelets <75 x 109/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 not be randomised to receive an arm that contains the contraindicated IMP.   Exclusion criteria for randomisation into the CE arm: Carboplatin is contraindicated in patients with actively bleeding tumours.  Therefore, patients with actively bleeding tumours are not eligible for the CE randomisation.  Exclusion criteria for randomisation into the IFOS and CE arms: glomerular filtration rate that would preclude use of ifosfamide or carboplatin   1. Patients and investigators may decline randomisation to one or more trial regimens. 2. Patients who have previously received one of the trial regimens off-trial may not be randomised to receive that regimen again. 3. Patients who have received cyclophosphamide during first line therapy **may** be randomised to receive the TC arm and 4. Patients who have had ifosfamide during first line therapy **may** receive the ifosfamide arm. There is no requirement for a minimum time between receiving first line ifosfamide and entry to rEECur. |

**Notes:**

The appearance of new bone lesions on bone scan or PET avid disease on PET scan requires confirmation with cross-sectional imaging.

Refractory disease is defined as disease progression during first line treatment or within 12 weeks of completion. Disease progression at or after 12 weeks of completion of first line treatment is defined as recurrent disease.

Patients with bone marrow, renal or other toxicity are eligible to enter the trial if they meet all inclusion and no exclusion criteria and do not have bone marrow, renal or other toxicity that would necessitate a dose modification as described in section 7. during cycle 1.

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.

1. Screening and Consent
   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.

* 1. 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 investigatoror 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.

1. 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. Randomisation

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

* TC 6 cycles of **Section 7.2.1**

intravenous topotecan and cyclophosphamide

* CE 6 cycles of **Section 7.2.2**

intravenous carboplatin and etoposide

* IFOS 4 cycles of intravenous ifosfamide **Section 7.2.3**

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

* 1. Procedure for randomisation

It is expected that patients will be randomised between all 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 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. At trial entry, each patient will be assessed for suitability for each treatment and the appropriate randomisation options will be selected:

3-way options:

TC or CE or IFOS

2-way options:

TC or CE

TC or IFOS

CE or IFOS

Patients will be allocated in a 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/rEECur**](https://www.cancertrials.bham.ac.uk/rEECur)**Live/**

In order to randomise a patient, a paper Eligibility Checklist must be completed followed by an online 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 emailed through to the UK Coordinating Centre using the details below:

**RANDOMISATION**

(09:00 to 17:00 GMT, Monday to Friday)

🕿 🕿 +44 (0)121 415 9877 or [reecur@trials.bham.ac.uk](mailto: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.

1. Treatment Details
   1. Trial treatment

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

* Carboplatin
* Cyclophosphamide
* Docetaxel
* Etoposide
* 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.
  1. Treatment schedules and dose modifications
     1. Topotecan and Cyclophosphamide (TC)

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

* + - 1. Agents and dosage

Cycles of TC should be given at 21 +/-3 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.

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

|  |  |  |  |
| --- | --- | --- | --- |
| **TC** | | | |
| **T**OPOTECAN | 0.75 mg/m2  (IV infusion, 30 min) | d1, d2, d3, d4, d5 | (Total dose: 3.75 mg/m2/cycle) |
| **C**YCLOPHOSPHAMIDE | 250 mg/m2  (IV infusion, 1 h) | d1, d2, d3, d4, d5 | (Total dose: 1.25 g/m2/cycle) |
| **G-CSF** | Not mandatory - refer to section 7.10.5 | | |

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.

* + - 1. Patient monitoring and assessments

Refer to sections 7.4 to 7.6.

* + - 1. 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 should be delayed if possible until completion of protocol defined treatment (6 cycles). Details of local control treatments will be captured on the Case Report Form (CRF).

* + - 1. Stem cell mobilisation and myeloablative therapy

Stem cell harvesting may be carried out in patients for whom high dose therapy is planned. However, if an alternative chemotherapy regimen is planned for stem cell mobilisation, it should be delayed if possible until completion of protocol defined treatment (6 cycles), or as a minimum must be delayed until after the response assessment following cycle 4.

Details of myeloablative therapy will be captured on the on the CRF.

* + - 1. 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.

* + - 1. 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 ml/m2/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
  + 1. Carboplatin and Etoposide (CE)

A screenshot of a cell phone

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

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

* + - 1. Agents and dosage

Cycles of CE should be given at 21 +/-3 day intervals or on haematological recovery to ANC ≥1.0 x 109/L, platelets ≥75 x 109/L, whichever is later.

Body surface area should be calculated according to institutional practice.

|  |  |  |  |
| --- | --- | --- | --- |
| **CE** | | | |
| **C**ARBOPLATIN | 400 mg/m2 (IV infusion, 1hr) | d1 | (Total dose: 400mg/m2 /cycle) |
| **E**TOPOSIDE | 120 mg/m2 (IV infusion, 2 h) | d1, d2, d3 | (Total dose: 360 mg/m2/cycle) |
| **G-CSF** | **Mandatory - refer to section 7.10.5** | | |

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

* + - 1. Patient monitoring and assessments

Refer to sections 7.4 to 7.6

* + - 1. 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 should be delayed until completion of protocol defined treatment (6 cycles). Details of local control treatments will be captured on the Case Report Form (CRF)..

* + - 1. Stem cell mobilisation and myeloablative therapy

Stem cell harvesting may be carried out in patients for whom high dose therapy is planned. However, if an alternative chemotherapy regimen is planned for stem cell mobilisation, it should be delayed if possible until completion of protocol defined treatment (6 cycles), or as a minimum must be delayed until after the response assessment following cycle 4 .

Details of myeloablative therapy will be captured on the on the CRF.

* + - 1. Duration of treatment

In the absence of disease progression, a minimum of 6 cycles of CE 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 CE 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.

* + - 1. Toxicity

##### Haematological toxicity

G-CSF support is mandatory for CE cycles. 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 dose of etoposide by 20% and reduce dose of carboplatin to 300 mg/m2 for next CE cycle

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

* Reduce dose of etoposide by 20% and reduce dose of carboplatin to 300 mg/m2 for next CE cycle

In the event of further episodes of toxicity, reduce the dose of etoposide by an additional 20% and reduce the dose of carboplatin to 200 mg/m2 for the next CE cycle. If toxicity recurs after a second dose reduction, discontinue study treatment.

##### Nephrotoxicity / Renal function monitoring

Glomerular Filtration Rate (GFR)

Serum creatinine and GFR should be monitored prior to each cycle of CE.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. Investigators are encouraged to use an isotope clearance method to measure GFR in children in preference to a calculated estimate based on creatinine clearance. The following calculations should be performed if an isotope GFR is not possible.

*Bedside Schwartz’s Formula (1-17 years) [*[*77*](#_ENREF_77)*]*

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

Ccrea = ml/min/1.73 m2

0.413 x height [cm]

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

serum creatinine [mg/dl]

*Cockcroft- Gault Formula (≥18 years)* [[79](#_ENREF_79)]



**Females** or



**Males** or

PLEASE NOTE:

* These formulae have not been confirmed in patients receiving repeated cycles of intensive chemotherapy or in adolescents. Renal function may be overestimated by these methods.
* The bedside Schwartz's formula estimate of creatinine clearance is corrected for surface area (units: ml/min/1.73m2); the Cockgroft-Gault formula estimate is not corrected (units: ml/min) and must be corrected for a surface area of 1.73m2 before deciding whether a dose reduction is required.

|  |  |
| --- | --- |
| **GFR corrected for surface area** | **Action** |
| ≥ 90 ml/min/1.73 m2 | Continue carboplatin dose 100% |
| 61-90 ml/min/1.73 m2 | Reduce carboplatin to 300 mg/m2/dose |
| 30-60 ml/min/1.73 m2 | Reduce carboplatin to 200 mg/m2/dose |
| <30 ml/min/1.73 m2 | Omit carboplatin |

Tubular function (Tp/Ccrea or Tmp/GFR), [[80](#_ENREF_80)] [[81](#_ENREF_81)]

Tubular function should be monitored prior to each cycle (TmP/GFR, serum bicarbonate and electrolytes) and electrolytes should be adequately supplemented if renal losses occur. No chemotherapy delays or dose reductions are required for electrolyte loss. However, investigator discretion is allowed to reduce dose or discontinue carboplatin if electrolyte loss is significant.

Maximal phosphate reabsorption per unit volume of glomerular filtrate (TmP/GFR) can be calculated using fasting paired urine and serum samples as follows:





Reference range for children aged 2-15 years: 1.15-2.44 umol/ml. Reference range for adults approximately: 0.8 - 1.44, varying with age and sex.

##### Posterior reversible encephalopathy syndrome (PRES)

##### If PRES develops during therapy

* Institute supportive measures including blood pressure control and anti-seizure medication
* Permanently discontinue study treatment

##### Liver toxicity

Hepatic injury, including fatal hepatic failure and veno-occlusive dsease (VOD), has been reported in some patients treated with carboplatin. Liver function tests should be performed prior to each cycle of CE. If abnormal, clinicians should assess the benefit/risk prior to initiating carboplatin, including the potential for fatal hepatic failure.

##### Haemolytic-uraemic syndrome

##### Study treatment should be discontinued at the first sign of haemolytic-uraemic syndrome.

##### Hearing Loss

##### Long term audiometric follow-up is recommended for patients receiving carboplatin.

##### Anticoagulants:

##### Increased monitoring is recommended for patients receiving anticoagulation therapy.

##### 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 etoposide and/or a dose reduction of carboplatin to 300 mg/m2 depending which agent is responsible for toxicity. If neither agent is clearly responsible for toxicity, both agents should be reduced.

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

* a second 20% dose reduction of etoposide should be made and/or carboplatin dose should be reduced to 200 mg/m2 depending which agent is responsible for toxicity. If neither agent is clearly responsible for toxicity, both agents should be reduced.

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

* discontinue study treatment
  + 1. Ifosfamide (IFOS)

A screenshot of a cell phone

Description automatically generated

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.

* + - 1. Agents and dosage

Cycles of IFOS should be given at 21 +/- 3 day intervals or on haematological recovery to ANC ≥1.0 x 109/L, platelets ≥75 x 109/L, whichever is later.

Body surface area should be calculated according to institutional practice.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **IFOS** | | | | |
| **I**FOSFAMIDE | 3 g/m2  (IV infusion, 24 h) | d1, d2, d3, d4, d5 | (Total dose: 15 g/m2/cycle) | plus MESNA and hydration\* |
| **G-CSF** | **Mandatory starting 48 hours after final IFOS infusion - refer to section 7.10.5** | | | |
| **MESNA** | **According to local practice** | | | |
| **Hydration** | **According to local practice (see also below).** | | | |

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

Sufficient hydration (2-3 L/m²/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.

* + - 1. Patient monitoring and assessments

Refer to sections 7.4 to 7.6

* + - 1. 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 should be delayed if possible until completion of protocol defined treatment (4 cycles).

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

* + - 1. Stem cell mobilisation and myeloablative therapy

Stem cell harvesting may be carried out in patients for whom high dose therapy is planned. However, if an alternative chemotherapy regimen is planned for stem cell mobilisation, it should be delayed if possible until completion of protocol defined treatment (4 cycles).

Details of myeloablative therapy will be captured on the on the CRF.

* + - 1. Duration of treatment

In the absence of disease progression, a maximum of 4 cycles of IFOS will generally be given. This ifosfamide regimen is toxic. However, for patients with stable disease or an OR on imaging after 4 cycles, additional cycles may be given with caution at the discretion of the responsible clinician.

* + - 1. 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 or

Repeated episodes of neutropenic sepsis grade 3 or 4 after ≥ 2 cycles:

* Discontinue study treatment.

##### Nephrotoxicity / Renal function monitoring

Serum creatinine and GFR should be monitored prior to each cycle of IFOS.

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. Investigators are encouraged to use an isotope clearance method to measure GFR in children in preference to a calculated estimate based on creatinine clearance. The following calculations should be performed if an isotope GFR is not possible.

*Bedside Schwartz’s Formula (1-17 years), [*[*77*](#_ENREF_77)*]*

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

Ccrea = ml/min/1.73 m2

0.413 x height [cm]

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

serum creatinine [mg/dl]

*Cockcroft- Gault Formula (≥18 years)* [[79](#_ENREF_79)]



**Females** or



**Males** or

PLEASE NOTE:

* These formulae have not been confirmed in patients receiving repeated cycles of intensive chemotherapy or in adolescents. Renal function may be overestimated by these methods.
* The bedside Schwartz's estimate of creatinine clearance is corrected for surface area (units: ml/min/1.73m2); the Cockgroft-Gault estimate is not corrected (units: ml/min) and must be corrected for a surface area of 1.73m2 before deciding whether a dose reduction is required.

|  |  |
| --- | --- |
| **GFR** | **Action (apply worst grade)** |
| ≥60 (ml/min/1.73 m2) | Continue ifosfamide dose 100% |
| <60 (ml/min/1.73 m2) | Delay treatment and recheck renal function after one week. If grade 2-4 toxicity persists after one week, discontinue study treatment. |

Tubular function [[80](#_ENREF_80), [81](#_ENREF_81)]

Tubular function should be monitored prior to each cycle (TmP/GFR, serum bicarbonate and electrolytes) and electrolytes should be adequately supplemented if renal losses occur. No chemotherapy delays or dose reductions are required for electrolyte loss. However, investigator discretion is allowed to reduce dose or discontinue carboplatin if electrolyte loss is significant.

Maximal phosphate reabsorption per unit volume of glomerular filtrate (TmP/GFR) can be calculated using fasting paired urine and serum samples as follows:





Reference range for children aged 2-15 years: 1.15-2.44 umol/ml. Reference range for adults approximately: 0.8 - 1.44, varying with age and sex .

##### 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

There have been occasional reports of serotonin syndrome in patients treated with serotonin uptake inhibitor antidepressants who receive methylene blue. Investigators are advised to use caution in this setting.

##### 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 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
  1. 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.

* 1. Schedule of assessments

The assessments included in the Schedule of Events in the Trial Synopsis (page xi) 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.

* 1. Assessments at diagnosis

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

* + 1. Diagnosis of ES and Ewing-like sarcoma

Diagnosis of ES or Ewing-like sarcoma 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.
* CD 99 (Mic-2) positivity.
  + 1. Histological confirmation of ES and Ewing-like 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.

* + 1. 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) [[82](#_ENREF_82)], or WHO Performance Status (age ≥16) (see Appendix 4).
* Menstrual history and pregnancy test if indicated.
  + 1. 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 parents/guardians to children over the age of 2 years) 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. The UK Coordinating Centre (CRCTU) will assume the responsibility for entering QoL data onto the eRDC database on behalf of all participating sites

* + 1. 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 7.2.3.6.
* Tubular function. See section 7.2.3.6.
  + 1. Haematology
* Blood count
  + 1. 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.
  + 1. 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.

* + 1. 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.

* 1. 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.

* + 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 or CE – see section 7.2.3.6. GFR and tubular function should also be assessed after the final cycle of IFOS or CE.
  + 1. 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.

* + 1. Quality of Life assessments

A member of the site research team should ask patients over the age of 5 years (and if applicable parents/guardians to children over the age of 2 years) to complete the relevant age group QoL Booklet at the following time points:

* After completion of chemotherapy cycle 2.
* After completion of chemotherapy cycle 4.

The UK Coordinating Centre (CRCTU) will assume the responsibility for entering QoL data onto the eRDC database on behalf of all participating sites (see Appendix 3).

* 1. 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 the CRF.

* 1. 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.

* 1. 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.

* 1. Supportive Treatment
     1. Venous Access

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

* + 1. Antiemetics

Patients should be treated with antiemetics appropriate to the anticipated emetogenicity of the allocated treatment schedule according to institutional practice.

* + 1. Neutropenic fever

Neutropenic fever should be managed using broad spectrum agents according to institutional practice.

* + 1. *Pneumocystis jirovecii* infection prophylaxis

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

* + 1. 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 CE 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 a minimum of 24 hours prior to chemotherapy commencing.

* + 1. Blood products

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

* + 1. 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 being evaluated in the recently closed 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 and CE or cycles 1 to 4 of IFOS).

* 1. General Warnings

The use of live vaccines should be avoided.

* 1. Concomitant Medication

Investigators should review the relevant Summary of Product Characteristics to avoid concomitant use with contraindicated medications.

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.

* 1. Patient Withdrawal
     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 or parent/guardian withdraws consent to further trial treatment (see section 7.13.2)
* Unacceptable toxicity (see also section 7.2)
* Disease progression whilst on therapy
* 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 7.13.2).

* + 1. 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/or 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.

* + 1. 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.

1. 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.

* 1. Questionnaires

The QoL Sub-study will utilise the following questionnaires:

* PedsQL™ 4.0 [[83](#_ENREF_83)] 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 [[84](#_ENREF_84)] (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.

* 1. 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

Teen QoL Booklet PedsQL™ Generic Core Scales Child Self Report Age 13-17

PedsQL™ Cancer Specific Module Child Self Report Age 13-17

Young Adult QoL Booklet PedsQL™ Generic Core Scales Self Report Age 18-25

PedsQL™ Cancer Specific Module Self Report Age 18-25

EORTC-QLQ30

Adult QoL Booklet PedsQL™ Generic Core Scales Self Report

Over 26

PedsQL™ Cancer Specific Module Self Report Over 26

EORTC-QLQ30

Parent/Guardian Toddler QoL Booklet PedsQL™ Generic Core Scales Parent-Proxy Report Age 2-4

PedsQL™ Cancer Specific Module Parent-Proxy Report Age 2-4

Parent/Guardian Young Child QoL Booklet PedsQL™ Generic Core Scales Parent-Proxy Report Age 5-7

PedsQL™ Cancer Specific Module Parent-Proxy Report Age 5-7

Parent/Guardian Child QoL Booklet PedsQL™ Generic Core Scales Parent-Proxy Report Age 8-12

PedsQL™ Cancer Specific Module Parent-Proxy Report Age 8-12

Parent/Guardian Teen QoL Booklet PedsQL™ Generic Core Scales Parent-Proxy Report Age 13-17

PedsQL™ Cancer Specific Module Parent-Proxy Report Age 13-17

* 1. Eligibility for Quality of Life Study

All participating patients 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.

* 1. 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:

* No patient specific questionnaire is available for patient under the age of 5 years of age
* A Parent/Guardian QoL Booklet will be given to all parent/guardians of eligible patients aged ≥2 to ≤4 years of age.
* 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 randomisation. 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.

1. 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.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | At diagnosis / prior to cycle 1 | After cycle 2/prior to cycle 3 | After cycle 4/prior to cycle 5 | After cycle 6 a | At disease progression or relapse b |
| Frozen tumour – snap frozen. Ship on dry ice to reference centre | **X** |  |  |  | **X** |
| Paraffin embedded tumour block Send at room temperature to pathology reference centre | **X** |  |  |  | **X** |
| Bone marrow aspirate (0.5 ml x 2, right and left) into PAXgeneTM Blood RNA Tubes – DO NOT POOL. Store at -80°C. Ship on dry ice to reference centre. | **X** |  |  |  | **X** |
| Whole blood (2 ml x 1) into PAXgeneTM Blood RNA Tube. Store at -80°C. Ship on dry ice to reference centre. | **X** | **X** | **X** | **X** | **X** |
| 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. | **X** | **X** | **X** | **X** | **X** |
| Whole blood (5ml into EDTA) for sequencing of constiutional DNA Store at -80°C. Ship on dry ice to reference centre. | **X** |  |  |  |  |

a In treatment arms TC and CE 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.

1. 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.

* 1. Reporting Requirements
     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.

* + 1. 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.

* + - 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 investigation or 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

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 Centreas 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.

* + 1. 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.

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.

* 1. Reporting Procedure
     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 emailed to the UK Coordinating Centre using the contact details provided below as soon as possible and no later than 24 hours after the Site Research Team first becoming aware of the event:

IF email is unavailable then sites may fax the SAE together with a SAE Fax Cover Sheet.

To report an SAE,

Email: reg@trials.bham.ac.uk

Or, if email unavailable, 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 3700

**General Enquiries**

🕿 +44 (0)121 415 9877 or [reecur@trials.bham.ac.uk](mailto:reecur@trials.bham.ac.uk)

On receipt the UK Coordinating Centre will allocate each SAE a unique reference number. This number will be provided 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. Where faxed, the SAE Fax Cover Sheet will be completed by the UK Coordinating Centre and faxed back to the site as proof of receipt. All correspondence 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.

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).

* + 1. 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.

* + 1. Reporting to the Competent Authority and Ethics Committee

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. .

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.

Adverse Events

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

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.

* + 1. 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.

* + 1. Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will review all SAEs (see section 15.5).

1. Data Handling and Record Keeping
   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/rEECur**](https://www.cancertrials.bham.ac.uk/rEECur)**Live/**

**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.

* 1. 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.

1. Quality Management
   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.

* 1. On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the UK Quality Management and International Monitoring plans (see Appendix 3).

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

* 1. 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.

* 1. 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.

* 1. 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.

The National Coordinating Centre will notify the UK Coordinating Centre of any serious breaches.

1. 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.

1. Statistical Considerations

rEECur is a MAMS randomised phase II/phase III clinical trial. The trial will include multiple arms with randomisation possible between any combination of arms (e.g. if four arms are open, 4-way, 3-way or 2-way randomisation is possible), with arms to be either: i) dropped after the first stage, ii) dropped after the second stage; iii) continued to a phase III evaluation. Randomisation to all arms will continue while awaiting interim analysis of the data.

Only concurrently randomised patients will be compared. For example, for the CE arm, patients allocated to CE will be compared only with patients allocated to the other open arms over the same time period and for whom the CE arm was selected as one of those to be randomised.

* 1. Definition of Outcome Measures
     1. Primary outcome measure

Phase II: For the initial four-way and three-way randomisation, imaging response by CT or MRI after 4 cycles of trial treatment was the primary outcome measure (see below for the definition).

From protocol version 6: EFS is the primary outcome measure and 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.

* + 1. Secondary outcome measures

Imaging response by CT or MRI after 2, 4 and 6 cycles (not for the IFOS arm) of trial treatment and at the end 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. For comparisons involving the CE arm, EFS (as defined above) is the primary outcome measure.

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.

PET-CT response after cycle 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.

* 1. Sample Size Calculations
     1. Phase II

First stage – At least 50 patients in each arm

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

**For OR:** See previous versions of the protocol.

**For EFS:** Simulations for OR, showed that there was only a small probability of dropping a regimen that was much more effective than the others. Similar considerations will apply for EFS and will be documented in the Statistical Analysis Plan.

* + 1. 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 [[85](#_ENREF_85)]. Pragmatically, the sample size for the phase III part of the trial will depend on: the actual outcomes observed (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 20% and 25% 1-year EFS with one treatment and 200 patients per arm):

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **1-yr EFS**  **Arm A** | **Improvement** | **1-yr EFS**  **Arm B** | **Total**  **Events** | **Hazard**  **Ratio (HR)** | **P(HR < 1.00)**  **(%)** | **P(HR < 0.86)**  **(%)** | **P(HR < 0.75)**  **(%)** |
| 0.20 | 0.00 | 0.20 | 320 | 1.00 | 0.50 | 0.09 | 0.01 |
| 0.20 | 0.05 | 0.25 | 310 | 0.86 | 0.91 | 0.50 | 0.11 |
| 0.20 | 0.10 | 0.30 | 300 | 0.75 | 0.99 | 0.88 | 0.50 |
| **1-yr EFS**  **Arm A** | **Improvement** | **1-yr EFS**  **Arm B** | **Total**  **Events** | **Hazard**  **Ratio (HR)** | **P(HR < 1.00)** | **P(HR < 0.87)** | **P(HR < 0.76)** |
| 0.25 | 0.00 | 0.25 | 300 | 1.00 | 0.50 | 0.11 | 0.01 |
| 0.25 | 0.05 | 0.30 | 290 | 0.87 | 0.88 | 0.50 | 0.12 |
| 0.25 | 0.10 | 0.35 | 280 | 0.76 | 0.99 | 0.87 | 0.50 |
| **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.

* 1. 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.

* + 1. Primary outcome measures

Phase II: See below A 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 [[19](#_ENREF_19)]. The priors will be combined with the observed data (likelihood) using conjugate analysis to obtain posterior distributions.

Phase III: 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.

* + 1. Secondary outcome measures

OR:The analysis populations for OR will be all patients with measurable disease. For each treatment arm and overall, the number (and proportion) of responders (CR or PR) 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. Credible intervals (CrI) will be provided. Analysis adjusting for the minimisation factors will also be presented.

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.

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.

* 1. Planned Sub Group Analyses

Exploratory subgroup analyses will be undertaken by the minimisation parameters.

* 1. Planned Interim Analyses
     1. Phase II

Interim analyses in Phase II will be performed once a minimum of 50 (stage 1) and 75 (stage 2) patients have been recruited to the CE arm. Randomisation to all open arms will continue while awaiting interim analysis of the data. Recruitment to the GD and IT arms was stopped after the first and second interim analysis.

At each interim analysis, the CE arm may be dropped if its EFS is worse than the other two arms. This decision criterion will be considered as a guideline and other factors – such as toxicity – will be taken into account before making the clinical decision as whether to drop the CE arm. The DMC will make recommendations on this basis.

* 1. Planned Main Analyses
     1. Phase III

The first main analysis for each arm is planned once that arm has been closed and patients in that arm have been followed up for a minimum of one year.

The decision as to which treatment will be considered the better treatment will be based on clinical opinion. It is expected that, if the Pr(true HR < 1.0 | data) > 70%, this will be sufficient to accept this treatment as the better one, while taking account of toxicity. If the probability is below 70%, the result could be considered as ambiguous or uncertain in which case the toxicity and other important secondary outcome measures will be taken into account, or the randomisation could continue in a future trial.

1. Trial Organisational Structure
   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.

* 1. 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.

* 1. 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.

* 1. 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.

* 1. 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 theSponsor and funders, where applicable.

* 1. 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.

1. 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 2001/20/EC** of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (Official Journal L21, 01/05/2001 P. 0034 – 0044) and detailed guidance.
  + **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).
  + **Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data (**Official Journal L 281 , 23/11/1995 P. 0031 – 0050).
  + 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.

1. 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.

1. 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.

1. 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.

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APPENDIX 1 – RECIST criteria

From the revised RECIST guideline (version 1.1)[[18](#_ENREF_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 aremet, 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:

<http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm>

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 indicting 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.

## 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 all participating sites.

## On-site Monitoring

Monitoring will be carried out as required following a Risk Assessment and as documented in the rEECurUK 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

|  |  |
| --- | --- |
| **Score** | **Descriptor** |
| 100 | Fully active, normal |
| 90 | Minor restrictions in strenuous physical activity |
| 80 | Active, but gets tired more quickly |
| 70 | Both greater restriction of play *and* less time spent in active play |
| 60 | Up and around, but minimal active play; keeps busy with quieter activities |
| 50 | Gets dressed but lying around much of the day but no active play; able to participate in all quiet play and activities |
| 40 | Mostly in bed; participates in quiet activities |
| 30 | In bed; needs assistance even for quiet play |
| 20 | Often sleeping; play entirely limited to very passive activities |
| 10 | No play; does not get out of bed |
| 0 | Unresponsive |
| **Table 6: Lansky score** [[82](#_ENREF_82)] [[82](#_ENREF_82)] | |

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

|  |  |
| --- | --- |
| **Score** | **Descriptor** |
| 0 | Asymptomatic (Fully active, able to carry on all predisease activities without restriction) |
| 1 | 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) |
| 2 | Symptomatic, <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) |
| 3 | Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours) |
| 4 | Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair) |
| 5 | Death |
| **Table 7: WHO score**  [[86](#_ENREF_86)] | |

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

See rEECur FDG-PET-CT Manual.