A prospective randomised controlled phase III trial of gemcitabine and docetaxel compared with doxorubicin as first line treatment in previously untreated advanced unresectable or metastatic soft tissue sarcomas

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Funder reference: CRUK/10/004
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UK CTA no: 20363/0285/001-0001
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Protocol version no: 8.0
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3/4/16

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Please note: This trial protocol must not be applied to patients treated outside the GeDDiS trial. UCL CTC can only ensure that approved trial investigators are provided with amendments to the protocol.
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<td>Dr. Regula Lustenberger</td>
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<td>SAKK CC, Bern</td>
</tr>
</tbody>
</table>

In addition to the information in the GeDDiS protocol sites in Switzerland should also refer to their Country Specific Appendix. Sites should refer to BOTH the protocol and the Swiss-specific appendix at all times.

Trial documentation is available on the SAKK website, by using the following link:

Members → Trials → Sarcomas → GeDDiS
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# 1. Protocol Summary

## 1.1. Summary of trial design

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<th>A prospective randomised controlled phase III trial of gemcitabine and docetaxel compared with doxorubicin as first line treatment in previously untreated locally advanced unresectable or metastatic soft tissue sarcomas</th>
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<tbody>
<tr>
<td>Short Title/Acronym:</td>
<td>GeDDiS</td>
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<tr>
<td>EUDRACT no:</td>
<td>2009-014907-29</td>
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<tr>
<td>Sponsor name &amp; reference:</td>
<td>University College London (UCL 09/0060)</td>
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<tr>
<td>Funder name &amp; reference:</td>
<td>Cancer Research UK (CRUK/10/004)</td>
</tr>
<tr>
<td>ISRCTN no:</td>
<td>ISRCTN07742377</td>
</tr>
<tr>
<td>Design:</td>
<td>Randomised, controlled phase III multi-national trial</td>
</tr>
<tr>
<td>Overall Aim:</td>
<td>To determine whether the combination of gemcitabine and docetaxel is associated with an improved clinical outcome (progression free and overall survival) compared with single agent doxorubicin as first line treatment in patients with locally advanced unresectable/metastatic soft tissue sarcoma</td>
</tr>
<tr>
<td>Primary endpoint:</td>
<td>Proportion of patients alive and progression free at 24 weeks after randomisation</td>
</tr>
<tr>
<td>Secondary endpoints:</td>
<td>Proportion of patients alive and progression free at 12 weeks after randomisation</td>
</tr>
<tr>
<td></td>
<td>Median progression-free survival</td>
</tr>
<tr>
<td></td>
<td>Overall survival</td>
</tr>
<tr>
<td></td>
<td>Time to progression</td>
</tr>
<tr>
<td></td>
<td>Time from start of treatment to progression or death (whichever occurs first)</td>
</tr>
<tr>
<td></td>
<td>Objective response rate by RECIST (v1.1)</td>
</tr>
<tr>
<td></td>
<td>Objective response rate by Choi criteria (retrospective analysis)</td>
</tr>
<tr>
<td></td>
<td>Adverse Events (CTCAE v4.03)</td>
</tr>
<tr>
<td></td>
<td>Quality of life</td>
</tr>
<tr>
<td></td>
<td>Health economic evaluation</td>
</tr>
<tr>
<td>Target number of patients:</td>
<td>250</td>
</tr>
<tr>
<td>Inclusion &amp; Exclusion criteria:</td>
<td>Inclusion criteria:</td>
</tr>
<tr>
<td></td>
<td>• Locally advanced or metastatic soft tissue sarcoma, incurable by surgery or radiotherapy</td>
</tr>
<tr>
<td></td>
<td>• Histological confirmation of high grade disease (Trojani grade 2 or 3 sarcoma)</td>
</tr>
<tr>
<td></td>
<td>• Evidence of disease progression within the previous 6 months</td>
</tr>
<tr>
<td></td>
<td>• No prior chemotherapy regimen for sarcoma and no prior doxorubicin containing regimen for any previously treated cancer.</td>
</tr>
<tr>
<td></td>
<td>• WHO performance status 0 – 2</td>
</tr>
<tr>
<td></td>
<td>• Age ≥13 years</td>
</tr>
<tr>
<td></td>
<td>• Histological material available for central review</td>
</tr>
<tr>
<td></td>
<td>• Measurable disease evaluable by RECIST criteria v1.1</td>
</tr>
<tr>
<td></td>
<td>• Life expectancy of at least 3 months</td>
</tr>
<tr>
<td></td>
<td>• Adequate organ function:</td>
</tr>
</tbody>
</table>
- Neutrophils $\geq 1.0 \times 10^9/L$
- Platelets $\geq 100 \times 10^9/L$
- Bilirubin $\leq 1.5 \times$ ULN
- AST or ALT $\leq 3.0 \times$ ULN
- ALP $\leq 3.0 \times$ ULN, if ALP $\geq 3.0 \times$ ULN, patients can be entered if this is shown to be the bone isoenzyme
- Measured or calculated creatinine clearance $\geq 30$ ml/min
- Ejection fraction (measured according to local practice) within normal limits for the site

- Patients agree to use contraception for the duration of the trial, where applicable
- Able to complete quality of life questionnaires
- Able to give written informed consent

Exclusion criteria:
- Soft tissue sarcoma of the following types:
  - Alveolar soft part sarcoma
  - Gastrointestinal stromal tumour
  - Ewing’s sarcoma family of tumours
  - Alveolar or embryonal rhabdomyosarcoma
  - Desmoplastic small round cell tumour
  - Extra-skeletal myxoid chondrosarcoma
  - Dermatofibrosarcoma protuberans
  - Malignant mixed mesodermal tumour/carcinosarcoma of the uterus
  - Smooth muscle tumours of uncertain malignant potential (STUMP)
- Known active/uncontrolled brain metastases
- Grade 3 or 4 peripheral neuropathy
- Active uncontrolled infection
- Prior history of malignancy other than sarcoma, except for basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, breast or prostate, and unless the patient has been free of malignancy for a period of 3 years prior to first dose of trial drug.
- Women who are pregnant or lactating
- Any serious and/or unstable pre-existing medical, psychiatric or other condition that could interfere with patient safety or obtaining informed consent

<table>
<thead>
<tr>
<th>Planned number of sites:</th>
<th>Approximately 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target countries:</td>
<td>UK, Switzerland</td>
</tr>
</tbody>
</table>
| Treatment summary:       | Standard arm – doxorubicin 75 mg/m² i.v. day 1 every three weeks for up to 6 cycles  
                           | Experimental arm – gemcitabine 675 mg/m² i.v. days 1 and 8, docetaxel 75 mg/m² i.v. day 8 every three weeks for up to 6 cycles |
| Anticipated duration of recruitment: | 3 years |
| Duration of patient follow up: | After treatment, patients will be followed up no less frequently than 12 weekly with clinical evaluation and scanning until disease progression, or death, for up to 24 months after randomisation. Patients who have not progressed after 24 months should be scanned according to local practice. Following disease progression, or after 24 months in the absence of progression, patients will be assessed for survival up every 12 weeks until death |
| Definition of end of trial: | 5 years after the last administration of protocol treatment or death of the last surviving patient, whichever is sooner |
| Translational component: | To investigate the influence of pharmacogenomics on response and toxicity in patients with soft tissue sarcoma treated with gemcitabine/docetaxel or doxorubicin |
1.2. Trial Schema

**Eligible patients:** high or intermediate grade locally advanced or metastatic soft tissue sarcoma, incurable by surgery or radiotherapy (n=250)

Baseline CT/MRI scan

Quality of life assessment

Randomise 1:1

**ARM A**
Doxorubicin 75mg/m²
Day 1 q21 for 6 cycles (n=125)

CT/MRI at week 12, week 24, then 12 weekly until disease progression

Quality of life assessments at 12, 18 and 24 weeks

After disease progression assessment for survival every 12 weeks

**ARM B**
Gemcitabine 675 mg/m²
days 1 and 8
Docetaxel 75mg/m² Day 8
q21 for up to 6 cycles (n=125)

CT/MRI at week 12, week 24, then 12 weekly until disease progression

Quality of life assessments at 12, 18 and 24 weeks

After disease progression assessment for survival every 12 weeks
2. Introduction

2.1. Background

Sarcomas are rare tumours and account for approximately 1% of all cancer diagnoses. The annual incidence rate was 2,025 cases in the UK in 2006, including bone and soft tissue sarcomas[1-4], although this is probably an underestimate.

The current standard of care for first line palliative chemotherapy in locally advanced or metastatic soft tissue sarcoma is doxorubicin[5]. As a single agent it is associated with response rates of 12 – 24%, and an overall survival of up to 12 months[6-10]. Ifosfamide was the next drug to show consistent activity in soft tissue sarcoma. It was first introduced in the 1960s, but it was not until after the introduction of mesna in 1979 to prevent the dose-limiting toxicity of haemorrhagic cystitis that its use in soft tissue sarcoma was established, with response rates of 18 – 38% as a single agent[11-16]. Combination regimens including doxorubicin and ifosfamide were then investigated in phase II studies, as doxorubicin and ifosfamide alone[17-18], or in combination with other drugs such as dacarbazine (DTIC) in the MAID regimen[19]. In the early 1990s, three large prospective randomised controlled phase III studies were completed, two comparing doxorubicin with combination chemotherapy[6, 10], and a third comparing doxorubicin and DTIC with MAID[20], summarised in table 1. The combination regimens were associated with higher response rates, but with greater toxicity, and no significant improvement in overall survival. This may have been in part because the addition of inactive agents required dose reduction of the active doxorubicin and ifosfamide, with consequent loss of activity.

Table 1 Phase III studies of combination doxorubicin and ifosfamide in metastatic soft tissue sarcoma.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>RR</th>
<th>TTP (weeks)</th>
<th>OS (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG (1993)[6]</td>
<td>279</td>
<td>20%</td>
<td>-</td>
<td>35</td>
</tr>
<tr>
<td>Doxorubicin 80 mg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin 60 mg/m²/ ifosfamide 7.5 g/m²</td>
<td>34%</td>
<td>-</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin 40 mg/m²/ mitomycin C 8 mg/m²/ cisplatin 60 mg/m²</td>
<td>32%</td>
<td>-</td>
<td>25</td>
<td>NS</td>
</tr>
<tr>
<td>Intergroup (1993)[20]</td>
<td>340</td>
<td>17%</td>
<td>17</td>
<td>56</td>
</tr>
<tr>
<td>Doxorubicin 60 mg/m²/ DTIC 1000 mg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin 60 mg/m²/ DTIC 1000 mg/m² /ifosfamide 7.5 g/m² (MAID)</td>
<td>32%</td>
<td>p&lt;0.005</td>
<td>26</td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>EORTC 62851 (1995)[10]</td>
<td>663</td>
<td>23%</td>
<td>46</td>
<td>52</td>
</tr>
<tr>
<td>Doxorubicin 75 mg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYVADIC 1</td>
<td></td>
<td>28%</td>
<td>48</td>
<td>51</td>
</tr>
<tr>
<td>Doxorubicin 50 mg/m² / ifosfamide 5 g/m²</td>
<td>28%</td>
<td>NS</td>
<td>44</td>
<td>NS</td>
</tr>
</tbody>
</table>

1 CYVADIC – cyclophosphamide 500 mg/m², vincristine 1.5 mg/m², doxorubicin 50 mg/m² and DTIC 750 mg/m²
RR = response rate; TTP = time to progression; OS = overall survival

A subsequent series of phase II studies sought to investigate dose intensification of the doxorubicin and ifosfamide combination using growth factor support, allowing escalation of doses of both drugs[18, 21-23]. These studies confirmed feasibility, with response rates of 45 – 66%, but at the expense of significant toxicity. Overall, it seems that doxorubicin and ifosfamide are the best single agents in soft tissue sarcoma, and there is a demonstrable dose-response for both agents. Combination treatment results in higher response rates, but with higher toxicity even with growth factor support. It is still not known how the dose-
intensified growth factor supported regimens compare with single agent doxorubicin, and whether these will finally confer an overall survival benefit. To this end, the EORTC Soft Tissue and Bone Sarcoma Group are currently conducting the 62012 study, a prospective randomised phase III study which compares doxorubicin 75 mg/m², with doxorubicin 75mg/m² and ifosfamide 10g/m². Until this study is completed and reports, the standard of care for metastatic soft tissue sarcoma first line chemotherapy remains single agent doxorubicin.

Doxorubicin and ifosfamide, either alone or in combination, have been the mainstay of therapy for metastatic soft tissue sarcoma since the 1980’s. However, there has been continuing interest in identifying additional active agents. Gemcitabine (2’,2’-difluorodeoxycytidine) is an anti-metabolite, a fluorinated analogue of the nucleoside deoxycytidine (dCTP). The parent drug is inactive, but intracellular phosphorylation yields active di- and tri-phosphate metabolites. The diphosphate form inhibits ribonucleotide reductase; the triphosphate form is incorporated into DNA and competes with dCTP as a ‘bogus’ base dFdCTTP. This results in DNA chain synthesis termination, and in addition, the ‘bogus’ base is resistant to excision by DNA repair enzymes. A number of studies have been carried out with gemcitabine in metastatic soft tissue sarcoma in both first and second line settings[24-33]. The majority of studies have shown only low objective response rates, and concluded that further investigation was not warranted. Work in pancreatic cancer has indicated that prolonged infusion rate gemcitabine (10 mg/m²/minute) results in higher clinical response rates than bolus infusions[34]. The majority of the studies in sarcoma had used short 30 minute infusion rates. This, in addition to the inclusion of large numbers of patients with ‘gastrointestinal leiomyosarcomas’ (which in retrospect were probably gastrointestinal stromal tumours, known to be chemo-resistant), may account at least in part for the low response rates. A single sarcoma study has investigated a longer 150 minute infusion rate against the ‘standard’ widely used 30 minute infusion rate, showing that the longer infusion duration was associated with a increase by 1.4 fold in concentration of the active metabolite GTP in peripheral blood monocytes[29], suggesting an advantage to longer infusion times.

Docetaxel, a taxane, stabilises tubulin, thereby disrupting the microtubule network of the cell, resulting in inhibition of mitotic and interphase cellular functions. It has been investigated in soft tissue sarcoma in a phase II study carried out by the EORTC Soft Tissue and Bone Sarcoma Group[35]. Pre-treated patients received docetaxel 100mg/m² as a 60 minute infusion every 3 weeks. A response rate of 17% was observed, leading to a randomised phase II study, comparing docetaxel 100 mg/m² with doxorubicin 75 mg/m², used first line in soft tissue sarcoma[58]. However, following randomisation of 83 patients, the response rates for doxorubicin and docetaxel were 30% and 0%, and the time to progression 24 and 7 weeks, respectively, leading to the conclusion that docetaxel was inactive, and to the abandonment of a planned phase III component of the study.

Gemcitabine and docetaxel have been used in combination in a range of tumour types[37]. A number of studies have investigated the utility of the combination in soft tissue sarcoma (table 2). Initial work was carried out by Hensley et al[38]. In a phase II study of 34 patients with leiomyosarcoma (29 with uterine leiomyosarcoma, 5 with leiomyosarcomas at other sites) who had received between 0 - 2 previous chemotherapy regimens, patients received up to eight cycles (median 6, range 1 - 8). Results were impressive, with 3 patients achieving a complete response, and a further 15 achieving a partial response, giving an objective response rate (CR and PR) of 53%. A further 8 patients experienced a minor response or stable disease. The median time to progression was 5.6 months, and the median overall survival was 17.9 months. The regimen was tolerable, and comparing with historical results, appeared to show significant activity, thus heralding further investigation of the combination.
A subsequent report\[39\] presented retrospective data of the combination in 35 patients (28 had received previous chemotherapy) with a range of sarcoma histological subtypes. Patients received a median of 5 cycles. The objective response rate was 43% (CR 5, PR 10, SD 13). The median time to progression was 6.7 months. In a larger retrospective study of 133 patients with advanced or refractory soft tissue sarcoma, patients received a median of 3 cycles of gemcitabine and docetaxel. In this unselected population, the objective response rate was 18.4%, and the median survival was 12.1 months\[40\].

Table 2 Studies of gemcitabine and docetaxel in advanced and metastatic soft tissue sarcoma.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Study type</th>
<th>Histology</th>
<th>RR</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hensley et al, 2002[38]</td>
<td>34</td>
<td>Phase II</td>
<td>Leiomyosarcoma</td>
<td>53%</td>
<td>PFS 5.6 months OS 17.9 months</td>
</tr>
<tr>
<td>Leu et al, 2004[39]</td>
<td>35</td>
<td>Retrospective</td>
<td>All types</td>
<td>43%</td>
<td>TTP 6.7 months</td>
</tr>
<tr>
<td>Bay et al, 2006[40]</td>
<td>133</td>
<td>Retrospective</td>
<td>All types</td>
<td>18.4%</td>
<td>Median OS 12.1 months</td>
</tr>
<tr>
<td>Maki et al, 2007[41]</td>
<td>73</td>
<td>Randomised</td>
<td>All types</td>
<td>16%</td>
<td>Median PFS 6.2 months Median OS 17.9 months</td>
</tr>
<tr>
<td>Ebeling et al, 2008[42]</td>
<td>34</td>
<td>Retrospective</td>
<td>All types</td>
<td>15%</td>
<td>PFR at 3 months 38%</td>
</tr>
<tr>
<td>Seddon et al, 2009[43]</td>
<td>44</td>
<td>Phase II</td>
<td>Leiomyosarcoma</td>
<td>27%</td>
<td>PFR at 3 months 68.9% PFR at 6 months 57.8%</td>
</tr>
</tbody>
</table>

RR – response rate; PFS – progression-free survival; OS – overall survival; TTP – time to progression; PFR – progression free rate

These results supported the previous study, and fuelled further interest in the regimen. A multi-centre randomised phase II study was carried out by the Sarcoma Alliance for Research through Collaboration (SARC) comparing gemcitabine and docetaxel with gemcitabine alone\[41\]. One hundred and twenty two patients with relapsed metastatic soft tissue sarcoma received a median of 4 cycles of chemotherapy. The primary end point (complete or partial response, or stable disease after more than 24 weeks) was reached by 13 patients (27%) receiving gemcitabine, and 23 patients (32%) receiving gemcitabine and docetaxel. The RECIST partial response rate for patients receiving gemcitabine-docetaxel (16%; 12 of 73) was greater than the partial response rate for gemcitabine alone (8%; four of 49). Moreover, a number of patients who did not have objective responses had prolonged stable disease (18% in the gemcitabine arm, 15% in the combination arm), lending support to the concept of stable disease as an important clinical end point for patients with metastatic soft tissue sarcomas. Median PFS was 6.2 months for gemcitabine and docetaxel versus 3.0 months for gemcitabine alone. Median OS was 17.9 months with gemcitabine-docetaxel versus 11.5 months with gemcitabine. These results mirror those of the phase II study of Hensley et al\[38\], albeit in all soft tissue sarcoma subtypes, and are impressive given the size and multi-centre nature of the study. They confirm the use of gemcitabine and docetaxel as an effective salvage therapy for doxorubicin- and/or ifosfamide-refractory patients.

Two further studies have contributed information. A single centre retrospective series has been published of 34 patients with soft tissue sarcomas of all types treated with gemcitabine and docetaxel. Partial responses were seen in 15% of patients, with a further 13 (38%) achieving stable disease, giving an overall clinical benefit rate of 53%. The progression free survival rate at 3 months was 38%\[42\]. Finally, a prospective UK phase II study using gemcitabine and docetaxel in leiomyosarcoma in the first line setting has been carried out by University College Hospital and the Royal Marsden Hospital\[43\]. Forty-four patients with locally advanced or metastatic leiomyosarcoma were treated. Partial responses were observed in 12 (27%), stable disease in 21 (48%), and progressive disease in 11 (25%). Median OS and PFS were 578 (95% CI 131-322) and 216 (95% CI 24–169) days.
Progression free rates at 3 and 6 months were 68.9% (95% CI 55.1-82.7%) and 57.8% (95%CI 43.1-72.5%).

These data taken together have led to the adoption by the world-wide sarcoma treating community of gemcitabine and docetaxel as an additional useful regimen for relapsed disease in soft tissue sarcoma. However, there is a need to better define where the combination fits into the current soft tissue sarcoma treatment algorithm, and specifically, whether gemcitabine and docetaxel represents a combination that will produce longer progression free survival than the current standard of care doxorubicin for first line treatment of locally advanced or metastatic soft tissue sarcoma, with acceptable toxicity and good quality of life. Progression-free survival is now recognised as a valid endpoint in the evaluation of new drugs or regimens in soft tissue sarcoma[44]. The proposed trial aims to answer these questions by comparing gemcitabine and docetaxel with doxorubicin in a prospective randomised phase III trial in this patient population.

The precise administration of the gemcitabine and docetaxel appears to be crucial to the efficacy of the regimen. The optimal sequence has been evaluated in vitro in sarcoma and breast cell lines[38]. The addition of docetaxel to gemcitabine resulted in a significant decrease in the IC50 values for gemcitabine. In contrast, docetaxel followed by gemcitabine was mostly antagonistic in the sarcoma cell lines. The rate of gemcitabine infusion also appears to be vital to maximising its anti-tumour activity. The accumulation of intracellular gemcitabine triphosphate, the active form of the drug, is saturated at dose rates that produce plasma gemcitabine concentrations of 10–20 μmol/L. Comparison of gemcitabine plasma levels achieved with infusion rates of 90 minutes and the more standard 30 minutes has shown that while the mean area under the curve did not differ, the duration of the plasma gemcitabine concentration remaining above the 10 μmol/L threshold was 50% longer with the 90 minute infusion as compared with the 30 minute bolus[38].

The previous studies of the combination have used eight cycles of gemcitabine and docetaxel at doses of 900 mg/m2 (days 1 and 8) and 100 mg/m2 (day 8) respectively, with a 25% dose reduction for patients who had had previous pelvic radiotherapy. However, in the largest study by Maki et al[41], concerns were raised about the toxicity of the regimen at full dose. Specifically, 46% of patients required at least 1 dose reduction. Toxicities included CTCAE v3.0 grade 3 or 4 thrombocytopenia in 40% (15% requiring platelet transfusions), febrile neutropenia in 6%, grade 3 fatigue in 25%, and myalgias and muscle weakness in 25%. More than 40% of patients stopped chemotherapy for a variety of non-haematological toxicities within 6 months of starting chemotherapy, despite dose reductions. The investigators concluded that ‘the dose and schedule are too high for long term use’. In the UK phase II study carried out at University College Hospital and the Royal Marsden Hospital[43], we also found significant toxicity with the full doses and 8 cycle schedule used by Hensley et al[38] and Maki et al[41]. Four patients came off study due to toxicity, two due to pulmonary toxicity (pneumonitis), one due to an anaphylactic reaction to docetaxel, and one due to severe fatigue. CTCAE v3.0 grade 3 – 4 dyspnoea occurred in 16% of patients, anaemia in 17%, and fatigue in 30%. One patient died of sepsis. Thirty four patients achieved stable disease or better, while ten patients experienced progressive disease (and hence stopped treatment early). Responders received 2 – 8 cycles, with only 26% of responders receiving the full eight cycles, and 32% receiving 6 cycles, such that 42% did not receive even six cycles. Twenty five percent of patients required a dose reduction. On the basis of these findings, the current protocol uses 6 cycles of gemcitabine and docetaxel, at the reduced dose of 675mg/m2 (days 1 and 8) and 75 mg/m2 (day 8), respectively, with the aim of making the combination tolerable as a palliative regimen, with toxicity of an equivalent grade of severity as experienced with doxorubicin.
2.2. Proposed Trial

2.2.1. Trial objectives

The objective of the trial is to compare doxorubicin, the current standard treatment for patients with metastatic soft tissue sarcoma, with gemcitabine and docetaxel, a new combination chemotherapy regimen in this tumour type. The trial will compare progression free survival associated with the two treatments, but will also compare the relative toxicity experienced by patients, and their quality of life. A health economic analysis will be performed to compare the cost-effectiveness of the two treatments. A translational study will be undertaken to investigate the pharmacogenomic profiles of patients, to evaluate if there is a correlation between a pharmacogenomic profile, and both the relative toxicities experienced and response to treatment.

Primary objective

- To compare the efficacy and effectiveness of gemcitabine and docetaxel with that of doxorubicin

Secondary objectives

- To compare the toxicity observed with the two regimens
- To compare the quality of life of patients treated with gemcitabine and docetaxel with those treated with doxorubicin
- To compare the cost-effectiveness of the two regimens
- To investigate the influence of pharmacogenomic profiles of patients on disease response and treatment toxicity of the two regimens

2.2.2. Primary and secondary endpoints

Primary endpoint

- Proportion of patients alive and progression free at 24 weeks after the date of randomisation

Secondary endpoints

- Proportion of patients alive and progression free at 12 weeks after the date of randomisation
- Median progression-free survival
- Overall survival
- Time to progression
- Time from start of treatment to progression or death (whichever occurs first)
- Objective response rate assessed prospectively by RECIST version 1.1 (Appendix 2)
- Objective response rate assessed retrospectively by Choi criteria (UCLH only)
- Adverse events defined by NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03
- Quality of life evaluation measured in >18 years by EORTC QLQ-C30 and FA-13, and in 13 – 18 years by PedsQL Quality of Life Inventory, Cancer Module and Multidimensional Fatigue Scale (Appendix 3)
- Health economic evaluation including EQ-5D & EQ-5D-Y (Appendix 4)
2.2.3. **Trial design**

This is a prospective randomised controlled phase III trial which aims to compare the combination of gemcitabine and docetaxel with the current standard treatment, single agent doxorubicin, when used as first line treatment in locally advanced unresectable or metastatic soft tissue sarcoma. Patients will be randomised to receive up to six cycles of either chemotherapy regimen, and will be assessed for trial endpoints every 12 weeks until disease progression. Response will be assessed prospectively by RECIST version 1.1, and retrospectively by Choi criteria in an exploratory analysis[45]. Quality of life will be assessed prospectively at four time points during the trial. An analysis of the comparative health economic impact of the two regimens will be performed. Patients will be stratified according to age (≤18 years, >18 years) and histological subtype as follows:

- **Uterine leiomyosarcoma**
- **Synovial sarcoma**
- **Pleomorphic sarcoma** (including pleomorphic liposarcoma, pleomorphic rhabdomyosarcoma, sarcoma not otherwise specified [NOS], myxofibrosarcoma, malignant fibrous histiocytoma)
- **Other types of eligible soft tissue sarcomas** (including non-uterine leiomyosarcoma, myxoid liposarcoma, de-differentiated liposarcoma)

This stratification is because a previous study has indicated differential responses for these groups[41]. Patients will be randomised with UCL CTC prior to starting treatment and after verification of eligibility criteria. The trial will include a screening visit, assessments while on treatment, and post-treatment follow-up visits. During the treatment phase, patients will undergo regular assessments for safety and clinical response.

2.2.4. **Translational research**

A translational research component to the trial will investigate the influence of pharmacogenomics on response and toxicity in patients treated with the two chemotherapy regimens.

2.2.5. **Trial treatment**

Patients will be randomised to receive either of the following treatments:

- **Standard arm** – doxorubicin 75 mg/m² intravenously (i.v.) on day 1 every three weeks for up to 6 cycles
- **Experimental arm** – gemcitabine 675 mg/m² i.v. administered over 90 minutes on days 1 and 8, docetaxel 75 mg/m² i.v. administered over 60 minutes after gemcitabine, on day 8 every three weeks for up to 6 cycles

Cycles will be repeated every 21 days for up to six cycles unless the patient experiences unacceptable toxicity, progressive disease, or withdraws consent.

Refer to section 7.3 (Trial Treatment Details) for full details of trial treatment.
2.3. Trial activation

UCL CTC will ensure that all trial documentation has been reviewed and approved by all relevant bodies and that the following have been obtained prior to activating the trial:

- Research Ethics Committee approval
- Clinical Trial Authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA)
- ‘Adoption’ into NIHR portfolio
- NHS permission
- Adequate funding for central coordination
- Confirmation of sponsorship
- Adequate insurance provision

In addition, the following must have been obtained prior to the trial being activated in Switzerland:

- a signed International Country Coordinating Centre Agreement between UCL CTC and the CCC
- Clinical Trial Authorisation from Swissmedic
3. Selection of Sites/Site Investigators

3.1. Site selection
In this protocol trial “Site” refers to the hospital or site where trial-related activities are conducted.

Sites must be able to comply with:

- Trial treatments, imaging, clinical care, follow up schedules and all requirements of the trial protocol
- Requirements of the Research Governance Framework and the Medicines for Human Use (clinical trials) Act (SI 2004/1031 and all amendments)
- Data collection requirements, including adherence to CRF submission timelines as per section 9.0
- Sample collection, processing and storage requirements
- Monitoring requirements, as outlined in the protocol (section 12 and trial monitoring plan)

Non-UK sites must comply with all local regulations governing clinical trials.

3.1.1. Selection of Principal Investigators and other investigators at sites
UK Sites must have an appropriate Principal Investigator (PI), i.e. a consultant oncologist authorised by the site, ethics committee and regulatory authority to lead and coordinate the work of the trial on behalf of the site. The PI must be a core or extended member of the designated Sarcoma Network MDT.

Other investigators at sites wishing to participate in the trial must be medical doctors and be trained and approved by the PI. The PI must ensure that all other investigators have adequate knowledge and experience to perform the duties delegated to them.

Non-UK Sites must have an appropriate Principal Investigator (PI), i.e. a consultant oncologist authorised by the site, ethics committee and regulatory authority to lead and coordinate the work of the trial on behalf of the site.

3.1.2. Training requirements for site staff
All site staff must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log.

CVs for all staff must be kept up-to-date, signed and dated and copies held in the Investigator Site File (ISF). An up-to-date, signed copy of the CV for the PI must be forwarded to UCL CTC upon request.

In the UK GCP training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing Institution, or 2 yearly where the Institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials. For non-UK sites the requirement for and frequency of GCP training will be dictated by that country’s policy on training.
3.2. Site initiation and activation

3.2.1. Site initiation

Before a UK site is activated, the UCL CTC trial team will arrange a site initiation, with the site which the PI, the pharmacy lead and site research team must attend. The site will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked.

Site initiation will be performed at each site by a site visit or teleconference.

For non-UK sites, Site initiation will be carried out by the CCC and will be carried out by a site visit or teleconference.

3.2.2. Required documentation

For UK sites:

The following documentation must be submitted to UCL CTC prior to a site being activated by UCL CTC trial team:

- Trial specific Site Registration Form (identifying relevant local staff)
- All relevant institutional approvals (e.g. local NHS permission)
- A completed site delegation log, signed and dated by the PI
- A copy of the PI’s current CV, signed and dated

The UCL CTC trial team will ensure that:

- If the site was not included in the original CSP application, the Part C is updated and the R&D form is resubmitted to CSP (who will notify the lead CLRN of the new site)
- An SSI form is transferred to the site via IRAS
- If the site was not included on the original REC application, a substantial amendment is submitted to and approved by the REC
- If the site was not included on the original CTA application, the CTA is updated and the MHRA notified at the next substantial amendment to the MHRA.

In addition, the following agreements must be in place:

- A signed Clinical Trial Site Agreement (CTSA) between the Sponsor and the relevant institution (usually a NHS Trust)

For non-UK Sites:

The following documentation must be submitted to the CCC for forwarding to UCL CTC prior to a site being activated by UCL CTC trial team:

- Trial specific Site Registration Form (identifying relevant local staff)
- All relevant institutional approvals (e.g. local ethics committee approval)
- A completed site delegation log, initialled and dated by the PI
- A copy of the PI’s current CV, signed and dated
- A signed International Clinical Trials Site Agreement (ICTSA) between the CCC and the relevant institution

3.2.3. Site activation letter

Once the UCL CTC trial team has received all required documentation and the site has been initiated, a site activation letter will be issued to the PI, at which point the site may start to recruit patients (N.B. no trial-related activities may be performed prior to site activation).
Once the site has been activated by UCL CTC, the PI is responsible for ensuring:

- Adherence to the most recent version of the protocol
- All relevant site staff are trained in the protocol requirements
- Appropriate recruitment and medical care of patients in the trial
- Timely completion and return of CRFs (including assessment of all adverse events)
- Prompt notification and assessment of all serious adverse events
- That the site has facilities to provide **24 hour medical advice** for trial patients
4. Informed consent

4.1. Informed consent in adults

Sites are responsible for assessing a patient’s capacity to give informed consent.

Sites must ensure that all patients have been given the current approved version of the patient information sheet(s), are fully informed about the trial and have confirmed their willingness to take part in the trial by signing the current approved consent form.

Sites in the UK must assess a patient’s ability to understand verbal and written information in English and whether or not an interpreter would be required to ensure fully informed consent. If a patient requires an interpreter and none is available, the patient should not be considered for the trial.

The PI, or, where delegated by the PI, other appropriately trained site staff, are required to provide a full explanation of the trial and all relevant treatment options to each patient prior to trial entry. During these discussions, the current approved patient information sheet(s) for the trial should be discussed with the patient. A minimum of 24 hours should be allowed for the patient to consider and discuss participation in the trial. However, in order to prevent unnecessary return visits patients may consent on the same day as being given the information sheet, provided the member of staff taking consent is satisfied that the patient understands the trial and implications. A member of the research team at the hospital must then phone the patient a few days later to confirm that they are still willing to participate in the trial. Written informed consent on the current approved version of the consent form for the trial must be obtained before any trial-specific procedures are conducted. This discussion and consent process must be documented in the patient’s medical notes.

Site staff are responsible for:

- Checking that the correct approved versions of the patient information sheets and consent form are used;
- Checking that information on the consent form is complete and legible;
- Checking that the patient has completed/initialled all relevant sections and signed and dated the form;
- Checking that an appropriate member of staff has countersigned and dated the consent form to confirm that they provided information to the patient;
- Checking that an appropriate member of staff has made dated entries in the patient’s medical notes relating to the informed consent process (i.e. information given, consent signed etc.);
- Giving the patient a copy of their signed consent form, patient information sheet, patient diary and patient contact card;
- Following randomisation: adding the patient trial number to all copies of the consent form, which should be filed in the patient’s medical notes and investigator site file.

The right of the patient to refuse to participate in the trial without giving reasons must be respected. All patients are free to withdraw at any time (see section 13 – withdrawal of patients).

Non-UK Sites must consent patients to the trial according to local practice and regulatory and/or ethical requirements.
4.2. Additional information for obtaining informed consent in teenagers (UK only)

The person with parental responsibility or legal guardianship of the child must be informed of all aspects of the trial. The child must also be informed about the trial to the extent compatible with their understanding. The same information must be provided to children of all ages, however the level of detail is age appropriate. Information sheets are available for patients aged 13 – 15 years old. There are also information sheets available for parents/legal guardians.

A minimum of twenty-four hours should be allowed for the child and parent/legal guardian to consider and discuss participation in the trial. However, in order to prevent unnecessary return visits children and parents/legal guardians may consent on the same day as being given the information sheet, provided the member of staff taking consent is satisfied that they understand the trial and implications. A member of the research team at the hospital must then phone the child and parent/legal guardian a few days later to confirm that they are still willing to participate in the trial. This process must be documented clearly in the child’s medical notes.

If capable the child may give assent by personally signing and dating the informed consent form, in addition to the parent or legal guardian.

A child’s refusal to participate in the trial must be respected.

n.b. sites in Switzerland will not be entering patients aged <18 years of age.
5. Selection of patients

5.1. Pre-randomisation evaluation

Patients must have proven histological confirmation of soft tissue sarcoma prior to trial entry. The following assessments or procedures are required to evaluate the suitability of patients for the trial. Any non-routine procedures or investigations must not be performed prior to informed consent being taken.

Within 14 days prior to randomisation:

- Full medical history including demographics (age, gender)
- Cancer signs and symptoms
- Clinical examination, height and weight
- Assessment of performance status by the WHO scale (Appendix 5)
- Blood tests for haematology (haemoglobin, white cell count, neutrophil count and platelets) and biochemistry (sodium, potassium, urea, creatinine, bilirubin, ALP, AST or ALT, albumin). These may be carried out at a hospital other than the Trial Site as all investigations would normally be part of routine care
- Pathology samples available for central review (see section 8.7 (central pathology review) for details)
- Informed consent
- Pregnancy test (urine or blood) in females of child bearing potential

Within 21 days prior to randomisation:

- Baseline documented disease assessment with CT or MRI scanning of tumour lesions

Within 12 weeks prior to randomisation:

- Ejection fraction measured according to local practice (Echocardiogram or MUGA).

The following is not required for evaluation of eligibility but should be carried out within 14 day prior to randomisation:

- Quality of life assessment (Appendix 3)

This QoL assessment may be carried out after randomisation, however, it must be completed prior to informing the patient of their treatment allocation.

5.2. Screening Log

A screening log must be maintained by the site and kept in the Investigator Site File. This must record each patient screened for the trial and the reasons why they were not randomised if this is the case. The log must be sent to UCL CTC (or via the CCC for non-UK sites) when requested with patient identifiers removed prior to sending.
5.3. **Patient eligibility**

There will be no exception to the eligibility requirements at the time of randomisation. Ensuring patient eligibility is the responsibility of the PI or other delegated Investigator(s). Queries in relation to the eligibility criteria must be raised with UCL CTC prior to calling/faxing for randomisation. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria applies.

5.3.1. **Patient inclusion criteria**

- Locally advanced or metastatic soft tissue sarcoma, incurable by surgery or radiotherapy
- Histological confirmation of high grade disease (Trojani grade 2 or 3 sarcoma)
- Prior to trial enrolment, patients must have evidence of disease progression. Disease progression is defined as radiological progression when comparing current imaging to a prior disease assessment carried out within the previous 6 months. Some patients may present with evidence of clinical progression for whom there is concern regarding treatment delays incurred by awaiting radiological disease progression prior to trial entry – these cases must be discussed with the Chief Investigator to determine eligibility
- No prior chemotherapy regimen for sarcoma and no prior doxorubicin containing regimen for any previously treated cancer.
- WHO performance status 0 – 2
- Age ≥13 years
- Histological material available for central review (see section 8.7)
- Measurable disease evaluable by RECIST criteria version 1.1. New lesions occurring in previously irradiated fields, and progression of previously irradiated lesions, will be eligible
- Life expectancy of at least 3 months
- Adequate organ function:
  - Neutrophils ≥1.0 × 10^9/L
  - Platelets ≥100 × 10^9/L
  - Bilirubin ≤1.5 x upper limit of normal (ULN)
  - AST or ALT ≤3.0 x ULN
  - ALP ≤3.0x ULN, if ALP ≥ 3.0 x ULN, patients can be entered if this is shown to be the bone isoenzyme.
  - Measured or calculated creatinine clearance ≥30 ml/min
  - Ejection fraction (measured according to local practice) within normal limits for the site
- Patients to agree to use contraception for the duration of the trial, where applicable (see section 5.3.3)
- Able to complete quality of life questionnaires
- Able to give informed consent

5.3.2. **Patient exclusion criteria**

- Soft tissue sarcoma of the following types:
  - Alveolar soft part sarcoma
  - Gastrointestinal stromal tumour
  - Ewing’s sarcoma family of tumours
  - Alveolar or embryonal rhabdomyosarcoma
  - Desmoplastic small round cell tumour
  - Extra-skeletal myxoid chondrosarcoma
- Dermatofibrosarcoma protruberans
- Malignant mixed mesodermal tumour/carcinosarcoma of the uterus
- Smooth muscle tumours of uncertain malignant potential (STUMP)
- Known active/uncontrolled brain metastases
- Grade 3 or 4 peripheral neuropathy
- Active uncontrolled infection
- Prior history of malignancy other than sarcoma, except for basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, breast or prostate, and unless the patient has been free of malignancy for a period of 3 years prior to first dose of trial drug
- Women who are pregnant or lactating
- Any serious and/or unstable pre-existing medical, psychiatric or other condition that could interfere with patient safety or obtaining informed consent

5.3.3. Pregnancy, Birth Control and Infertility

Pregnancy Testing
All women of childbearing potential who are at risk of becoming pregnant must undergo a pregnancy test prior to randomisation.

A woman of childbearing potential is a sexually mature woman (i.e. any female who has experienced menstrual bleeding) who has not:
- undergone a hysterectomy or bilateral oophorectomy/salpingectomy
- been postmenopausal for 24 consecutive months (i.e. who has had menses at any time in the preceding 24 consecutive months without an alternative medical cause)

Contraceptive Advice
Due to the effects of doxorubicin, gemcitabine and docetaxel during pregnancy and lactation, patients must consent to use one of the following acceptable methods of contraception during and for at least 6 months after last treatment administration.

Acceptable methods of effective contraception for this trial are:
- Established use of oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository). The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted:
  - Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore the use of additional spermicides does confer additional theoretical contraceptive protection.
  - However, spermicides alone are inefficient at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and must not be used alone.
- Male sterilisation (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients, the vasectomised male partners must be the sole partner for that patient. Please note that sterilisation is not usually regarded as completely reliable enough on its own to ensure that pregnancy can never occur.
- Absolute and continuous abstinence: When this is in line with the preferred and usual lifestyle of the patient. Please note that periodic abstinence (e.g. calendar, ovulation,
symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Male patients aged ≥ 16 years with partners of childbearing potential or partners who are pregnant must consent to use acceptable methods of contraception during and for at least 6 months after last treatment administration.

Male patients aged 13 – 15 years must be advised on the use of contraception precautions during and for at least 6 months after treatment if deemed applicable.

Female patients must be advised of the risks to a foetus if they become pregnant.

Male patients should be provided information on sperm banking prior to treatment due to the possibility of treatment-related infertility.

If a patient or the partner of a male trial patient becomes pregnant during the trial UCL CTC must be informed immediately (See section 10.0 (Pharmacovigilance) for details on the reporting procedure).

Patients must not breast-feed during the trial due to the possible concentration of these drugs in human milk and potential adverse effects to a baby.
6. Randomisation procedures
Patient randomisation will be undertaken centrally at UCL CTC and this must be performed prior to commencement of any trial treatment.

Treatment allocation will be by minimisation, incorporating a random element and will be carried out by computer at UCL CTC. Patients will be stratified by:

- Age (≤18 or >18 years)
- Histological subtype (uterine leiomyosarcoma, synovial sarcoma, pleomorphic sarcoma, and other eligible sarcomas)

6.1. Randomisation
Following pre-treatment evaluations (as detailed in section 5.1), confirmation of eligibility and consent of a patient at a site the randomisation form must be fully completed prior to telephoning UCL CTC. The eligibility criteria will be reviewed during the randomisation telephone call using the same form at UCL CTC.

A trial number and treatment allocation will be assigned for the patient during the call and must be recorded at site by the caller.

For UK sites UCL CTC will fax confirmation of the patient’s inclusion in the trial, their trial number and treatment allocation to the main contact and pharmacy. Case report forms will be sent to the main contact at site.

For non-UK sites UCL CTC will email confirmation of the patient's inclusion in the trial, their trial number and treatment allocation to the main contact and the CCC.

| Randomisation telephone number: | +44 (0)20 7679 9880 |
| Randomisation fax number: | +44 (0)20 7679 9871 |
| Office hours: | 09:00 to 17:00 Monday to Friday (UK time) |

Once a patient has been randomised onto the trial they must be provided with the following:

- A copy of their signed consent form and patient information sheet
- UK patients only: A patient diary. Patients should be asked to use this to record any adverse events or symptoms and also non-hospital medical visits. Patients must be reminded to bring this with them every time they visit the hospital.
- UK patients only: A patient contact card. Site on-call contact details for out-of-hours medical care must be added to this card and patients advised to carry this with them at all times while on the trial
7. Trial Treatment

7.1. Treatment summary

For the purpose of this protocol, the IMPs are doxorubicin, gemcitabine and docetaxel. Patients will be randomised to receive one of following treatments:

- Standard arm – doxorubicin 75 mg/m² i.v. day 1 every three weeks for up to 6 cycles
- Experimental arm – gemcitabine 675 mg/m² i.v. days 1 and 8, docetaxel 75 mg/m² i.v. day 8 every three weeks for up to 6 cycles

7.2. Summary Treatment Schedule

<table>
<thead>
<tr>
<th>Day</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
<th>Cycle 5</th>
<th>Cycle 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Arm</td>
<td></td>
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<tr>
<td>Doxorubicin 75 mg/m² iv</td>
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<td>Experimental Arm</td>
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<tr>
<td>Gemcitabine 675 mg/m² iv</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>Docetaxel 75 mg/m² iv</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
</tr>
</tbody>
</table>

Whilst not mandated, it is strongly recommended that all patients start treatment within 14 days of randomisation.

7.3. Trial Treatment Details

Dose will be calculated according to body surface area. Dose capping may be applied according to local policy.

**Doxorubicin**

In the UK doxorubicin is licensed for use as an anticancer cytotoxic agent.

For all sites, doxorubicin will be supplied from hospital stock and will be administered at a dose of 75 mg/m² on day 1 of a 3 week cycle. Doxorubicin should be reconstituted and administered according to local institutional guidelines. Dose banding according to local institution policy is acceptable, to a variance of +/- 5%[46]. Antiemetics should be administered according to local institutional policy for each site; for example, dexamethasone 20 mg iv and ondansetron 8mg iv prior to doxorubicin, and dexamethasone 4mg bd orally for 3 days and domperidone 20 mg qds orally for 5 days after chemotherapy.

**Gemcitabine and docetaxel**

In the UK gemcitabine is licensed for use in breast, lung, ovarian and pancreatic cancer. It is not licensed for use in soft tissue sarcoma.

For all sites, gemcitabine will be provided from hospital stock and should be reconstituted according to local institutional practice. Gemcitabine will be administered at a dose of 675 mg/m² on day 1 as a 90 minute infusion, and on day 8 at a dose of 675mg/m² as a 90 minute infusion prior to docetaxel. Dose banding according to local institution policy is acceptable, to a variance of +/- 5%[46]. **The infusion duration of gemcitabine should not be shortened as this duration is associated with optimal pharmacokinetics. Additionally, gemcitabine will always be administered prior to docetaxel, and this sequencing should not be reversed, as it has been shown in vitro to contribute to the efficacy of the regimen**[39].
In the UK docetaxel is licensed for use in breast cancer, non-small cell lung cancer, hormone refractory prostate cancer, gastric adenocarcinoma, and head and neck cancer. It is not licensed for use in soft tissue sarcoma.

For all sites, docetaxel will be provided from hospital stock and will be administered at a dose of 75mg/m$^2$ as an intravenous infusion over 60 minutes. Dose banding according to local institution policy is acceptable, to a variance of +/- 5%\citep{46}. Patients should be premedicated with dexamethasone 8 mg bd orally on the day prior to receiving docetaxel (day 7), which will be continued on days 8 and 9. After 2 cycles without hypersensitivity reaction, the dexamethasone dosing schedule may be adjusted at the discretion of the treating investigator. However, all patients should receive some form of corticosteroid medication prior to each docetaxel infusion.

Anti-emetics should be administered according to local institutional policy for these drugs at each site. For example, metoclopramide 20mg i.v. is administered immediately prior to the gemcitabine on day 1, and ondansetron 8 mg iv prior to gemcitabine and docetaxel on day 8, in addition to the oral dexamethasone given with the docetaxel (see above).

### 7.3.1. Criteria for administration of chemotherapy on day 1 of each cycle

Blood tests should be carried out prior to day 1 (usually ≤48 – 72 hours), as per local practice. The following criteria must be met:

- Absolute neutrophil count ≥ 1.0 x 10$^9$/L
- Platelet count ≥ 100 x 10$^9$/L
- Total bilirubin ≤ 1.5 x ULN
- ALT or AST ≤ 3.0 x ULN

### 7.3.2. Criteria for administration of chemotherapy on day 8 of each cycle

Blood tests should ideally be carried out ≤ 48 – 72 hours prior to chemotherapy. To receive day 8 of gemcitabine and docetaxel, the following criteria must be met:

- Absolute neutrophil count ≥ 1.0 x 10$^9$/L
- Platelet count ≥ 75 x 10$^9$/L

### 7.3.3. Pharmacy responsibilities

All pharmacy aspects of the trial at participating sites are the responsibility of the Principal Investigator, who may delegate this responsibility to the local pharmacist, or other appropriately qualified personnel, who will be the Pharmacy Lead. The delegation of duties must be recorded on the site staff delegation log.

The IMPs to be used in this trial must be stored, handled and dispensed as detailed in the Summary of Product Characteristics, supplied handling instructions, or according to locally agreed guidelines (a copy of which must be submitted to UCL CTC prior to site activation).

The IMPs are to be supplied from commercial hospital stock as detailed in the Pharmacy file. In the UK patient specific labels must be added by the site on dispensing. UCL CTC will provide the required text.

For non-UK sites labels must be applied according to the terms of the Clinical Trial Authorisation received from that country’s regulatory authority.

### 7.3.4. Drug accountability

The Pharmacy Lead will ensure that appropriate records are maintained.
These records must include accountability for each drug detailing dispensing. Template accountability forms will be provided, however sites may be permitted to use their own drug accountability records providing the same information is captured as a minimum. Such in-house records must be submitted to UCL CTC for review and authorisation for use prior to patient enrolment.

Copies of completed drug accountability logs must be submitted to UCL CTC for all trial patients following completion of/withdrawal from treatment or upon request. Also refer to section 12.2 (Central Monitoring).

7.4. **Dose modifications**

Adverse events will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

7.4.1. **Doxorubicin**

Doxorubicin chemotherapy is a standard regimen, and as such it is intended that adverse events should be managed at the discretion of local investigators according to local guidelines. Suggested management, as guidance only, is given below.

**Haematological toxicity**

**Thrombocytopenia**

If platelet count is <100 x 10⁹/L, delay chemotherapy for a week or until resolution to ≥100 x 10⁹/L. If treatment is delayed for more than 2 weeks, then the patient should be withdrawn from the trial.

**Neutropenia**

If neutrophil count is <1.0 x 10⁹/L, delay chemotherapy for a week or until resolution to ≥1.0 x 10⁹/L. If treatment is delayed for more than 2 weeks, then the patient should be withdrawn from the trial.

**Non-haematological toxicity**

**Febrile neutropenia**

If febrile neutropenia occurs, GCSF could be introduced. Alternatively, or if further episodes of febrile neutropenia occur after introduction of GCSF, doxorubicin dose can be modified according to the table below for subsequent cycles. The decision to administer GCSF will be at the discretion of the treating clinician and should be given according to local institutional policy.

**Cardiotoxicity**

Further measurements of LVEF by MUGA scan or echocardiography during treatment will be performed according to local institutional rules, acknowledging that some sites may not perform further measurements unless there is clinical concern. If LVEF <45% or 20% decrease, consideration should be given to discontinuing treatment.

**Other non-haematological toxicities**

For grade 3 or 4 non-haematological toxicities delay doxorubicin for a week, or until the toxicity is ≤ grade1. If treatment is delayed for >3 weeks the patient should be withdrawn from the trial.

**Dose modifications**

For a patient requiring a dose reduction for toxicity as described above, dose modifications may be made according to local guidelines, or according to the following suggested schedule:
Doxorubicin 75 mg/m²

<table>
<thead>
<tr>
<th>Reduction</th>
<th>Dose Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st reduction</td>
<td>20% (60 mg/m²)</td>
</tr>
<tr>
<td>2nd reduction</td>
<td>33% (50 mg/m²)</td>
</tr>
<tr>
<td>3rd reduction</td>
<td>Stop treatment</td>
</tr>
</tbody>
</table>

**Treatment overdose**
Recommendations for managing treatment overdoses as stated in the SPC for doxorubicin is given below, however, sites may follow local procedures as appropriate.

Acute overdose with doxorubicin will result in gastrointestinal toxic events and generally appears early after drug administration. Most patients recover from this within three weeks.

Delayed cardiac failure may occur up to six months after the overdosage. Patients should be observed carefully and should signs of cardiac failure arise, be treated along conventional lines.

### 7.4.2. Gemcitabine and docetaxel

**Haematological toxicity**

**Thrombocytopenia**
If pre-chemotherapy platelet count is <100 x 10⁹/L, delay chemotherapy for one week or until resolution to ≥100 x 10⁹/L.

If the patient is delayed at day 8, but toxicity has resolved sufficiently by day 15, the gemcitabine and docetaxel can be administered but with a dose reduction as indicated in the table below for all subsequent cycles. If treatment is delayed for more than 2 weeks, then the patient should be withdrawn from the trial.

**Neutropenia**
If neutrophil count is <1.0 x 10⁹/L on day 1, delay chemotherapy for one week or until resolution to ≥1.0 x 10⁹/L.

If the patient is delayed at day 8, but toxicity has resolved sufficiently by day 15, the gemcitabine and docetaxel can be administered but with a dose reduction as indicated in the table below for all subsequent cycles. If treatment is delayed for more than 2 weeks, then the patient should be withdrawn from the trial.

**Non-haematological toxicity**

**Febrile neutropenia**
If febrile neutropenia occurs at any time during a treatment cycle, no further treatment will be administered during that cycle. Following an episode of febrile neutropenia, GCSF may be introduced for subsequent cycles. If further episodes of febrile neutropenia occur, the doses of both gemcitabine and docetaxel should be modified according to the table below for all subsequent cycles.

**Infection with grade 3 or 4 neutrophil count**
If a patient experiences any grade 3 or 4 infection with grade 3 or 4 neutrophil count during treatment, no additional anticancer agents will be administered during that cycle. Following an episode of infection with grade 3 or 4 neutrophil count, GCSF may be introduced for subsequent cycles. If further episodes occur, the doses of both gemcitabine and docetaxel should be modified according to the table below for all subsequent cycles.

**Neuropathy**
Patients who experience grade 2 neuropathy (motor or sensory) during a treatment cycle will have no further treatment during that cycle and for all subsequent cycles both the gemcitabine and docetaxel will be modified according to the table below.
Patients who experience grade 3 or 4 neuropathy (motor or sensory) at any time will be withdrawn from the trial.

**Pulmonary**
Patients who experience any grade pulmonary toxicity that is attributable to gemcitabine or docetaxel will have no further treatment during that cycle and for all subsequent cycles both the gemcitabine and docetaxel will be modified according to the table below for all subsequent cycles.

Any patient who experiences grade 3 pulmonary fibrosis or any grade 4 pulmonary toxicity at any time will be withdrawn from the trial.

**Hypersensitivity reactions**
Grade 1 or 2 allergic reactions/hypersensitivity that are attributable to docetaxel will be managed by interrupting the docetaxel infusion, decreasing the rate of infusion, and administration of chlorphenamine and/or additional corticosteroids. No dose reduction is required; however, pre-treatment with dexamethasone and chlorphenamine will be required for all subsequent cycles.

Patients who experience a grade 3 or 4 allergic reaction/hypersensitivity that are attributable to docetaxel will be withdrawn from the trial.

**Weight gain/fluid retention**
Grade 1 or 2 weight gain attributable to docetaxel administration does not require a dose reduction. Patients experiencing Grade 3 weight gain (>20% increase from baseline) attributable to docetaxel will be withdrawn from the trial.

**Other non-haematological toxicities**
For grade 3 or 4 non-haematological toxicities not listed above that are related to either gemcitabine or docetaxel, both agents should be withheld until the toxicity is ≤ grade 1. If the non-haematological toxicity resolves to ≤ grade 1 by day 35 of a treatment cycle, both agents may be restarted at a reduced dose as outlined in the table below. If the toxicity has not resolved to ≤ grade 1 by day 35 of a treatment cycle, the patient will be withdrawn from the trial.

**Dose Modifications**
For a patient requiring a dose reduction for toxicity as described above, the following dose modification should be used. Up to two dose modifications are permitted. If further toxicity is experienced, the patient should be withdrawn from the trial.

<table>
<thead>
<tr>
<th></th>
<th>Gemcitabine 675 mg/m²</th>
<th>Docetaxel 75mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; reduction</td>
<td>20% (540 mg/m²)</td>
<td>20% (60 mg/m²)</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; reduction</td>
<td>33% (450 mg/m²)</td>
<td>33% (50 mg/m²)</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; reduction</td>
<td>Stop treatment</td>
<td>Stop treatment</td>
</tr>
</tbody>
</table>

**Treatment overdose**
Recommendation for managing treatment overdoses as stated in the SPC for the trial treatments is given below, however, sites may follow local procedures as appropriate.

Gemcitabine: There is no known antidote for overdose of gemcitabine. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and receive supportive therapy, as necessary.

Docetaxel: There is no known antidote for docetaxel overdose. In case of overdose, the patient should be kept in a specialised unit and vital functions closely monitored. In cases of overdose, exacerbation of adverse events may be expected. The primary anticipated complications of overdose would consist of bone marrow suppression, peripheral
neurotoxicity and mucositis. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

7.5. Support medication
All details of support medication used during this trial are included in section 7.3 (Trial Treatment Details).

7.6. Clinical management after treatment discontinuation
If a patient withdraws consent or stops treatment due to adverse events, then further treatment will be at the discretion of the treating clinician.

Also refer to section 13 (Withdrawal of Patients) for further details regarding treatment discontinuation, patient withdrawal from trial treatment and withdrawal of consent to data collection.
8. Assessments

Whilst not mandated, it is strongly recommended that all patients start treatment within 14 days after randomisation.

Assessments will be carried out according to the following schedule:

<table>
<thead>
<tr>
<th></th>
<th>Pre-randomisation</th>
<th>Pre-treatment</th>
<th>TREATMENT</th>
<th>AFTER TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Within 12 weeks prior to randomisation</td>
<td>Within 21 days prior to randomisation</td>
<td>Within 14 days prior to start of treatment</td>
<td>Day 1 of each cycle</td>
</tr>
<tr>
<td>Medical history</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed consent</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer symptoms/toxicity assessment</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Clinical examination</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance status</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Vital signs</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient diary review (UK only)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUGA/ECHO1</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematology2</td>
<td></td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Biochemistry3</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>CT/MRI4</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of life assessment5</td>
<td></td>
<td>●</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Pathology review6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood sample for TR</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment for survival8</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1Repeat during treatment as clinically indicated.
2Haematology should include: haemoglobin, white cell count, neutrophil count, platelets
3Biochemistry should include: sodium, potassium, urea, creatinine, bilirubin, alkaline phosphatase, AST or ALT, albumin
4Scans must be performed at 12 and 24 weeks after randomisation, irrespective of relationship to chemotherapy cycle, ± 1 week. Additional CT/MRI scans between these time points may be performed at discretion of the local PI. After the 24 week scan, scans should be performed every 12 weeks until disease progression for up to 24 months after randomisation. Patients who have not progressed after 24 months should be scanned according to local practice.
5Quality of life assessments at weeks 12 and 24 will coincide with CT/MRI scans. The assessment at week 18 may be carried out by post.
6Pathology samples should be submitted for central review within 3 months of trial entry (UK patients only).
7This blood sample may be taken at any time after randomisation and prior to commencement of treatment.
8Assessment of survival may be done by telephone if more convenient.
9Pre-treatment assessments do not need to be repeated if carried out within 14 days prior to commencement of treatment as part of the Pre-randomisation evaluation.
8.1. Pre-treatment assessments
The following assessment should be carried out prior to commencing treatment.
- Blood sample for translational research

The following pre-randomisation assessments (section 5.1) do not need to be repeated if carried out within 14 days prior to treatment commencing:
- Cancer signs and symptoms
- Clinical examination, including weight
- Assessment of performance status by WHO
- Blood tests for haematology (haemoglobin, white cell count, neutrophil count and platelets) and biochemistry (sodium, potassium, urea, creatinine, bilirubin, ALP, AST or ALT, albumin). These may be carried out at a hospital other than the trial site as all investigations would normally be part of routine care.

8.2. Assessments during treatment
During treatment the patient should be clinically assessed prior to each cycle and the following assessments performed (preferably within 72 hours prior to day 1):
- Assessment of cancer symptoms and treatment toxicity
- Assessment of adverse events using CTCAE v4.03
- Review of patient diary (UK patients only)
- WHO Performance Status
- Full blood count (haemoglobin, white cell count, neutrophil count and platelets) (also day 8 of experimental arm). These may be carried out at a hospital other than the trial site and should be done prior to day 1 and day 8 (usually ≤48 – 72 hours), as per local practice.
- Biochemistry (sodium, potassium, urea, creatinine, bilirubin, alkaline phosphatase, AST or ALT, albumin). These may be carried out at a hospital other than the trial site if all investigations would normally be part of routine care
- Quality of life will be assessed at weeks 12 and 18 (± 2 weeks)
- Disease reassessment by CT or MRI must be carried out 12 weeks (+ 1 week) after randomisation

UK patients must be reminded to bring their diary with them to every hospital visit. Any adverse events recorded by a patient must be transferred into the patient’s notes and trial CRFs. A copy of the relevant pages of the diary should be taken and sent to UCL CTC with the treatment CRFs and a copy kept with the patients CRF at site.

8.3. Assessments on completion of treatment
The following assessments should be performed 30 days post last trial treatment administration for all patients:
- Assessment of cancer symptoms and treatment toxicity
- Assessment of adverse events using CTCAE v4.03
- Review of patient diary (UK patients only)
- WHO Performance Status
- Blood tests for haematology (haemoglobin, white cell count, neutrophil count and platelet count) and biochemistry (sodium, potassium, urea, creatinine, bilirubin, ALP, AST or ALT, albumin). These may be carried out at a hospital other than the trial site if all investigations would normally be part of routine care
- Quality of life will be assessed at week 24 (± 2 weeks)

With patients consent please retain the patient diary and forward a copy to UCL CTC (UK patients only).

8.4. **Assessments during follow up**

During follow up the patient should be regularly assessed according to local institutional guidelines until disease progression or death, and should include the following assessments:

- Disease reassessment by CT or MRI **must be performed 24 weeks (± 1 week) after randomisation**, and thereafter approximately every 12 weeks until disease progression for up to 24 months after randomisation. Patients who have not progressed after 24 months should be scanned according to local practice.
- Assessment for survival (may be carried out by telephone) every 12 weeks

Following disease progression, or after 24 months in the absence of progression, assessment of survival will be done every 12 weeks.

8.5. **Quality of life assessments and Health Economic analysis**

The aim of these assessments is to determine the impact of these two different chemotherapy regimens on quality of life, to give a better understanding from patients’ perspective the nature of treatment related side effects. Quality of life will be measured prior to the first cycle of chemotherapy (preferably prior to randomisation but certainly before the patient is informed of their treatment allocation), at 12, 18 and 24 weeks following randomisation (these time points have been chosen as providing data prior to, during, and after chemotherapy, and are also linked to the timing of assessment imaging to facilitate trial administration). Quality of life tools will be age-specific:

- >18 years – EORTC QLQ-C30 and FA-13 fatigue questionnaires and the EuroQoL EQ-5D
- 13 - 18 years – PedsQL questionnaires (Cancer module version 3.0, Paediatric Quality of Life Inventory version 4.0, Multidimensional Fatigue Scale standard version) and the EuroQoL EQ-5D-Y

8.6. **Radiological disease evaluation**

The primary endpoint of the trial is the proportion of patients who are alive and progression free 24 weeks after randomisation. A secondary endpoint of the trial is the proportion of patients who are alive and progression free at 12 weeks after randomisation. Accordingly, during treatment patients will be scanned at 12 and 24 weeks (± 1 week). It is essential that patients are scanned **on time** for the 12 and 24 week time points for the validity of the primary and secondary endpoints. Thereafter, patients should be scanned approximately 12 weekly until disease progression or death, for up to 24 months after randomisation. Patients who have not progressed after 24 months should be scanned according to local practice. Investigators may wish to perform additional scans (for example, after cycle 2) during treatment to clinically assess response to chemotherapy; this is at the discretion of the investigator.
Scheduling of imaging related to chemotherapy cycles is as follows:

| Cycle | Baseline Scan* | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 |
| Week  | Scan           | * | **| * | **|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Scan  |                |   |   |   |   |° |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

*baseline scan performed within 3 weeks prior to randomisation
*additional scans between baseline and 12 weeks may be performed at discretion of investigator
**mandatory

Existing data for the chemotherapy regimens indicate that median progression-free survival for doxorubicin is approximately 3 – 4 months, and for gemcitabine and docetaxel is approximately 5 – 6 months. Thus it is likely that most patients will have experienced disease progression by six months. Response will be evaluated by RECIST version 1.1[47] (see Appendix 2). Note that confirmation of response is not required as the primary end point of the trial utilises progression free survival rather than objective response rate.

Objective tumour response is a secondary end-point and will be measured according to RECIST criteria version 1.1. Tumour measurements will be performed on the 12 and 24 week scans and on 12 weekly scans thereafter until disease progression.

Investigators are required to submit CDs of baseline, weeks 12 and 24 CT/MRI scans, and all post-treatment 12 weekly CT scans thereafter until disease progression, for review and confirmation of response. CT/MRI scans performed to confirm disease progression should also be submitted. CDs should be submitted, ideally as a single batch, together with the scan submission form and anonymised scan reports to:

GeDDiS Trial Coordinator
Cancer Research UK & UCL Cancer Trials Centre
90 Tottenham Court Road
London
W1T 4TJ
UK

Please note that CDs and all supporting documentation being submitted to UCL CTC must clearly display the patient’s trial number and any patient identifiers must be removed/blacked out prior to sending in order to maintain confidentiality in accordance with the Data Protection Act 1998.

Guidelines on submission of CT scans are provided in the Investigator Site File.

An exploratory endpoint of the study is the retrospective evaluation of disease response by Choi criteria in order to assess how it compares with RECIST and whether it is more representative of response and outcome. This will be performed on a cohort of patients at University College Hospital, to allow scans to be performed consistently to an agreed scanning protocol, which is necessary for analysis.
8.7. Central pathology review

Pathology specimens are to be reviewed centrally to confirm the diagnosis of sarcoma and subtyping of sarcoma. Pathology review is not required to be completed prior to randomisation, but as a change in diagnosis may impact on stratification according to histological subtype, pathology material for UK patients must be submitted within 3 months of randomisation. H&E stained slides and two representative tissue blocks should be forwarded for review. For patients who consent to the translational component of the trial, one block will be stored for future research. In those who have declined entry into the translational component of the trial, these will be returned after review is complete, together with the H&E stained slides.

Sites who have any questions regarding the submission of pathology material should contact the GeDDiS Trial Coordinator (see page 1 for contact details).

Slides and blocks will be sent to:

Professor Adrienne Flanagan
Consultant Histopathologist
Histopathology Department
Royal National Orthopaedic Hospital
Institute of Orthopaedics
Brockley Hill
Stanmore
Middlesex
HA7 4LP
UK

Please note that any supporting documentation being submitted with pathology material must clearly display the patient’s trial number and any patient identifiers must be removed/blacked out prior to sending in order to maintain confidentiality in accordance with the Data Protection Act 1998.

n.b. Central pathology review will be performed for all Swiss patients, however, Swiss sites must NOT submit any pathology material until requested to do so by UCL CTC.
9. Data Management Guidelines

Data will be collected from sites on version controlled case report forms (CRFs) designed for the trial and supplied by UCL CTC. Data entered onto CRFs must reflect source data at site.

Where supporting documentation (e.g. pathology reports, CT scan images etc) is being submitted to UCL CTC, the patient’s trial number must be clearly indicated on all material and any patient identifiers removed/blacked out prior to sending to maintain confidentiality.

9.1. Completing and Submitting Case Report Forms

All CRFs must be completed and signed by staff who are listed on the site staff delegation log and authorised by the PI to perform this duty. The PI is responsible for the accuracy of all data reported in the CRF.

Once completed the original CRFs must be sent to UCL CTC (or via the Country Coordinating Centre (CCC) for non-UK sites) and a copy kept at site. All CRF entries must be clear, legible and written in ball point pen. The use of abbreviations and acronyms must be avoided.

9.2. Corrections to CRFs

Any corrections made to a CRF at site must be made by drawing a single line through the incorrect item ensuring that the previous entry is not obscured. Each correction must be dated and initialled. Correction fluid must not be used. The amended CRF must be sent to UCL CTC or CCC (see above) and a copy retained at site.

9.3. Missing Data

To avoid the need for unnecessary data queries CRFs must be checked at site (and CCC if applicable) to ensure there are no blank fields before sending to UCL CTC. When data are unavailable because a measure has not been taken or test not performed, enter “ND” for not done. If an item was not required at the particular time the form relates to, enter “NA” for not applicable. When data are unknown enter the value “NK” (only use if every effort has been made to obtain the data).

9.4. Timelines for data return

UK sites must complete and submit the randomisation and baseline data CRFs within one week of the patient being randomised.

All other forms must be completed and submitted within one month of a patient completing a chemotherapy cycle or attending an assessment visit.

Non-UK sites with a Country Coordinating Centre must complete and submit randomisation and baseline CRFs to their CCC within two weeks of the patient being randomised and within one month of a patient completing a chemotherapy cycle or attending an assessment visit. CCCs must forward all CRFs to UCL CTC within 5 business days of receipt. If a delay is envisaged in forwarding the CRFs, the CCC must contact UCL CTC to inform them of this.

Sites who persistently do not return data within the required timelines may be suspended from recruiting further patients into the trial by UCL CTC and subjected to a ‘for cause’ monitoring visit. See section 12.3 (Non-Compliance/’for cause’ on-site monitoring) for details.
9.5. Data Queries
Data arriving at UCL CTC will be checked for legibility, completeness, accuracy and consistency, including checks for missing or unusual values. Query Reports will be sent to the data contact at site (or CCC where applicable). Further guidance on how data contacts should respond to Data Queries can be found on the Query Reports.
10. Pharmacovigilance

10.1. Definitions of Adverse Events

The following definitions have been adapted from Directive 2001/20/EC, ICH E2A “Clinical Safety Data Management: Definitions and Standards for Expedited Reporting” and ICH GCP E6:

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

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

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)
An adverse event or adverse reaction that at any dose:
- Results in death
- Is life threatening (the term “life-threatening” refers to an event in which the 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.)
- Requires in-patient hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is otherwise medically significant (e.g. important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above)

Suspected Unexpected Serious Adverse Reaction (SUSAR)
A serious adverse reaction, the nature or severity of which is not consistent with the applicable trial treatment information.

10.2. Reporting Procedures

10.2.1. All Adverse Events (AEs)
All adverse events that occur between informed consent and 30 days post last trial treatment administration must be recorded in the patient notes and the trial CRFs. Those meeting the definition of a Serious Adverse Event (SAE) must also be reported to UCL CTC using the trial specific SAE Report. Refer to section 10.2.2 (Serious Adverse Events (SAEs)) for details.

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

Overdoses
All accidental or intentional overdoses, whether or not they result in adverse events, must be recorded in the patient notes and CRFs. Overdoses resulting in adverse events are classified as SAEs and must be reported to UCL CTC according to SAE reporting procedures. The fact that an overdose has occurred must be clearly stated on the SAE Report. Also refer to section 10.2.2 (Serious Adverse Events (SAEs)).
Sites must inform UCL CTC immediately when an overdose has been identified. Also refer to section 11.0 (Incident Reporting and Serious Breaches).

**Adverse Event Term**
An adverse event term must be provided for each adverse event, preferably using the term listed in the Common Terminology Criteria for Adverse Events (CTCAE) v4.03, available online at: http://evs.nci.nih.gov/ftp1/CTCAE

**Severity**
Severity for each adverse event must be determined by using the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 as a guideline, wherever possible. The criteria are available online at: http://evs.nci.nih.gov/ftp1/CTCAE

In those cases where the CTCAE criteria do not apply, severity should be coded according to the following criteria:

\[1 = \text{Mild (awareness of sign or symptom, but easily tolerated)}\]
\[2 = \text{Moderate (discomfort enough to cause interference with normal daily activities)}\]
\[3 = \text{Severe (inability to perform normal daily activities)}\]
\[4 = \text{Life threatening (immediate risk of death from the reaction as it occurred)}\]
\[5 = \text{Fatal (the event resulted in death)}\]

**Causality**
The PI, or other delegated site investigator, must perform an evaluation of causality for each adverse event. Causal relationship to each trial treatment must be determined as follows:

- **None**
  There is no evidence of any causal relationship.

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

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

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

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

**10.2.2. Serious Adverse Events (SAEs)**
All SAEs that occur between informed consent and 30 days post the last trial treatment administration (or after this date if the site investigator feels the event is related to the trial treatment) must be submitted to the UCL CTC by fax within **24 hours** of observing or learning of the event, using the trial specific SAE Report. All sections on the SAE Report...
must be completed. If the event is **not being reported within 24 hours** to UCL CTC, the circumstances that led to this must be detailed in the SAE Report to avoid unnecessary queries.

**Exemptions from SAE Report Submission**

For this trial, the following events are exempt from requiring submission on an SAE Report, but must be recorded in the relevant section(s) of the trial CRFs:

- events that occur after 30 days post last trial treatment administration that are not considered to be related to trial treatment
- disease progression (including disease related deaths)

Please note that hospitalisation for elective treatment or palliative care does not qualify as an SAE.

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**Completed SAE Reports must be faxed within 24 hours of becoming aware of the event to UCL CTC**

*Fax: +44 (0)20 7679 9871*
Adverse Event Reporting Flowchart

1. **Adverse event**
2. **Assign severity grade**
3. **Investigator to assess causality**
   - Is the event causally related to the trial treatment?
4. **Was the event serious?**
   - Criteria:
     - Results in death
     - Is life threatening
     - Results in persistent or significant disability/incapacity
     - Requires inpatient hospitalisation or prolongs existing hospitalisation
     - Results in a congenital anomaly or birth defect
     - Is otherwise medically significant
5. **Event exempt from requiring submission on an SAE Report?**
   - (as stated in protocol)
     - Yes
     - No
6. **Complete SAE Report**
7. **Fax Report to UCL CTC within 24 hours of becoming aware of the event**
8. **Complete CRF**
   - (to be submitted at time point stated in protocol)
SAE Follow-Up Reports
All SAEs must be followed-up until resolution and until there are no further queries. The PI, or other delegated site investigator, must provide follow-up SAE Reports if the SAE had not resolved at the time the initial report was submitted.

SAE Processing at UCL CTC
On receipt of the SAE Report, UCL CTC will check for legibility, completeness, accuracy and consistency. Expectedness will be evaluated to determine whether or not the case qualifies for expedited reporting, using the list of expected adverse events in the current SPC for doxorubicin, gemcitabine and docetaxel. n.b. there is no paediatric data published in the SPC for docetaxel and gemcitabine and therefore all events occurring in patients under the age of 18 in this arm of the trial will be considered unexpected.

The CI or their delegate (e.g. a clinical member of the TMG) may be contacted immediately to review the SAE and to perform an evaluation of causality on behalf of UCL CTC. If UCL CTC has considered expectedness difficult to determine, the CI, or their delegate, will be consulted for their opinion at this time.

Periodic SAE line listings for non-UK sites
SAE line listings will be provided to the Country Coordinating Centre in Switzerland every 6 months. These line listings will be processed according to the requirements of the country.

10.3. SUSARs
If the event is evaluated as a Suspected Unexpected Serious Adverse Reaction (SUSAR), i.e. unexpected events that are possibly, probably or definitely related to a trial treatment, UCL CTC will submit a report to the MHRA (for them to enter the case on the EudraVigilance Clinical Trial Module) within 5 calendar days for fatal/life threatening events (with a follow-up report within a further 6 calendar days) and 13 calendar days for all other events (reporting timeframes have been shortened to allow for submission to regulatory authority(ies) and ethics committee(s) outside the UK, as stated below). Where there are conflicting evaluations of causal relationship by the site and UCL CTC/CI, both opinions will be reported.

UCL CTC will also report all SUSARs originating in the UK to the UK REC.

UCL CTC will also submit the report to country co-ordinating centres (CCCs). CCCs must forward all SUSAR reports within 1 business day to their ethics committee(s), as required, their regulatory authority and sites within the country (for forwarding to the local ethics committee(s) within 1 business day). UCL CTC will ensure that consideration is given where the reporting deadline occurs at a weekend to allow reporting within the required timeframes.

Informing Sites of SUSARs
UCL CTC will inform all UK PIs of any SUSARs that occur on the trial. PIs will receive a quarterly line listing which must be processed according to local requirements.

For participating countries outside the UK, UCL CTC will submit reports to CCCs for forwarding to the PIs in their country within one business day.

10.4. Safety Monitoring
UCL CTC will provide safety information to the TMG and the IDMC on a periodic basis for review.

Trial safety data will be monitored to identify:

- new adverse reactions to the trial treatment regimen or individual trial treatments;
• a higher incidence in rare adverse events than is stated in the SPC for a trial treatment;
• trial related events that are not considered related to the trial treatment regimen.

Should UCL CTC identify or suspect any issues concerning patient safety at any point throughout the trial, the CI or TMG will be consultant for their opinion.

10.5. Pregnancy
If a female patient or the female partner of a male patient becomes pregnant at any point during the trial, a completed trial specific Pregnancy Report must be submitted to UCL CTC by fax within 24 hours of learning of its occurrence. Consent to report information regarding pregnancy outcomes must be obtained from the pregnant patient/partner. The trial-specific pregnancy monitoring information sheets and informed consent forms for trial patients and partners of trial patients must be used for this purpose.

All pregnancies must be reported by faxing a completed Pregnancy Report within 24 hours of becoming aware of the pregnancy to UCL CTC
Fax: +44 (0)20 7679 9871

Pregnancy Follow-Up Reports
All pregnancies must be followed-up until an outcome is determined. Follow-up Pregnancy Reports must be submitted to UCL CTC by fax within 24 hours of learning of the outcome. Reports must include an evaluation of the possible relationship of the trial treatment to the pregnancy outcome.

SAEs During Pregnancy
Any SAE occurring in a pregnant patient must be reported using the trial specific SAE Report, according to SAE reporting procedures. Refer to section 10.2.2 (Serious Adverse Events (SAEs)) for details.

Pregnancy Report Processing at UCL CTC
UCL CTC will submit a report as outlined in section 10.3 (SUSARs) should the pregnancy outcome meet the definition of a SUSAR.

10.6. Development Safety Update Reports (DSURs)
Safety data obtained from the trial will be included in DSURs that UCL CTC will submit to the MHRA, the UK REC and all CCCs. CCCs must forward all reports within 1 business day to their ethics committee(s) and regulatory authority as required.
11. Incident Reporting and Serious Breaches

11.1. Incident Reporting
Organisations must notify UCL CTC of all deviations from the protocol or GCP immediately. UCL CTC may require a report on the incident(s) and a form will be provided if the organisation does not have an appropriate document (e.g. Trust Incident Form for UK sites).

If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the UCL CTC trial team can be contacted immediately to discuss.

Where the incident has occurred in a site outside the UK, the CCC must also notify the relevant ethics committee in accordance with local requirements. Where UCL CTC identifies an incident at a site outside the UK, the CCC where the incident occurred will be informed.

If a site in the CCC’s country identifies an incident, they must report it immediately to the CCC.

If the CCC is notified of any incidents occurring at a site, or identifies any incidents occurring at a site or within the CCC, the CCC should forward the report on to the UCL CTC.

UCL CTC will assess all incidents to see if they meet the definition of a serious breach.

11.2. Serious Breaches
Systematic or persistent non-compliance by a site with GCP and/or the protocol, including failure to report SAEs occurring on trial within the specified timeframe, may be deemed a serious breach.

In cases where a potential or actual serious breach has been identified, UCL CTC will inform the MHRA within 7 calendar days of becoming aware of the breach.

The serious breach report may also be forwarded to CCCs for submission to their regulatory authorities, as required.

UK sites must have written procedures for notifying the sponsor of serious breaches (see MHRA Guidance on the Notification of Serious Breaches).

UCL CTC will use an organisation’s history of non-compliance to make decisions on future collaborations.
12. Trial Monitoring and oversight

UK participating sites and PIs must agree to allow trial-related on-site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/documents as required. Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the consent form.

UCL CTC will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

Monitoring of non-UK sites will, as a minimum, be performed in accordance with the Central Monitoring requirements detailed below and the applicable monitoring plan.

12.1. Central monitoring

Sites will be requested to submit screening logs and staff delegation logs to UCL CTC at the frequency detailed in the UCL CTC trial monitoring plan or on request and these will be checked for consistency and completeness. Also refer to section 3.2.2 (Required Documentation) and 5.2 (Screening Logs).

Ensuring patient eligibility is the responsibility of the PI or other delegated Investigator(s). Checks of the criteria listed on the randomisation form will be undertaken by an appropriately trained UCL CTC staff member prior to randomisation. Also refer to section 6.1 (Randomisation).

Details relating to the informed consent process will be collected on the randomisation form and are subject to review by CTC as part of patient eligibility.

Copies of the drug accountability logs will be collected at UCL CTC for all trial patients. Sites will be required to submit logs following a patient’s completion of/withdrawal from trial treatment, or on request. A proportion of these will be monitored centrally to ensure completeness and correlation with data captured in the CRF. Also refer to section 7.3.4 (Drug Accountability)

Sites will be requested to conduct quality control checks of documentation held within the Investigator Site file and Pharmacy Site File at the frequency detailed in the UCL CTC trial monitoring plan. Checklists detailing the current version/date of version controlled documents will be provided for this purpose.

Central pathology review is also being performed for all patients. See section 8.7 (Central Pathology Review) for details.

Data received at UCL CTC will be subject to review in accordance with section 9.5 (Data Queries).

Where central monitoring of data and/or documentation submitted by sites indicates that a patient may have been placed at risk (e.g. evidence of an overdose having been administered, indication that appropriate dose reductions or stopping rules for an IMP were not observed following an adverse reaction, etc.), the matter will be raised urgently with site staff (and/or CCC where applicable) and escalated as appropriate (refer to section 11 – Incident Reporting and Serious Breaches, and section 12.3 – ‘For cause’ on-site monitoring, for further details).

For non-UK sites, in addition to return of the above, the CCC must return a completed Reconciliation Summary document at the frequency specified in the UCL CTC Monitoring plan.
12.2. 'For cause’ on-site monitoring

On-site monitoring visits may be scheduled where there is evidence or suspicion of non-compliance at a site with important aspect(s) of the trial protocol/GCP requirements. Sites will be sent a letter in advance outlining the reason(s) for the visit. The letter will include a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities, who will be performing the visit and when the visit is likely to occur.

Following a monitoring visit, the Trial Monitor/Trial Coordinator will provide a report to the site, which will summarise the documents reviewed and a statement of findings, deviations, deficiencies, conclusions, actions taken and/or actions required. The PI at each site will be responsible for ensuring that monitoring findings are addressed in a timely manner, and by the deadline specified.

For non-UK sites, this duty may be delegated to the CCC.

UCL CTC will assess whether it is appropriate for the site to continue participation in the trial and whether the incident(s) constitute a serious breach. Refer to section 11.0 (Incident Reporting and Serious Breaches) for details.

12.3. Oversight Committees

12.3.1. Trial Management Group (TMG)

The TMG will include the Chief Investigator, clinicians and experts from relevant specialities and GeDDiS trial staff from UCL CTC (see page 1). The TMG will be responsible for overseeing the trial. The group will meet at least twice a year (or more frequently if required) and will send updates to PIs (via newsletters or at Investigator meetings) and to the NCRI Sarcoma, Teenage and Young Adult and Gynaecology Clinical Studies Groups.

The TMG will review substantial amendments to the protocol prior to submission to the MHRA and the REC. All PIs will be kept informed of substantial amendments through their nominated responsible individuals.

A TMG charter will summarise the roles and responsibilities of the TMG and each member will be required to sign this prior to the first meeting.

12.3.2. Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision for the trial of the Trial. The TSC will review the recommendations of the Independent Data Monitoring Committee and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder and Sponsor.

A TSC charter will summarise the roles and responsibilities of the TSC and each member will be required to sign this prior to the first meeting.

12.3.3. Independent Data Monitoring Committee (IDMC)

The role of the IDMC is to provide independent advice on data and safety aspects of the trial. Meetings of the Committee will be held annually to review interim analyses, or as necessary to address any issues. The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC.

An IDMC charter will summarise the roles and responsibilities of the IDMC and each member will be required to sign this prior to the first meeting.
12.3.4. Role of UCL CTC

UCL CTC will be responsible for the day to day coordination and management of the trial and will act as custodian of the data generated in the trial (on behalf of UCL). UCL CTC is responsible for all duties relating to pharmacovigilance which are conducted in accordance with section 10.0 (Pharmacovigilance).
13. Withdrawal of patients

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

Withdrawal from Trial Treatment

A patient may be withdrawn from trial treatment whenever continued participation is no longer in the patient’s best interests, but the reasons for doing so must be recorded. Reasons for discontinuing treatment may include:

- Disease progression whilst on therapy
- Unacceptable toxicity
- Intercurrent illness which prevents further treatment
- Patients or parent/legal guardian withdrawing consent to further trial treatment
- Any alterations in the patient’s condition which justifies the discontinuation of treatment in the site investigator’s opinion
- Any delays in treatment that is greater than 35 days
- If patient requires more than two dose reductions
- If a patient becomes pregnant or fails to use adequate birth control (for patients of childbearing potential)
- If the patient is non-compliant with trial procedures

In these cases patients remain within the trial for the purposes of follow-up and data analysis according to the treatment option to which they have been allocated.

If a patient wishes to withdraw from trial treatment, sites should explain the importance of remaining on trial follow-up, or failing this of allowing routine follow-up data to be used for trial purposes and for allowing existing collected data to be used. If a patient gives a reason for their withdrawal, this should be recorded.

Future Data Collection

If a patient explicitly states they do not wish to contribute further data to the trial their decision must be respected, with the exception of safety data, and recorded on the relevant CRF. In this event details should be recorded in the patient’s hospital records, no further CRFs must be completed and no further data, other than safety data, sent to UCL CTC (or CCC for non-UK sites).

Losses to follow-up

If a patient moves from the area, every effort should be made for the patient to be followed up at another participating trial site and for this new site to take over the responsibility for the patient, or for follow-up via their GP. Details of participating trial sites can be obtained from the UCL CTC trial team who must be informed of the transfer of care and follow up arrangements.

If a patient is lost to follow-up at a site every effort should be made to contact the patient’s GP (if consented) to obtain information on the patient’s status.
14. Trial Closure

14.1. End of Trial

For regulatory purposes the end of the trial will be five years after last administration of protocol treatment or death of the last surviving patient, whichever is sooner. At this point the 'declaration of end of trial' form will be submitted to regulatory authorities and ethical committees, as required.

Following this, UCL CTC will advise sites on the procedure for closing the trial at the site.

14.2. Archiving of Trial Documentation

At the end of the trial, UCL CTC will archive securely all centrally held trial related documentation for a minimum of 5 years. Arrangements for confidential destruction will then be made. It is the responsibility of Principal Investigators to ensure data and all essential documents relating to the trial held at site are retained for a minimum of 5 years after the end of the trial, in accordance with national legislation and for the maximum period of time permitted by the site.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of Good Clinical Practice and all applicable regulatory requirements.

UCL CTC will notify sites when trial documentation held at sites may be archived. All archived documents must still continue to be available for inspection by appropriate authorities upon request.

14.3. Early discontinuation of trial

The trial may be stopped before completion as an Urgent Safety Measure on the recommendation of the TSC or IDMC (see section 12.3.2 TSC and 12.3.3 IDMC). Sites will be informed in writing by UCL CTC of reasons for early closure and the actions to be taken with regards the treatment and follow up of patients.

14.4. Withdrawal from trial participation by a site

Should a UK site choose to close to recruitment the PI must inform UCL CTC in writing. Follow up as per protocol must continue for all patients recruited into the trial at that site and other responsibilities continue as per CTSA.

Should a non-UK site choose to close to recruitment the PI must inform the CCC in writing. Follow up as per protocol must continue for all patients recruited into the trial at that site and other responsibilities continue as per the International CTSA.
15. Statistics

15.1. Population for analysis
Three populations will be defined:

**Intention to Treat (ITT)/Safety Population:** This population will consist of patients who have been randomised to trial treatment and have received at least one dose of doxorubicin in any cycle, or at least one dose of either gemcitabine or docetaxel in any cycle.

**Evaluable Population:** This will include all the patients in the ITT/safety population and who in addition:
- have measurable disease (using RECIST version 1.1) at baseline, and
- have at least one evaluable post-baseline tumour assessment

**Per Protocol Population:** This population will be a subset of the ITT/Safety Population and in addition:
- Patients who have received at least 80% of randomised trial medication or have completed at least 4 cycles of their allocated trial treatment.

15.2. Analysis of the trial endpoints

**Primary Endpoint**

Proportion of patients alive and progression free at 24 weeks:
The proportion of patients who are alive and progression free at 24 weeks will be derived and compared between treatment groups. This will be derived by constructing the Kaplan Meier (KM) survival plots and estimating the proportion of patients who are alive and progression free at 24 weeks. Where stratified variables are used, adjusted KM plots will be used to estimate the proportion of patients who are alive and progression free at 24 weeks. The estimate of the hazard ratio will be used for deriving 95% confidence intervals for the odds ratio at 24 weeks. In addition a 95% confidence interval for the difference in the proportion who are alive and progression free at 24 weeks will be constructed. If the 95% confidence interval excludes the value of 0 (where absolute differences are being calculated), then a statistically significant result will be declared for this endpoint. Where differences are expressed as an odds ratio, the 95% confidence interval should exclude 1 for statistical significance at the 2 sided 5% level. The analysis will also be repeated after adjusting for stratified factors. This endpoint will be analysed using the ITT and the per protocol populations.

**Secondary Endpoints**

Proportion of patients alive and progression free at 12 weeks:
This endpoint will be analysed in the same way as the primary endpoint for the ITT and per protocol populations.

Median progression free survival:
This is defined as the period from the date of randomisation to the date of progression, or death from any cause, whichever occurs first. For each patient who is known not to have progressed or was alive, PFS duration will be censored at the date the subject was last known to be alive and progression free.

The primary test for differences between PFS curves between the two arms will be determined using a stratified log rank test. Furthermore, Kaplan-Meier plots using the Life table method will be presented to describe PFS distribution over time. The 95% confidence
intervals for the median PFS time will be reported. In addition, PFS will be analysed using a Cox proportional hazards model using the stratification variables age and histological subtype as covariates. The hazard ratio adjusted for covariates along with a 95% confidence interval for the estimate of the hazard ratio will be derived and reported. Additional covariates may also be included for exploratory reasons. Progression will be based on clinical or radiological progression. This endpoint will be analysed only using the ITT population.

**Overall survival:**
This is measured from the date of randomisation to the date of death from any cause. For each subject who is not known to have died, OS duration will be censored at the date the subject was last known to be alive. This endpoint will be analysed using similar methods to the PFS endpoint, and will be analysed using the ITT population only.

**Time to progression:**
This is measured from date of randomisation to date of first documented progression. Subjects with no progression recorded will be censored at the last date where progression was confirmed, or at the last known date alive. Progression will be based on clinical or radiological progression.

This endpoint will be analysed using similar methods to the PFS endpoint, and will be analysed using the ITT population only.

**PFS defined as Time from start of treatment to progression or death:**
This endpoint is the same as PFS except that it is measured from date of start of treatment (first dose) to date of first documented progression, or death, whichever occurs first. Subjects with no progression recorded will be censored at the last date where progression was confirmed, or at the last known date alive. Progression will be based on clinical or radiological progression. This endpoint will be analysed using similar methods to the PFS endpoint, and will be analysed using the ITT population only. The justification for this endpoint is to take into account the potential delay in patients receiving treatment after randomization.

**Objective response rate by RECIST:**
This is measured as the proportion of subjects who achieve complete response (CR), or partial response (PR). For this analysis, all subjects in the analysis population who do not meet the criteria as specified by RECIST version 1.1 for a CR, PR, or SD will be included as if they have progressed. Disease control will be categorised by the best overall response (CR, PR, or SD) recorded from randomisation. In RECIST version 1.1, for studies in which objective response rate is not a primary endpoint, a confirmatory examination documenting the response is not required.

Objective response rate will be summarised by arm and strata using frequencies and percentages. Chi-squared tests controlling for stratification factors will be used when appropriate to compare response rates. This endpoint will be analysed using the evaluable population only.

**Adverse events/safety**
Adverse event data will be summarised using frequencies and percentages. No formal statistical analysis is planned. The following Safety data will be summarised by treatment group:

- AEs ≥grade 3
- Treatment related AEs ≥grade 3
- All SAEs
- SAEs ≥grade 3
- Treatment related SAEs ≥grade 3
- Dose reductions
- Specific SAEs ≥grade 3 (e.g. thrombocytopenia, febrile neutropenia and others)
- Patients who withdrew from trial treatment due to adverse events
- Treatment exposure expressed as the proportion of patients who received all cycles and other proportions, in responders and non-responders

**Quality of life:**
The assessment of quality of life will be an important aspect of this trial, as it will inform the choice of treatment, especially if survival differences are small. Every effort should be made to ensure all patients complete as many scheduled quality of life assessments as possible. The questionnaires used will be the EORTC QLQ-C30 and FA-13 for patients over 18 years of age, and the PedsQL Paediatric Quality of Life inventory version 4.0, Cancer module version 3.0, and Multidimensional Fatigue scale for patients aged 13 -18 years. The EuroQol EQ-5D will be used for patients aged ≥18 years and the EQ-5D-Y (version for children) will be used for patients aged <18 years. The analysis from these questionnaires will also be used in the economic evaluation. Quality of life analysis will be based on ITT population only.

The EORTC QLQC-30 and FA-13 questionnaires will be analysed using Mixed Effects Models, and differences in scores between arms will be presented with 95% confidence intervals at each time point and overall. Changes from baseline will also be presented. The algorithm for core construction will be based on that provided by the QLQC-30 manual.

Data from the PedsQL questionnaires will be summarised and presented using a General Linear Model.

Data from the EQ-5D will be presented and summarised and analysed using categorical or appropriate methods.

Data from the EQ-5D-Y will be presented and summarised and analysed using categorical or appropriate methods.

**Health economic evaluation:**
Since individual level data is being collected, estimates of probabilities of patients alive will be derived through using the empirical survival distribution or fitting an appropriate survival model. Results will be reported as the incremental cost-effectiveness ratio based on quality adjusted life years. The cost effectiveness acceptability curve will be generated. Uncertainty will be evaluated through sensitivity analysis (probabilistic or otherwise). All costs will be discounted at the 3.5% p.a rate, in order to account for the influence of inflation on future costs.

In addition to costs and consequences of the treatment regimens being different as a result of the nature of the treatment (combination versus single agent), there are also likely to be different adverse event profiles and efficacy, which may translate into different costs, effects and cost-effectiveness. Therefore the following data will be collected from a number of sources including clinical report forms, SAE or SUSAR forms and patient diaries:

- administered trial treatment
- unexpected trial treatment-related hospitalisations
- use of supportive treatments including GCSF and antibiotics
- management of serious adverse events
- extra trial treatment-related unscheduled hospital visits
- extra trial treatment-related unscheduled non-hospital visits/encounters (including GP, district nurses, community palliative care nurses)
The EuroQoL EQ-5D and EQ-5D-Y, collected as part of the quality of life measurement process, will attempt to provide a widely used source of data for the calculation of quality-adjusted life-years (QALYs).

15.3. Sample size calculation
Using a median PFS of 5.5 months for gemcitabine and docetaxel and a median PFS of 3.5 month for doxorubicin, which corresponds to a 24 week PFS rate of about 47% (i.e. 47% who are alive and progression free) for gemcitabine and docetaxel, and a 24 week PFS rate of about 30% (i.e. 30% who are alive and progression free) for doxorubicin respectively, in order to detect differences in the proportion of patients who have progressed or died of about 17% at 6 months, 122 patients per arm will be required (244 patients in total), assuming at least 80% power and a 2 sided type I error of 5%.

In addition, 125 patients per arm (250 patients in total) will provide at least 80% power to detect differences in the median PFS (PFS as a time to event endpoint) of 5 months versus 3.5 months (hazard ratio of 0.7) for gemcitabine and docetaxel versus doxorubicin, respectively, based on 3 years of recruitment and 1 year of follow up (5% type I error)\textsuperscript{48}. Therefore, a total of 250 patients will be recruited to answer the objectives of this trial.

15.4. Interim analysis
An interim analysis will be carried out on a calendar yearly basis to assess safety and futility for efficacy. The expected information rates (rates of either patient accrual or events) are expected to be 30%, 50% and 75% over the 4 year period. That is, a futility analysis for efficacy will only be conducted when 30%, 50% and 75% of the total sample size is reached and each patient has a follow up of at least 24 weeks. The conditional power will be derived as an aid to deciding to stop for futility. This provides the probability of a statistically significant result at the end of the trial after analysing the data at each of the above time points (i.e. when 30%, 50% and 75% of data (i.e. PFS events) is available). If this probability is low (typically < 20%), then stopping for futility may be considered. Futility analysis will be based only on the primary endpoint. A decision to terminate the trial for futility will not be made purely on this probability – other clinical criteria and endpoints will also be considered before a trial is terminated for futility. More details will be provided in a separate Statistical Analysis Plan. The Statistical Analysis Plan will be finalised before the last patient is recruited into the trial.
16. Ethical and Regulatory Approvals

In conducting the Trial the Sponsor, UCL CTC and sites shall also comply with all laws and statutes, as amended from time to time, applicable to the performance of clinical trials including, but not limited to:

- the principles of ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) and any applicable local GCP laws or regulations in the relevant country(ies)
- Human Rights Act 1998
- Data Protection Act 1998
- Freedom of Information Act 2000
- Human Tissue Act 2004
- Human Tissue Act (Scotland) 2006
- Medicines Act 1968
- Medicines for Human Use (Clinical Trials) UK Regulations SI 2004/1031, and subsequent amendments
- Good Manufacturing Practice
- the Research Governance Framework for Health and Social Care, issued by the UK Department of Health (Second Edition 2005) or the Scottish Health Department Research Governance Framework for Health and Community Care (Second Edition 2006)

All non-UK sites shall comply with all their local laws and statutes applicable to the performance of clinical trials.

16.1. Ethical Approval

The trial will be conducted in accordance with the World Medical Association Declaration of Helsinki entitled ‘Ethical Principles for Medical Research Involving Human Subjects’ (1996 version) and in accordance with the terms and conditions of the ethical approval given to the trial.

In the UK, the trial has received a favourable opinion from the London – Bloomsbury Research Ethics Committee.

UCL CTC will submit Annual Progress Reports to the REC, which will commence one year from the date of ethical approval for the trial.

For non-UK sites, the trial must have received appropriate ethics committee approval.

16.2. Regulatory Approval

A Clinical Trial Authorisation (CTA) has been granted for the trial in each country.

The trial will be conducted at approved trial sites in accordance with the trial protocol and the terms of the CTA granted by the MHRA (UK) and Swissmedic (Switzerland).

16.3. Local Site Approval

Evidence of local Trust R&D approval must be provided to UCL CTC prior to site activation. The trial will only be conducted at sites where all necessary approvals for the trial have been obtained.

All non-UK sites must provide a signed copy of the International CTSA and confirmation of approval of their local institutions.
16.4. Protocol Amendments
UCL CTC will be responsible for gaining ethical and regulatory approvals, as appropriate, for all amendments made to the protocol and other trial-related documents. Once approved, UCL CTC will ensure that all amended documents are distributed to sites and CLRNs as appropriate.

Site staff will be responsible for acknowledging receipt of documents and for implementing all amendments.

For non-UK sites, the CCC will be responsible for gaining regulatory approval for all amendments made to the protocol and other trial-related documents as appropriate and distributing the amendments to Sites for submission to their local ethics committees. The CCC is responsible for ensuring that all applicable approvals have been obtained prior to implementation of an amendment at a Site.

The CCC will forward all documentation on to UCL CTC as required.

16.5. Patient Confidentiality & Data Protection
In the UK patient identifiable data, including initials, date of birth and NHS number will be required for the randomisation process and will be provided to UCL CTC. UCL CTC will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a secure manner and UCL CTC trials are registered in accordance with the Data Protection Act 1998 with the Data Protection Officer at UCL.

Non-UK Sites will not provide patient identifiable data. Patients will be identified by patient trial number and initials only.
17. Sponsorship and Indemnity

17.1. Sponsor Details:

<table>
<thead>
<tr>
<th>Sponsor Name:</th>
<th>University College London</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address:</td>
<td>Joint Research Office</td>
</tr>
<tr>
<td></td>
<td>Gower Street</td>
</tr>
<tr>
<td></td>
<td>London</td>
</tr>
<tr>
<td></td>
<td>WC1E 6BT</td>
</tr>
<tr>
<td></td>
<td>UK</td>
</tr>
<tr>
<td>Contact:</td>
<td>Managing Director Research Support Centre</td>
</tr>
<tr>
<td>Tel:</td>
<td>020 3447 9995/2178 (unit admin)</td>
</tr>
<tr>
<td>Fax:</td>
<td>020 3447 9937</td>
</tr>
</tbody>
</table>

17.2. Indemnity

University College London holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital’s duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or not. This does not affect the participant’s right to seek compensation via the non-negligence route.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor’s Insurers, via the Sponsor’s office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.
18. Funding
Cancer Research UK is supporting the central coordination of the trial through UCL CTC. In Switzerland, the trial is supported by St. Gallen CTU Commission and the State Secretariat for Education and Research.
19. Publication Policy
All publications and presentations relating to the trial will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group. Members of the TMG will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal’s policy. Contributing Site investigators will also be acknowledged. Site investigators contributing >5% of patients will be included as a named author. Data from all sites will be analysed together and published as soon as possible. Participating sites may not publish trial results prior to the first publication by the TMG or without prior written consent from the TMG. The trial data is owned by UCL as Sponsor. The ISRCTN number (ISRCTN07742377) allocated to this trial will be quoted in any publications resulting from this trial.
20. Translational Research

20.1. Background

The primary aim of the proposed study is to investigate the influence of pharmacogenomics on response and toxicity in patients with soft tissue sarcoma treated with gemcitabine and docetaxel, or doxorubicin, within the GeDDiS Trial.

Pharmacogenomics, the study of inherited differences in drug response at whole genome level, may allow for personalised cancer chemotherapy and has been studied in a number of malignancies. Single nucleotide polymorphisms (SNPs) that influence gemcitabine and doxorubicin toxicity and efficacy have been studied in breast cancer[49-51] and a number of SNPs have been found to influence survival and toxicity after docetaxel treatment in patients with prostate cancer[52]. There are however, few published data on the influence of pharmacogenomics in patients with sarcoma mainly due to its heterogeneous nature and rarity. Within the London Sarcoma Service a pharmacogenomic study in osteosarcoma using genome-wide SNP arrays has been completed, which has demonstrated a number of SNPs associated with response and toxicity[53-54]. Other genetic or epigenetic studies may also provide data that leads to improved outcome and tolerance of therapy.

A single peripheral blood sample will be collected and stored from all patients who provide informed consent upon study entry. In addition, paraffin-embedded tumour tissue will be stored, where available, for these studies.

20.2. Sample collection and processing

This is an optional part of the trial. Sites will be asked to confirm whether patients have consented to this part of the trial at randomisation.

For additional information please refer to the arrangements for pathology sample document held in the Investigator Site File.

Types of samples to be collected

In patients who have consented the following will be collected:

- Blood – a single blood sample into a 10ml EDTA tube
- Tumour tissue – one representative tissue block that has been sent to Professor Flanagan at the Royal National Orthopaedic Hospital (RNOH) for central pathology review will be stored for future research, unless sites specifically request the blocks to be returned.

Blood samples

How samples collected in the UK are to be processed and sent

No processing of samples is required at treatment site.

Blood samples should be collected into pre-labelled tubes (labels will be provided by UCL CTC). Samples should be left at room temperature, and must be sent within 24 hours of collection. Preferably, samples should be shipped on the day of collection. To avoid samples arriving on weekends samples should be sent on Mondays, Tuesdays or Wednesdays only. Royal Mail Safeboxes will be provided by UCL CTC for the mailing of
the samples. To avoid delays in samples being delivered please post safeboxes directly into Royal Mail postboxes (i.e. do not send safeboxes through the hospitals post room).

A blood sample worksheet must be completed for each sample being posted and included in the safebox. Copies of the worksheet are held in the Investigator Site File.

Samples will be sent to:

John Hartley
GeDDiS Trial
ECMC GLP Laboratory
Ground Floor
UCL Cancer Institute
Paul O’Gorman Building
72 Huntley Street
London
WC1E 6BT
UK

A fax cover sheet and a copy of the blood sample worksheet should be sent to notify the UCL Cancer Institute when a sample is posted. A confirmation fax will be sent back to the Site when the sample arrives in the post. Copies of the fax cover sheet are held in the Investigator Site File.

Samples will be stored in the UCL Cancer Institute at -80°C until analysis.

**How samples collected outside the UK are to be processed and sent**

Blood samples collected for patients outside the UK should be stored at site at -20°C. These will be transported to the UK by courier. The courier and all transport materials will be supplied by UCL CTC.

Prior to storage at -20°C, blood samples must be transferred into a labelled cryovial(s) or similar which is suitable for freezing. Samples should be frozen on the same day as collection.

**What analyses are to be performed on the samples**

DNA will be extracted and genetic analyses, including typing for functional polymorphisms, will be carried out to examine their influence on response and toxicity to treatment.

Any future research on these samples would be subject to separate ethical approval(s).

**Tumour tissue**

The stored tumour tissue is to be analysed to assess prognostic immune biomarkers and to develop an immunoscore, and to evaluate whether these can be used to predict response to chemotherapy and immune therapies.
21. References


# APPENDIX 1: ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ALP</td>
<td>Alkaline phosphatase</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine transaminase</td>
</tr>
<tr>
<td>AR</td>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>bd</td>
<td>Twice daily</td>
</tr>
<tr>
<td>CCC</td>
<td>Country Coordinating Centre</td>
</tr>
<tr>
<td>CI</td>
<td>Chief Investigator</td>
</tr>
<tr>
<td>CR</td>
<td>Complete response</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CT</td>
<td>Computerised Tomography</td>
</tr>
<tr>
<td>CTA</td>
<td>Clinical Trial Authorisation</td>
</tr>
<tr>
<td>CTCAE</td>
<td>National Cancer Institute Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>CTSA</td>
<td>Clinical Trial Site Agreement</td>
</tr>
<tr>
<td>CV</td>
<td>Curriculum vitae</td>
</tr>
<tr>
<td>DSUR</td>
<td>Development Safety Update Report</td>
</tr>
<tr>
<td>EC</td>
<td>Ethics Committee</td>
</tr>
<tr>
<td>EudraCT</td>
<td>European Clinical Trials Database</td>
</tr>
<tr>
<td>G-CSF</td>
<td>Granulocyte Colony Stimulating Factor</td>
</tr>
<tr>
<td>ICH GCP</td>
<td>International Conference of Harmonisation-Good Clinical Practice</td>
</tr>
<tr>
<td>IDMC</td>
<td>Independent Data Monitoring Committee</td>
</tr>
<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
</tr>
<tr>
<td>ISF</td>
<td>Investigator Site File</td>
</tr>
<tr>
<td>ISRCTN</td>
<td>International Standard Randomised Controlled Trial Number</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention To Treat</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Image</td>
</tr>
<tr>
<td>MHRA</td>
<td>Medicines and Healthcare products Regulatory Agency</td>
</tr>
<tr>
<td>NCRI</td>
<td>National Cancer Research Institute</td>
</tr>
<tr>
<td>OS</td>
<td>Overall Survival</td>
</tr>
<tr>
<td>PD</td>
<td>Progressive Disease</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression Free Survival</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PR</td>
<td>Partial Response</td>
</tr>
<tr>
<td>qds</td>
<td>Four times daily</td>
</tr>
<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
</tr>
<tr>
<td>RECsT</td>
<td>Response Evaluation Criteria in Solid Tumours</td>
</tr>
<tr>
<td>RNOH</td>
<td>Royal National Orthopaedic Hospital</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAKK</td>
<td>Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung</td>
</tr>
<tr>
<td>SAKK CC</td>
<td>SAKK Coordinating Center</td>
</tr>
<tr>
<td>SAR</td>
<td>Serious Adverse Reaction</td>
</tr>
<tr>
<td>SD</td>
<td>Stable Disease</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>TMG</td>
<td>Trial Management Group</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>TSC</td>
<td>Trial Steering Committee</td>
</tr>
<tr>
<td>UCL CTC</td>
<td>CR UK and UCL Cancer Trials Centre</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper Limit of Normal</td>
</tr>
</tbody>
</table>
APPENDIX 2: RECIST CRITERIA
Response Evaluation Criteria in Solid Tumours (RECIST)\textsuperscript{[47]}

Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint.

**Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

**Measurable lesions** – Tumour lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with callipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant lymph nodes: For malignant lymph nodes to be considered pathologically enlarged and measurable, a lymph node must be:

- ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

**Non-measurable lesions** – All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitis, involvement of skin or lung abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

**Measurement of lesion**: All measurements should be taken and recorded in metric notation, using callipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

**Clinical lesions**: Clinical lesions will only be considered measurable when they are superficial and ≥ 10mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion, is recommended.

**Chest X-ray**: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on the chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

- CT is the best currently available and reproducible methods to measure target lesions selected for response assessment. CT scans of the chest, abdomen and pelvis should be contiguous throughout all the anatomic region of interest. As a general rule,
the minimum size of a measurable lesion at baseline should be no less than double the slice thickness and also have minimum size of 10mm.

Baseline documentation of “Target” and “Non-Target” lesions

- All measurable lesions up to a maximum of two lesions per organ and 5 lesions in total, representative of all involved organs should be identified as **target lesions** and recorded and measured at baseline.

- Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs and should be those that lend themselves to reproducible repeated measurements. On occasion, the largest lesion may not lend itself to reproducible measurement, in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

- Only the short axis of **lymph nodes** identified as target lesions contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour.

- A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterise the objective tumour.

- All other lesions (or sites of disease) including pathological lymph nodes should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases ‘unequivocal progression’ of each should be noted throughout follow-up. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g. multiple enlarged pelvic lymph nodes or multiple liver metastases).
Response Criteria

<table>
<thead>
<tr>
<th>Evaluation of target lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete Response (CR):</strong> Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to &lt;10 mm</td>
</tr>
<tr>
<td><strong>Partial Response (PR):</strong> At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters</td>
</tr>
<tr>
<td><strong>Progressive Disease (PD):</strong> At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of one or more new lesions is also considered progression).</td>
</tr>
<tr>
<td><strong>Stable Disease (SD):</strong> Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evaluation of non-target lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete Response (CR):</strong> Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (&lt;10 mm short axis)</td>
</tr>
<tr>
<td><strong>Incomplete Response/Non-CR/Non-PD:</strong> Persistence of one or more non-target lesion(s) or/and maintenance of tumour marker level above the normal limits</td>
</tr>
<tr>
<td><strong>Progressive Disease (PD):</strong> Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)</td>
</tr>
</tbody>
</table>

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

Special notes on the assessment of target lesions:
Lymph nodes identified as target lesions should always have the actual short axis measurements recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10mm on study. This means when lymph nodes are included as targets lesions, the sum of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10mm.

New lesions:
The finding of new lesions should be unequivocal i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour. A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example, because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.
Evaluation of best overall response

- The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into the account the requirements for confirmation.
- When no imaging/measurements is done at all at a particular time point, the patient is not evaluable (NE) at that time point.
- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response.
- For equivocal findings of progression (e.g. very small and uncertain new lesions, cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression in confirmed, the date of progression should be the earlier date when progression was suspected.

Confirmation

- Confirmation of PR and CR is required to ensure responses identified are not the result of measurement error.
- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumour measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded on study. The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest sum on the study (if the baseline sum is the smallest, this is the reference for calculation of PD)
APPENDIX 3: QUALITY OF LIFE QUESTIONNAIRES (UK)

Quality of Life questionnaires in languages other than English will be supplied separately.

EORTC QLQ-C30 (version 3)

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

Patient trial number: [GED] [____] - [____]
Please fill in your initials: [____] [____]
Your birthdate (Day, Month, Year): [____] [____] [____]
Today's date (Day, Month, Year): [____] [____] [____]

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

During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Were you limited in doing either your work or other daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Were you limited in pursuing your hobbies or other leisure time activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Were you short of breath?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. Have you had pain?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. Did you need to rest?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. Have you had trouble sleeping?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. Have you felt weak?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. Have you lacked appetite?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14. Have you felt nauseated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15. Have you vomited?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Please go on to the next page
### During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>16. Have you been constipated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>17. Have you had diarrhea?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18. Were you tired?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19. Did pain interfere with your daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>21. Did you feel tense?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>22. Did you worry?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>23. Did you feel irritable?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>24. Did you feel depressed?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>25. Have you had difficulty remembering things?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>26. Has your physical condition or medical treatment interfered with your family life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>27. Has your physical condition or medical treatment interfered with your social activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>28. Has your physical condition or medical treatment caused you financial difficulties?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Question</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>29. How would you rate your overall health during the past week?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Excellent</td>
</tr>
<tr>
<td>30. How would you rate your overall quality of life during the past week?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Excellent</td>
</tr>
</tbody>
</table>

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EORTC QLQ-FA13

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

**During the past week:**

1. Have you lacked energy?  
   - Not at All  
   - A Little  
   - Quite a Bit  
   - Very Much

2. Have you felt exhausted?  
   - Not at All  
   - A Little  
   - Quite a Bit  
   - Very Much

3. Have you felt slowed down?  
   - Not at All  
   - A Little  
   - Quite a Bit  
   - Very Much

4. Did you feel sleepy during the day?  
   - Not at All  
   - A Little  
   - Quite a Bit  
   - Very Much

5. Did you have trouble getting things started?  
   - Not at All  
   - A Little  
   - Quite a Bit  
   - Very Much

6. Did you feel discouraged?  
   - Not at All  
   - A Little  
   - Quite a Bit  
   - Very Much

7. Did you feel helpless?  
   - Not at All  
   - A Little  
   - Quite a Bit  
   - Very Much

8. Did you feel frustrated?  
   - Not at All  
   - A Little  
   - Quite a Bit  
   - Very Much

9. Did you have trouble thinking clearly?  
   - Not at All  
   - A Little  
   - Quite a Bit  
   - Very Much

10. Did you feel confused?  
    - Not at All  
    - A Little  
    - Quite a Bit  
    - Very Much

11. Did you have trouble completing things?  
    - Not at All  
    - A Little  
    - Quite a Bit  
    - Very Much

12. Did tiredness interfere with your daily activities?  
    - Not at All  
    - A Little  
    - Quite a Bit  
    - Very Much

13. Did you feel that your tiredness is (was) not understood by the people who are close to you?  
    - Not at All  
    - A Little  
    - Quite a Bit  
    - Very Much

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**PedsQL™**

**Paediatric Quality of Life Inventory**

Version 4.0 – UK English

**TEENAGER REPORT (ages 13-18)**

Patient trial number: GED

Please fill in your initials: __________

Your birthdate (Day, Month, Year): __________

Today's date (Day, Month, Year): __________

---

**DIRECTIONS**

On the following page is a list of things that might be a problem for you. Please tell us how much of a problem each one has been for you during the **PAST MONTH** by circling:

- **0** if it is *never* a problem
- **1** if it is *almost never* a problem
- **2** if it is *sometimes* a problem
- **3** if it is *often* a problem
- **4** if it is *almost always* a problem

There are no right or wrong answers. If you do not understand a question, please ask for help.
In the **PAST MONTH**, how much of a **problem** has this been for you …

### About My Health and Activities (PROBLEMS WITH…)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. It is hard for me to walk more than a couple of streets (about 100 metres)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. It is hard for me to run</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. It is hard for me to do sports activities or exercise</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. It is hard for me to lift heavy things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. It is hard for me to have a bath or shower by myself</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. It is hard for me to do chores around the house</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. I have aches and pains</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. I feel tired</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### About My Feelings (PROBLEMS WITH…)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I feel afraid or scared</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I feel sad</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I feel angry</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I have trouble sleeping</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I worry about what will happen to me</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### How I Get On with Others (PROBLEMS WITH…)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I have trouble getting on with other teenagers</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Other teenagers do not want to be my friend</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Other teenagers tease me</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I cannot do things that other teenagers my age can do</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. It is hard to keep up with other teenagers my age</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### About School / College (PROBLEMS WITH…)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. It is hard to pay attention in class</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I forget things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I have trouble keeping up with my school / college work</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I miss school / college because of not feeling well</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I miss school / college to go to the doctor or hospital</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
PedsQL™ Cancer Module

Version 3.0

TEEN REPORT (ages 13-18)

Patient trial number: GED_____•_____•
Please fill in your initials: ________
Your birthdate (Day, Month, Year): ________ ________ ________
Today's date (Day, Month, Year): ________ ________ ________

DIRECTIONS

Teens with cancer sometimes have special problems. Please tell us how much of a problem each one has been for you during the past one month by circling:

- 0 if it is never a problem
- 1 if it is almost never a problem
- 2 if it is sometimes a problem
- 3 if it is often a problem
- 4 if it is almost always a problem

There are no right or wrong answers. If you do not understand a question, please ask for help.
In the past *one month*, how much of a problem has this been for you …

<table>
<thead>
<tr>
<th>Pain and Hurt <em>(PROBLEMS WITH…)</em></th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I ache or hurt in my joints and/or muscles</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I hurt a lot</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nausea <em>(PROBLEMS WITH…)</em></th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I become sick to my stomach when I have medical treatments</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Food does not taste very good to me</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I become sick to my stomach when I think about medical treatments</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I feel too sick to my stomach to eat</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Some foods and smells make me sick to my stomach</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Procedural Anxiety <em>(PROBLEMS WITH…)</em></th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Needle sticks (i.e. injections, blood tests, IV’s) hurt</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I get scared when I have to have blood tests</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I get scared about having needle sticks (i.e. injections, blood tests, IV’s)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Anxiety <em>(PROBLEMS WITH…)</em></th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I get scared when I am waiting to see the doctor</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I get scared when I have to go to the doctor</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I get scared when I have to go to the hospital</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Worry <em>(PROBLEMS WITH…)</em></th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I worry about side effects from medical treatments</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I worry about whether or not my medical treatments are working</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I worry that my cancer will come back or relapse</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cognitive Problems <em>(PROBLEMS WITH…)</em></th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. It is hard for me to figure out what to do when something bothers me</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I have trouble solving math problems</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I have trouble writing school papers or reports</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. It is hard for me to pay attention to things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. It is hard for me to remember what I read</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
In the past *one month*, how much of a *problem* has this been for you …

<table>
<thead>
<tr>
<th>Perceived Physical Appearance</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I feel I am not good looking</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I don’t like other people to see my scars</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I am embarrassed when others see my body</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Communication</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. It is hard for me to tell the doctors and nurses how I feel</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. It is hard for me to ask the doctors and nurses questions</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. It is hard for me to explain my illness to other people</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
**PedSQL™**

**Multidimensional Fatigue Scale**

Standard Version - UK English

**TEEN REPORT** (ages 13-18)

Patient trial number: GED [___] - [___]

Please fill in your initials: [___] [___] [___]

Your birthdate (Day, Month, Year): [___] [___] [___] [___] [___] [___]

Today's date (Day, Month, Year): [___] [___] [___] [___] [___] [___]

---

**DIRECTIONS**

On the following page is a list of things that might be a problem for you. Please tell us how much of a problem each one has been for you during the past ONE month by circling:

- 0 if it is **never** a problem
- 1 if it is **almost never** a problem
- 2 if it is **sometimes** a problem
- 3 if it is **often** a problem
- 4 if it is **almost always** a problem

There are no right or wrong answers. If you do not understand a question, please ask for help.
In the past **ONE month**, how much of a **problem** has this been for you

<table>
<thead>
<tr>
<th>General Fatigue (<strong>PROBLEMS WITH…</strong>)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I feel tired</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I feel physically weak (not strong)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I feel too tired to do things that I like to do</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I feel too tired to spend time with my friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I have trouble finishing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. I have trouble starting things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sleep/Rest Fatigue (<strong>PROBLEMS WITH…</strong>)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I sleep a lot</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. It is hard for me to sleep through the night</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I feel tired when I wake up in the morning</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I rest a lot</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I take a lot of naps</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. I spend a lot of time in bed</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cognitive Fatigue (<strong>PROBLEMS WITH…</strong>)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. It is hard for me to keep my attention on things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. It is hard for me to remember what people tell me</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. It is hard for me to remember what I just heard</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. It is hard for me to think quickly</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I have trouble remembering what I was just thinking</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. I have trouble remembering more than one thing at a time</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
PedsQL™
Paediatric Quality of Life Inventory
Version 4.0 - UK English

PARENT REPORT for TEENS (ages 13-18)

Patient trial number: GED____-____
Patient initials: ______
Birthdate (Day, Month, Year): ______
Today's date (Day, Month, Year): ______

DIRECTIONS

On the following page is a list of things that might be a problem for your teen. Please tell us how much of a problem each one has been for your teen during the past ONE month by circling:

0 if it is never a problem
1 if it is almost never a problem
2 if it is sometimes a problem
3 if it is often a problem
4 if it is almost always a problem

There are no right or wrong answers. If you do not understand a question, please ask for help.
In the past **ONE month**, how much of a **problem** has your teen had with

<table>
<thead>
<tr>
<th>Physical Functioning (PROBLEMS WITH...)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Walking 100 metres</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Running</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Participating in sports activities or exercise</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Lifting something heavy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Taking a bath or shower by him or herself</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. Doing chores around the house</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Having aches or pains</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Low energy levels</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Emotional Functioning (PROBLEMS WITH...)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling afraid or scared</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Feeling sad</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Feeling angry</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Trouble sleeping</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Worrying about what will happen to him or her</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Social Functioning (PROBLEMS WITH...)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Getting on with other teens</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Other teens not wanting to be his or her friend</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Getting teased by other teens</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Not being able to do things that other teens his or her age can do</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Keeping up with other teens</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>School Functioning (PROBLEMS WITH...)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Paying attention in class</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Forgetting things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Keeping up with schoolwork</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Missing school because of not feeling well</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Missing school to go to the doctor or hospital</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
PedsQL™
Cancer Module
Version 3.0

PARENT REPORT for TEENS (ages 13-18)

Patient trial number: GED ______ - _______
Patient initials: ______
Birthdate (Day, Month, Year): ______
Today's date (Day, Month, Year): ______

DIRECTIONS

Teens with cancer sometimes have special problems. On the following page is a list of things that might be a problem for your teen. Please tell us how much of a problem each one has been for your teen during the past one month by circling:

0 if it is never a problem
1 if it is almost never a problem
2 if it is sometimes a problem
3 if it is often a problem
4 if it is almost always a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.
In the past **month**, how much of a **problem** has your teen had with …

### Pain and Hurt (**PROBLEMS WITH...**)  
<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Aches in joints and/or muscles</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Having a lot of pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### Nausea (**PROBLEMS WITH...**)  
<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Becoming nauseated during medical treatments</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Food not tasting very good to him/her</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Becoming nauseated while thinking about medical treatments</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Feeling too nauseous to eat</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Some foods and smells making him/her nauseous</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### Procedural Anxiety (**PROBLEMS WITH...**)  
<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Needle sticks (i.e. injections, blood tests, IV’s) causing him/her pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Getting anxious about having blood drawn</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Getting anxious about having needle sticks (i.e. injections, blood tests, IV’s)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### Treatment Anxiety (**PROBLEMS WITH...**)  
<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Getting anxious when waiting to see the doctor</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Getting anxious about going to the doctor</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Getting anxious about going to the hospital</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### Worry (**PROBLEMS WITH...**)  
<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Worrying about side effects from medical treatments</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Worrying about whether or not his/her medical treatments are working</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Worrying that the cancer will reoccur or relapse</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### Cognitive Problems (**PROBLEMS WITH...**)  
<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Difficulty figuring out what to do when something bothers him/her</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Trouble solving math problems</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Trouble writing school papers or reports</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Difficulty paying attention to things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Difficulty remembering what he/she reads</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
In the past **one month**, how much of a **problem** has your teen had with …

<table>
<thead>
<tr>
<th>Perceived Physical Appearance (PROBLEMS WITH…)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling that he/she is not good looking</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Not liking other people to see his/her scars</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Being embarrassed about others seeing his/her body</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Communication (PROBLEMS WITH…)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Difficulty telling the doctors and nurses how he/she feels</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Difficulty asking the doctors or nurses questions</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Difficulty explaining his/her illness to other people</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
PedsQL™
Multidimensional Fatigue Scale
Standard Version - UK English

PARENT REPORT for TEENS (ages 13-18)

Patient trial number: GED [ ] [ ] [ ] [ ]
Patient initials: [ ] [ ] [ ]
Birthdate (Day, Month, Year): [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]
Today's date (Day, Month, Year): [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

DIRECTIONS

On the following page is a list of things that might be a problem for your child. Please tell us how much of a problem each one has been for your child during the past ONE month by circling:

0 if it is never a problem
1 if it is almost never a problem
2 if it is sometimes a problem
3 if it is often a problem
4 if it is almost always a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.
In the past **ONE month**, how much of a **problem** has this been for your child?

### General Fatigue (PROBLEMS WITH…)

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling tired</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Feeling physically weak (not strong)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Feeling too tired to do things that he/she likes to do</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Feeling too tired to spend time with his/her friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Trouble finishing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. Trouble starting things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### Sleep/Rest Fatigue (PROBLEMS WITH…)

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Sleeping a lot</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Difficulty sleeping through the night</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Feeling tired when he/she wakes up in the morning</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Resting a lot</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Taking a lot of naps</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. Spending a lot of time in bed</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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</tbody>
</table>

### Cognitive Fatigue (PROBLEMS WITH…)

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Difficulty keeping his/her attention on things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Difficulty remembering what people tell him/her</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Difficulty remembering what he/she just heard</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Difficulty thinking quickly</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Trouble remembering what he/she was just thinking</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. Trouble remembering more than one thing at a time</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
APPENDIX 4: HEALTH ECONOMIC QUESTIONNAIRES

Health Questionnaire

Patient trial number: GED [ ] [ ] [ ]
Please fill in your initials: [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]
Your birthdate (Day, Month, Year): [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]
Today's date (Day, Month, Year): [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

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

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

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

Usual Activities (e.g. work, study, housework, family or leisure activities)
I have no problems with performing my usual activities
I have some problems with performing my usual activities
I am unable to perform my usual activities

Pain/Discomfort
I have no pain or discomfort
I have moderate pain or discomfort
I have extreme pain or discomfort

Anxiety/Depression
I am not anxious or depressed
I am moderately anxious or depressed
I am extremely anxious or depressed
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

© 1998 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group
Patient trial number: GED [redacted] - [redacted]
Please fill in your initials: [redacted]
Your birthdate (Day, Month, Year): [redacted]
Today's date (Day, Month, Year): [redacted]

**Describing your health TODAY**

Under each heading, mark ONE box that best describes your health TODAY

**Mobility (walking about)**
I have no problems walking about [redacted]
I have some problems walking about [redacted]
I have a lot of problems walking about [redacted]

**Looking after myself**
I have no problems washing or dressing myself [redacted]
I have some problems washing or dressing myself [redacted]
I have a lot of problems washing or dressing myself [redacted]

**Doing usual activities (for example, going to school, hobbies, sports, playing, doing things with family or friends)**
I have no problems doing my usual activities [redacted]
I have some problems doing my usual activities [redacted]
I have a lot of problems doing my usual activities [redacted]

**Having pain or discomfort**
I have no pain or discomfort [redacted]
I have some pain or discomfort [redacted]
I have a lot of pain or discomfort [redacted]

**Feeling worried, sad or unhappy**
I am not worried, sad or unhappy [redacted]
I am a bit worried, sad or unhappy [redacted]
I am very worried, sad or unhappy [redacted]
How good is your health TODAY

- We would like to know how good or bad your health is TODAY.
- This line is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the line that shows how good or bad your health is TODAY.

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## APPENDIX 5: PERFORMANCE STATUS SCALES

<table>
<thead>
<tr>
<th>WHO Performance Status (Age ≥16 years)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Able to carry out all normal activity without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out light work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry out any selfcare; totally confined to bed or chair.</td>
</tr>
</tbody>
</table>
APPENDIX 6: DOSE REDUCTIONS OR MODIFICATIONS

Dose modifications
Adverse events will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

Doxorubicin
Doxorubicin chemotherapy is a standard regimen, and as such it is intended that adverse events should be managed at the discretion of local investigators according to local guidelines. Suggested management, as guidance only, is given below.

Haematological toxicity
Thrombocytopenia
If platelet count is <100 x 10^9/L, delay chemotherapy for a week or until resolution to ≥100 x 10^9/L. If treatment is delayed for more than 2 weeks, then the patient should be withdrawn from the trial.

Neutropenia
If neutrophil count is <1.0 x 10^9/L, delay chemotherapy for a week or until resolution to ≥ 1.0 x 10^9/L. If treatment is delayed for more than 2 weeks, then the patient should be withdrawn from the trial.

Non-haematological toxicity
Febrile neutropenia
If febrile neutropenia occurs, GCSF could be introduced. Alternatively, or if further episodes of febrile neutropenia occur after introduction of GCSF, doxorubicin dose can be modified according to the table below for subsequent cycles. The decision to administer GCSF will be at the discretion of the treating clinician and should be given according to local institutional policy.

Cardiotoxicity
Further measurements of LVEF by MUGA scan or echocardiography during treatment will be performed according to local institutional rules, acknowledging that some sites may not perform further measurements unless there is clinical concern. If LVEF <45% or 20% decrease, consideration should be given to discontinuing treatment.

Other non-haematological toxicities
For grade 3 or 4 non-haematological toxicities delay doxorubicin for a week, or until the toxicity is ≤ grade1. If treatment is delayed for >3 weeks the patient should be withdrawn from the trial.

Dose modifications
For a patient requiring a dose reduction for toxicity as described above, dose modifications may be made according to local guidelines, or according to the following suggested schedule:

<table>
<thead>
<tr>
<th>Reduction</th>
<th>Doxorubicin 75 mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st reduction</td>
<td>20% (60 mg/m²)</td>
</tr>
<tr>
<td>2nd reduction</td>
<td>33% (50 mg/m²)</td>
</tr>
<tr>
<td>3rd reduction</td>
<td>Stop treatment</td>
</tr>
</tbody>
</table>

Treatment overdose
Recommendations for managing treatment overdoses as stated in the SPC for doxorubicin is given below, however, sites may follow local procedures as appropriate.
Acute overdose with doxorubicin will result in gastrointestinal toxic events and generally appears early after drug administration. Most patients recover from this within three weeks.

Delayed cardiac failure may occur up to six months after the overdosage. Patients should be observed carefully and should signs of cardiac failure arise, be treated along conventional lines.

**Gemcitabine and docetaxel**

**Haematological toxicity**

**Thrombocytopenia**

If pre-chemotherapy platelet count is \(<100 \times 10^9/L\) delay chemotherapy for one week or until resolution to \(\geq 100 \times 10^9/L\).

If the patient is delayed at day 8, but toxicity has resolved sufficiently by day 15, the gemcitabine and docetaxel can be administered but with a dose reduction as indicated in the table below for all subsequent cycles. If treatment is delayed for more than 2 weeks, then the patient should be withdrawn from the trial.

**Neutropenia**

If neutrophil count is \(<1.0 \times 10^9/L\) on day 1, delay chemotherapy for one week or until resolution to \(\geq 1.0 \times 10^9/L\).

If the patient is delayed at day 8, but toxicity has resolved sufficiently by day 15, the gemcitabine and docetaxel can be administered but with a dose reduction as indicated in the table below for all subsequent cycles. If treatment is delayed for more than 2 weeks, then the patient should be withdrawn from the trial.

**Non-haematological toxicity**

**Febrile neutropenia**

If febrile neutropenia occurs at any time during a treatment cycle, no further treatment will be administered during that cycle. Following an episode of febrile neutropenia, GCSF may be introduced for subsequent cycles. If further episodes of febrile neutropenia occur, the doses of both gemcitabine and docetaxel should be modified according to the table below for all subsequent cycles.

**Infection with grade 3 or 4 neutrophil count**

If a patient experiences any grade 3 or 4 infection with grade 3 or 4 neutrophil count during treatment, no additional anticancer agents will be administered during that cycle. Following an episode of infection with grade 3 or 4 neutrophil count, GCSF may be introduced for subsequent cycles. If further episodes occur, the doses of both gemcitabine and docetaxel should be modified according to the table below for all subsequent cycles.

**Neuropathy**

Patients who experience grade 2 neuropathy (motor or sensory) during a treatment cycle will have no further treatment during that cycle and for all subsequent cycles both the gemcitabine and docetaxel will be modified according to the table below.

Patients who experience grade 3 or 4 neuropathy (motor or sensory) at any time will be withdrawn from the trial.

**Pulmonary**

Patients who experience any grade pulmonary toxicity that is attributable to gemcitabine or docetaxel will have no further treatment during that cycle and for all subsequent cycles both the gemcitabine and docetaxel will be modified according to the table below for all subsequent cycles.
Any patient who experiences grade 3 pulmonary fibrosis or any grade 4 pulmonary toxicity at any time will be withdrawn from the trial.

**Hypersensitivity reactions**
Grade 1 or 2 allergic reactions/hypersensitivity that are attributable to docetaxel will be managed by interrupting the docetaxel infusion, decreasing the rate of infusion, and administration of chlorphenamine and/or additional corticosteroids. No dose reduction is required; however, pre-treatment with dexamethasone and chlorphenamine will be required for all subsequent cycles.

Patients who experience a grade 3 or 4 allergic reaction/hypersensitivity that are attributable to docetaxel will be withdrawn from the trial.

**Weight gain/fluid retention**
Grade 1 or 2 weight gain attributable to docetaxel administration does not require a dose reduction. Patients experiencing Grade 3 weight gain (>20% increase from baseline) attributable to docetaxel will be withdrawn from the trial.

**Other non-haematological toxicities**
For grade 3 or 4 non-haematological toxicities not listed above that are related to either gemcitabine or docetaxel, both agents should be withheld until the toxicity is ≤ grade 1. If the non-haematological toxicity resolves to ≤ grade 1 by day 35 of a treatment cycle, both agents may be restarted at a reduced dose as outlined in the table below. If the toxicity has not resolved to ≤ grade 1 by day 35 of a treatment cycle, the patient will be withdrawn from the trial.

**Dose Modifications**
For a patient requiring a dose reduction for toxicity as described above, the following dose modification should be used. Up to two dose modifications are permitted. If further toxicity is experienced, the patient should be withdrawn from the trial.

<table>
<thead>
<tr>
<th></th>
<th>Gemcitabine 675 mg/m²</th>
<th>Docetaxel 75mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; reduction</td>
<td>20% (540 mg/m²)</td>
<td>20% (60 mg/m²)</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; reduction</td>
<td>33% (450 mg/m²)</td>
<td>33% (50 mg/m²)</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; reduction</td>
<td>Stop treatment</td>
<td>Stop treatment</td>
</tr>
</tbody>
</table>

**Treatment overdose**
Recommendation for managing treatment overdoses as stated in the SPC for the trial treatments is given below, however, sites may follow local procedures as appropriate.

Gemcitabine: There is no known antidote for overdose of gemcitabine. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and receive supportive therapy, as necessary.

Docetaxel: There is no known antidote for docetaxel overdose. In case of overdose, the patient should be kept in a specialised unit and vital functions closely monitored. In cases of overdose, exacerbation of adverse events may be expected. The primary anticipated complications of overdose would consist of bone marrow suppression, peripheral neurotoxicity and mucositis. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.
APPENDIX 7: SCHEDULE OF ASSESSMENTS

Whilst not mandated, it is strongly recommended that all patients start treatment within 14 days of randomisation.

Assessments will be carried out according to the following schedule:

<table>
<thead>
<tr>
<th>Pre-randomisation</th>
<th>TREATMENT</th>
<th>AFTER TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 12 weeks prior to randomisation</td>
<td>Day 1 of each cycle</td>
<td>30 days post last trial treatment</td>
</tr>
<tr>
<td>Within 21 days prior to randomisation</td>
<td>Day 8 of each cycle</td>
<td>24 weeks after randomisation</td>
</tr>
<tr>
<td>Within 14 days prior to randomisation</td>
<td>12 weeks after randomisation</td>
<td>Every 12 weeks after PD</td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>18 weeks after randomisation</td>
<td></td>
</tr>
</tbody>
</table>

- **Medical history**
- **Informed consent**
- **Cancer symptoms/toxicity assessment**
- **Clinical examination**
- **Performance status**
- **Vital signs**
- **Adverse events**
- **Patient diary review (UK only)**
- **MUGA/ECHO**
- **Haematology**
- **Biochemistry**
- **CT/MRI**
- **Quality of life assessment**
- **Pathology review**
- **Blood sample for TR**
- **Assessment for survival**

1. Repeat during treatment as clinically indicated.
2. Haematology should include: haemoglobin, white cell count, neutrophil count, platelets
3. Biochemistry should include: sodium, potassium, urea, creatinine, bilirubin, alkaline phosphatase, AST or ALT, albumin
4. Scans must be performed at 12 and 24 weeks after randomisation, irrespective of relationship to chemotherapy cycle, ± 1 week. Additional CT/MRI scans between these time points may be performed at discretion of the local PI. After the 24 week scan, scans should be performed every 12 weeks until disease progression, for up to 24 months after randomisation. Patients who have not progressed after 24 months should be scanned according to local practice.
5. Quality of life assessments at weeks 12 and 24 will coincide with CT/MRI scans. The assessment at week 18 may be carried out by post.
6. Pathology samples should be submitted for central review within 3 months of trial entry (UK patients only).
7. This blood sample may be taken at any time after randomisation and prior to commencement of treatment.
8. Assessment of survival may be done by telephone if more convenient.
9. Pre-treatment assessments do not need to be repeated if carried out within 14 days prior to commencement of treatment as part of the Pre-randomisation evaluation.
## APPENDIX 8: VERSION HISTORY

<table>
<thead>
<tr>
<th>Protocol:</th>
<th>Amendments:</th>
<th>Summary of main changes from previous version.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Version no.</strong></td>
<td><strong>Date</strong></td>
<td><strong>Protocol Section (no./title)</strong></td>
</tr>
<tr>
<td>1</td>
<td>01/07/10</td>
<td>n/a</td>
</tr>
<tr>
<td>2</td>
<td>17/08/10</td>
<td>3 (selection of sites/site investigators)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16.1 (ethical approval)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16.5 (patient confidentiality &amp; data protection)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20.2 (sample collection &amp; processing)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>3.2.2 (secondary endpoints)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.1.2 (training requirements for site staff) &amp; 3.2.1 (site initiation)</td>
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<td>3</td>
<td>12/04/11</td>
<td>4 (informed consent)</td>
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<tr>
<td></td>
<td></td>
<td>5.2 (screening log) &amp; 5.3.3 (pregnancy, birth control &amp; infertility)</td>
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<td></td>
<td>6.1 (randomisation procedure)</td>
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<tr>
<td></td>
<td></td>
<td>7.3 (treatment details), 7.3.3 (pharmacy responsibilities), 7.3.4 (drug accountability) &amp; 7.4 (dose modifications)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 (assessments), 8.1 (pretreatment assessments), 8.2 (assessments during treatment), 8.3 (assessments on completion of treatment), 8.4 (haematological drug effects) &amp; 8.5 (haematological disease assessment) &amp; 8.7 (central pathology review)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 (pharmacovigilance)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12.2 (central monitoring), 12.4.1 (trial management group) &amp; 12.4.4 (role of UCL CTC)</td>
</tr>
<tr>
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<td>14.2 (archiving of trial documents)</td>
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<td>17.1 (sponsor details)</td>
</tr>
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<td></td>
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<td>20 (translational research)</td>
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<td></td>
<td>21 (references)</td>
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<td>Amendments:</td>
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</tr>
<tr>
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<td>-----------------</td>
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<td><strong>Date</strong></td>
<td><strong>Protocol Section (no./title)</strong></td>
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<td>4</td>
<td>19/10/11</td>
<td>3.2.2 (required documentation)</td>
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<td>5</td>
<td>04/03/13</td>
<td>1.1 (summary of trial design)</td>
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<td>Protocol:</td>
<td>Amendments:</td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>Version no.</td>
<td>Date</td>
<td>Protocol Section (no./title)</td>
</tr>
<tr>
<td>6</td>
<td>07/06/13</td>
<td>8.0 Table of Assessment 8.3 Assessment at completion of treatment</td>
</tr>
<tr>
<td>7</td>
<td>27/07/15</td>
<td>10.6 Development Safety Update Reports (DSURs) 20.2 Sample Collection and Processing</td>
</tr>
<tr>
<td>8</td>
<td>22/03/16</td>
<td>1.1 Summary of Trial Design 8. Assessments 8.4 Assessments during follow up 8.6 Radiological Disease Evaluation</td>
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