International Randomised Controlled Trial for the Treatment of Newly Diagnosed Ewing's Sarcoma Family of Tumours

Euro Ewing 2012

Version 5.0

2nd June 2017

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Euro Ewing 2012 Trial protocol version 5.0 2nd June 2017

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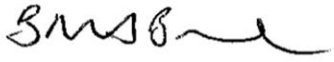
Signature:  **Date:** 6.6.17

This protocol describes the Euro Ewing 2012 trial and provides information about procedures for patients taking part in the Euro Ewing 2012 trial. The protocol should not be used as a guide for treatment of patients not taking part in the Euro Ewing 2012 trial.

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	3rd March 2014	2.0	Substantial amendment	Removal of randomisations to Busulfan and Melphalan (R2loc and R2pulm). Renaming of R2zol as R2 VAC, R2 VAI and R2 IEVC
				Amendment to eligibility criteria for R2
				Reduction in recruitment target for R2
				Change of treatment for Arm A patients (localised disease) from 1 cycle VAI plus 7 cycles VAC to 8 cycles VAC
				Change in number of bone marrow aspirate assessments from 4 to 1
				Amended length of time contraception is required for males patients post treatment
				Inclusion of treatment guidance for hypocalcaemia
				Removal of reference to Chemotherapy Guidelines
				Inclusion of central pathology review
				Clarification of details for biological studies
				Renumbering of Appendices and inclusion of a new Appendix 1: Country specific quality and trial management plan
				Minor changes to wording and terminology used in other sections for the purposes of clarity, especially with regard to international coordinating centre
2	23rd January 2015	3.0	Substantial amendment	Change of treatment for Arm A patients (good risk localised disease) from 8 cycle VAC to 1 cycle VAI plus 7 cycles VAC
				Change of terminology from co-sponsor to national coordinating centre throughout
				Changes to pharmacovigilance reporting requirements
				Inclusion of dose modifications for febrile neutropenia for patients in arm B.
				Updated diagnosis section 8.2.7 and eligibility criteria to include ‘Ewing’s like’ tumours which are EWSR1 negative.
				Change of dose for patients >18yrs receiving zoledronic acid, and change of infusion time.
				Addition of treatment advice for allergic reaction to methylene blue.
				Addition of allowing MRI and CT scans as end of treatment assessment.
				Clarification that lung radiotherapy is only recommended not mandated.
6	4th March 2016	4.0	Substantial amendment	Change of eligibility criteria to include any patient with newly diagnosed ESFT.
				Addition of analysis of occurrences of ear osteonecrosis to secondary outcome measures.
				Addition of a recommended bone marrow re-assessment for patients with metastatic

				bone disease, preferably following 2 cycles of VIDE (arm A) or 3 cycles VDC/IE (arm B) induction chemotherapy.
				Addition of a bone marrow sample for biological studies from patients with bone metastatic disease, preferably following 2 cycles of VIDE (if arm A) or 3 cycles of VDC/IE (if arm B) induction chemotherapy.
				Amendment of treatment schedules to allow leeway in timing of chemotherapy and zoledronic acid by +/- 3 days.
				Clarifications to biological studies and inclusion of new analysis that will be performed for research purposes.
				Change of biological studies blood sample timepoint from pre- cycle 3 for all to following cycle 2 and pre-cycle 3 (if arm A) and following cycle 4 and pre-cycle 5 (if arm B) induction chemotherapy.
				Addition of 5ml blood sample at diagnosis for biological studies.
				Addition of two extra blood samples for biological studies - to be taken after completion of zoledronic acid treatment and one year later.
				Clarification that growth parameters will be assessed only for patients entering the second randomisation who are less than 18 years of age.
				Clarification that the first follow-up form is due 18months after randomisation.
				Updated wording in regard to allergic reactions to methylene blue updated.
				Clarification that all SARs should continue to be reported in an expedited manner regardless of how long after IMP administration.
				Removal of Appendix 4 (Declaration of Helsinki) and updated wording regarding 'Ethical Considerations'.
				Updated personnel contact details and other minor corrections to spelling and wording throughout.
11.0	2nd June 2017	5.0	Substantial amendment	Change of consolidation treatment for patients with poor risk localised disease to 1 cycle VAI plus BuMel (for both arms A and B).
				Addition of IMPs busulfan and melphalan
				Addition to the exclusion criteria for the second randomisation (R2) of a history of jaw fracture.
				Minor changes to wording and terminology used in throughout for the purposes of clarity.
				Updated personnel contact details, change of phone number for emergency randomisation and change of fax number for SAE reporting.
				Clarification of time-points for blood samples for biological studies.

TRIAL SYNOPSIS

Title

International Randomised Controlled Trial for the Treatment of Newly Diagnosed Ewing's Sarcoma Family of Tumours (ESFT)

Acronym

Euro Ewing 2012 (EE2012)

Trial Design

The Euro Ewing 2012 trial is an international, phase III, open-label, randomised controlled trial.

Objectives

The objective of the induction/consolidation chemotherapy randomisation (R1) is to compare the VIDE strategy (VIDE induction and VAI/VAC/BuMel consolidation) with the VDC/IE strategy (compressed VDC/IE induction and IE/VC/Bu-Mel consolidation). The event-free survival (EFS) of the two chemotherapy regimens will be compared, and also the relative toxicity experienced by patients both before and after local control of the primary tumour.

The objective of the zoledronic acid randomisation (R2) is to determine whether the addition of zoledronic acid to consolidation chemotherapy, as assigned at R1, is associated with improved clinical outcome.

The objective of the biological studies associated with this trial is to identify informative prognostic biomarkers for assessment of disease status and response at diagnosis and throughout the disease course. Whether they are predictive of response to therapy and may be used to improve stratification of patients and whether they might predict those patients that may not tolerate a particular therapy will be explored.

Outcome Measures

Primary outcome measure

- Event-free survival (EFS)

Secondary outcome measures

- Overall Survival (OS)
- Adverse events and toxicity, defined by NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0
- Histological response of the primary tumour to induction chemotherapy if surgery is performed as local control
- Response of primary tumour, regional lymph nodes and/or metastases
- Achievement of local control at the end of treatment
- Growth parameters and jaw/ear osteonecrosis (R2 only)

Patient Population

Any newly diagnosed patient with ESFT

Sample Size

Randomisation R1 – minimum of 600

Randomisation R2 – minimum of 750 (including 400 from the Ewing 2008 trial)

Key Eligibility Criteria

There are two randomisations: R1 and R2

	Randomisation 1	Randomisation 2
Inclusion criteria	• Any histologically and genetically confirmed ESFT of bone or soft tissue, or round cell sarcomas 'Ewing's-like' but negative for EWSR1 gene rearrangement. • Age >2 years and <50 years • Randomisation ≤45 days after diagnostic biopsy/surgery • Patient medically fit to receive the randomised treatment • No prior treatment other than surgery	• Age >5 years • Localised tumour OR • Metastatic disease and/or regional lymph node(s) involvement only at diagnosis and at least partial response of metastases and/or regional lymph node(s) • Consolidation chemotherapy as per protocol intended • Medically fit to receive zoledronic acid
Exclusion criteria	• Contra-indication to the treatment in R1 • Second malignancy • Pregnant or breastfeeding women	• History of dental surgery 6 months preceding start of zoledronic acid, or planned dental surgery during treatment or within 6 months after the end of treatment. • History of jaw fracture • Ewing's tumour of the maxilla or of the mandible • Progression of the primary tumour or appearance of new lesions

Trial Duration

Anticipated accrual time for different randomisations:

- Randomisation R1: 5 years
- Randomisation R2: 5 years

After treatment, patients will be followed up with clinical evaluation and scanning for 5 years, or until disease progression or death if sooner. Patients will be followed up for progression and death until all trial objectives have been met.

The first main analysis will be performed once all patients have a minimum of 2 years follow-up.

Treatment Summary

Randomisation R1

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

ARM A (VIDE strategy): VIDE induction; VAI/VAC consolidation

Induction chemotherapy:	6 cycles of VIDE
Consolidation chemotherapy:	1 cycle of VAI plus 7 cycles of VAC (good risk localised disease)
	OR
	1 cycle of VAI plus one cycle of BuMel (poor risk localised disease without contraindication to BuMel)
	OR
	8 cycles of VAI (poor risk localised disease with contraindication to BuMel, and/or regional lymph node(s) involvement and/or metastatic disease)

OR

Arm B (VDC/IE strategy): VDC/IE induction; IE/VC consolidation

Induction chemotherapy:	9 cycles of alternating VDC and IE
Consolidation chemotherapy:	5 cycles of alternating IE and VC (good risk localised disease, and/or regional lymph node(s) involvement and/or metastatic disease, or poor risk localised disease with contraindication to BuMel).
	OR
	1 cycles of VAI plus one cycle of BuMel (poor risk localised disease without contraindication to BuMel)

Randomisation R2

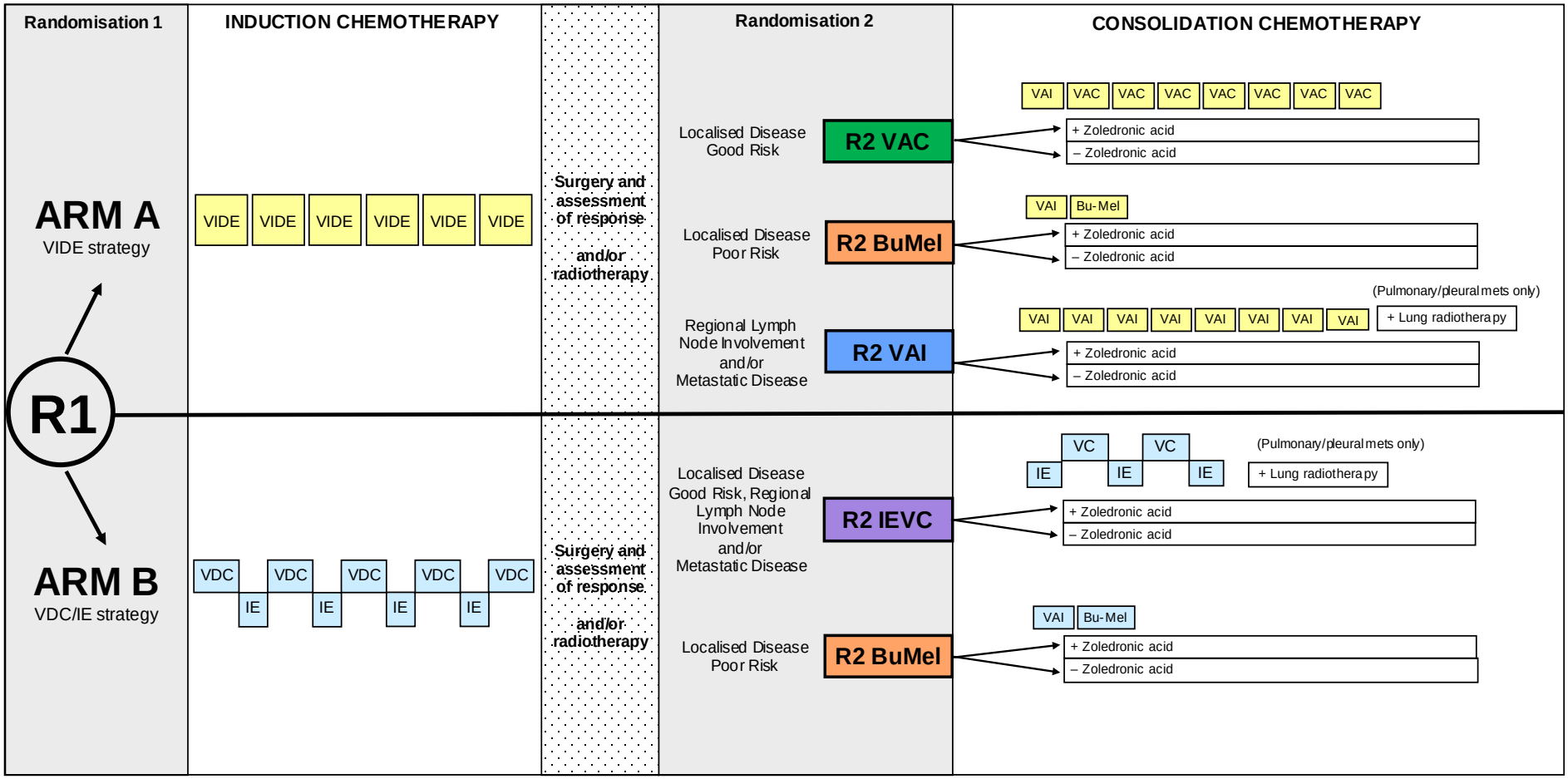
Following induction chemotherapy, patients who fulfil the eligibility criteria for R2 and consent to take part in the randomisation will receive consolidation chemotherapy as allocated at trial entry and be randomised to receive either:

- **9 cycles of zoledronic acid** following the first cycle of consolidation chemotherapy (VAI (Arm A) or IE (Arm B))

OR

- **No zoledronic acid**

TRIAL SCHEMA



VIDE Vincristine, Ifosfamide, Doxorubicin, Etoposide
VDC Vincristine, Doxorubicin, Cyclophosphamide
IE Ifosfamide, Etoposide

VAI Vincristine, Actinomycin D, Ifosfamide
VAC Vincristine, Actinomycin D, Cyclophosphamide
IE Ifosfamide, Etoposide
VC Vincristine, Cyclophosphamide
Bu Busulfan
Mel Melphalan

ABBREVIATIONS

ABPI	Association of the British Pharmaceutical Industry
AE	Adverse Event
AR	Adverse Reaction
ALP	Alkaline Phosphatase
ALT	Alanine Transferase
AST	Aspartate Aminotransferase
ATP	Adenosine triphosphate
ANC	Absolute Neutrophil Count
BP	Bisphosphonate
BuMel	Busulfan-Melphalan
CCrea	Creatinine Clearance
CESS	Cooperative Ewing's Sarcoma Study
CGH	Comparative Genomic Hybridisation
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Intervals
COG	Children's Oncology Group
CRCTU	Cancer Research UK Clinical Trials Unit
CRF	Case Report Form
CT	Computerised Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DSUR	Development Safety Update Report
ECHO	Echocardiography
EDTA	Ethylenediaminetetraacetic Acid
EFS	Event-Free Survival
ESFT	Ewing's Sarcoma Family of Tumours
FISH	Fluorescence In Situ Hybridisation
FPP	Farnesyl Diphosphate Synthase
FS	Fractional Shortening
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GFR	Glomerular Filtration Rate
GP	General Practitioner
HE	Hematoxylin and Eosin
HDT	High Dose Therapy
HR	Hazard RatioICF Informed Consent Form
IDMC	Independent Data Monitoring Committee
IE	Ifosfamide – Etoposide
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISG	Italian Sarcoma Group

ITT	Intention-To-Treat
LVEF	Left Ventricular Ejection Fraction
MDT	Multi Disciplinary Team
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
N-BP	Nitrogen-containing Bisphosphonate
NCI	National Cancer Institute
OS	Overall Survival
PAS	Periodic-Acid-Schiff
PBSC	Peripheral Blood Stem Cell
PET	Positron Emission Tomography
PIS	Patient Information Sheet
RDE	Remote Data Entry
REC	Research Ethics Committee
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SMN	Second Malignant Neoplasm
SSG	Scandinavian Sarcoma Group
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
Tm_p/GFR	Renal tubular threshold for phosphate
Tp/Ccrea	Fractional phosphate reabsorption
TSC	Trial Steering Committee
UDCA	Ursodeoxycholic Acid
UK	United Kingdom
VAC	Vincristine – Actinomycin D – Cyclophosphamide
VAI	Vincristine – Actinomycin D – Ifosfamide
VC	Vincristine – Cyclophosphamide
VDC	Vincristine – Doxorubicin – Cyclophosphamide
VIDE	Vincristine – Ifosfamide – Doxorubicin – Etoposide
WMA	World Medical Association

1. BACKGROUND AND RATIONALE

1.1 *Background*

1.1.1 Characterisation of ESFT

Ewing's sarcoma, malignant peripheral neuroectodermal tumour, Askin tumour and atypical Ewing's sarcoma are part of a family of tumours known collectively as the Ewing's sarcoma family of tumours (ESFT). These tumours consist of small, round malignant cells that may exhibit varying degrees of neural differentiation. ESFT are characterised by a re-arrangement of chromosome 22, in the form of an 11;22 translocation in more than 95% of cases [1-7]. The gene rearrangement results in the production of a transcription factor – in the majority, EWS-FLI1 transcription.

Most ESFT arise in bony sites. Staging procedures identify approximately 30% of patients as metastatic at diagnosis. During the past 30 years, the prognosis has dramatically improved owing to the introduction of multimodal treatment including combination chemotherapy, surgery and radiotherapy.

1.1.2 Treatment results in localised disease

The 5-year survival rate in localised ESFT ranges from 60 to 70% with chemotherapy regimens including A (actinomycin D), D (doxorubicin), E (etoposide), C (cyclophosphamide), V (vincristine) and I (ifosfamide), with different doses and schedules of administration.

The Italian/Scandinavian ISG/SSG III trial was designed for standard risk patients. Induction treatment consisted of VAC, V, VAI and EI cycles. Patients were stratified according to histological response and allocated accordingly to different treatment arms: good responders received 9 cycles of conventional chemotherapy; poor responders received high-dose busulfan-melphalan (BuMel) [8].

More recent analyses from other groups have confirmed R2 as a poor prognostic group [9, 10].

The EURO-E.W.I.N.G. 99 trial employed VIDE induction chemotherapy [11] followed by risk-adapted randomised treatment. In patients with localised disease, the volume of the primary tumour and the histological response to induction chemotherapy were critical factors for stratification into the standard or high risk group. Standard risk patients were randomised for consolidation treatment with either VAI or VAC (R1). High risk patients were randomised to high-dose Bu-Mel versus VAI (R2loc).

Accrual into the R1 randomisation is now closed and the results have led to the recommendation of VAC regimen as maintenance treatment for standard risk patients [12]. Accrual into the R2loc randomisation has been prematurely closed after the independent Data Monitoring Committee (IDMC) recommendations in November 2013 because of insufficient recruitment. The analysis of these patients has now been performed. The results have been presented at ASCO in June 2016 [13]. Between 2000 and 2013, 216 patients with high risk localised disease were randomized to VAI (107) or BuMel (109). Median follow up was 8.0 years, with only 3 patients lost to follow up before 3 years. Overall, the 3yr EFS was 60% and OS, 74%. In the intention to treat analysis, the risk of an event was significantly decreased by BuMel compared to VAI: HR =0.64 (95%CI, 0.43-0.94) p=.024; 3yr-EFS of 67% (57.6-75.0) vs. 53% (43.6-62.3). O.S. also favoured BuMel, 78% vs. 70%, HR=0.60 (0.39-0.92) p=.019. Therefore, in patients with poor histological response to VIDE and/or with tumour volume>200ml in whom prior resection or radiotherapy prevents histological response data being available, BuMel improves EFS and OS without unacceptable excess toxicity. Therefore, BuMel should be standard of care for patients with high risk localised disease in whom there is no contraindication to receiving BuMel and radiotherapy, which they generally all require.

1.1.3 Treatment results in patients with primary pulmonary metastases and regional lymph nodes

Ewing's tumours with lung-only metastases treated with conventional chemotherapy have a poor prognosis and event-free survival (EFS) ranges from 23% to 36% [14-17]

The first US Intergroup study demonstrated that “prophylactic” lung irradiation was effective in controlling microscopic lung metastases in patients who were not given doxorubicin-containing chemotherapy [18]. In the Cooperative Ewing’s Sarcoma Study (CESS) studies, lung irradiation was an only option for patients with lung metastases at diagnosis who achieved a complete clinical response to chemotherapy. In a multivariate analysis, lung irradiation was associated with improved survival [15].

The use of high-dose chemotherapy including busulfan seemed to improve the prognosis of patients with lung-only metastases in a non-randomised French study where the EFS of 44 consecutive patients treated by BuMel consolidation chemotherapy was 52% [17]. This was the rationale of the R2pulm randomisation in the EURO-E.W.I.N.G. 99. Despite of the importance of the question, accrual into the R2pulm randomisations has been prematurely closed after IDMC recommendations in November 2013 because of insufficient accrual. The analysis, however has been performed and presented at ASCO in June 2016 [19] and demonstrated a similar EFS and OS in both arms. Therefore VAI and lung radiotherapy will continue in the EE2012 protocol (R2 VAI).

There are no separate data on patients with regional lymph nodes and their outcome. It can be assumed, however, that they do at least as badly as those with metastases to lungs and/or pleura.

1.1.4 Treatment results in patients with disseminated disease

Within the EURO-E.W.I.N.G. 99 trial, 192 patients with primary dissemination, i.e. dissemination to bone and/or other sites and possibly additional pulmonary dissemination, were registered. In contrast to the distribution in the entire group of patients with Ewing sarcomas, the primary site in this subgroup was extremity in only 57 patients and axial/other in 135 patients (41% pelvis). The recommended treatment scheme included six cycles of VIDE induction, one cycle of VAI, and high dose chemotherapy followed by reinfusion of autologous haematopoietic stem cells. The VIDE induction cycles were completed by 168 patients (85%) and 116 patients were referred to high dose chemotherapy with busulfan (Bu), 600mg/m², and melphalan (Mel), 140mg/m², followed by reinfusion of autologous haematopoietic stem cells (SCR). The overall survival at 3 years in the total group of 188 evaluable patients was 29% (SE=0.04). Regarding patients who received BuMel/SCR, 37 patients younger than 14 years achieved an EFS of 47% in comparison with an EFS of 22% (p=0.03) in their older counterparts >14 years. The multivariate analysis identified two major risk factors at diagnosis: primary tumour volume >200ml (p<0.001 (RR 2.25)) and >5 bone metastases (p=0.06 (RR 2.11)). Given the uncontrolled nature of this study, no reliable conclusions on the efficacy of high dose therapy can be reached and the results must be considered biased by the selection of a favourable group for high dose chemotherapy: 15% of patients with disseminated Ewing sarcoma did not complete the VIDE induction mainly due to early progression. Furthermore, it has to be considered that busulfan-containing high dose chemotherapy is not compatible with radiotherapy to the central axis and patients with large pelvic tumours (associated with a poor outcome even in patients with localised disease) who required radiotherapy were excluded from BuMel/SCR [19].

1.1.5 The value of bisphosphonates in the treatment of ESFT

Bisphosphonates (BPs) are effective inhibitors of bone resorption and have been widely used for the treatment of osteoporosis, osteogenesis imperfecta, systemic osteolytic bone disease or local bone loss, but also for the treatment of bone metastases in patients with breast cancer [21, 22], multiple myeloma [22] and prostate cancer [23].

Osteoclasts are the preferred target cells of bisphosphonate action. Bisphosphonates show a high affinity to hydroxyapatite. They are resorbed by activated osteoclasts and subsequently inhibit osteoclast activity [24]. Non-nitrogen containing bisphosphonates are intracellularly metabolised to cytotoxic analogues of adenosine triphosphate (ATP) leading to an early cell death of target cells. Nitrogen-containing bisphosphonates (N-BPs), which are much more potent at inhibiting bone resorption *in vivo*, act by inhibiting farnesyl diphosphate synthase (FPP), a key enzyme of the mevalonate pathway. Consequently N-BPs inhibit farnesylation and geranylgeranylation of small G-proteins such as Ras, Rap1 and Rho [25-28].

1.1.5.1 Anti tumour effects of N-bisphosphonates

The anti-tumour effects of N-BPs are also correlated with an inhibition of FPP, as *in vitro* studies have shown that some of the effects can be reversed by replenishing tumour cells with downstream products of the mevalonate pathway, i.e. farnesol or geranylgeranol, which are required for farnesylation and geranylgeranylation of small G-proteins. Furthermore, some N-BPs have been shown to inhibit angiogenesis *in vitro* and *in vivo* [29-31] and to lower serum levels of proangiogenic vascular endothelial growth factor and platelet derived growth factor in cancer patients [32, 33]. Similar mechanisms are responsible for the induction of apoptosis of cancer cells [34-36].

1.1.5.2 Effect of N-bisphosphonates in ESFT cells

In vitro and *in vivo* data have proven the anti-tumour activity of N-BPs against ESFT cells:

i. The N-BP pamidronate inhibits growth in eight different ESFT cell lines via inhibition of the mevalonate pathway [36].

ii. Zhou et al showed significant inhibition in the development of bone metastases after injection of zoledronic acid *in vivo*. N-BPs induced apoptosis and inhibited osseous metastases [37].

iii. Zoledronic acid has a direct inhibitory effect on the growth of ESFT cells *in vitro* which is induced by apoptosis associated with caspase 3 activation and cell cycle arrest in S phase. This effect was enhanced by alkylating agents. Using an *in vivo* mouse model, zoledronic acid exerted a strong inhibitory effect on the growth of bone ESFT and little effect on the growth of intramuscularly injected ESFT. When combined with ifosfamide, zoledronic acid exerted synergistic effects in the soft tissue model: its combination with one cycle of ifosfamide resulted in an inhibitory effect similar to three cycles of ifosfamide alone [38].

iv. The effects on ESFT cells described in i) and ii) were obtained at concentrations which are not achieved *in vivo*. Serum levels of N-BPs have been reported to reach 10µM. The concentrations used in the above cited studies were 40µM. The strong affinity of N-BPs to bone mineral does, however, lead to much higher concentrations in bone [39].

1.1.5.3 Clinical studies with bisphosphonates and experience in children

New N-BPs have frequently been used in children with osteolytic bone disease such as osteonecrosis following chemotherapy. In two prospective clinical studies, pamidronate was given to 11 infants with a median age of 3.6 months over a period of 3-6 years [40] and 18 children and adolescents aged 6-21 years [41]. No serious adverse effects were observed in these studies. To evaluate the safety and efficacy of N-BPs in adolescents with osteoporosis, 22 patients with an average age of 13.3 years (range 4.3-19 years) were treated over 1-3 years. Again, no side effects were observed [42]. Eighteen children and adolescents between 6.2 and 17.5 years with moderate polyostotic fibrodysplasia received pamidronate for 1.2-9.1 years (average treatment duration 3.8 years) with no serious side effects [43].

By contrast, some adult patients treated for osseous metastases have shown osteonecrosis of the jaw after 2-3 years of treatment with novel N-BPs such as pamidronate and zoledronic acid [44]. In the Euro Ewing 2012 study, treatment duration will be restricted to nine months. As yet, no irreversible side effects such as osteonecrosis have been reported within this time limit. Furthermore the OS2006 trial with 10 monthly injections of Zoledronic acid has not raised any safety concerns [45].

1.2 *Trial Rationale*

1.2.1 Rationale for an international study

Although these tumours are the second commonest malignant bone tumour in children, adolescents and young adults, they remain rare tumours (less than 70 cases per year in the UK and 100 in France) and hence any randomised trials must be international.

1.2.2 Rationale for a VIDE and VAC/VAI versus VDC/IE/VC randomisation

Internationally, the standard treatment of ESFT is not defined. The EURO-E.W.I.N.G. 99 trial employed VIDE induction chemotherapy (6 cycles of vincristine, ifosfamide, doxorubicin and etoposide given approximately every 3 weeks prior to local control), followed by risk adapted randomised treatment of either vincristine, actinomycin D and ifosfamide or cyclophosphamide (VAI/VAC) as consolidation chemotherapy or high-dose busulfan/melphalan. The toxicity of VIDE induction chemotherapy has been published [11]. In summary, 12% had grade III or IV stomatitis, 3% had cardiac left ventricular dysfunction as determined by fractional shortening, there were 5 toxic related deaths out of 851 patients giving a rate of 0.6%, and grade II, III and IV infections occurred in 40%, 9% and 0.6% respectively. As yet, the data on second malignant neoplasms (SMNs) have not been published but in the current EURO-E.W.I.N.G. 99 trial between 1 September 2001 and 1 September 2005, there have been 5 SMNs (2 leukaemias and 3 solid tumours) in the 462 registered patients with localised disease (Marie-Cécile Le Deley, personal communication).

The other widely used treatment regimen for ESFT, employed mainly in the USA, is that from the Children's Oncology Group (COG) AEWS0031 trial. In this study, patients with localised ESFT received alternating cycles of vincristine-doxorubicin-cyclophosphamide and ifosfamide-etoposide (VDC/IE) as induction chemotherapy, and alternating cycles of ifosfamide-etoposide and vincristine-cyclophosphamide (IE/VC) as consolidation chemotherapy. There was an upfront randomisation to compare 3-weekly cycles of this treatment (standard arm) with 2-weekly cycles (experimental arm). At a median of 3 years, there was significantly superior EFS of 76% in the compressed 2-weekly VDC/IE/VC, compared to 65% in the standard arm (p= 0.028), and also improved overall survival (p=0.026). This compressed induction regimen has now become the standard regimen for localised ESFT in the USA.

Regarding short term toxicity, there was one toxic death in the compressed arm B. In arm B, despite compression of the chemotherapy cycles, stomatitis occurred in 3% and colitis or typhilitis in 0.4% of chemotherapy cycles. There were no episodes of acute cardiac left ventricular dysfunction and grade III/IV infectious toxicities occurred as follows: febrile neutropenia 7%, infection with grade 3/4 neutropenia 5%, infection without neutropenia 2% and infection (white cell count unknown) 0.3%.

The total doses of drugs received between compressed VDC/IE/VC versus VIDE and VAI/VAC are shown in the table below.

	Compressed VDC/IE/VC (14 cycles)	VIDE x 6 / VAI x 8	VIDE x 6 / VAC x 8
Vincristine	14 mg/m^2	21 mg/m^2	21 mg/m^2
Doxorubicin	375 mg/m^2	360 mg/m^2	360 mg/m^2
Cyclophosphamide	8.4 g/m^2	0 mg/m^2	12 g/m^2
Ifosfamide	63 g/m^2	102 g/m^2	54 g/m^2
Etoposide	3.5 g/m^2	2.7 g/m^2	2.7 g/m^2
Actinomycin D	0 mg/m^2	12 mg/m^2	12 mg/m^2

In the 568 randomised patients, there were 16 SMNs, not differently distributed between the two arms, 9 on the standard arm and 7 on the intensive arm.

As yet, long term data on late toxicity has not been published for either regimen (VIDE and VAC or compressed VDC/IE/VC) but there would be an expectation for infertility and cardiac toxicity with the use of doxorubicin in both regimens [46] and renal impairment due to ifosfamide [47].

Therefore an upfront randomisation between VIDE and VAI/VAC versus VDC/IE/VC is necessary to establish which is the regimen of choice, taking account of both clinical outcome (EFS and OS) and toxicity (short and long term).

1.2.3 Rationale for zoledronic acid randomisation

Standard risk patients are those with the most favourable outcome, with expected overall survival at 5 years of close to or above 70%. Still, there is about a 30% risk of relapse. In high risk localised disease the risk of relapse is higher from 50-60 %. Ewing's tumours with lung-only metastases treated with conventional chemotherapy have a poorer prognosis with an EFS between 23% to 36%.

Recurrence of disease is associated with a poor outcome [48, 49]. Hence, there is clearly a need to improve survival in this group of patients.

The use of more intensive conventional chemotherapy appears to have clear limits due to toxic effects. More than 80% of relapses occur early, i.e. within the first two years following diagnosis. Therefore, the Euro Ewing 2012 trial will test whether add-on treatment with zoledronic acid improves EFS in localised ESFT or those with pulmonary and/or pleural metastatic disease only.

A similar randomisation in the same group of patients is already underway in the German Ewing 2008 trial. A prospective combined analysis of the two trials will take place.

2. OBJECTIVES AND OUTCOME MEASURES

2.1 *Objectives*

1. The objective of the induction/consolidation chemotherapy randomisation (R1) is to compare:
   – VIDE strategy: vincristine, ifosfamide, doxorubicin and etoposide (VIDE) as induction chemotherapy and vincristine, actinomycin D and ifosfamide (VAI), vincristine, actinomycin D cyclophosphamide (VAC) or busulfan and melphalan (BuMel) as consolidation chemotherapy

   with

   – VDC/IE strategy: alternating cycles of vincristine, cyclophosphamide, doxorubicin (VDC) and ifosfamide, etoposide (IE) as induction chemotherapy and alternating cycles of ifosfamide, etoposide (IE) and vincristine, cyclophosphamide (VC) or busulfan and melphalan (BuMel) as consolidation chemotherapy

   as first line treatment in all patients with ESFT, with respect to clinical outcome and toxicity.

2. The objective of the zoledronic acid randomisation (R2) is to determine whether the addition of zoledronic acid to the consolidation chemotherapy assigned at R1 is associated with improved clinical outcome in patients in the EE2012 trial.

3. The objective of the biological studies associated with this trial is to identify informative prognostic biomarkers for assessment of disease status and response at diagnosis and throughout the disease course. Whether they are predictive of response to therapy and may be used to improve stratification of patients and whether they might predict those patients that may not tolerate a particular therapy will be explored.

2.2 *Outcome Measures*

2.2.1 Primary outcome measure

- Event-free survival (EFS)

2.2.2 Secondary outcome measures

- Overall Survival (OS)
- Adverse events and toxicity, defined by NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0
- Histological response of the primary tumour to induction chemotherapy if surgery is performed as local control.
- Response of the primary tumour, regional lymph nodes and/or metastases
- Achievement of local control at the end of treatment
- Growth parameters and jaw/ear osteonecrosis (R2 only)

3. TRIAL DESIGN

Euro Ewing 2012 is an international, multicentre, phase III, open-label randomised controlled trial. There are two randomisations: R1 and R2 Patients are randomised at two different time points, at entry to the trial (R1) and following local control therapy (R2).

4. ELIGIBILITY

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

4.1 *Randomisation R1*

Inclusion criteria	• Any histologically and genetically confirmed ESFT of bone or soft tissue, or round cell sarcomas which are 'Ewing's-like' but negative for EWSR1 gene rearrangement (see section 8.2.7) • Age >2 years and <50 years (from second birthday to 49 years 364 days) at the date of randomisation • Randomisation ≤45 days after diagnostic biopsy/surgery • Patient assessed as medically fit to receive the treatment in either of the R1 treatment arms • No prior treatment for ESFT other than surgery • Documented negative pregnancy test for female patients of childbearing potential • Patient agrees to use contraception during therapy and for 12 months after last trial treatment (females) or 6 months after last trial treatment (males), where applicable • Written informed consent from the patient and/or the parent/legal guardian
Exclusion criteria	• Contra-indication to the treatment in either of the R1 treatment arms • Second malignancy

	• Pregnant or breastfeeding women • Follow-up not possible due to social, geographic or psychological reasons

4.2 *Randomisation R2*

Inclusion criteria	• Age >5 years (from fifth birthday) at date of randomisation • Localised tumour OR • Metastatic disease and/or regional lymph node(s) involvement only at diagnosis and at least partial response of the metastases and/or regional lymph node(s) • Consolidation chemotherapy as per protocol intended • Patient assessed as medically fit to receive zoledronic acid if allocated • Written informed consent from the patient and/or the parent/legal guardian
Exclusion criteria	• History of dental surgery (extraction or jaw surgery) in the 6 months preceding the start of zoledronic acid treatment, or planned dental surgery within the treatment period or within 6 months after the end of treatment. • History of jaw fracture • Ewing's tumour of the maxilla or of the mandible • Progression of the primary tumour or appearance of new lesions

5. SCREENING AND CONSENT

5.1 *Screening*

All assessments relating to patient eligibility are performed as standard practice. There are no additional screening procedures required specifically for the trial. For the complete list of assessments required at diagnosis, see section 8.2.

5.2 *Informed Consent*

It is the responsibility of the Principal Investigator or co-investigator, if this duty has been delegated to a suitably qualified individual as captured on the site signature and delegation log (or country specific equivalent), to obtain written informed consent for each patient prior to performing any trial related procedure. Consent must be obtained separately for each randomisation in this trial. Country specific Patient/Parent Information Sheets (PIS) are provided for each randomisation to facilitate this process. Investigators must ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the patient and/or parent/legal guardian as appropriate. The Investigator should also stress that the patient and/or parent/legal guardian is completely free to refuse to take part or withdraw from the trial at any time. The patient and/or parent/legal guardian should be given sufficient 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. The patient and/or parent/legal guardian must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the patient and/or parent/legal guardian to refuse to participate in the trial without giving a reason must be respected.

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 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 which will be documented in the patient's medical records.

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 R1 Informed Consent Form (ICF). The patient and/or parent/legal guardian will have the option of consenting to the collection, storage and analysis of additional tumour, blood and bone marrow samples for use in biological studies associated with the trial. The Investigator must then sign and date the form on the same day. 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 filed in the ISF. If allowed by country specific legislation/guidance (as specified in the country specific quality and trial management plan, see Appendix 1) and if the patient and/or parent/legal guardian has given explicit consent, a copy of the signed ICF must be sent in the post to the applicable National Coordinating Centre for review.

Prior to the second randomisation (R2), the PIS for the appropriate randomisation should be provided to the patient and/or parent/legal guardian. If the patient and/or parent/legal guardian agrees to participate in the second randomisation, they should be asked to sign and date the latest version of the ICF for the appropriate R2 randomisation. As described above, the ICF should be filed and where applicable sent for in-house review.

Details of the informed consent discussions should be recorded in the patient's medical records; this 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 respected.

Electronic copies of the PIS and ICF are available from the applicable National Coordinating Centre and should be printed or photocopied onto the 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 1).

With the patient's prior consent, their medical practitioner (General Practitioner (GP) in the UK) should also be informed that they are taking part in the trial. A GP Letter is provided electronically for this purpose but it is anticipated that both this letter and the PIS are translated and adapted in accordance with national practices.

6. RANDOMISATION

6.1 *Randomisation R1*

Patients can be entered into the trial once the applicable National Coordinating Centre has confirmed that all regulatory requirements have been met by the trial 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 (R1). 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 8.2.
At trial entry, patients will be randomised to one of two treatment arms. Consolidation chemotherapy will be administered according to treatment arm randomisation and risk group.

- **Arm A (VIDE strategy): VIDE induction; VAI/VAC/BuMel consolidation**

  Induction chemotherapy: 6 cycles of VIDE **See section 7.2.2**

  Consolidation chemotherapy: 1 cycle of VAI plus 7 cycles of VAC (good risk localised disease) - R2 VAC **See section 7.2.4**

  OR

  1 cycle VAI plus one cycle of BuMel (poor risk localised disease without contraindication to BuMel)* - R2 BuMel **See section 7.2.5**

  OR

  8 cycles of VAI (poor risk localised disease with contraindication to BuMel, and/or regional lymph node(s) involvement and/or metastatic disease) - R2 VAI **See section 7.2.3**

OR

- **Arm B (VDC/IE strategy): VDC/IE induction; IE/VC /BuMel consolidation**

  Induction chemotherapy: 9 cycles of alternating VDC and IE **See section 7.3.2**

  Consolidation chemotherapy: 5 cycles of alternating IE and VC - R2 IE/VC (good risk localised disease, and/or regional lymph node(s) involvement and/or metastatic disease, or poor risk localised disease with contraindication to BuMel) **See section 0**

  OR

  1 cycle VAI plus BuMel (poor risk localised disease without contraindication to BuMel)* **See section 7.2.5**

* For BuMel contraindications see section 7.2.6.1

6.2 *Randomisation R2*

Following induction chemotherapy, patients who fulfil the eligibility criteria for R2 and consent to take part in the randomisation will be randomised to receive zoledronic acid or not in addition to the consolidation chemotherapy allocated in R1;

Consolidation chemotherapy as assigned at R1;

with the addition of 9 cycles of zoledronic acid **See section 7.2.7**

following the first cycle of chemotherapy

OR

without zoledronic acid

R2 randomisation must take place after completion of induction chemotherapy. R2 randomisation should ideally take place at least 7 days prior to the start of the second cycle of consolidation chemotherapy or BuMel (VAC, VAI, BuMel for Arm A patients or VC or BuMel for Arm B patients). The first dose of zoledronic acid must be given at least 24 hours before the start of the second cycle of consolidation chemotherapy or the start of BuMel treatment (as applicable).

Patients with localised disease need to be assigned to a risk group to determine their consolidation chemotherapy. Table 1 provides the definition of poor risk localised disease. Patients with localised disease not defined in table 1 are therefore considered good risk.

Table 1. Definition of poor risk localized disease and indications for busulfan and melphalan (BuMel) high dose therapy

Case	Localised disease	Resected at diagnosis	Volume ≥200ml	Pre-operative RT	Histological response ≥10% viable tumour	Unresectable tumour treated with RT alone	Volume < 200ml but poor radiological response i.e. <50% regression with chemotherapy	Radiotherapy contraindications to BuMel** (see section 7.2.6.1)	Other medical contraindications to BuMel**	BuMel recommended
1	N	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	N
2	Y	Y	N	n/r	n/r	n/r	n/r	n/r	n/r	N
3	Y	Y	Y	n/r	n/r	n/r	n/r	N	N	Y
4	Y	N	N	n/r	Y	n/r	n/r	N	N	Y
5	Y	N	N	Y	Y	n/r	n/r	N	N	Y
6	Y	N	Y	N	Y	n/r	n/r	N	N	Y
7	Y	N	Y	Y	Y	n/r	n/r	N	N	Y
8	Y	N	Y	Y	N	n/r	n/r	N	N	Y
9	Y	N	Y	Y	n/a***	n/r	n/r	N	N	Y
10	Y	N	Y	N	n/a	Y	n/r	N	N	Y
11	Y	N	N	N	n/a	Y	Y	N	N	Y
	Notes: n/r: not relevant n/a: not available ** if response is Yes then high dose therapy (HDT) is contraindicated; *** e.g. if extracorporeal irradiation of primary tumour used prior to re-implantation									

If the response assessment results are not available before the start of the second cycle, patients will receive another chemotherapy cycle (VAI for Arm A patients or VC for Arm B patients). If the results become available before the start of the third cycle, patients may still be randomised to R2. Patients randomised to receive zoledronic acid in this situation must start zoledronic acid treatment at least 24 hours prior to the third cycle of consolidation chemotherapy

Patients must not be randomised to R2 following the start of the third cycle of consolidation chemotherapy.

6.3 *Procedure for online randomisation*

Informed consent for randomisation must be obtained prior to performing the randomisation. Randomisation should be performed by sites using the online remote data capture (eRDC) system at the protocol specified time point. In order to randomise a patient, an eligibility checklist must be completed. All of the required information – e.g. on stratification factors – must be available at the time of randomisation.

Randomisation of patients can be achieved by logging on to the Euro Ewings 2012 eRDC system:

https://www.cancertrials.bham.ac.uk/EE2012Live/

The program will confirm eligibility and allocate treatment via a computerised minimisation algorithm, developed by the UK Coordinating Centre based at the Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham. For each randomisation, patients will be allocated in a 1:1 ratio.

The R1 randomisation will be stratified by

- age at R1 randomisation (<14 years; ≥14 years),
- gender,
- disease type (no metastases or involvement of lymph nodes only; lung or pleural metastases only; other metastases),
- volume of tumour at diagnosis (<200ml; ≥200ml) and
- country (UK, France or other)

to ensure that there is a balance between treatments within the strata defined by these key prognostic factors.

The R2 randomisation will be stratified by

- allocated treatment in the R1 randomisation,
- age at R1 randomisation (<14 years; ≥14 years),
- gender,
- disease status (localised disease or regional lymph node involvement only at diagnosis and good risk after induction, localised disease or regional lymph node involvement only at diagnosis and poor risk after induction, lung or pleural metastases at diagnosis, other metastasis at diagnosis),
- country (UK, France or other).

A copy of each randomisation result should be printed and retained in the ISF and the patient's hospital records.

If allowed by country specific legislation/guidance (as specified in the country specific quality and trial management plan, see Appendix 1) a copy of the patient's ICF must be sent to the applicable National Coordinating Centre, if explicit consent has been given for this.

6.4 *Emergency randomisation*

In case of any problems with online randomisation, the appropriate eligibility checklist and randomisation form should be completed. These details can be phoned through to the UK Coordinating Centre at the CRCTU using the numbers below:

RANDOMISATION

09:00 to 17:00 GMT / BST
Monday to Friday

☎ +44 (0)121 415 9877 / 3798

7. TREATMENT DETAILS

7.1 *Investigational Medicinal Products (IMPs)*

The following drugs are regarded as Investigational Medicinal Products (IMPs) for the purposes of this trial:

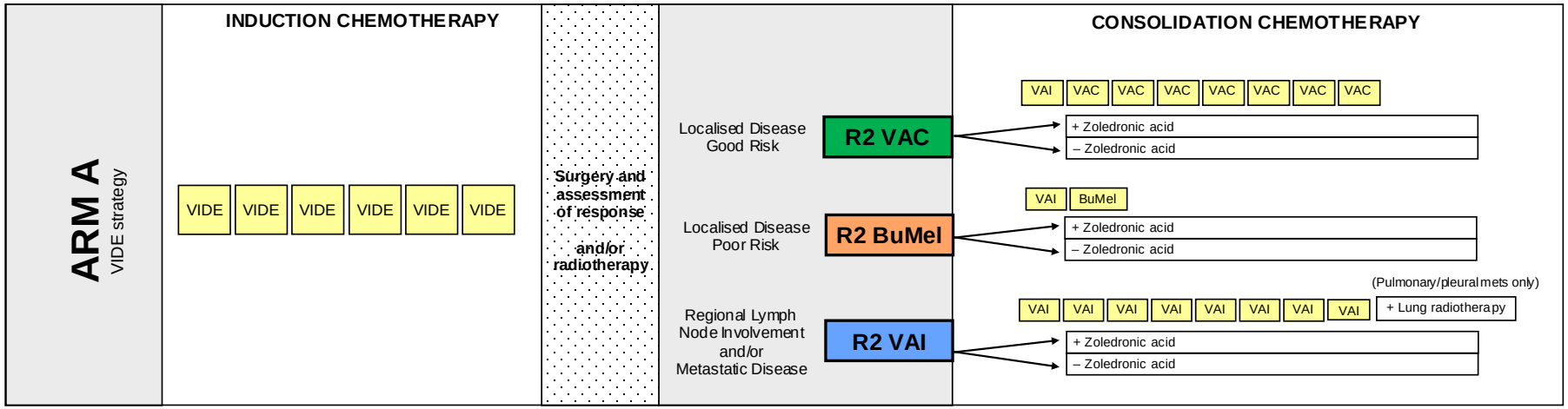
- Vincristine
- Ifosfamide
- Doxorubicin
- Etoposide
- Actinomycin D
- Cyclophosphamide
- Zoledronic acid
- Busulfan
- Melphalan

The following drug is a Non-Investigational Medicinal Product (NIMP) in this trial:

- Clonazepam

7.2 *Arm A treatment schedule*

7.2.1 Arm A: Overview



VIDE Vincristine, Ifosfamide, Doxorubicin, Etoposide

VAI Vincristine, Actinomycin D, Ifosfamide
VAC Vincristine, Actinomycin D, Cyclophosphamide
Bu Busulfan
Mel Melphalan

7.2.2 Arm A: VIDE chemotherapy

Agents and dosage

Cycles of VIDE should be given at 21 day intervals (+/- 3 days) and on haematological recovery to absolute neutrophil count (ANC) ≥1.0x10^9/L, platelets ≥80x10^9/L.

VIDE				
VINCRISTINE	1.5 mg/m^2 (IV push or short infusion)	d1	(1.5 mg/m^2/cycle)	*(max. single dose: 2 mg)*
IFOSFAMIDE	3 g/m^2/d (IV infusion, 1-3 h)	d1, d2, d3	(9 g/m^2/cycle)	plus MESNA and hydration*
DOXORUBICIN	20 mg/m^2/d (IV infusion, 4 h)	d1, d2, d3	(60 mg/m^2/cycle)	
ETOPOSIDE (etopophos can be used)	150 mg/m^2/d (IV infusion, 2 h)	d1, d2, d3	(450 mg/m^2/cycle)	
G-CSF	Refer to section 7.7.3.2.			
*MESNA and hydration should be given according to institutional guidelines				

Please refer to the Pharmacy Manual for further details.

Patients whose surface area (SA) is > 2 m^2 should have their doses capped and calculated with a SA of 2 m^2.

Patient monitoring and assessments

Refer to section 8.3.

Local treatment following VIDE

Whenever feasible, proceed to surgery after cycle 6 on haematological recovery (ANC ≥1.0x10^9/L, platelets ≥80x10^9/L). It is not advised that deviations to this timescale are made for purely logistical reasons. Please contact the EE2012 trial office if you wish to discuss a specific case.

Please refer to the "Surgery Guidelines" document for recommendations.

The next chemotherapy cycle (VAC/VAI) should be planned to commence no later than 14 days after surgical resection.

Surgical specimens should be sent for histopathological assessment of response to chemotherapy. Results should be available within 3 weeks of surgery.

Peripheral blood stem cell (PBSC) mobilisation and harvesting

This is recommended after VIDE chemotherapy if defined as poor risk localised disease (see section 6.2). PBSC mobilisation and harvesting should be performed according to institutional guidelines. Refer to "PBSC Mobilisation and Harvesting Guidelines" document for recommendations.

7.2.3 Arm A: VAI chemotherapy

Agents and dosage

Cycles of VAI should be given at 21 day intervals (+/- 3 days) and on haematological recovery to ANC ≥1.0x10^9/L, platelets ≥80x10^9/L.

VAI				
VINCRISTINE	1.5 mg/m^2 (IV push or short infusion)	d1	(1.5 mg/m^2/cycle)	*(max. single dose: 2 mg)*
ACTINOMYCIN D	0.75 mg/m^2/d (IV push)	d1, d2	(1.5 mg/m^2/cycle)	*(max. single dose per day: 1.5 mg)*
IFOSFAMIDE	3 g/m^2/d (IV infusion, 1-3 h)	d1, d2	(6 g/m^2/cycle)	plus MESNA and hydration*
G-CSF	Refer to section 7.7.3.2.			
*MESNA and hydration should be given according to institutional guidelines				

Please refer to the Pharmacy Manual for further details.

Patients whose SA is > 2 m^2 should have their doses capped and calculated with a SA of 2 m^2.

Patient monitoring and assessments

Refer to section 8.3.

VAI and radiotherapy

Radiotherapy is recommended to be given concurrently with consolidation chemotherapy to the primary site. In patients with pulmonary and/or pleural metastatic disease whole lung radiotherapy is recommended to be given on completion of consolidation chemotherapy. Radiotherapy to boney metastases may be given either during consolidation or at the end.

Please refer to the “Radiotherapy Guidelines” document for recommendations

PLEASE NOTE: Actinomycin D should be omitted during radiotherapy and resumed after completion of radiotherapy according to clinical symptoms. Omitted doses are not to be given subsequently.

7.2.4 Arm A: VAC chemotherapy

Agents and dosage

Cycles of VAC should be given at 21 day intervals (+/- 3 days) and on haematological recovery to ANC ≥1.0x10^9/L, platelets ≥80x10^9/L.

VAC				
VINCRISTINE	1.5 mg/m^2 (IV push or short infusion)	d1	(1.5mg/m^2/cycle)	*(max. single dose: 2 mg)*
ACTINOMYCIN D	0.75 mg/m^2/d (IV push)	d1, d2	(1.5mg/m^2/cycle)	*(max. single dose per day: 1.5 mg)*
CYCLOPHOSPHAMIDE	1500 mg/m^2 (IV infusion, 1-3 h)	d1	(1500mg/m^2/cycle)	plus MESNA and hydration*
G-CSF	Refer to section 7.7.3.2.			
*MESNA and hydration should be given according to institutional guidelines				

Please refer to the Pharmacy Manual for further details.

Patients whose SA is > 2 m^2 should have their doses capped and calculated with a SA of 2 m^2.

Patient monitoring and assessments

Refer to section 8.3.

VAC and radiotherapy

Radiotherapy is recommended to be given concurrently with consolidation chemotherapy to the primary site. In patients with pulmonary and/or pleural metastatic disease whole lung radiotherapy is given on completion of consolidation chemotherapy. Radiotherapy to boney metastases may be given either during consolidation or at the end.

Please refer to the “Radiotherapy Guidelines” document for recommendations.

PLEASE NOTE: Actinomycin D should be omitted during radiotherapy and resumed after completion of radiotherapy according to clinical symptoms. Omitted doses are not to be given subsequently.

7.2.6 Arm A: BuMel

BuMel should be given on haematological recovery to absolute neutrophil count (ANC) ³1.0x10^9/L, platelets ³80x10^9/L.

Agents and dosage

	Day	-7	-6	-5	-4	-3	-2	-1	0
Busulfan, IV (total of 16 doses) Adults: 0.8mg/kg. body weight (BW)	T = 0		X	X	X	X			
Children and adolescents: <9kg: 1mg/kg. BW 9 - <16kg: 1.2mg/kg. BW	T = 6	(X)	X	X	X	(X)			
16 - 23kg: 1.1mg/kg. BW >23 - 34kg: = 0.95mg/kg. BW >34kg: 0.8mg/kg. BW	T = 12	X	X	X	X				
	T = 18	X	X	X	X				
Melphalan, IV 140mg/m² IV infusion over 30 min.							X		
Clonazepam, orally or IV 0.025 to 0.1mg/kg/day		X	X	X	X	X	X	X	
Stem cell re-infusion (min. 3 x 10^6/kg. CD34$^+$)									X

Hydration should be given according to institutional guidelines.

G-CSF, see section 7.7.3.2.

Patients whose SA) is > 2 m^2 should have their doses capped and calculated with a SA of 2 m^2.

Heparin or allopurinol or ursodeoxycholic acid (UDCA) (Days -7 to +8) may be added according to institutional guidelines.

If the patient develops veno-occlusive disease, the management should be as institutional guidelines.

Please refer to the Pharmacy manual for further details.

BuMel and radiotherapy

Radiotherapy must not commence until 10 weeks after BuMel.

Please refer to the “Radiotherapy Guidelines” document for recommendations.

7.2.6.1 Contraindication to BuMel (Busulfan and Melphalan)

BuMel HDT may interact with radiotherapy, potentially resulting in significant toxicity after delivery of high radiotherapy doses to spinal cord/cauda equina, lung or bowel. This may compromise the ability to deliver an effective radiotherapy dose to central axial sites (spine, sacrum, pelvis) or when lung or bowel are within the radiotherapy treatment fields. BuMel HDT is therefore contra-indicated for primary tumours for which radiotherapy will deliver:

- > 45 Gy to gastrointestinal tract and rectum (unless small volumes < 10 cc^3)
- > 50 Gy to bladder (unless very small volumes< 10 cc^3)
- > 30 Gy to spinal cord
- > 36 Gy to cauda equina including sacrum and nerve routes
- Any dose to the lung, for either primary rib tumours (unless very small volumes), or whole lung radiotherapy

Consideration should be given to the use of techniques that can minimise dose to normal tissues or exclude normal tissues from radiotherapy treatment fields:

- Spacer devices can be used in the pelvis to displace bowel away from treatment volumes
- Intensity modulated radiotherapy [IMRT] techniques (fixed field IMRT, volumetric modulated arc therapy, tomotherapy)
- Proton beam therapy or carbon ion therapy (if available)

7.2.7 Arm A: Zoledronic acid treatment

Agent and dosage

Patients randomised to zoledronic acid will receive 9 cycles of zoledronic acid at 28 day intervals (+/- 3 days). All patients less than 18 years old will receive 0.05 mg/kg (maximum dose 4 mg). Patients 18 years or older will receive 4mg. The dose should be administered as an IV infusion over not less than 15 minutes.

The first dose of zoledronic acid should be given at least 24 hours before or 12 hours after the start of the second cycle of consolidation chemotherapy. Parallel to consolidation chemotherapy cycles, the medication must then continue to be given at least 24 hours before or at least 12 hours after chemotherapy.

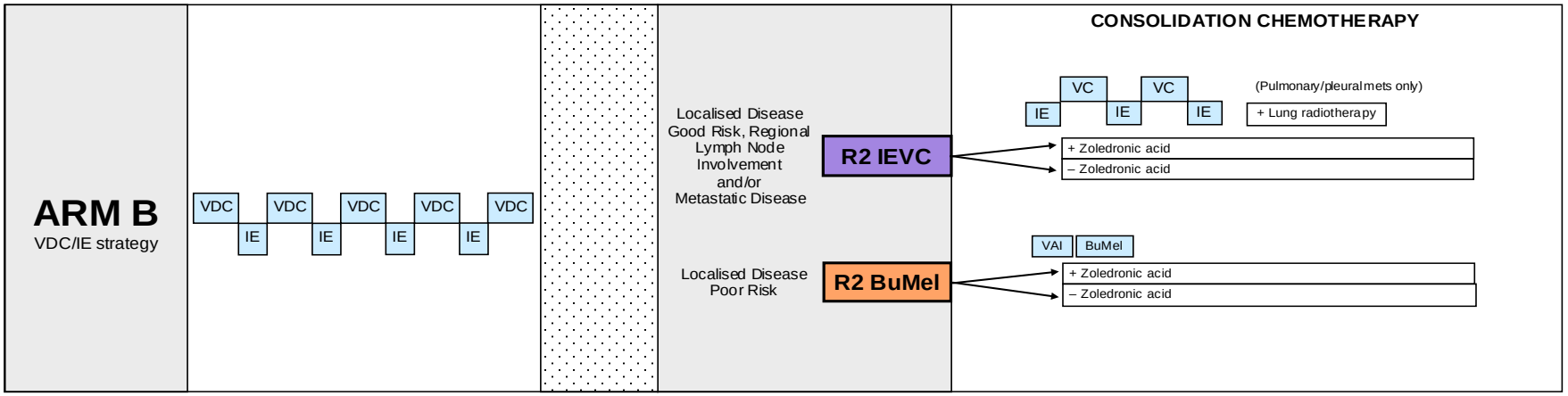
PLEASE NOTE: The maximum dose is 4mg. Patients must undergo an appropriate dental examination prior to treatment with zoledronic acid. Six-monthly dental examinations are required at the time of treatment with zoledronic acid and for a follow up period of five years after the end of treatment. While on treatment, the patients should avoid invasive dental procedures if possible.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Prior to administering zoledronic acid, ensure adequate hydration of the patient in accordance with local practice Normal creatinine clearance, electrolytes, calcium, magnesium, phosphate, bicarbonate, alkaline phosphatase	**X**					
Zoledronic acid 0.05 mg/kg by IV infusion (maximum dose 4 mg). Patients 18 years or older will receive 4mg. The dose should be administered as an IV infusion over not less than 15 minutes.	**X**					
Hydration 250ml/m^2 (post zoledronic acid)	**X**					
Oral calcium and vitamin D in accordance with local practice	**X**	**X**	**X**	**X**	**X**	**X**
Paracetamol in case of flu-like symptoms, in accordance with local practice	**X**	**X**	**X**	**X**	**X**	**X**

Please refer to the Pharmacy Manual for further details.

7.3 *Arm B treatment schedule*

7.3.1 Arm B: Overview



VDC Vincristine, Doxorubicin, Cyclophosphamide
IE Ifosfamide, Etoposide

IE Ifosfamide, Etoposide
VC Vincristine, Cyclophosphamide
Bu Busulfan
Mel Melphalan

7.3.2 Arm B: VDC/IE chemotherapy

Agents and dosage

Alternating cycles of VDC and IE should be given at 14 day intervals (+/- 3 days) and on haematological recovery to absolute neutrophil count (ANC) ≥0.75x10^9/L, platelets ≥75x10^9/L. Blood counts should be obtained on day 7 and 14 of the cycle and every Monday, Wednesday, and Friday after Day 14, until the criteria for beginning the next cycle are satisfied.

VDC				
VINCRISTINE	2 mg/m^2 (IV push or short infusion)	d1	(2 mg/m^2/cycle)	*(max. single dose: 2 mg)*
DOXORUBICIN	37.5 mg/m^2/d (IV infusion, 24 hrs)	d1, d2	(75 mg/m^2/cycle)	
CYCLOPHOSPHAMIDE	1200 mg/m^2 (IV infusion, 1 hr)	d1	(1200 mg/m^2/cycle)	plus MESNA and hydration*
G-CSF	Refer to section 7.7.3.2.			
*MESNA and hydration should be given according to institutional guidelines				

IE				
IFOSFAMIDE	1800 mg/m^2/d (IV infusion, 1 h)	d1, d2, d3, d4, d5	(9 g/m^2/cycle)	plus MESNA and hydration*
ETOPOSIDE (etopophos can be used)	100 mg/m^2/d (IV infusion, 2 h)	d1, d2, d3, d4, d5	(500 mg/m^2/cycle)	
G-CSF	Refer to section 7.7.3.2.			
*MESNA and hydration should be given according to institutional guidelines				

Please refer to the Pharmacy Manual for further details.

Patients whose SA is > 2m^2 should have their doses capped and calculated with a SA of 2m^2.

Patient monitoring and assessments

Refer to section 8.3.

Local treatment following VDC/IE

Whenever feasible, proceed to surgery after cycle 9 on haematological recovery (ANC ≥0.75x10^9/L, platelets ≥75x10^9/L). It is not advised that deviations to this timescale are made for purely logistical reasons. Please contact the EE2012 trial office if you wish to discuss a specific case.

Please refer to the "Surgery Guidelines" document for recommendations.

The next chemotherapy cycle (IE) should be planned to commence no later than 14 days after surgical resection.

Surgical specimens should be sent for histopathological assessment of response to chemotherapy. Results must be available within 3 weeks of surgery.

Peripheral blood stem cell (PBSC) mobilisation and harvesting

This is recommended after VDC/IE chemotherapy if defined as poor risk localised disease (see section 6.2). PBSC mobilisation and harvesting should be performed according to institutional guidelines. Refer to "PBSC Mobilisation and Harvesting Guidelines" document for recommendations.

7.3.3 Arm B: IE/VC chemotherapy

Agents and dosage

Alternating cycles of IE and VC should be given at 14 day intervals (+/- 3 days) and on haematological recovery to ANC $\geq 0.75 \times 10^9$/L, platelets $\geq 75 \times 10^9$/L. Blood counts should be obtained on day 7 and 14 of the cycle and every Monday, Wednesday, and Friday after Day 14, until the criteria for beginning the next cycle are satisfied.

IE				
IFOSFAMIDE	1800 mg/m^2/d (IV infusion, 1 h)	d1, d2, d3, d4, d5	(9 g/m^2/cycle)	plus MESNA and hydration*
ETOPOSIDE (etopophos can be used)	100 mg/m^2/d (IV infusion, 2 h)	d1, d2, d3, d4, d5	(500 mg/m^2/cycle)	
G-CSF	Refer to section 7.7.3.2.			
*MESNA and hydration should be given according to institutional guidelines				

VC				
VINCRISTINE	2 mg/m^2 (IV push or short infusion)	d1	(2 mg/m^2/cycle)	*(max. single dose: 2 mg)*
CYCLOPHOSPHAMIDE	1200 mg/m^2 (IV infusion, 1 hr)	d1	(1200 mg/m^2/cycle)	plus MESNA and hydration*
G-CSF	Refer to section 7.7.3.2.			
*MESNA and hydration should be given according to institutional guidelines				

Please refer to the Pharmacy Manual for further details.

Patients whose SA is > 2 m^2 should have their doses capped and calculated with a SA of 2 m^2.

Patient monitoring and assessments

Refer to section 8.3.

IE/VC and radiotherapy

Radiotherapy is recommended to be given concurrently with consolidation chemotherapy to primary site. In patients with pulmonary and/or pleural metastatic disease whole lung radiotherapy is given on completion of consolidation chemotherapy. Radiotherapy to boney metastases may be given either during consolidation or at the end.

Please refer to the "Radiotherapy Guidelines" document for recommendations.

7.3.4 Arm A: BuMel

As per section 7.2.5 for Arm A.

7.3.5 Arm B: Zoledronic acid treatment

As per section 0 for Arm A.

7.4 *Dose Modifications*

7.4.1 VIDE/VAI/VAC chemotherapy (Arm A)

7.4.1.1 Haematological toxicity

Dose/time intensity is regarded as an essential aspect of induction strategy. In case of significant bone marrow toxicity, preference should be given to early G-CSF support rather than dose reduction in order to maintain dose intensity.

For VIDE chemotherapy if significant toxicity continues as defined by:

Haematological recovery (ANC ≥1.0x10^9/L, platelets ≥80x10^9/L) delayed >6 days:

- Reduce etoposide dose by 20% for next VIDE cycle

Febrile Neutropenia grade 3 or 4:

- Reduce etoposide dose by 20% for next VIDE cycle

In the event of further episodes of toxicity, the etoposide dose is to be reduced by an additional 20%. If necessary it is advised to omit etoposide completely rather than reducing the doses of the other three drugs. If after the omission of etoposide the toxicity of VIDE remains intolerable, the dose of ifosfamide per VIDE cycle may be reduced from 9 g/m²/cycle to 6 g/m²/cycle (2g/m^2/d x 3).

7.4.1.2 Gastrointestinal toxicity

Mucositis/gastrointestinal (GI) toxicity grade 3 or 4:

- Reduce etoposide dose by 20%

In the event of further episodes of toxicity, the etoposide dose is to be reduced by an additional 20%. If necessary it is advised to omit etoposide completely rather than reducing the doses of the other three agents.

7.4.1.3 Nephrotoxicity / Renal function monitoring

Glomerular Filtration Rate (GFR)

Serum creatinine should be monitored prior to each cycle of ifosfamide or cyclophosphamide. Glomerular function is to be assessed according to national / group guidelines, applying either isotope clearance, or calculated creatinine clearance.

Schwartz's Formula (1-18 years) (Schwartz, 1987)

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

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

where **F** is proportional to body muscle mass, hence depending on age and gender:

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

Normal values [ml/min/1.73m²]:

- Normal 120
- Normal range 90-120

Cockcroft- Gault Formula (>18 years) [50]

Females

$$\frac{1.05\,(140 - \text{age (yrs)})\,\text{wt(kg)}}{\text{Crea}_{\text{serum}}[\,\mu\text{mol/L}]}$$

Or

$$\frac{0.85\;(140 - \text{age (yrs)})\,\text{wt(kg)}}{72 \text{ x Crea}_{\text{serum}}[\text{mg/dl}]}$$

Males

$$\frac{1.25\,(140 - \text{age (yrs)})\,\text{wt(kg)}}{\text{Crea}_{\text{serum}}[\,\mu\text{mol/L}]}$$

Or

$$\frac{(140 - \text{age (yrs)})\,\text{wt(kg)}}{72 \text{ x Crea}_{\text{serum}}[\text{mg/dl}]}$$

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

Tubular function (Tp/Ccrea or Tmp/GFR) [51, 52]

Tubular function should be monitored prior to each cycle of ifosfamide. For tubular function, serum electrolyte and bicarbonate (HCO_3) levels, and the calculation of fractionated phosphate reabsorption, relative amino acid reabsorption and/or fractionated Na excretion from single urine samples may be calculated according to Rossi et al.:

Fractionated phosphate reabsorption:

$$T_p/C_{crea} = \text{Phosphate}_{serum} - \frac{\text{Phosphate}_{urine}\; x\; \text{Creatinine}_{serum}}{\text{Creatinine}_{urine}}[\mu mol/ml]$$

$$T_p/C_{crea} = \text{Phosphate}_{serum} - \frac{\text{Phosphate}_{urine}\; x\; \text{Creatinine}_{serum}}{\text{Creatinine}_{urine}} 1x0{,}323[mg/dl]$$

Reference value for children >1 year or adult: mean = 1.5, inferior limit = 1.07

Ifosfamide adjustment to renal function

Classify toxicity as grade 0/1, 2, or 3/4 and adjust ifosfamide treatment as indicated (or as per local practice) if either GFR or Tp/Ccrea (Tm_p/GFR) or HCO_3 is reduced.

Toxicity grade*	GFR (ml/min/1.73 m^2)	Tp/Ccrea (Tm_p/GFR) (mmol/l)	HCO_3** (mmol/l)	Action (apply worst grade)
Grade 0/1	≥60	≥1.00	≥17.0	Continue ifosfamide dose 100%
Grade 2	40-59	0.80-0.99	14.0-16.9	Use cyclophosphamide instead, 1500 mg/m²/d, d1
Grade 3/4	≤40	≤0.80	≤14.0	Use cyclophosphamide instead, 1500 mg/m²/d, d1

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

** Low values of HCO_3 should be re-checked when the patient is clinically stable (to rule out infection as a cause, etc.) before modifying ifosfamide dose / treatment.

Etoposide adjustment to renal function

GFR <60ml/min/1.73m^2:

- Reduce etoposide dose by 30%

7.4.1.4 Haematuria or haemorrhagic cystitis

Microscopic during ifosfamide/cyclophosphamide infusion - give additional bolus doses of Mesna 600mg/m^2 then continuous infusion at double dose.

≥ Grade 2 discontinue ifosfamide/cyclophosphamide, continue double dose Mesna and hydration for 24 hours after ifosfamide.

7.4.1.5 Cardiac toxicity (relevant to treatment phases using doxorubicin)

Fractional shortening (FS) <28% or left ventricular ejection fraction (LVEF) <40% or decrease by an absolute value of ≥10 percentile points from previous tests:

Delay chemotherapy cycle for 7 days and repeat echocardiography. If FS has recovered to 29% or greater then proceed to next cycle. If FS remains below 29% then omit doxorubicin and substitute with actinomycin D 1.5 mg/m² on day 1 only (maximum dose: 1.5 mg).

Repeat cardiac tests prior to next doxorubicin-containing cycle. If results have normalised, continue doxorubicin at normal dosage. If FS remains abnormal, substitute with actinomycin D 1.5 mg/m² on day 1 only (maximum dose: 1.5 mg).

7.4.1.6 Central neurotoxicity

If grade 3 or 4 central neurotoxicity occurs, consider using methylthioninium chloride (methylene blue) as follows:

Adults: 50 mg (5ml ampoule of 1% solution) 4 hourly, IV slow bolus

Children: 1 mg/kg/dose 4 hourly, IV slow bolus

Patients who have had an episode of ifosfamide-induced encephalopathy 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:

Adults: 50 mg (5ml ampoule of 1% solution) 6 hourly, IV slow bolus

Children: 1 mg/kg/dose 6 hourly, IV slow bolus

In the case of allergic reactions to methylene blue or concomitant monoamine oxidase inhibitor, prophylaxis for central neurotoxicity in subsequent cycles could be given with Thiamine administered: 100 mg diluted in 100 ml of normal saline, in 10-min infusions every 4 h until resolution.

Repeated grade 3 or 4 central neurotoxicity:

Consider withholding ifosfamide and substitute with cyclophosphamide 1500 mg/m² on day 1 only.

7.4.2 VDC/IE/VC chemotherapy (Arm B)

7.4.2.1 Haematological toxicity

If neutrophil and platelet recovery (ANC $\geq 0.75 \times 10^9$/L, platelets $\geq 75 \times 10^9$/L) does not occur by Day 22 from last chemotherapy, decrease doxorubicin, cyclophosphamide, ifosfamide, and etoposide doses in subsequent cycles by 25% during the current phase of treatment (i.e. induction or consolidation). If neutrophil and platelet recovery still does not occur by Day 22 from subsequent chemotherapy, reduce doses a further 25%. Increase doses by 25% in subsequent cycles if ANC criterion is met by Day 18.

For Febrile Neutropenia grade 3 or 4:

- For VDC chemotherapy - reduce doxorubicin, cyclophosphamide in subsequent cycles by 25%.
- For IE chemotherapy - reduce etoposide in subsequent cycles by 25%.
- For VC chemotherapy - reduce cyclophosphamide in subsequent cycles by 25%.

7.4.2.2 Gastrointestinal toxicity

For Grade 3 or 4 mucositis after VDC which persists beyond Day 15 from start of chemotherapy, decrease the doxorubicin dose by 25% in subsequent cycles.

For Grade 3 or 4 mucositis which persists more than 21 days after an IE cycle, reduce both the ifosfamide and etoposide doses by 25% in subsequent cycles.

7.4.2.3 Nephrotoxicity / Renal function monitoring

Renal function monitoring as per section 7.4.1.3 following VIDE/VAI/VAC.

Ifosfamide adjustment to renal function

Classify toxicity as grade 0/1, 2, or 3/4 and adjust ifosfamide treatment as indicated (or as per local practice) if either GFR or Tp/Ccrea (Tm_p/GFR) or HCO_3 is reduced.

Toxicity grade*	GFR (ml/min/1.73 m^2)	Tp/Ccrea (Tm_p/GFR) (mmol/l)	HCO_3** (mmol/l)	Action (apply worst grade)
Grade 0/1	≥60	≥1.00	≥17.0	Continue ifosfamide dose 100%
Grade 2	40-59	0.80-0.99	14.0-16.9	Use cyclophosphamide instead, 2100 mg/m²/d, d1
Grade 3/4	≤40	≤0.80	≤14.0	Use cyclophosphamide instead, 2100 mg/m²/d, d1

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

** Low values of HCO_3 should be re-checked when the patient is clinically stable (to rule out infection as a cause, etc.) before modifying ifosfamide dose / treatment.

7.4.2.4 Haematuria or haemorrhagic cystitis

As per section 7.4.1.4 following VIDE/VAI/VAC.

7.4.2.5 Cardiac toxicity (relevant to treatment phases using doxorubicin)

As per section 7.4.1.5 following VIDE/VAI/VAC.

7.4.2.6 Central neurotoxicity

If grade 3 or 4 central neurotoxicity occurs, consider using methylthioninium chloride (methylene blue) as follows:

Adults: 50 mg (5ml ampoule of 1% solution) 4 hourly, IV slow bolus

Children: 1 mg/kg/dose 4 hourly, IV slow bolus

Patients who had an episode of ifosfamide-induced encephalopathy 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:

Adults: 50 mg (5ml ampoule of 1% solution) 6 hourly, IV slow bolus

Children: 1 mg/kg/dose 6 hourly, IV slow bolus

Repeated grade 3 or 4 central neurotoxicity:

Consider withholding ifosfamide and substitute with cyclophosphamide 2100 mg/m²/cycle

7.4.3 Zoledronic acid (Arms A and B)

7.4.3.1 Osteonecrosis

If osteonecrosis of the jaw or middle ear develops during treatment, zoledronic acid must be discontinued and not recommenced.

7.4.3.2 Nephrotoxicity

Zoledronic acid adjustment to renal function:

GFR (ml/min/1.73 m^2)	Action
≥ 60	Continue zoledronic acid dose 100%
50-59	Reduce zoledronic acid dose by 12.5%
40-49	Reduce zoledronic acid dose by 17.5%
30-39	Reduce zoledronic acid dose by 25%
<30	Pause until recovery

7.4.3.3 Hypocalcaemia

In case of severe hypocalcaemia, defined as calcium levels less than 1.8 mmol/l, zoledronic acid should be reduced by 30% for subsequent doses.

Hypocalcaemia should be treated as per institutional guidelines.

7.5 *Treatment Compliance*

Compliance for IMP treatment will be monitored by each National Co-ordinating Centre and as specified in the country specific Pharmacy Manual and by the data on the treatment forms of the Case Report Form (CRF). All IMPs are administered intravenously, in hospital, and therefore patient drug diaries and pharmacy reconciliation is not required for this trial.

7.6 *IMP Handling*

All IMPs are held as standard hospital stock and should therefore be stored and handled according to local institutional policy. Labels will be produced by each National Co-ordinating Centre in accordance with Annex 13 guidelines.

7.7 *Supportive Treatment*

7.7.1 Venous Access

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

7.7.2 Antiemetics

Patients should be treated with appropriate antiemetics according to institutional practice.

It is advised that aprepitant is not used for patients given ifosfamide.

7.7.3 Neutropenia

7.7.3.1 Neutropenic fever

Antibiotic coverage is at the discretion of the Investigator using broad spectrum cover.

7.7.3.2 G-CSF

Treatment intensity is essential in the treatment of ESFT. G-CSF support is preferable to dose reduction following VIDE chemotherapy and is recommended following VDC/IE chemotherapy. The dose or type of G-CSF – i.e. daily G-CSF or Pegfilgrastim – is according to institutional guidelines. Daily G-CSF must be stopped 24 hours prior to chemotherapy commencing.

7.7.4 Blood products

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

7.7.5 *Pneumocystis carinii* infection prophylaxis

Pneumocystis carinii prophylaxis according to the recommendations of the national groups.

7.7.6 Hydration

Sufficient hydration (2-3L/m²/day) with appropriate electrolyte supplementation must be provided during chemotherapy. Monitoring of blood pressure, cardiac and respiratory frequencies, body weight, and diuresis is mandatory; the application of diuretics may become necessary in case of oedema or hypertension.

7.8 *Concomitant Medication*

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

7.9 *Patient Follow Up*

Following completion of treatment, the frequency of follow-up assessments should be as per local practice. The first Follow-up Form should be completed 18 months after trial entry, and those therafter will be requested yearly from trial entry.

Disease related follow-up checks for the first 5 years must include:

- Physical examination at each visit
- Appropriate imaging of primary tumour
- Chest X-ray

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

7.10 *Patient Withdrawal*

7.10.1 Withdrawal from Euro Ewing 2012 trial treatment

If a patient stops Euro Ewing 2012 protocol treatment, the reason should be recorded in the patient's medical records and be reported to the applicable National Coordinating Centre whether it is due to either the patient's, parent/legal guardian's or clinician's decision. Reasons for withdrawal from protocol treatment may include, but are not limited to:

- The patient/parent/guardian withdraws consent to further trial treatment
- Unacceptable toxicity
- Disease progression whilst on therapy

Euro Ewing 2012 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 7.10.2).

7.10.2 Withdrawal of consent to data collection

A patient's and/or parent/legal guardian's wishes with respect to their data must be respected. If a patient and/or parent/legal guardian explicitly states that they do not wish for any further data to be collected, this must be recorded on a Withdrawal Form. Details should also be recorded in the patient's hospital records and no further forms must be completed.

7.10.3 Loss to follow-up

If a patient is lost to follow-up, every effort should be made to contact the patient's medical practitioner (GP in the UK) (if consented) to obtain information on the patient's status. Similarly, if a patient's care is transferred to another clinician, the applicable National Coordinating Centre should be informed.

8. PATIENT MONITORING AND ASSESSMENT

The following are the recommended assessments and monitoring before and during treatment. Further monitoring can be performed according to institutional guidance.

These may be carried out at a hospital other than the trial site as all investigations would normally be part of routine care.

8.1 *Overview – Schedule of assessments*

	At diagnosis	Prior to the start of each cycle of induction	During treatment with doxorubicin (VIDE or VDC)	Following cycle 2 of VIDE (Arm A patients) or cycle 3 of VDC/IE (Arm B patients)	Post induction chemotherapy	Prior to the start of BuMel	Prior to the start of each cycle of consolidation or BuMel	Prior to the start of each cycle of zoledronic acid	At the end of treatment
Informed consent	X (R1)				X[a] (R2)				See section 8.4
Fertility preservation						X[e]			
Height, weight and surface area	X	X					X		
Assessment of performance status by Lansky score (age <16), or WHO Performance Status (age ≥16)	X								
Menstrual history and pregnancy test if indicated	X								
Sodium, potassium, magnesium, phosphate, calcium, creatinine, urea, ALP, ALT or AST, bilirubin, albumin	X	X					X		
GFR (calculated creatinine clearance (Ccrea) or isotopic). See section 7.4.1.3	X	X					X	X	
Tubular function. See section 7.4.1.3	X	X[b]					X[b]		
Full blood count	X	X					X		
Plain radiograph in two planes of primary tumour	X								
MRI or CT scan of primary site	X			X	X[c]				
Chest CT scan	X			X[d]					
Radionuclide scan of skeleton	X			X[j]					
PET scan (not mandatory)	X			X[j]					
Cardiac function assessed by ECHO	X		X[e]		X[f]				
Bone marrow aspirate and trephine of at least 1 site. See section 8.2.5 and 8.3.4	X			X[k]					
Estimation of primary tumour volume (and lymph node involvement if applicable). See section 8.2.6	X								
Confirmation of diagnosis/central pathology Review	X[g]								
Assessment of treatment toxicity		X[h]					X[h]		
Assessment of adverse events using CTCAE v4.0		X[h]					X[h]		
Dental assessment					X[i] (R2)				

The above table provides a summary of assessment timings. Please refer to sections 8.2, 8.3 and 8.4 for more information.

[a] see section 6 for the timing of the R2 randomisation

[b] prior to ifosfamide chemotherapy

[c] prior to local control of the primary tumour

[d] patients with pulmonary/pleural metastatic disease only

[e] according to institutional guidelines

[f] 3 weeks post induction chemotherapy (usually prior to surgery or radiotherapy)

[g] to be performed within 3 months of diagnosis

[h] not applicable prior to first cycle

[i] required before entering R2, and then at 6 monthly intervals during treatment with zoledronic acid.

[j] if metastatic disease at diagnosis

[k] if metastatic bone marrow disease at diagnosis

8.2 *Assessments at diagnosis*

8.2.1 Basic patient information

- Height, weight and surface area
- Assessment of performance status by Lansky score (age <16), or WHO Performance Status (age ≥16)
- Menstrual history and pregnancy test if indicated

8.2.2 Blood chemistry

- Sodium, potassium, magnesium, phosphate, calcium, creatinine, urea, alkaline phosphatase (ALP), alanine transferase (ALT) or aspartate aminotransferase (AST), bilirubin, albumin
- GFR (calculated creatinine clearance (Ccrea) or isotopic). See section 7.4.1.3.
- Tubular function. See section 7.4.1.3.

8.2.3 Haematology

- Full blood count

8.2.4 Radiological assessments

- Plain radiograph in two planes of primary tumour
- MRI or CT scan of primary site
- Chest CT scan
- Radionuclide scan of skeleton
- PET scan (not mandatory)

8.2.5 Other assessments

- Cardiac function assessed by ECHO
- Bone marrow aspirate and trephine of at least 1 site

8.2.6 Estimation of tumour involvement

Primary tumour volume

- Estimation of the tumour volume according to the formula:

Tumour volume = a x b x c x F,		
where a, b, and c represent the maximum tumour dimensions (in centimetres) in three planes		
with	F = 0.52	for spherical tumours,
or	F = 0.785	for cylindrical tumours

- Estimation of lymph node involvement:
The diameter of the largest node (or group if not separate) should be measured.

8.2.7 Diagnosis of ESFT

The diagnosis has to be confirmed in every patient. The diagnosis is based on the examination of routinely stained material supplemented by additional diagnostic methods as defined by the World Heath Organisation Classification of Tumours of Soft tissue and Bone (2013).

Hematoxylin and eosin (HE) is necessary for preliminary classification, followed and supplemented by immunohistochemistry and molecular genetics studies.

Fresh tumour tissue should be saved and snap frozen for additional investigations as defined in the biological studies section (section 9).

CD99 immunohistochemistry is obligatory in the diagnostic work-up of ESFT, as >95% of ESFT show membranous CD99 expression. However, other tumours (lymphoblastic leukaemia, lymphoma, myeloid sarcoma) may demonstrate membranous CD99 expression and it should be assessed in the context of the absence of lymphoma markers expression (such as CD45 and TdT).

The definitive diagnosis should be based on examination of routinely stained material demonstrating morphological and immunohistochemical features consistent with ESFT***plus*** the detection of *EWSR1* gene rearrangement (by Florescence *In Situ* Hybridisation, RT-PCR or similar method).However round cell sarcomas 'Ewing's-like' that are negative for EWSR1 gene rearrangement may be included in the trial.

Failure to perform test for *EWSR1* gene rearrangement will exclude the subject from the study.

8.2.7.1 Central Pathology Review

Diagnostic pathology samples are to be reviewed centrally within each country to confirm the diagnosis of ESFT, and should be conducted in line with national/study group guidelines. Pathology review is not required to be completed before randomisation but pathology material must be submitted within 3 months of diagnosis. H&E slides and a minimum of 1 representative block should be forwarded for review.

For patients who consent to the biological studies component of the study, the block will be stored for construction of tissue microarrays. For those who have declined entry into the biological studies, these will be returned after review is complete together with the H&E sections. For processes for shipping of pathology samples, please refer to the country-specific Laboratory Manual.

8.2.8 Definition of pulmonary/pleural metastatic disease

As a rule, one pulmonary/pleural nodule of >1 cm, or more than one nodule of >0.5 cm are 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.

In patients with chest wall tumours, pleural effusion with or without pleural nodules is not regarded as proof for lung/pleural metastases, but is considered to represent loco-regional disease.

8.2.9 Regional lymph node involvement

As a rule, these are lymph nodes within the drainage of the primary tumour as detected by clinical examination CT/MRI scan or ultra sound scan. It is recommended that suspicious nodes are confirmed by biopsy or cytology.

Definition of regional nodal disease:

- Nodal extension involving the first anatomical nodal drainage group.
- Hilar lymph nodes on the same side as the lung/pleural metastases.

8.3 *Assessments during treatment*

8.3.1 Prior to each cycle of chemotherapy

During treatment the patient should be clinically assessed and the following assessments performed prior to start of each cycle:

- Height, weight and surface area
- Assessment of treatment toxicity (not applicable prior to first cycle)
- Assessment of adverse events using CTCAE v4.0 (not applicable prior to first cycle)
- Full blood count (haemoglobin, white cell count, neutrophil count and platelets)
- Biochemistry (sodium, potassium, magnesium, phosphate, calcium, creatinine, urea, ALP, ALT or AST, bilirubin, albumin)
- GFR (calculated creatinine clearance (Ccrea) or isotopic) – see section 7.4.1.3
- Tubular function prior to ifosfamide chemotherapy – see section 7.4.1.3

8.3.2 Cardiac assessments

- Cardiac function assessments during treatment with doxorubicin, according to institutional guidelines using ECHO.
- To assess toxicity post induction chemotherapy, where applicable assessment should be performed 3 weeks post induction chemotherapy usually prior to surgery or radiotherapy

8.3.3 Radiological assessments

- Primary tumour site disease re-evaluation: CT scan or MRI (with measurements) should be performed to assess response or progression at the following time points:
  - following the second cycle of induction chemotherapy (Arm A patients) or following the third cycle of induction chemotherapy (Arm B patients)
  - prior to local control of primary tumour
- In patients with pulmonary/pleural metastatic disease, a CT scan of the chest should be performed to assess response or progression following the second cycle of induction chemotherapy (Arm A patients) or following the third cycle of induction chemotherapy (Arm B patients).
- In patients with other metastases, appropriate imaging should be performed to assess response or progression following the second cycle of induction chemotherapy (Arm A patients) or following the third cycle of induction chemotherapy (Arm B patients).

8.3.4 Bone Marrow assessments

- In patients with bone marrow metastases, it is recommended that bone marrow aspirates and trephines should be performed to assess response or progression. This is recommended to be done following the second cycle of induction chemotherapy (Arm A patients) or following the third cycle of induction chemotherapy (Arm B patients), but alternative timepoints are acceptable, and this assessment may be omitted if it is not clinically indicated or not usual local practice.

8.4 *Assessments at the end of treatment*

For patients who received radiotherapy only as local control and who had residual disease pre-radiotherapy, an end of treatment MRI or CT scan should be performed.

If the end of treatment scan shows residual disease, another scan should be performed six months after the end of treatment.

9. BIOLOGICAL STUDIES

The complete set of samples and which may be taken from consenting patients and the studies for which these samples will be used are described below. Not all countries will participate in every study. Therefore the details on which samples should be collected, processing and transport instructions, are provided in the accompanying country specific Laboratory Manuals supplied by the relevant National Coordinating Centre.

If a country is participating in the biological studies, subject to patient consent and appropriate centre facilities, the following should be collected from patients entered into EE2012 to achieve the common collective objectives described below.

- Whole genome sequence and RNA profile will be determined in DNA and RNA isolated from tumour; constitutionally normal DNA will be required in each case for genomic analysis (this is obtained from the whole blood sample collected into EDTA).

- Patient specific EWS-ETS fusion type will be identified using DNA isolated from frozen tumour.

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

- In blood, the association of molecular bone remodelling factors with bone growth will be determined.

- Tumour micro-arrays (TMAs) will be prepared from paraffin embedded tumour. See section 8.2.7.1.

The independent prognostic and predictive power of these studies will be compared to other methods for assessment of patient risk including (but not exclusively) age at diagnosis, site of disease and toxicity.

Given the rapid pace of disease characterisation at the molecular level, additional studies may become appropriate during the course of the trial. Any sample that remains after the primary research objectives of the biological studies described above have been reached should be banked and provide a valuable resource for future ethically approved biological studies that may arise.

	At diagnosis/prior to R1	Following cycle 2 and pre cycle 3 (if arm A) or following cycle 4 and pre cycle 5 (if arm B) induction therapy	Following cycle 2 and pre cycle 3 of VIDE (if arm A) or following cycle 3 and pre cycle 4 of VDC/IE (if arm B)	Pre start of consolidation therapy	At the end of consolidation therapy	One year after the end of consolidation therapy
Frozen tumour – snap frozen in (ideally) liquid nitrogen. Ship on dry ice to reference centre.	X					
Paraffin embedded tumour block	X					
Bone marrow aspirate (0.5 ml x2, right and/or left) into PAXgene Blood RNA Tubes - DO NOT POOL. Store at -80^{o}C. Ship on dry ice to reference centre.	X		X*			
Whole blood (2 ml x 1) into PAXgene Blood RNA Tube. Store at -80^{o}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^{o}C. Ship on dry ice to reference centre.	X	X		X	X	X
Whole blood (5ml) into EDTA tube. Store at -20 or -80^{o}C. Ship on dry ice to reference centre.	X					

*For patients with bone marrow metastatic disease only (where bone marrow aspirates are taken as part of response assessment: see Section 8.3.4)

For information on sample collection and processing from patients in each participating country please see the country specific Laboratory Manual.

If you do not have a laboratory manual please contact the applicable National Coordinating Centre.

10. ADVERSE EVENT REPORTING

The collection and reporting of Adverse Events (AEs) will be in accordance with 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 2. 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 - source data) with reference to the compendium of Summary of Product Characteristics.

10.1 *Reporting Requirements*

10.1.1 Adverse Events and Adverse Reactions

For definitions of Adverse Event (AEs) and Adverse Reactions (ARs) refer to Appendix 2.

As the safety profiles of the IMPs used in this trial are well characterised, only ARs experienced during treatment will be reported on the treatment forms of the CRF. The highest grade of AR experienced during each cycle of chemotherapy will be recorded only.

10.1.2 Serious Adverse Events

Investigators should report AEs that meet the definition of an SAE (see Appendix 2 for definition) and that are not excluded from the reporting process as described below.

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

The following events should not be reported on an SAE Form:

- Hospitalisations for:
  - Protocol defined treatment
  - Pre-planned elective procedures unless the condition worsens
  - Treatment for 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

Hospitalisations for the following events, or symptoms associated with them if considered related to the treatment, should be reported on an **Expected SAR Form** rather than an SAE Form:

- Neutropenia, fever and febrile neutropenia
- Infections
- Haematological toxicity (e.g. haemoglobin, WBC, granulocytes, platelets)
- Gut toxicity (e.g. mucositis/stomatitis, nausea, vomiting, diarrhoea)

  Unless the condition is life threatening or proves fatal

Expected SAR Forms should be completed by sites as soon as possible once the event has resolved and sent via post to the UK Coordinating Centre for data entry.

10.1.2.2 Monitoring pregnancies for potential Serious Adverse Events

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

In the event that a patient or their partner becomes pregnant during the SAE reporting period, please complete a Pregnancy Notification Form (providing the patient's details). If it is the patient who is pregnant, outcome data should be provided on a follow-up Pregnancy Notification Form. Where the patient's partner is pregnant, consent must first be obtained and the patient should be given a Release of Medical Information Form to give to their partner. If the 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, details of the outcome of the pregnancy should be provided on a follow-up Pregnancy Notification Form. If appropriate, an SAE Form should also be completed as detailed below.

10.1.3 Reporting period

Details of all ARs and SAEs (except those listed above) will be documented and reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment.

10.1.4 Post study SARs and SUSARs:

SAEs that are judged to be at least possibly related to the IMP(s) must still be reported in an expedited manner irrespective of how long after IMP administration the reaction occurred.

10.2 *Reporting Procedure*

10.2.1 Site

10.2.1.1 Adverse Reactions

ARs experienced during treatment should be recorded in the toxicity section of the Induction and Consolidation Chemotherapy Forms. ARs will be reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (see Appendix 3). Any ARs experienced by the patient but not included in the CTCAE should be graded by an Investigator and recorded on the AR Form using a scale of (1) mild, (2) moderate or (3) severe. For each sign/symptom, the highest grade observed since the last visit should be recorded.

10.2.1.2 Serious Adverse Events

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

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 version 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 form should be faxed together with a SAE Fax Cover Sheet to the UK Coordinating Centre, based at the CRCTU, using one of the numbers listed below as soon as possible and no later than 24 hours after first becoming aware of the event:

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

+44 (0) 121 414 9520 or +44 (0) 121 414 3700

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

For SAE Forms completed by someone other than the Investigator, the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the UK Coordinating Centre in the post and a copy kept in the ISF.

Investigators should also report SAEs within their own institution in accordance with local practice.

10.2.1.3 Provision of follow-up information

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

10.2.2 UK Coordinating Centre

On receipt of an SAE Form, seriousness and causality will be determined independently by a Clinical Coordinator. An SAE judged by the Investigator or Clinical Coordinator to have a 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. not defined in the Reference Safety Information), it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

10.2.3 Reporting to the Competent Authority and Research Ethics Committee

10.2.3.1 Suspected Unexpected Serious Adverse Reactions

The UK Coordinating Centre will report individual events categorised as SUSARs to the EORTC Pharmacovigilance Unit. The EORTC will report SUSARs to the EudraVigilance Clinical Trial Module (EVCTM) and were 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 SUSARs reports to the National Coordinating Centres who will report SUSARs to the relevant REC, within the time frame specified above, and Principal Investigators within their country. The UK Coordinating Centre will assume responsibility for reporting to these parties in the UK.

10.2.3.2 Development Safety Update Report

The UK Coordinating Centre will include details of all SAEs, SARs (including SUSARs) in a Development Safety Update Report (DSUR) produced annually from the date of the first Clinical Trial

Authorisation received for the trial to the submission of the End of Trial Declaration. National Coordinating Centres will be provided with a copy of this report and where contractually required to do so will forward this report to the relevant Competent Authority and REC. The UK Coordinating Centre will assume responsibility for reporting in all other countries.

10.2.3.3 Adverse Reactions

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

10.2.3.4 Other safety issues identified during the course of the trial

The National Coordinating Centres will notify the relevant Competent Authority and REC immediately if a significant safety issue is identified during the course of the trial. The UK Coordinating Centre will notify the MHRA and UK REC.

10.2.4 Investigators

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the ISF.

10.2.5 Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review all SAEs.

11. DATA HANDLING AND RECORD KEEPING

11.1 *Data Collection*

This trial will use an eRDC system which will be used for completion of the CRF. Access to the eRDC system will be granted to individuals via the UK Coordinating Centre. The Euro Ewings 2012 eRDC system can be accessed from:

https://www.cancertrials.bham.ac.uk/EE2012Live

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 National Coordinating Centre for data entry. SAE reporting will be paper-based (see section 9).

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 listed above.

Entries on the paper CRF should be made in ballpoint pen, in blue or black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be indicated on the form. Missing and ambiguous data will be queried. All sections are to be completed before being submitted.

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.

Trial forms may be amended by the UK Coordinating Centre, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, 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 if required.

11.2 *Archiving*

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source records (e.g. signed Informed Consent Forms, ISF, Pharmacy Files, patients' medical records, copies of SAE forms etc) at their site are securely retained for at least 10 years after the end of the trial. National Coordinating Centres will notify sites when documentation can be destroyed as specified in the country specific quality and trial management plan (see Appendix 1).

12. QUALITY MANAGEMENT

12.1 *Site Set-up and Initiation*

Sites will be set up and initiated in accordance with the applicable National Coordinating Centre quality and trial management plan (see Appendix 1). 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 Co-ordinating Centre. The applicable National Coordinating Centre must be informed immediately of any change in the site research team.

12.2 *On-site Monitoring*

Monitoring will be carried out as required following a risk assessment and as documented in the country specific quality and trial management plan (see Appendix 1).

Investigators will allow the Euro Ewing 2012 trial research staff access to source documents as requested.

12.3 *Central Monitoring*

If allowed by country specific legislation/guidance (as specified in the country specific quality and trial management plan, see Appendix 1) and if the patient and/or parent/legal guardian has given explicit consent sites are requested to send in copies of signed Informed Consent Forms 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 Good Clinical Practice (GCP), and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group (TMG), Trial Steering Committee (TSC) and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol.

12.4 *Audit and Inspection*

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

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

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

12.5 *Notification of Serious Breaches*

Country specific legislation may require the National Coordinating Centre of the trial to notify the Competent Authority and REC 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 regulatory authorities where required and in undertaking any corrective and/or preventive action.

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

See Appendix 1 for country specific requirements.

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

13. END OF TRIAL DEFINITION

The trial will remain open until all trial objectives have been met. The applicable National Coordinating Centre will notify the relevant Competent Authority and REC 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 trial.

14. STATISTICAL CONSIDERATIONS

14.1 *Definition of Outcome Measures*

14.1.1 Primary outcome measure

For each randomisation, EFS is defined as the time from randomisation to first event, where an event is progression without complete remission, recurrence (following complete remission), diagnosis of second malignancy or death.

Patients who have not had an event will be censored at their last follow-up date. Patients lost to follow-up without an event will be censored at the date of their last consultation.

14.1.2 Secondary outcome measures

14.1.2.1 Overall survival

For each randomisation, 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.

14.1.2.2 Adverse events and toxicity (CTCAE v4.0)

Adverse events and toxicity will be graded using CTCAE version v4.0.

14.1.2.1 Primary tumour, lung and/or pleural metastases, other metastasis and regional lymph node response,

The volume of the primary tumour, the number of lung and/or pleural and other metastases, the diameter of the largest node (or group if not separate) will be recorded at four time points – at the baseline, after course 2 or 3 (depending on the treatment arm), prior to local control of primary tumour and at the end of treatment.

14.1.2.2 Histological response of the primary tumour to induction chemotherapy if surgery is performed as local control

Patients with good histological response are defined as follows:

No viable tumour cells	(Salzer-Kuntschik: grade 1)
1% - <5% viable tumour cells	(Salzer-Kuntschik: grade 2)
≥5% - <10% viable tumour cells	(Salzer-Kuntschik: grade 3)

Patients with poor histological response are defined as follows:

≥10% - <50% viable tumour cells	(Salzer-Kuntschik: grade 4)
≥50% viable tumour cells	(Salzer-Kuntschik: grade 5+6)

The percentage of viable tumour cells in the resected primary tumour specimen will be determined at the time of surgery following induction chemotherapy.

14.1.2.3 Achievement of local control at the end of treatment

The definition of local control is either:

- complete surgical resection following induction chemotherapy
- no measurable disease, assessed by end of treatment MRI or CT scan
- no increase in measurable residual tumour over a six month period from the end of treatment, assessed by MRI or CT scan at the end of treatment and six months after the end of treatment

14.1.2.4 Growth parameters and jaw/ear osteonecrosis (R2 only)

Growth parameters will be assessed using patient's height measured at baseline, treatment and throughout follow up for all patients who enter the second randomisation and who are less than 18 years of age at entry.

Whether the patient was diagnosed with jaw and ear osteonecrosis will be recorded at the end of or during treatment for all patients who were randomised to R2.

14.2 *Induction/consolidation chemotherapy randomisation: general principles*

The two conventional chemotherapy strategies (VIDE; VDC/IE/VC) will be compared to evaluate whether one is better than the other with respect to EFS; if there is likely to be an absolute difference in EFS of <5%, toxicity will be used to decide which regimen should become the standard. In the absence of reliable evidence on the comparative efficacy of the two regimens, no prior assumptions have been made as to which might be better than the other.

A likelihood Bayesian approach will be adopted for this randomisation (a conventional sample size calculation is also provided). This randomisation compares two standard induction and consolidation regimens – one from Europe, one from the USA. The clinicians involved at the design stage of the trial were asked how certain they would need to be that one treatment was not more than 5% worse than the other in terms of 3-year EFS; a consensus was reached that they would want to be about 75% to

80% certain, on the basis that two standard treatments were being compared rather than a novel agent being added and this will be the decision rule (although the toxicity will be taken into account).The 20-25% probability of selecting a treatment that is actually more than 5% worse is thereafter referred to as the limit of clinical acceptability.

14.3 *Sample Size Calculations*

14.3.1 Induction/consolidation randomisation (R1)

Likelihood Bayesian approach:

With a 5 year accrual period, it will be possible to randomise at least 600 patients in the UK and France, and over 800 if Germany and associated countries take part in the induction randomisation. Hence, these figures are used as the basis for the calculations; with 600 and 800 patients, and a minimum of two years and a maximum of 7 years follow-up, there will be at least 150 and 200 events respectively.

Non-informative priors will be used, so the posterior distribution gives Pr(parameter|data) – i.e. the probability of the treatment effect. The ln(hazard ratio) is assumed to be normally distributed with variance 4/n, where n=total number of events in both arms [53]. Based on the EURO-E.W.I.N.G. 99 data, 3-year EFS is anticipated to be about 70% with VIDE. The tables below show the probability that one treatment is better than the other, or not more than 5% worse, for a range of observed hazard ratios (HR) (a HR of 1.21, or inversely 0.81, represents about a 5% absolute difference in 3-year EFS – i.e. HR = ln(0.75)/ln(0.70) = 0.81; HR= ln(0.65)/ln(0.70) = 1.21).

600 patients:

Observed 3-year EFS			Observed HR			P (HR<1.00)	P (HR<0.81)	P (HR>1.21)
VIDE	Diff.	VDC/IE	# Events	HR	ln(HR)			
0.70	0.00	0.70	180	1.00	0.00	0.50	0.07	0.10
0.70	0.05	0.75	165	0.81	-0.21	0.92	0.50	0.00
0.70	-0.05	0.65	195	1.21	0.19	0.09	0.00	0.50
0.70	0.025	0.725	173	0.90	-0.10	0.75	0.23	0.03
0.70	-0.025	0.675	188	1.10	0.10	0.25	0.02	0.27

800 patients:

Observed 3- year EFS			Observed HR			P (HR<1.00)	P (HR<0.81)	P (HR>1.21)
VIDE	Diff.	VDC/IE	# Events	HR	ln(HR)			
0.70	0.00	0.70	240	1.00	0.00	0.50	0.05	0.07
0.70	0.05	0.75	220	0.81	-0.21	0.94	0.50	0.00
0.70	-0.05	0.65	260	1.21	0.19	0.06	0.00	0.50
0.70	0.025	0.725	230	0.90	-0.10	0.78	0.20	0.01
0.70	-0.025	0.675	250	0.10	0.10	0.22	0.01	0.23

With 600 patients, it can be seen that:

- with an observed HR of 1.00 (no apparent difference between the randomised groups in terms of EFS), there would be probabilities of 10% or 7% that VDC/IE was actually more than 5% worse or better respectively than VIDE, with a cumulative probability of 17% i.e. within the limits of clinical acceptability. It would then be reasonable to base the decision on which regimen is preferable on toxicity.

- with observed HR of 0.81 (an observed improvement of about 5% in EFS with VDC/IE compared to VIDE), there would be a 8% probability that the apparently better regimen, i.e. VDC/IE, was actually worse – i.e. within the limits of clinical acceptability.

- with an observed HR of 0.90 (i.e. about a 2.5% absolute difference in EFS favour of VDC/IE), there would be a probability of 25% that the apparently better regimen was actually worse and probability of 3% that it was more than 5% worse – i.e. at the limit of clinical acceptability;

With 800 patients, the corresponding probabilities are:

- with an observed HR of 0.81, there would be a 6% probability that the apparently better regimen was actually worse;

- with an observed HR of 0.90, there would be a probability of 22% that the apparently better regimen was actually worse and probability of <2% that it was more than 5% worse;

- with an observed HR of 1.00, there would be probabilities of 5% or 7% that VDC/IE was actually more than 5% better or worse than VIDE, with a cumulative probability of 12%.

These calculations have been performed for various sample size, leading to the conclusion that a sample size of minimum 600 patients was sufficient to provide adequate estimates of outcome to enable clinical decision making.

Conventional sample size:

A conventional frequentist sample size has not been used because of the difficulty in coming up with a plausible design, and also because we do not wish to make assumptions as to whether we will find superiority of one regimen over the other, or “equivalent” EFS. To detect, in a superiority trial, a 5% difference in 3-year EFS from 70% in the VIDE arm to 75% or 65% in the VDC/IE arm would require about 2500 and 2800 patients in total respectively, using a two-sided p=0.05 and 80% power. This number is not achievable within a reasonable timeframe (to detect a 10% difference would require an achievable 600 to 700 patients but such a difference is not considered clinically plausible). Similarly, an equivalence trial with an equivalence margin of 5% - i.e. EFS is not more than 5% worse in one arm – would require about 3500 patients under the assumption of no actual difference between the two regimens, at 2p=0.05 and 80% power (a 10% margin would require about 900 patients but is considered too large a margin to be clinically acceptable).

Another scenario that has been considered plausible by some clinicians, based on a non-randomised comparison of the published data on VIDE and VDC/IE, is that VDC/IE will produce 5% better EFS but will be less toxic. On this basis – i.e. assuming a 5% EFS benefit for VDC/IE and wishing to eliminate a 5% adverse effect – about 700 patients would be needed, at 2p=0.05 and 80% power. This fits with the Bayesian sample size.

Pragmatically, randomising several hundred patients between regimens will provide a considerable amount of useful information and will be a more efficient use of patients than in the preceding EURO-E.W.I.N.G. 99 trial, in which there was no induction randomisation, meaning that over half of the patients registered did not undergo any randomisation and, hence, did not provide information on treatment efficacy. If, at the end of the trial, the result was felt to be inconclusive, it would be possible to continue this randomisation into the subsequent trial.

14.3.2 Zoledronic acid randomisation (R2)

Assuming 3-year EFS of 70% in the no zoledronic acid arm, to detect an 9% increase to 79% with zoledronic acid, a total of about 750 patients will be needed, at 2p=0.05 with 80% power. To detect a larger difference of 10% would require about 600 patients.

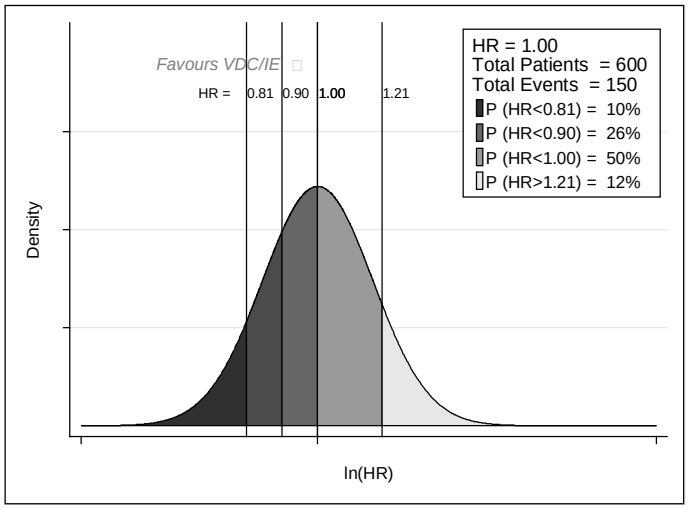
The majority of patients (c. 80%) will be responders so, with accrual of at least 600 patients to the R1 randomisation, it should be possible to randomise about 400 in the R2 randomisation. The agreed prospective analysis in conjunction with the German Ewing 2008 trial (where the zoledronic acid randomisation is restricted to good responders), which will have a similar or greater number of patients randomised, will enable to reach the accrual target of at least 750 patients.

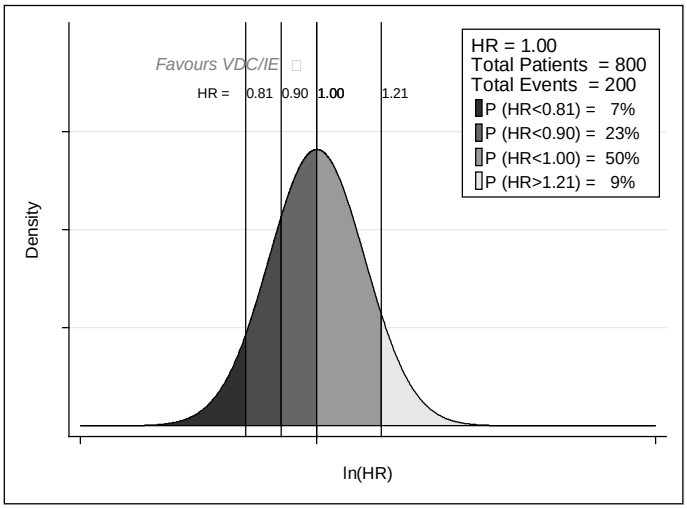
14.4 *Analysis of Outcome Measures*

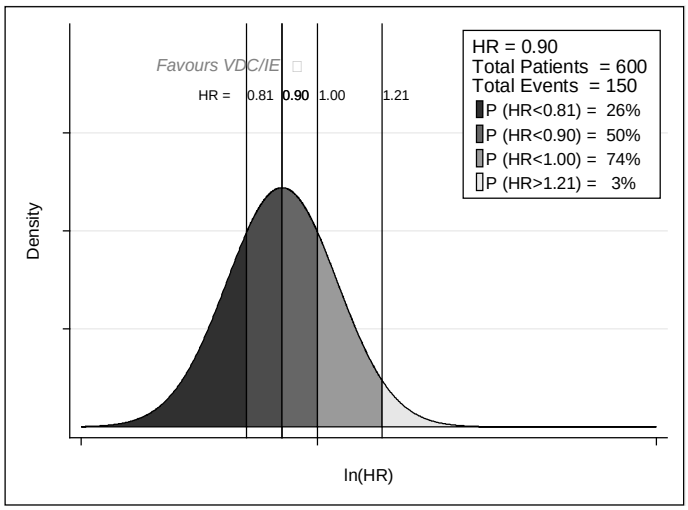
For each randomisation, the main analyses will be intention-to-treat (ITT) with all patients analysed in the arm to which allocated at randomisation. Analyses of the zoledronic acid randomisation will be stratified by trial (Euro Ewing 2012, Ewing 2008).

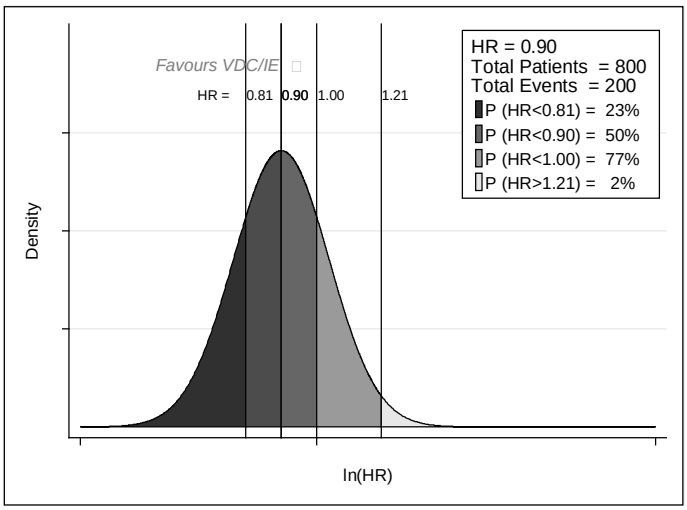
Induction/consolidation chemotherapy randomisation:

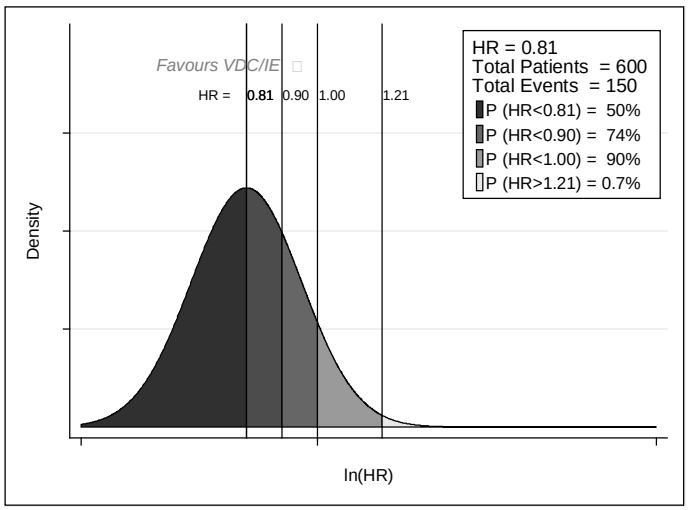
Posterior probability distributions will be plotted for the primary outcome measure of EFS, and the secondary outcome measure of OS, based on the HR as calculated from the Cox model and the number of events observed. Examples are given below for observed HRs of 1.00, 0.90 and 0.81 and, conservatively, for about 150 and 200 events in 600 and 800 patients respectively. If larger numbers of events are observed, the probabilities will be smaller (except for the probability of 50%).

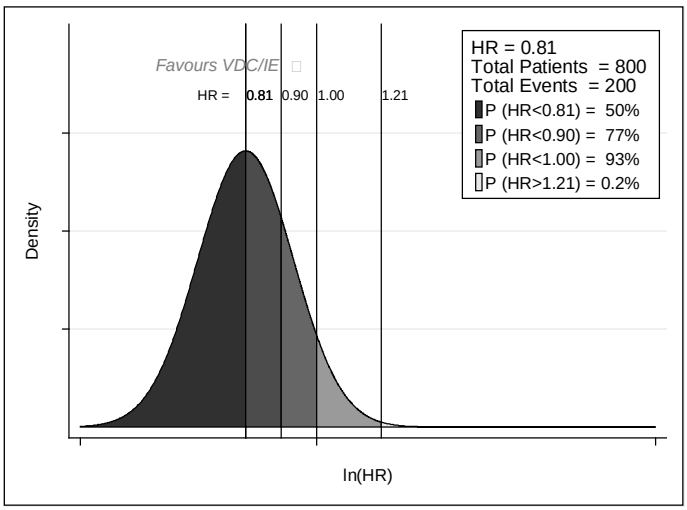












For time-to-event data – EFS and OS – Kaplan-Meier life tables will also be produced and the data plotted as survival curves for visual representation. Secondary conventional analyses will be reported: logrank tests, with 95% confidence intervals (CI). For each toxicity type, toxicity grades will be compared between the two randomised groups; analyses will include consideration of all chemotherapy cycles (e.g. repeated data per patient analysed using mixed models) and consideration of the worse grade observed per patient on the whole treatment course.

The main analysis will be performed on the whole set of patients included in the R1 randomisation.

Zoledronic acid randomisation:

Conventional statistical analyses will be performed: Kaplan-Meier life tables will be constructed for time-to-event data (with date of randomisation as reference time point) and arms will be compared by means of the logrank test; continuous variables will be compared across arms by means of t-tests or Wilcoxon tests as appropriate. Multivariable analysis using Cox regression will be used to adjust for baseline co-variates as appropriate.

Analyses of zoledronic acid randomisation will be performed on the total data sets for all trials combined (with stratification by trial). Multivariable analysis using Cox regression will be used to adjust/stratify on the following variables: country, allocated treatment in the R1 randomisation, trial (EE2012, Ewing 2008) and prognostic factors, as appropriate. Heterogeneity of the treatment effect according to these factors will be evaluated.

14.5 *Planned Subgroup Analyses*

Exploratory subgroup analyses will be performed, where appropriate, by: age (<14 years; ≥14 years), gender, country, disease site and volume of tumour. Given the well-known dangers, all subgroup analyses will be treated as exploratory and hypothesis-generating.

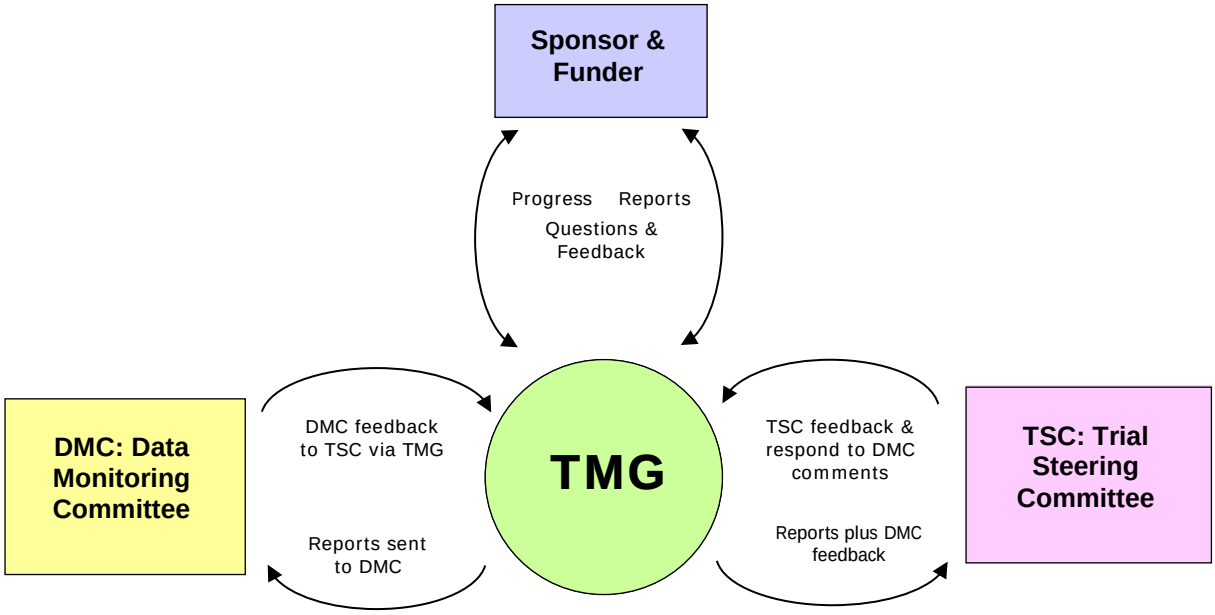
14.6 *Planned Interim Analysis*

Interim analyses of accrual and safety will be supplied at least annually to the independent DMC (see section 15.5). Interim analyses of efficacy outcome measures in each randomised comparison will be performed according to a pre-specified plan annually using Haybittle-Peto guideline.

14.7 *Planned Main Analyses*

The first main analysis of the trial will be performed when the last patient entered into each randomisation has been followed up for a minimum of two years. Patients will be followed up long-term for death, recurrence and late side-effects.

15. TRIAL ORGANISATIONAL STRUCTURE



15.1 *Coordinating-sponsor*

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

National Coordinating Centres are responsible for the conduct of the trial within their own country.

15.2 *National Coordinating Centres*

The Coordinating 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 Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham. The trial will be set-up, managed and analysed in the UK in accordance with CRCTU standard policy and procedures.

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

15.3 *Trial Management Group*

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

15.4 *Trial Steering Committee*

The TSC will provide independent oversight of the trial and provide advice through its independent chair. The TSC will include members of the Euro Ewing Consortium (EEC) External Advisory Board, a patient representative and a sponsor's representative. The Chief Investigator will report to the committee on behalf of the TMG. The TSC will assume responsibility for the oversight of the trial on behalf of the Coordinating Sponsor. The TSC will meet or hold teleconferences at least once a year, or more often if required.

15.5 *Data Monitoring Committee*

Analyses will be supplied in confidence by the trial statistician 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 Euro Ewing 2012 trial have provided **both** (i) "proof beyond reasonable doubt"[1] 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 local lead 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

[1] Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely but, in general terms, a difference of at least three standard errors in an interim analysis of a major endpoint would be needed to justify halting, or modifying, a randomisation prematurely. This criterion has the practical advantage that the exact number of interim analyses is of little importance.

trial. Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified.

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

15.6 *Finance*

This is an investigator-initiated and investigator-led trial funded by Cancer Research UK in the UK and the Seventh framework programme of the European Community for research and technological development including demonstration activities (FP7) internationally.

No individual per patient payment will be made to sites, Investigators, patients or other third parties from this funding.

16. ETHICAL CONSIDERATIONS

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

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

The National Coordinating Centres and Investigators shall consider all relevant guidance with respect to commencing and conducting the study in accordance to 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 pharmaceutical 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)).

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local site specific approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

17. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the relevant data protection legislation in the member state. With the patient's consent (and where national legislation/guidance permits) their full name, date of birth, hospital number, medical practitioner details and national registry numbers (e.g. National Health Service (NHS) Number in the UK) will be collected at trial entry to allow long-term follow-up via other health care professionals (e.g. patient's medical practitioner) and national cancer registries.

Patients will be identified using only their unique trial number and, if national legislation permits, their initials and date of birth on the header section of the eRDC screens and 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 regulatory authorities, 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 Euro Ewing 2012 trial research team may be required to have access to patients' medical records for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

18. INSURANCE AND INDEMNITY

The National Coordinating Centres are responsible for obtaining insurance to set up and run the Euro Ewing 2012 trial in their respective countries and for ensuring that sites in their country are adequately covered.

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

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

19. PUBLICATION POLICY

Results of this trial will be submitted for publication in peer reviewed journals. The 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 lead of the UK Coordinating Centre at the CRCTU and the Chief Investigator. 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 National Coordinating Centres and the clinical study site agreement (or country specific equivalent) between the National Coordinating Centres and sites.

Individual National Coordinating Centres will be allowed to publish their efficacy results. However, the publication of efficacy results from the whole trial will precede efficacy result publications of individual countries, unless the TMG decides otherwise.

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APPENDIX 1 – 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. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

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 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 Visit and will be provided with a Pharmacy File containing the Pharmacy Manual, protocol, labels and accountability logs.

When patients are randomized into the trial the Responsible Pharmacist will be sent a Pharmacy Notification by fax.

On-site Monitoring

Monitoring will be carried out as required following a Risk Assessment and as documented in the Euro Ewing 2012 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 2 – 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 IMP, whether or not related to the IMP.

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:

- Results in death unrelated to original cancer
- Is life-threatening*
- Requires hospitalisation** or prolongation of existing inpatient 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 SAEs.

*** 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 patient 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 applicable product information.

A SUSAR should meet the definition of an AR, UAR and SAR.

Unexpected Adverse Reaction

An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product).

When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.

APPENDIX 3 – COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

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 (NCI) website, the following address was correct when this version of the protocol was approved:

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