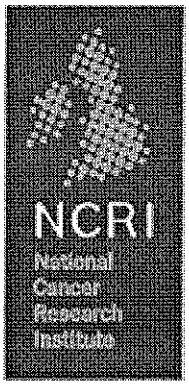

R-CODOX-M/IVAC for DLBCL or BL

A Phase II Single Arm Study of the use of CODOX-M/IVAC with Rituximab (R-CODOX-M/IVAC) in the treatment of patients with Diffuse Large B-Cell Lymphoma (DLBCL) or Burkitt's Lymphoma (BL) of International Prognostic Index (IPI) High or High Intermediate Risk

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Authorised by Sponsor Representative	Professor Jonathan Ledermann
Signature & Date approved	3/9/09

A trial developed by the National Cancer Research Institute Lymphoma Study Group and adopted by the National Cancer Research Network

Table of Contents

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The protocol may be revised periodically. If so, participating sites will be informed. New sites are advised to check with the Lymphoma team, UCL CTC that they have the current version of the protocol.

Section 2: STUDY SYNOPSIS

Study Title	A Phase II Single Arm Study of the use of CODOX-M/IVAC with Rituximab (R-CODOX-M/IVAC) in the treatment of patients with Diffuse Large B-Cell Lymphoma (DLBCL) or Burkitt's lymphoma of International Prognostic Index (IPI) High or High-Intermediate Risk
Short study title	R-CODOX-M/IVAC for DLBCL or BL
Start and end dates of study	Start date: February 2006 Patients will be recruited over 2-3 years and followed until death
Primary Objectives	To evaluate the improvement in complete response rate and assess toxicity of Rituximab combined with CODOX-M/IVAC
Primary endpoint	Progression Free Survival
Clinical Phase	Phase II
Study design	A multicentre, single arm trial assessing the use of Rituximab (8 doses) with CODOX-M/IVAC (2 cycles) in patients with newly diagnosed CD20 positive diffuse large B cell or Burkitt's lymphoma of International Prognostic Index (IPI) High or High-Intermediate Risk
Number of patients	150 patients (DLBCL or Burkitt's lymphoma)
Inclusion criteria	• Patients with histological diagnosis of diffuse large B-cell or Burkitt's lymphoma according to the World Health Organisation classification whatever the subtype.[1] The B-cell nature of the proliferation must have been verified by the positivity with an anti-CD20 antibody before randomisation • International Prognostic Index High or High-Intermediate Risk Patients • Stage II-IV • Aged 18-60yrs (consideration of individual patients' ability to tolerate intensive chemotherapy required) • Not previously treated **(although pre-treatment with steroids is acceptable)** • Patients who have signed an informed consent form
Treatment	R-CODOX-M/IVAC: 8 doses of Rituximab 2 cycles of CODOX-M/IVAC
Treatment length	16 weeks

Section 3: BACKGROUND

Disease Background

Non-Hodgkin's lymphoma (NHL) is increasing in incidence with more than 287,000 cases world-wide and 9,000 cases in UK diagnosed each year.[2] Diffuse large B cell NHL (DLBCL) is the most frequently occurring NHL, constituting approximately 31% of all NHL. The 5 year survival rate for patients with diffuse large B cell lymphoma with IPI high-intermediate and high risk is 43% and 26% respectively with conventional treatment.[3]

Study Drugs Background

CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) given every 3 weeks has been considered as standard care for all patients with DLBCL. There are a number of studies that suggest dose intensification beyond standard dose CHOP might be efficacious in increasing complete remission rate and possibly long term survival. Pettengell et al (1982) demonstrated that the use of granulocyte colony stimulating factor (G-CSF) in patients receiving intensive chemotherapy for NHL enabled more patients to complete therapy and allowed delivery of the planned dose on time in a greater proportion of patients.[4] G-CSF treated patients received on average 12% greater dose intensity without significantly increased toxicity. Two independent studies by the German High Grade Non-Hodgkin's Lymphoma Study Group have compared dose intensification using G-CSF support. Two weekly CHOP with standard 3 weekly CHOP and the addition of etoposide to CHOP (CHOEP) 2 and 3 weekly have been compared.[5,6] Both studies have demonstrated an increased response rate in the dose intensification arm.

Rituximab is a chimeric anti-CD20 antibody containing human IgG lambda and kappa constant regions with murine variable regions. Rituximab and CHOP chemotherapy have non-overlapping toxic effects with some evidence of *in vitro* synergy in terms of efficacy. A French study organised by Groupe d'Etude des Lymphomes de l'Adulte (GELA) investigated the addition of rituximab to CHOP (R-CHOP). This study reported a complete response rate of 76% with R-CHOP and a decreased risk of death at 2 years of 12% in the Rituximab arm.[7] Data for R-CHOP in age adjusted IPI high-intermediate and high risk patients is limited but preliminary data demonstrates 2 year progression free and overall survival of 64% and 74% respectively.[8]

Further studies have considered escalating therapy by using upfront high dose therapy with stem cell rescue. An Italian study demonstrated a benefit of upfront high dose therapy (HDT) and autografting in patients with an age adjusted IPI score of 2 but not for those with an age adjusted IPI score of 3.[9] Final analysis of the LNH87 GELA study suggested that HDT benefited higher risk patients but this was on retrospective analysis of the IPI.[10] The MISTRAL study comparing 8 courses of CHOP versus high dose therapy with autografting was closed to recruitment prematurely in 2003 in the UK. NICE

guidelines had recommended the use of Rituximab in all patients with aggressive NHL stages 2-4 and neither arm of this trial included Rituximab. A recent paper by Milpied suggests a better outcome of upfront autografting over chemotherapy alone.[11] In this paper patients received 2 courses of CEEP chemotherapy which is an intensive regime and it may be that the use of intensive chemotherapy was the salient feature rather than the role of autografting in improving these patients' outcome.

Excellent results with complete response rates of 86-95% have been reported using CODOX-M/IVAC in Burkitt Lymphoma (BL).[12,13] In the study by Magrath, event free survival was 92% at 2 years. These results were confirmed by Mead whose study involving BL and Burkitt- like DLBCL patients, showed event free survival of 65% and overall survival of 73% at 2 years. BL has also been successfully treated with CODOX-M/IVAC in the preceding NCRI LY10[25] trial of CODOX-M/IVAC in Burkitt and Burkitt-like NHL with proliferation index of 100%. All studies demonstrated that this highly intensive schedule could be safely delivered in adult patients. Of note in the Magrath study is that the high risk patients tolerated the chemotherapy equivalently to the low risk group. A study by Davidson using CODOX-M/IVAC in primary refractory or relapsed HGNHL was terminated early because of the high incidence of long term toxicity in this group.[14] It is likely in this group of patients that their ability to tolerate highly intensive regimens had been jeopardised by previous chemotherapy.

It therefore seems appropriate to test CODOX-M/IVAC in a single arm phase II study in patients with newly diagnosed high and intermediate-high risk DLBCL as current regimens result in poor outcome and data suggests a better outcome with more intensive treatment. Though doses are intensified in the initial CODOX-M schedule, it includes all drugs that are in standard CHOP chemotherapy. The recent NICE guideline on the management of aggressive NHL states that all patients with a diagnosis of DLBCL eligible for CHOP should receive R-CHOP chemotherapy. For this reason Rituximab will be added to the protocol. No study incorporating Rituximab has produced data suggesting that the addition of Rituximab to chemotherapy causes a clinically significant increase in toxicity and so the addition of Rituximab is unlikely to alter the tolerability of this schedule.

Biological prognostic factors can be used in combination with the IPI to predict overall survival in DLBCL. In newly presenting patients with DLBCL treated with standard CHOP based chemotherapy regimens the presence of a germinal centre (GC) immunophenotype (defined by expression of BCL6 and CD10) is a favourable feature.[15] Rearrangement of the BCL6 gene at 3q27, the presence of a t(14;18) and/or BCL2 protein expression, deregulation of P53 (defined by over-expression of P53 in the absence of P21) and uniform high expression of FOX-P1 are adverse prognostic factors.[15-18] It has been shown that using these prognostic factors in combination with the IPI significantly improves risk stratification in DLBCL treated with CHOP based therapy. DLBCL patients with an intermediate IPI and adverse biological risk

factors have a similar outcome to patients with high IPI, considerably increasing the number of poor risk patients who may benefit from novel therapeutic regimens. It is therefore proposed that biological risk factors be assessed as patients are registered into this trial in order to evaluate the prognostic model prospectively in patients treated with CODOX-M/IVAC and Rituximab.

The CODOX-M/IVAC schedule includes frequent intrathecal therapy with Cytosine and Methotrexate. IPI high-intermediate and high risk patients are at significant risk of CNS relapse. The intrathecal therapy will be administered 8 times, or 12 times in patients with suspected or proven CNS disease at diagnosis according to the schedule in 6.2.

3.1 RATIONALE OF THE STUDY

Rationale for Diffuse Large B-Cell Lymphoma patients

Complete response rate for patients with diffuse large B cell lymphoma with IPI high-intermediate and high risk is 53% and 55% respectively, with 5-year survival rate of 43% and 26% respectively, with conventional treatment. Current chemotherapy regimens continue to show poor outcome data. Excellent results with CODOX-M/IVAC in Burkitt's lymphoma (highly aggressive NHL) and the prolongation of event-free and overall survival with Rituximab in aggressive NHL suggest a rationale for the use of CODOX-M/IVAC with Rituximab in this DLBCL patient population with poor survival after standard treatment. Preliminary evidence from current trials suggests earlier dose intensification can be beneficial.

Rationale for Burkitts Lymphoma patients

In the case of Burkitts lymphoma where CODOX-M/IVAC is established as the UK Gold standard the question is whether Rituximab may improve outcome in combination with this schedule. The results for R-HYPER CVAD show an improvement of more than 20% in outcome (Thomas et al, Cancer 2006:106, 1569-80). This potential significant improvement in outcome now needs to be assessed by adding Rituximab to the combination of CODOX-M and IVAC, which is the current UK standard management of Burkitts Lymphoma.

3.2 STUDY OBJECTIVES

This single arm, multicentre phase II study will test this hypothesis:

Does the combination of Rituximab and CODOX-M/IVAC improve the progression free survival in patients with newly diagnosed diffuse large B cell lymphoma or Burkitt's lymphoma of international prognostic index high or high-intermediate risk?

Primary Outcome Measure:

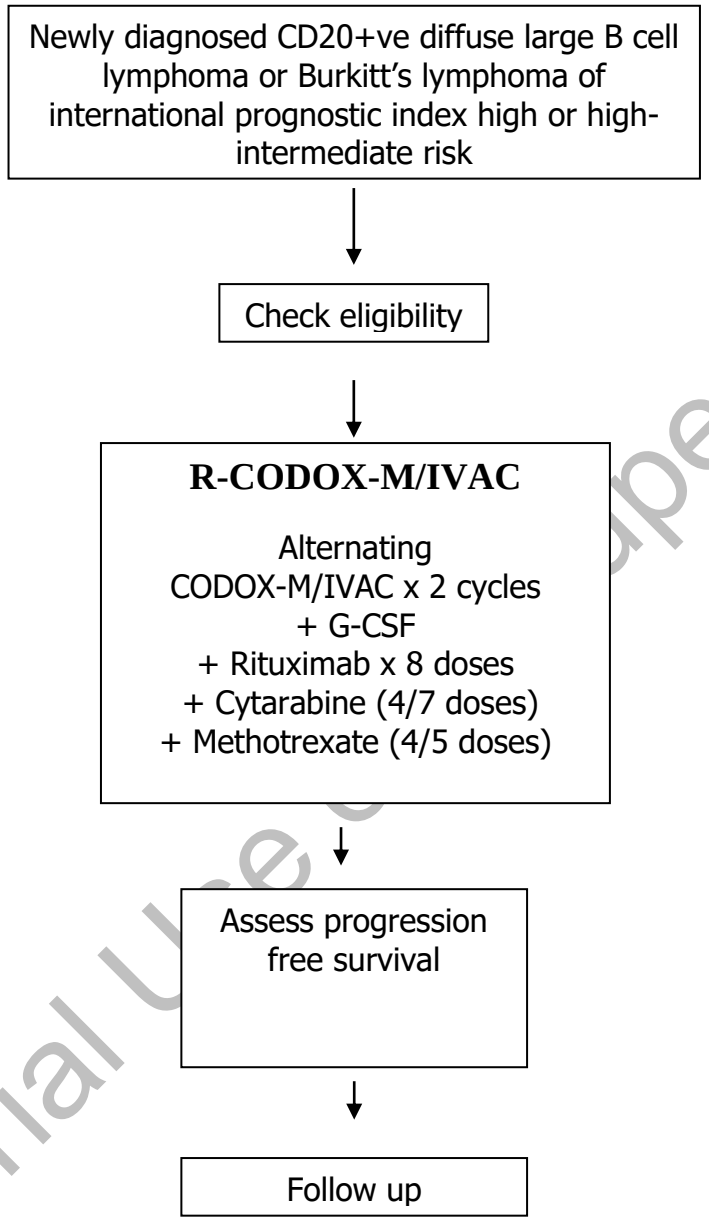
Progression Free Survival

Secondary Outcome Measure:

(1) Complete response rate (CR and Cru)

(2) Toxicity

3.3 Figure 1: R-CODOX-M/IVAC TRIAL OUTLINE



Section 4: CENTRE SELECTION

All investigators will be required to sign a declaration of participation. Each centre will be required to provide a complete list of clinicians, research nurses and data managers involved in conducting the trial. This protocol involves intensive therapy, which should only be given in expert centres. Therefore, it is recommended that only centres with expertise in the management of chemotherapy for Acute Myeloid Leukaemia given with curative intent (BCSH level 2) take part in this trial.

Participating investigators will keep a complete anonymised log of all patients screened for eligibility. The information collected will include:

- Patient Initials
- Age
- Gender
- The reason why not eligible for trial participation
- Whether eligible but declined.

The lymphoma team, UCL CTC will collect this information every 3 months.

Before the first patient is registered from each centre it will be ensured Site Specific Assessment approval has been obtained.

4.1 DISEASE EVALUATION

Baseline investigations

a) Complete medical history.
b) Concomitant diseases and treatment.
c) Physical examination.
d) Vital signs.
e) WHO performance status (Appendix 2).
f) Assessment of extranodal sites. Note: Spleen does not count as an extranodal site. Record the sites of extranodal lymphomatous involvement as bone marrow, gastrointestinal tract, liver, lung, central nervous system and 'other sites', and record the numbers of extranodal disease sites as 0, 1, or> 1.
g) Electrocardiogram.
h) Echocardiogram or nuclear medicine scan (MUGA) should be performed if past history of diabetes, cardiac disease, hypertension or abnormal resting ECG.
i) Contrast enhanced CT scan of the neck, thorax, abdomen and pelvis
j) Full blood count.
k) Serum electrolytes, urea and creatinine,
l) Creatinine clearance (measured either by 24 hour urinary collection or radio-isotope methods) measured no more than 72 hours before initial high dose methotrexate
m) Serum bilirubin, liver transaminases, alkaline phosphatase, albumin, total proteins, calcium, magnesium, phosphate level, uric acid
n) Serum lactate dehydrogenase (LDH) and β2 microglobulin.
o) Bone marrow biopsy.
p) Cerebrospinal fluid examination if clinically indicated or lymphomatous involvement in peripheral blood, bone marrow, nasal/paranasal sinuses, orbit or testis.

All investigations to be performed within 14 days prior to entering trial

For patients pre-treated with steroids, investigations should be performed within 14 days prior to entering trial but before steroid treatment.

Scan should be performed within 28 days prior to entering trial.

4.2 ELIGIBILITY CRITERIA

4.2.1 Inclusion criteria

a) Age 18-60 years (inclusive).
b) Histologically proven diffuse large B cell non-Hodgkin's lymphoma (DLBCL) and all morphological variants or Burkitt's lymphoma, according to the current World Health Organisation classification[1]. The B cell nature of the proliferation must be verified by the positivity with an anti-CD20 antibody. All histology will be reviewed by a central Lymphoma Trials Office pathology panel.
c) IPI score high-intermediate (score=3) or high (score=4,5). IPI defined as stage III or IV, raised LDH and poor performance status – WHO performance status >/= 2. (See Appendix 1).
d) No previous chemotherapy, radiotherapy or other investigational drug for this indication **(although pre-treatment with steroids is acceptable)**
e) Adequate bone marrow function with platelets > $100x10^9$/l; neutrophils > $1.5x10^9$/l at the time of study entry unless attributed to bone marrow infiltration by lymphoma.
f) Serum creatinine < 150μmol/l, serum bilirubin < 35μmol/l and transaminases < 2.5× upper limit of institutional normal range unless attributed to lymphoma.
g) Normal MUGA or echocardiogram without areas of abnormal contractility and left ventricular ejection fraction (LVEF) ≥50%. (only applicable if past history of diabetes, cardiac disease or hypertension or abnormal resting ECG).
h) No concurrent uncontrolled medical condition.
i) No active malignant disease other than basal or squamous cell carcinoma of the skin or carcinoma in situ of the uterine cervix in the last 10 years.
j) Life expectancy > 3 months.
k) Adequate contraceptive precautions for all patients of childbearing potential.l) Written, informed consent.

4.2.2 Exclusion criteria

a) T-cell lymphoma.
b) Previous history of treated or non-treated indolent lymphoma. However, diffuse large B cell patients not previously diagnosed who have some small cell infiltration in bone marrow or lymph node may be included.
c) Past history of heart failure or uncontrolled angina pectoris.
d) Cardiac contra-indication to doxorubicin (abnormal contractility on echocardiography or nuclear medicine examination [MUGA]).
e) Neurological contra-indication to vincristine (e.g. pre-existing diabetic neuropathy).
f) Any other serious active disease.
g) General status that does not allow the administration of 2 cycles of CODOX-M/IVAC according to the investigator.
h) Positive serology for HIV, Hepatitis B or Hepatitis C
i) Medical or psychiatric conditions that compromise the patient's ability to give informed consent.

Section 5: TRIAL REGISTRATION

- Each patient must be given a patient information sheet (Appendix 3) and provide written, informed consent, witnessed and signed by the researcher (Appendix 4).
- The registration and baseline assessment forms must be completed.
- Only patients fulfilling all eligibility criteria should be entered
- ANY queries should be addressed directly to the Lymphoma team, UCL CTC before registration. Tel. No. 020 7679 9860

To enter

- Completed registration and baseline assessment forms together with the signed informed consent form should be faxed to

Fax number 020 7679 9861

Between 09.00 and 17.00 Monday to Friday

Section 6: TREATMENT REGIMEN

Drug supply

Neulasta® (Filgrastim) will be provided free of charge by Amgen for this study. All other drugs will be supplied from the hospital pharmacy at the treating centre.

6.1 Initial preparation

At presentation, patients should be evaluated for problems requiring urgent attention, including impending airway obstruction, central nervous system disease, uric acid nephropathy, renal outflow obstruction, metabolic problems, or fever.

Patients entered into this trial are at high risk of developing tumour lysis syndrome. It is anticipated that all participating sites will have procedures for prevention and treatment of tumour lysis syndrome in place. Appendix 3 has guidance on the prevention of acute tumour lysis syndrome and Appendix 4 guidance on the management of other metabolic disturbances that may arise during treatment.

Patients can be pre-treated with Steroids, for a maximum of 7 days (10 days if over a weekend) prior starting treatment.
This would normally be Dexamethasone 8mg bd by either oral or intravenous route, prednisolone or methyl prednisolone. Other schedules at Physician's discretion are acceptable. The performance status score used at registration will be that before the pre treatment with steroids.

For patients pre-treated with steroids, it is acceptable to give rituximab on day –3 if required.

6.2 CODOX-M/IVAC

2 cycles of alternating CODOX-M/IVAC will be given.

6.2.1 CODOX-M

The table below shows the ideal schedule for delivering CODOX-M. However, because of the national guidance regarding the administration of intrathecal chemotherapy, it may not always be possible to adhere to this schedule. It is important that drugs are delivered at full dose and as close to the schedule shown below as possible.

Day	Drug	Dose	Method	Time
1	Rituximab	375 mg/m^2	IV	Infusion rate as per section 6.4
1	Cyclophosphamide Vincristine Doxorubicin	800mg/m^2 1.5mg/m^2 (max 2mg) 40mg/m^2	IV IV IV	
1	Cytarabine	70mg	**INTRATHECAL**	
2-5	Cyclophosphamide	200mg/m^2	IV	Daily
3	Cytarabine	70mg	**INTRATHECAL**	
5	Cytarabine [Patients with proven or suspected CNS disease* see section 6.7]	70mg	**INTRATHECAL**	
8	Vincristine	1.5mg/m^2 (max 2mg)	IV	
10	Methotrexate[a]	300mg/m^2 2700mg/m^2	IV IV	1 hour Given over next 23 hours
11	Rituximab	375 mg/m^2	IV	
11	Leucovorin[b]	15mg/m^2 15mg/m^2 15mg/m^2	IV IV IV	At hour 36 Every 3 hrs between 36-48 hrs Then every 6 hrs until methotrexate level is <5 x 10^{-8}M
13	Pegylated G-CSF (Neulasta)	6 mg	SC	
15	Methotrexate	12mg	**INTRATHECAL**	
17	Methotrexate[Patients with proven or suspected CNS disease* see section 6.7]	12mg	**INTRATHECAL**	
Commence IVAC on the day that the unsupported absolute granulocyte count is >1.0x10^9/l, with an unsupported platelet count of >75x10^9/l.				

* Proven or suspected CNS disease by scan or definite neurological condition e.g. cranial neural palsy.

[a]**Methotrexate:** This IV infusion of Methotrexate (see Appendix 5) should only be given in the presence of a normal serum creatinine for the patient's age and a measured creatinine clearance of >50 ml/min/m^2. Commence methotrexate regardless of blood counts. Stop infusion at hour 24 regardless of dose given.

[b]**Leucovorin:** Commence Leucovorin at hour 36 from start of methotrexate infusion. Continue Leucovorin until serum methotrexate level <$5x10^{-8}$M. Leucovorin may be given orally after the first 24 hours if patients are compliant, not vomiting, and otherwise without complication.

National guidance for the administration of intrathecal chemotherapy must be strictly followed at all times. This may require the intrathecal chemotherapy to be administered on a different day to that specified in the protocol and this is permissible as long as all planned doses are completed within each cycle. Intrathecal chemotherapy should not be given within 48 hours of the high dose methotrexate or during folinic acid rescue. During R-CODOX-M cycles, strict adherence to the timing of intrathecal cytarabine and methotrexate with respect to the administration of the intravenous chemotherapy drugs, as per National Guidance, must be observed.

6.2.2 M-IVAC

The table below shows the ideal schedule for delivering CODOX-M. However, because of the national guidance regarding the administration of intrathecal chemotherapy, it may not always be possible to adhere to this schedule. It is important that drugs are delivered at full dose and as close to the schedule shown below as possible.

Day	Drug	Dose	Method	Time
Start day 1 of IVAC on the first day after CODOX-M that the unsupported absolute granulocyte count is >$1.0x10^9$/l, with an unsupported platelet count of >$75x10^9$/l.				
1	Rituximab	375 mg/m^2	IV	Infusion rate as per section 6.4
1-5	Etoposide	60mg/m^2 (in 500ml of N.saline or 5% dextrose)	IV	Daily over 1 hour
	Ifosfamide	1.5g/m^2	IV	Daily over 1 hour
	Mesna	300mg/m^2 (mixed with ifosfamide)	IV	Over 1 hour
		Then 900mg/m^2 (continuous infusion)	IV	Over 12 hours
1 & 2	Cytarabine	2g/m^2	IV	Over 3 hours, 12 hourly total of 4 doses
5	Methotrexate	12mg	**INTRATHECAL**	
7	Pegylated G-CSF (Neulasta)	6 mg	SC	
7	Cytarabine [Patients with proven or	70mg	**INTRATHECAL**	

	suspected CNS disease* see section 6.7]			
9	Cytarabine [Patients with proven or suspected CNS disease* see section 6.7]	70mg	**INTRATHECAL**	
Commence next cycle (CODOX-M) on the day that the unsupported absolute granulocyte count is >1.0x10^9/l, with an unsupported platelet count of >75x10^9/l.				

* Proven or suspected CNS disease by scan or definite neurological condition e.g. cranial neural palsy.

4 doses of Rituximab are given with 2 cycles of CODOX-M and 2 doses of Rituximab given with 2 cycles of IVAC. **Two further doses of Rituximab will be administered on Day 21 and 42 after day one of the final course of IVAC** to bring the total of Rituximab infusions to 8 in line with the GELA R-CHOP schedule. The neutrophil count should be > 1.0 x 10^9/l on the day of administration.

21	Rituximab	375 mg/m^2	IV	Infusion rate as per section 6.4
42	Rituximab	375 mg/m^2	IV	Infusion rate as per section 6.4

6.2.3 Pre-requisites for the continuation of R-CODOX-M/IVAC

a) Patient has passed the leucocyte and platelet nadir
b) Neutrophil count>1.0 x 10^9/l unsupported
c) Platelet count >75 $\times$ 10^9/l unsupported
d) No active infection
e) No serious organ or other toxicity

If the threshold counts for neutrophils and platelets are not achieved, the administration of further chemotherapy will be initially postponed for 3 days. If the threshold counts are still not achieved by this time, chemotherapy should be postponed for a further 3-4 days.

6.2.4 Growth factor support

Pegylated G-CSF (NEULASTA) s.c. on Day 13 of cycles 1 and 3. (CODOX-M)

Pegylated G-CSF (NEULASTA) s.c. on Day 7 of cycles 2 and 4. (IVAC)

6.3 Administration of Rituximab

- Rituximab 375mg/m^2 is given as an intravenous infusion. Prior to infusion, pretreatment with paracetamol (1g) and a suitable anti-histamine e.g. chlorpheniramine (10mg iv or 4mg po) will be administered. The administration of rituximab should be carried out via a peripheral or central line. Prior to infusion, adrenaline for subcutaneous injection and an anti-histamine e.g. chlorpheniramine for intravenous injection have to be available for the case of allergic or anaphylactic reactions. Facilities for immediate intervention in case of an anaphylactic reaction must be available.
- During the first hour, the infusion should run at a rate of 50mg/hour. During the administration of rituximab, vital signs (blood pressure, heart rate, respiration rate, and temperature) are monitored every 15 minutes during the first treatment. For all subsequent infusions, these parameters may be monitored every 30 minutes at the discretion of the treating physician if there were no complications during the first infusions. Provided there are no adverse events during the first hour of administration, the rate of infusion can be increased by 50mg/hour every half an hour up to 300mg/hour as the maximum rate.
- During the infusion of rituximab, the occurrence of infusion related reactions are possible. In the case of these infusion related reactions, the antibody infusion has to be interrupted. After the symptoms have disappeared, the infusion can be restarted at **half** the initial infusion rate.

- These infusion related reactions include:

a) Fever (temperature >38.5^{o}C)
b) Chills
c) Mucosal swelling
d) Bronchospasm
e) Hypotension (drop in blood pressure by 30mmHg)

- There is no dose reduction of rituximab in the case of adverse events. In case of mild side effects, continuation of therapy with rituximab is possible dependent on the physician's assessment. If side effects of toxicity grade 1 or 2 occur, therapy is delayed for one hour according to the physician's assessment. In the case of adverse events of toxicity grade 3 or 4, the infusion should be stopped until all symptoms have resolved and then restarted. The restarting dose of rituximab after an infusion related reaction should be half the rate of infusion previously given. If the same grade 3 and 4 adverse event occurs again, therapy is stopped completely.
- The rate of infusion for subsequent infusions is at the treating clinicians' discretion. The rituximab can be given at the conventional rate (start at 100mg/hour and be increased by 50mg/hour every half an hour up to 400mg/hour). Alternatively for patients who tolerated their first infusion of Rituximab at the standard recommended administration rate, second and subsequent courses of rituximab can be given as a rapid infusion (Reference: Sehn L et al**,** Rapid Infusion Rituximab in Combination with Steroid Containing Chemotherapy Can Be Given Safely and Substantially Reduces Resource Utilization. Blood 2004, 104 (11), abstract 1407). 20% of the total dose of rituximab is given over first 30 minutes and remaining 80% of dose of rituximab over 1 hour, total infusion time 90 mins.

6.4 Other medications

Co-trimoxazole 480mg bd po (Mon, Wed and Fri) during treatment and for six months post therapy. (See appendix 5 for further recommendations)

Mouth care, antacids and anti-emetics should be give according to local protocols and the following is a suggested regimen:

- Corsdyl 5ml qds mouthwash
- Nystatin 1ml qds po
- Lansoprazole 30mg od po
- Metoclopramide 10mg tds for 3 days

6.5 Radiotherapy

There is no evidence that radiotherapy is beneficial in the treatment of meningeal disease. Because several neurotoxic drugs (methotrexate, ifosfamide) will be used in the protocol, radiation will only be considered in the presence of a documented intracerebral mass (by CT or MRI scan). In patients with paraplegia, radiation is probably of no benefit, but adds significantly to myelotoxicity. Therefore, radiation will only be used in this situation if there are unique circumstances, e.g. chemotherapy cannot commence immediately because of metabolic abnormalities.

Following treatment with R-CODOX-M/IVAC, the use of radiotherapy to initial bulk disease or residual disease is left to the individual investigator's discretion. However,

it is strongly recommended that any residual masses are assessed by a PET scan (if available) prior to radiotherapy administration.

6.6 Central Nervous System (CNS) Prophylaxis and Treatment

Please note that in accordance with Health Service Circular HSC 2001/022, dated 6th November 2001, national guidelines on the safe administration of intrathecal (IT) chemotherapy must be followed.

Administration schedule:

- CNS risk increases with factors associated with systemic disease[20, 21]. Patients with IPI High or High-Intermediate risk are therefore considered to be at greater risk of CNS disease than DLBCL or BL patients as a whole, so in this study these patients (with proven or suspected CNS disease) will receive 7 doses of Cytarabine and 5 doses of Methotrexate. Selection of patients with involvement of specific extranodal areas will not be used.

- **DLBCL or BL patients without CNS disease will receive 4 intrathecal doses each of Cytarabine and Methotrexate**

Cycle	Day	Drug	Intrathecal Dose
CODOX-M 1	1	Cytarabine	70mg
	3	Cytarabine	70mg
	15	Methotrexate	12mg
IVAC 1	5	Methotrexate	12mg
CODOX-M 2	1	Cytarabine	70mg
	3	Cytarabine	70mg
	15	Methotrexate	12mg
IVAC 2	5	Methotrexate	12mg

- **DLBCL or BL patients with proven or suspected CNS disease will receive a total of 7 intrathecal doses of Cytarabine and 5 intrathecal doses of Methotrexate.**

  Additional doses given below (ONLY THE FIRST TWO CYCLES).

Cycle	Day	Drug	Intrathecal Dose
CODOX-M	5 17	Cytarabine Methotrexate	70mg 12mg
IVAC	7 & 9	Cytarabine	70mg

6.7 Management of Post Treatment Neutropenia (after completion of all therapy)

Rituximab has been associated with late onset of neutropenia after therapy is complete[22, 23]. Management of this will need to be discussed with the Chief Investigator - Dr McMillan. It is likely that G-CSF will be of value but if the neutropenia is not severe (< 2.0 x 10^9/l but > 0.5 x 10^9 /l) and asymptomatic, intervention may not always be necessary. If neutrophils are < 0.5 x 10^9/l then G-CSF (Filgrastim 300 μg) should be given until neutrophils > 1.0 x 10^9/l for more than 1 day).

If in any doubt as to the aetiology of neutropenia please carry out a bone marrow aspirate to document the cause prior to starting G-CSF.

Section 7: STUDY SCHEDULE

	Pre-treatment screening (within 14 days)	End of treatment				
		Cycle 1 CODOX-M	Cycle 1 IVAC	Cycle 2 CODOX-M	Cycle 2 IVAC	On completion of treatment
Informed consent	×					
History	×					
Physical examination	×					
Performance status	×					
Electro-cardiogram	×					
CT scan[a]	×					×
Bone marrow biopsy	×					(×)[g]
Serum biochemistry[b]	×	×	×	×	×	×
Haematology[c]	×	×	×	×	×	×
Echocardiogram[d]	×					(×)
Cerebrospinal fluid examination[e]	×					
Central pathology review[f]	×					
CODOX-M		×		×		
IVAC			×		×	
Rituximab (doses 1 week apart)		×x	×x	×x	×x	
Toxicity assessment		x	x	x	x	
Adverse events		x	x	x	x	

[a]Contrast enhanced CT scan of thorax, abdomen and pelvis (neck if indicated) should be carried out within 28 days of registration and one month after the end of treatment.
[b]Serum chemistry to include sodium, potassium, urea, creatinine, bilirubin, alanine transferase, alkaline phosphatase, lactate dehydrogenase, albumin and total proteins. Serum β2 microglobulin to be performed at baseline only.
[c]Full blood count to include haemoglobin, white blood cell, absolute neutrophil count and platelet.
[d]Echocardiogram or MUGA should be performed if past history of diabetes, cardiac disease or hypertension or abnormal resting ECG. Patients must have an acceptable left ventricular ejection fraction (LVEF) ≥50%. A repeat echocardiogram/MUGA should be considered at the end of treatment if performed initially and same assessment method should be used.
[e]Cerebrospinal fluid examination if clinically indicated or lymphomatous involvement in bone marrow, peripheral blood, orbit, nasal/paranasal sinuses and testis.
[f]Diagnostic histological material to be forwarded for central pathology review. However, results from central review do not need to be available before commencing treatment.
[g]Bone marrow biopsy to be repeated at the end of treatment if initially involved.

Follow-up: Clinic visit with physical examination monthly during the first 4 months, 2-monthly during the rest of the first year, 3-monthly during the second year, 4-monthly during the third year, 6 monthly during the fourth year and annually, thereafter. CT scans of chest, abdomen and pelvis at 4 months and 1 year after finishing treatment. FBC should be taken at each visit.

Section 8: TOXICITY AND DOSE MODIFICATIONS

This will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v 3.0 (CTCAE). This can be accessed via http://ctep.cancer.gov or alternatively via a supplementary document to this protocol.

8.1 Haematological toxicity

There will be no dosage modifications based on the degree or duration of myelosuppression.

8.2 Non-haematological toxicity

If grade >/=2 motor or grade >/=3 sensory neurological toxicity to vincristine appears, the dose will be decreased to 1mg per cycle. If the neurological toxicity increases despite dose reduction, vincristine will be stopped.

In cases of intolerable non-haematological toxicity attributable to CODOX-M/IVAC, rituximab can be continued.

8.2.1 Hepatic Impairment

Cytarabine	Bilirubin > 34µmol/L, give 50% Escalate doses in subsequent cycles in the absence of toxicity
Doxorubicin	If bilirubin (µmol/L) is 20-51, give 50% 51-85, give 25% > 85, omit If AST is 2-3 x ULN, give 75%
Etoposide	If bilirubin (µmol/L) is 26-51 or AST is 60-180, give 50% If bilirubin is > 51µmol/L or AST is > 180 – clinician's decision
Methotrexate	If bilirubin < 52µmol/L and AST < 180, give 100% If bilirubin is 53-84µmol/L or AST > 180, give 75% If bilirubin > 85µmol/L – omit

Vincristine	If bilirubin is 26-51µmol/L and AST/ALT is 60-180, give 50% If bilirubin > 51µmol/L with normal AST/ALT, give 50% If bilirubin > 51µmol/L with AST/ALT > 180, omit
Cyclophosphamide	Dose reduction not necessary
Ifosfamide	Clinician's decision

8.2.2 Renal Impairment

Cytarabine	High dose (1-3g/m^2): CrCl (ml/min) % of full dose >60 60% >45 50% <35 omit
Doxorubicin	Severe impairment – clinical decision
Etoposide	CrCl (ml/min) % of full dose 60 85% 45 80% 30 75% < 15 50% Subsequent doses should be based on clinical response
Methotrexate	CrCl (ml/min) % of full dose > 80 100% 60 65% 45 50% < 30 omit
Vincristine	No dose reduction
Cyclophosphamide	CrCL (ml/min) % of full dose > 50 100% 10-50 75% < 10 50% Consider whether patient is being treated with high dose treatment

Ifosfamide	CrCl (ml/min) % of full dose > 60 100% 40-59 70% < 40 clinician's decision If creatinine is > 120 µmol/L, not recommended

Section 9: CENTRAL PATHOLOGY REVIEW

A central review of the diagnosis is organised for each case by a panel under the direction of Dr Andrew Jack at the Haematological Malignancy Diagnostic Service in Leeds. Following registration, a letter will be sent from the Lymphoma team, UCL CTC to the local pathologist requesting that a representative histological block be provided for central review.

All histological material is to be sent to:

Lymphoma team, UCL CTC
CR UK and UCL Cancer Trials Centre
90 Tottenham Court Road
London
W1T 4TJ

The material will then be forwarded to Dr Jack in Leeds. Samples should be identified by a combination of trial number, initials and date of birth, sent in a Jiffy bag or other suitable packaging. Material will be returned to the local pathologist via the Lymphoma team, UCL CTC after the review has been completed. The registering centre will receive a copy of the review pathology report.

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

a) Review of the diagnosis of diffuse large B cell lymphoma as defined in the WHO classification
b) A definition of the sub-entity according to the WHO subgroups
c) Assessment/review of the diagnosis of B cell proliferation with an anti-CD20 antibody and an anti-CD79a antibody.
d) All cases will be characterised as germinal or non-germinal centre types in accordance to published criteria
e) Bcl-2 protein expression, determined by immunohistochemistry
f) Bcl-6 rearrangement at 3q27 by immunohistochemistry and interphase fluorescence *in situ* hybridisation (FISH) mutational analysis
g) t(14,18) translocation, evaluated by interphase FISH
h) deregulation of P53 (defined by over-expression of P53 in the absence of P21) will be assessed using a combination of interphase FISH and immunohistochemistry
i) expression of MUM-1(IRF4) and FOX-P1 by immunohistochemistry

Definition of Burkitt's Lymphoma (BL)

BL can be defined as:

- A tumour with a germinal centre phenotype
- Absence of BCL-2 expression
- Abnormal TP53 expression
- Cmyc rearrangement
- Absence of t(14,18)
- 3q27 re-arrangements

Ideally FISH will be carried out on air-dried un-fixed touch preparations from fresh or frozen tissue biopsies and paraffin blocks will be used for the immunohistochemistry and for FISH if touch preparations are unavailable.

Section 10: DISEASE EVALUATION ON TREATMENT

Before each treatment course

a) Physical examination.
b) Laboratory tests including full blood count, serum electrolytes, urea, creatinine, bilirubin, liver transaminases, alkaline phosphatase, lactate dehydrogenase, albumin and total proteins.
c) Toxicity and adverse event assessment.

Within one month after the second IVAC cycle

a) Physical examination
b) Laboratory tests including full blood count, serum electrolytes, urea, creatinine, serum bilirubin, liver transaminases, alkaline phosphatase, lactate dehydrogenase, albumin and total proteins.
c) CT scan of chest, abdomen and pelvis (+ neck, if indicated).
d) Bone marrow biopsy if initially involved.
e) Toxicity and adverse event assessment.

10.1 Follow Up

a) Clinic visit with physical examination at 1-4, 6, 8 10, 12, 15, 18, 21, 24, 28, 32, 36 months after completion of R-CODOX-M/IVAC, then 6 monthly for 1 year then annually.
b) CT scan of chest, abdomen and pelvis at 4 months and 1 year after finishing treatment.
c) No routine blood tests are required as part of the trial.

10.2 Treatment Withdrawal Criteria

a) Intolerable adverse effects as judged by the investigator or the patient.
b) Patient decision to discontinue treatment.
c) Recurrent grade 3 or 4 drug related toxicity despite dose modification as judged by the investigator.
d) Serious systemic allergic reaction to any of the study drugs e.g. angio-oedema, anaphylaxis.

Despite treatment withdrawal, patients will continue to be followed in the study unless they explicitly state that they wish to withdraw from treatment *and* all data collection.

Section 11: RESPONSE EVALUATION

Response will be assessed in accordance with the International Workshop Standardised Response Criteria for Non-Hodgkin's Lymphoma.[24]

Response criteria will be determined as follow:

Complete response (CR) requires **all** of the following criteria are met:

a) Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy and normalisation of those biochemical abnormalities (e.g. LDH definitely contributable to NHL)
b) All lymph nodes and nodal masses must have regressed to normal size (≤1.5cm in their greatest transverse diameter for nodes >1.5cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to ≤1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).
c) The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size. Any macroscopic nodules in any organs detectable on imaging techniques should no longer be present. Similarly, other organs considered enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.
d) If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site. Flow cytometric, molecular or cytogenetic studies are not considered part of routine assessment to document persistent disease at the present time.

Complete response, undocumented/unconfirmed (CRu):

This includes those patients who fulfil criteria a) and c) above, but with one or more of the following features:

a) A residual lymph node mass greater than 1.5cm in greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass.
b) Indeterminate bone marrow (increased number or size of aggregates without cytological or architectural atypia).

Partial response (PR) requires all of the following:

a) ≥50% decrease in SPD of the six largest dominant nodes or nodal masses.
b) No increase in the size of the other nodes, liver or spleen.
c) Splenic and hepatic nodules must regress by at least 50% in the SPD.
d) With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease

e) Bone marrow assessment is irrelevant for determination of a PR because it is assessable and not measurable disease
f) No new sites of disease

Stable disease (SD):
Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.

Progressive disease (PD) requires one of the following:
a) ≥50% increase from nadir in the SPD of any previously identified abnormal node for PRs or non-responders.
b) Appearance of any new lesion during or at the end of therapy.

Response Assessment

Response criteria	Physical examination	Lymph Nodes	Lymph Node Masses	Bone marrow
CR	Normal	Normal	Normal	Normal
CRu	Normal	Normal	Normal	Indeterminate
	Normal	Normal	>75% decrease	Normal or indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	≥ 50% decrease	≥ 50% decrease	Irrelevant
	Decrease in liver/spleen	≥ 50% decrease	≥ 50% decrease	Irrelevant
Relapse/PD	Enlarging liver/spleen; new disease sites	New or ≥ 50% increase	New or ≥ 50% increase	Reappearance

Relapsed disease (after **CR, CRu)** requires the following:

a) Appearance of any new lesion or increase by ≥50% in the size of previously involved sites
b) ≥50% increase in the greatest diameter of any previously identified node greater than 1cm in its short axis or in the SPD of more than one node.

Section 12: OUTCOME MEASURES

Progression Free Survival

This will be measured from date of registration to date of first appearance of disease progression or relapse. Patients alive without progression or relapse will be censored at date last known to be alive.

Response Assessment

This will be assessed by CT scan of the thorax, abdomen and pelvis (+ neck if clinically indicated) one month after the end of treatment.

For those patients who have a residual mass at end of treatment, we would recommend a PET scan is performed if possible. Any questions regarding this should be directed to the Chief Investigator - Dr McMillan.

Toxicity

This will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v 3.0 (CTCAE).

Section 13: STATISTICAL CONSIDERATIONS

Sample size

The primary outcome measure is progression-free survival calculated from the time of starting chemotherapy. It is anticipated that the 2-year PFS is around 40-50% for patients with age <=60 and IPI=3,4. Using the Fleming's single-stage design, 95 patients are required to detect an improvement of 15% with a 90% power and a 5% significance level (one-side); 55 patients are required to detect an improvement of 20% with at least a 90% power and a 5% significance level (one-side). It is planned to recruit a total of 150 patients. With an expected ratio of DLBCL: BL = 2:1, approximately, the study will have a 90% power and a 5% significance level (one-sided) to detect an improvement of 15% for DLBCL and 20% for BL.

Brief analysis plan

The analyses will be descriptive. Survival curves and estimates using the Kaplan-Meier approach will be presented.

Section 14: INTERIM ANALYSES AND DATA MONITORING

14.1 COMMITTEES

14.1.1 Independent Data Monitoring Committee (IDMC)

The IDMC has drawn up guidelines for examining trial data, and for advising on the trial's progress and continuation. The interim analyses will be performed for the IDMC who will review the data when the first 10 patients have been entered into the study from a safety point of view. At this first meeting, the IDMC will advise on the nature and frequency of the subsequent interim analyses. It is anticipated that this IDMC will meet at approximately yearly intervals. The exact frequencies will depend upon accrual, progression and death rates. This study may be terminated at the request of the Independent Ethics Committee if, during the course of the study, concerns about the safety of further dosing emerge. The interim analyses will be performed by a statistician at the Lymphoma team, UCL CTC and will be confidential unless the IDMC advises otherwise. The members of the IDMC will write an annual report with recommendations to the Trial Steering Committee. (See appendix 7 for IDMC members).

14.1.2 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial and to ensure that the trial is conducted in accordance with the International Conference on Harmonisation Good Clinical Practice (ICH GCP). This independent committee will review the recommendations from the IDMC. On consideration of this information, the TSC will decide on continuing or stopping the trial, or modifying its protocol. The TSC is to be appointed.

Source data verification will be performed on a random sample of patients entered into trial. The number of patients and data items to be assessed will be decided on after discussion with the IDMC.

SECTION 15: PHARMACOVIGILANCE

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

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

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

Serious Adverse Event (SAE) or Serious Adverse Reaction
An adverse event or adverse reaction that at any dose:

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

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

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

Reporting Procedures

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

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

Adverse Event Term
An adverse event term needs to be provided for each adverse event, preferably using the Short Name as listed in the Common Terminology Criteria for Adverse Events v3.0 (CTCAE), available online at: http://ctep.cancer.gov/forms/CTCAEv3.pdf.

Severity
Severity for each adverse event will be determined by using the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) as a guideline, wherever possible. The criteria are available online at http://ctep.cancer.gov/forms/CTCAEv3.pdf.

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

1 = Mild
2 = Moderate
3 = Severe
4 = Life threatening
5 = Fatal

Causality
Investigators must perform an evaluation of causality for each adverse event.
Causal relationship to the trial treatment must be determined as follows:

• **None**
There is no evidence of any causal relationship.
• **Unlikely**
There is little evidence to suggest a causal relationship (e.g. because the event did not occur within a reasonable time after administration of the trial

treatment). There is another reasonable explanation of the event (e.g. the patient's clinical condition, other concomitant medications).

- **Possible**

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

- **Probable**

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

- **Definitely**

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

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 investigator feels the event is related to the trial treatment) must be submitted to the UCL CTC by fax within **1 business day** of observing or learning of the event, using the trial specific SAE Report. All sections on the SAE Report must be completed.

Expectedness

Investigators must perform an evaluation of expectedness for all SAEs regardless of causal relationship to the trial treatment. This evaluation must be performed using the list of expected adverse events in appendix 9 and the Investigator Brochure (IB).

Expectedness of the event to the trial treatment must be determined as follows:

- **Expected**

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

- **Unexpected**

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

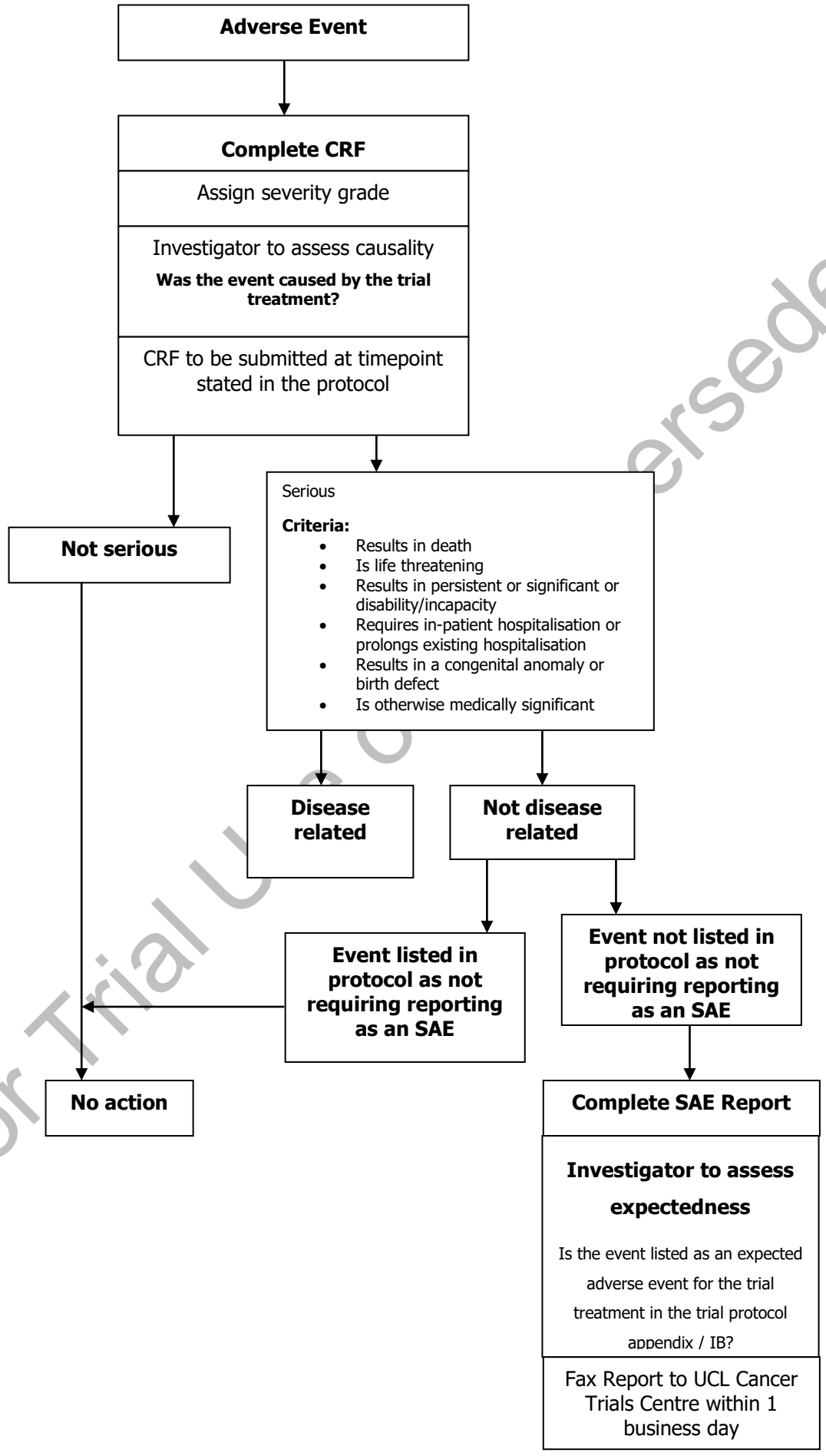
  - the event is life threatening or fatal (unless stated in the protocol appendix as expected).
  - the patient presents with an event which is considered to be moderate or severe, but only mild is listed as expected in the protocol appendix.

Events which do not Require Reporting as an SAE
The following events do not require reporting as an SAE but must be reported on the relevant sections of the CRF:

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

All SAEs must be reported by faxing a completed SAE Report within 1 business day of becoming aware of the event to the UCL CTC
Fax. No: 020 7679 9861

Adverse Event Reporting Flowchart



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

SAE Processing at the UCL CTC
The UCL CTC will fax all trial treatment related SAE Reports to Napp and Amgen within 1 business day.

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

SUSARs
If the event is evaluated by either the site or the UCL CTC as a Suspected Unexpected Serious Adverse Reaction (SUSAR), the UCL CTC will submit a report to the MHRA and MREC within 7 calendar days for fatal/life threatening events, with a follow-up report within a further 8 calendar days, and 15 calendar days for all other events.

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

The UCL CTC will forward reports regarding SUSARs that have occurred on other trials using the same trial treatment to all Principal Investigators. These must be processed according to local requirements and filed with the IB for the drug concerned.

Clinical Review
The UCL CTC will provide safety information to the Trial Management Group and the Independent Data Monitoring Committee on a periodic basis for review. Should the outcome of the review result in upgrading/downgrading of SAEs to SUSARs and vice versa, the UCL CTC will provide relevant reports to the MHRA and MREC.

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

If the UCL CTC detect a higher incidence in rare events than is stated in the IB(s)/SmPC(s) for the trial treatment, a report detailing the finding will be submitted to the MHRA/MREC.

Pregnancy

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

All pregnancies must be reported by faxing a completed Pregnancy Report within 1 business day of becoming aware of the event to the UCL CTC:
Fax. No: 020 7679 9867

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

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

Pregnancy Report Processing at the UCL CTC
The UCL CTC will fax all Pregnancy Reports to Napp and Amgen within 1 business day.

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

Annual Safety Reports
The UCL CTC will submit Annual Safety Reports to the MHRA and MREC. This will commence one year from the date of CTA approval obtained for the trial.

Serious Breaches of Safety
Systematic or persistent non-compliance by a site of the safety requirements set out in the protocol, including failure to report SAEs occurring on trial within the specified timeframe, may be deemed a serious breach. In cases where a serious breach has been identified, the UCL CTC will inform the MHRA within 7 calendar days of becoming aware of the breach.

SECTION 16: ETHICAL CONSIDERATIONS

16.1 Ethical conduct of the study

This study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) and Scotland (2000)) and the EU Directive.

The study protocol will be given approval by the MREC before patients are entered. Participants will only be allowed to enter the study provided they have given written informed consent (Appendix 4).

Subjects will be informed that they have the right to withdraw from the study at any stage without prejudice or without having to give reason.

This study may be terminated at the request of the Chief Investigator after discussion with the IDMC or TSC, or the independent Research Ethics Committee(s) if, during the course of the study, any concerns about safety emerge.

The Chief Investigator will update the ethics committee of any new information related to the study as appropriate.

16.2 Informed consent

Written informed consent should be obtained from each patient, in accordance with regulatory requirements, GCP and the Declaration of Helsinki. The subject will have the exact nature of the study explained to them in writing and verbally, including the known side-effects which they might expect and the risks. They will be advised that they are free to withdraw from the study or study treatment at any time without obligation. The consent form will also request permission for personnel involved in the research, including members of the Lymphoma team, UCL CTC, to have access to the subjects' medical records for the purposes of data verification and audit. Long-term follow-up will be conducted via the Office for National Statistics.

16.3 Indemnity & Compensation

Non-negligent harm: As sponsor, University College London (UCL) will provide insurance against claims for compensation for injury caused by participation in this clinical trial (ie non-negligent compensation). Patients wishing to make a claim should address their complaint in writing to the CI in the first instance.

Negligent harm: Where studies are carried out in a hospital, the hospital continues to have a duty of care to a patient being treated within the hospital, whether or not the patient is participating in this trial. UCL does not accept liability for a breach in the

hospital's duty of care, or negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not.

Section 17: REFERENCES

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APPENDICES

APPENDIX 1: INTERNATIONAL PROGNOSTIC INDEX

International Prognostic Index
One point is assigned for each of the following risk factors:

- Age greater than 60 years
- Stage III or IV disease
- Elevated serum LDH
- WHO performance status >/= 2.
- More than 1 extranodal site

The sum of the points allotted correlates with the following risk groups:

- Low risk (0-1 points) - 5-year survival of 73%
- Low-intermediate risk (2 points) - 5-year survival of 51%
- High-intermediate risk (3 points) - 5-year survival of 43%
- High risk (4-5 points) - 5-year survival of 26%

APPENDIX 2: WHO PERFORMANCE STATUS

0 Able to carry out all normal activity without restriction

1 Restricted in physically strenuous activity but ambulatory and able to carry light work

2 Ambulatory and capable of all self care but unable to carry out any work; up and about more than 50% of waking hours

3 Capable only of limited self care; confined to bed or chair more than 50% of waking hours

4 Completely disabled; cannot carry out any self care; totally confined to bed or chair

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Please note as a guide the following plain language version (from the CR UK website) may be used to aid discussion with patients:

0 You are fully active and more or less as you were before your illness
1 You cannot carry out heavy physical work, but can do anything else
2 You are up and about more than half the day; you can look after yourself, but are not well enough to work
2 You are in bed or sitting in a chair for more than half the day; you need some help in looking after yourself
3 You are in bed or a chair all the time and need a lot of looking after

APPENDIX 3: PREVENTION OF ACUTE TUMOUR LYSIS SYNDROME

The most important aspects of management of the acute tumour lysis syndrome are:

Prophylaxis

This necessitates the establishment of a good diuresis prior to therapy. Where necessary i.e., if output is significantly less than intake, diuretics e.g., Frusemide, should be given. In the presence of hyperuricaemia prior to therapy, alkalinisation should also be carried out prior to treatment to assist in rapid reduction of uric acid level.
Alkalinisation should be stopped as soon as the serum uric acid level is within the normal range (prior to commencing chemotherapy). Whenever possible uric acid should be normal at the start of therapy. If this cannot be achieved it will probably be necessary to institute haemodialysis prior to and during therapy. Such decisions will be taken in conjunction with a renal physician.
A suggested schema for hydration in a patient capable of having a diuresis is: In 24 hours:

1. 3 l/m^2 IV fluid as a minimum. 4.5 l/m^2 should be administered whenever possible i.e., if patient can excrete the water load; greater volumes may be administered in high risk patients under close monitoring in the critical care unit.
2. 75 mmols of sodium/l. If hypokalaemia below 3mmols/l is present, K+ may be added, especially if alkalinisation is required, but this should be done cautiously, and stopped before chemotherapy. Ideally plasma potassium should be between 3.0 and 3.5 mmol/l at the start of chemotherapy. It is possible that hyperkalaemia may exist in some patients with renal failure prior to therapy. This should be acutely managed as described below, but renal consultation will be necessary.

   Allopurinol should be commenced as soon as possible in all patients. The usual dose will be 300-800 mg daily, in three divided doses, depending upon age (10mg/kg/day). Diuresis should be vigorously maintained during the first few days of therapy. Diuresis can be discontinued in the absence of metabolic complications after 72 hours, or at such time as metabolic changes have normalised. **Patients who are allergic to allopurinol should receive treatment with rasburicase.**

   For sites that are able to use Rasburicase the following prophylactic treatment regimen is recommended

   Rasburicase can be used in Cycle 1 at the recommended dose of 0.2mg/kg/day, given as a once daily 30-minute infusion in 50ml of 0.9% sodium chloride solution. Duration of treatment should be between 3-5 days.

   Please note that rasburicase should not be given to patients with G6PDdeficiency

APPENDIX 4: OTHER TREATMENT ISSUES

Renal Problems

Occasionally patients present with established renal failure, requiring dialysis. These patients should be registered and discussed with the principal investigator. In general, initial therapy should be given at low dose, followed by CODOX-M when recovery of renal function has occurred.

Profound metabolic disturbances may occur shortly after commencement of chemotherapy, largely as a result of acute tumour lysis. The major possible changes are as follows.

Hyperkalaemia

This is relatively uncommon and is probably influenced by total body potassium, renal function, extracellular pH, tumour burden, and response to therapy or specific drug therapy.

Hyperkalaemia can occur within a few hours of the commencement of chemotherapy and close surveillance should be maintained in patients with large tumour burdens or any evidence of impaired renal function.

Serial plasma K+ levels, e.g. 2 hourly if renal function markedly impaired, supplemented by serial ECGs are mandatory in such patients and ideally, careful cardiac monitoring for the first 24-48 hours of treatment should be carried out. Further surveillance should be based on needs dictated by the clinical course.

Elevated blood urea and creatinine

Blood urea may begin to rise within 24 hours of the commencement of therapy. This may be followed shortly after by elevations in plasma creatinine.

Rapid deterioration of renal function will influence K+ clearance such that hyperkalaemia could be a persistent problem in the first few days. Blood urea elevation is in part a result of massive proteolysis secondary to tumour lysis but also results from impairment of renal function secondary to direct effects on the kidney of tumour breakdown products, e.g. phosphates and xanthines, which may give rise to tubular obstruction.

Elevations of blood urea and creatinine may persist for 7-10 days. Blood urea and creatinine should be monitored 4 to 6 hourly during the first 72 hours of therapy in patients with a large tumour burden, prior renal impairment or raised serum uric acid level.

Hyperphosphataemia and Hypocalcaemia

Changes in phosphate and calcium levels usually occur shortly after the earliest rise in blood urea is detected. Marked hyperphosphataemia, a result of the release of intracellular phosphates, may be sufficient to induce intraluminal renal tubular precipitation of calcium phosphate or amorphous phosphates that, in turn, may cause oliguria and worsen azotemia. It should be noted that phosphate solubility is decreased at an alkaline pH. Hypocalcaemia secondary to hyperphosphataemia may cause potentially fatal cardiac arrhythmias. Calcium and phosphate levels should be carefully monitored, e.g. 4-6 hourly, especially during the first 48-72 hours of therapy. Patients with relative oliguria, azotemia or tumour involvement of the renal tract are at particular risk for the development of serious consequences such as anuria (phosphates), tetany or cardiac arrhythmias (hypocalcaemia).

Appendix 5: METHOTREXATE ADMINISTRATION AND UROPROTECTION

Administration

24-hour collections for creatinine clearance and glomerular filtration rate (GFR) should be measured prior to the commencement of the initial methotrexate infusion. This should be done as close to the time of the infusion as possible, and after tumour lysis has ceased. Methotrexate should only be administered in the presence of a normal blood urea and serum creatinine and a creatinine clearance of at least 50ml/min after correction to a surface area of $1.73m^2$. If creatinine clearance has been previously normal, it will not be essential to repeat this so long as serum creatinine has not increased by more than 20% of its previous value (when the patient is well hydrated) and there has been no intervening reason for impairment of renal function. A creatinine clearance should be obtained while the patient is in the hospital. Methotrexate administration should be discussed with the principal investigator when there is any evidence of renal impairment.

Adequate hydration is essential during high dose methotrexate administration. **Normally 3 l/m^2 of intravenous fluid will be administered during the methotrexate infusion and for 24 hours afterwards wherever possible. Urine pH should be 7.0 or above prior to commencement and during the methotrexate administration and leucovorin rescue.** Normally 50-100 mmol/l sodium bicarbonate will be adequate to maintain alkalinisation, but more should be administered if necessary.

Serum creatinine should be checked daily after methotrexate while in the hospital. The duration of the infusion **must not exceed 24 hours, regardless of the total dose administered up to that point.**

Methotrexate Levels

Serum methotrexate levels should be obtained as follows:

1. Initially 48-hours after commencement of methotrexate.
2. Then daily until methotrexate level is below 5×10^{-8}M when rescue is stopped.

Leucovorin rescue is commenced at hour 36 from the start, i.e. 12 hours from the end of the infusion. This will be administered intravenously at a dose of $15mg/m^2$. Thereafter, Leucovorin is given IV or PO every 6 hours until the methotrexate level is below 5×10^{-8}M, or predicted to be below 5×10^{-8}M. Normally, during the first cycle a complete methotrexate disappearance curve will be obtained and the patient not discharged until the methotrexate level is below 5×10^{-8}M.

On subsequent cycles the patient is not discharged until 2 plasma samples have been obtained over the course of approximately 24 hours post methotrexate infusion. If there has been no increase in plasma creatinine and no other problems, patients can be discharged with oral Leucovorin. However, levels must be carefully checked and compared to those obtained in the first cycle. If consistent, Leucovorin is continued for 24 hours longer than the estimated time at which plasma methotrexate would be below 5×10^{-8}M. The patient should be given sufficient Leucovorin for the dose to be increased should this be necessary because of unusually high levels.

Drug interactions

Drugs which compromise real function eg. Aminoglycoside and cisplatin can decease clearance of methotrexate and lead to systemic toxicity. Avoid concurrent use of **NSAIDS including salicylates and sulphonamides.** Large doses of penicillin may interfere with the active renal tubular secretion of methotrexate. **It is recommended that prophylactic co-trimoxazole be stopped one week before HDMTX therapy.**

APPENDIX 6: EXPECTED TOXICITIES

General toxicity associated with chemotherapy:

1) Sore mouth
2) Diarrhoea, nausea and vomiting
3) Lowering of the blood count which increases the risk of getting infections, bruising and bleeding. Sometimes blood and platelet transfusions are necessary. Intravenous antibiotics are likely to be required
4) Loss of hair -the hair usually grows back shortly after the chemotherapy is stopped.
5) Numbness or tingling sensation in limbs
6) Reduced reproductive function
7) Increased risk of thromboembolism

Specific side effects of chemotherapy

Cyclophosphamide

- Bone marrow suppression (anaemia, leucopenia, thrombocytopenia)
- Bladder contracture and fibrosis
- Amenorrhoea and azoospermia
- Haematuria (chemical cystitis, sterile haemorrhagic cystitis)
- Secretion of anti-diuretic hormone, fluid retention and hyponatremia
- Myocardial toxicity
- Secondary acute leukaemia and bladder cancer
- Hyperglycaemia, Hypoglycaemia
- Thromboemolism
- Pneumonitis
- Haemolytic uraemic syndrome
- Nasal congestion
- Asthenia or sweating
- Redness, swelling or pain at injection site
- Myxoedema or sore lips
- Hepatotoxiciy
- Diarrhoea
- Sterility
- Alopecia
- Mucosal ulceration
- Pigmentation of skin, nails
- Interstitial pulmonary fibrosis
- Hepatic Toxicity
- Neoplasia
- Pancreatitis
- Macrocytosis
- Veno-occlusive disease
- Disseminated intravascular coagulation
- Hypersensitivity

- Dizziness
- Rash, hives or itching
- Toxic epidermal necrolysis
- Haemorrhagic colitis
- Stomatitis colitis
- Stomatitis
- Jaundice
- Anorexia
- Nausea
- Vomiting

Doxorubicin

- Bone marrow suppression (leucopenia, neutropenia, anaemia, thrombocytopenia)
- Immunosuppression/infection
- Anaphylaxis
- Anorexia
- Dehydration
- Hyperuricaemia
- Conjunctivitis, keratitis of the eye, lacrimation
- Cardiac toxicity (tachycardia, tachyarrythmias, ECG abnormalities, reduced left ventricular ejection fraction, cardiac failure)
- Nausea
- Vomitting
- Stomatitis/mucositis
- Oesophagitis
- Diarrhoea
- GI bleeds/erosions
- Abdominal pain
- Colitis
- Hepatic toxicity- abnormal LFTs
- Alopecia
- Rash
- Itching, erythema, urticaria and dysaesthesia
- Hyperpigmentation of skin, nails and oral mucosa
- Hypersensitivity
- Photosensitivity
- Thromboembolism
- Phlebitis
- Discolouration of urine
- Hot flushes
- Shock
- Menstrual changes
- Impaired spermatogenesis/infertility
- Secondary acute myeloid leukaemia, Lymphocytic leukaemia and myelogenous leukaemia
- Injection site reaction (thrombophlebitis, stinging, burning)

Vincristine

- Bone marrow suppression (leucopenia, anaemia, thrombocytopenia)
- Peripheral neuropathy
- Neuritic pain
- Constipation
- Abdominal cramps
- Ileus
- Diarrhoea
- Weight loss
- Nausea
- Vomiting
- Oral ulceration
- Intestinal necrosis and/or perforation
- Anorexia
- Alopecia
- Rash
- Renal toxicity – polyuria, dysuria and urinary retention
- Hearing loss
- Visual impairment
- Blindness and optic atrophy
- Shortness of breath
- Bronchospasm
- Jaw pain
- Pharyngeal pain
- Parotid gland pain
- Bone pain, back pain and limb pain
- Sensory loss
- Paraesthesiae
- Dizziness, nystagmus and vertigo
- Musculoskeletal pain and muscle wasting
- Loss of deep tendon reflexes
- Difficulty in walking
- Ataxia, paresis
- Convulsions, coma
- Anaphylaxis and oedema
- Coronary artery disease and myocardial infarction
- Hypertension and hypotension
- Fever
- Headache
- Injection site reaction

Etoposide

- Secondary cancer (acute promyelocytic leukaemia
- Bone marrow suppression (anaemia, leucopenia, thrombocytopenia)
- Anaphylaxis
- Fever

- Reversible loss of vision
- Fatigue
- Drowsiness
- Cardiac toxicity (tachycardia, arrhythmia, MI)
- Hypotension and hypertension
- Bronchospasm, coughing, cyanosis and laryngospasm
- Apnoea, interstitial pneumonitis or pulmonary fibrosis
- Hepatic dysfunction (elevated LFTs)
- Toxic epidermal necrolysis
- Stevens Johnson syndrome
- Alopecia
- Nausea
- Immunosuppression/infection
- Haemorrhage
- Vomiting
- Anorexia
- Abdominal pain
- Diarrhoea
- Mucositis and oesophagitis
- Constipation
- Dysphaia
- Rash, urticaria, pigmentation and pruritus
- Hyperuricaemia
- Peripheral neuropathy
- Weakness
- Paresthesiae
- Phlebitis

Please note: Inpatient admission will be necessary for administration of chemotherapy

Rituximab

For a complete list of expected AE'S please refer to the summary pf products characteristics (SmPC) for Rituximab

GCSF (Neulasta)

The most frequently reported study-drug related undesirable effect is bone pain.

Allergic- type reactions, including anaphylaxis, skin rash, urticaria, angioedema, dyspnoea and hypotension.

Reversible, mild to moderate elevations in uric acid, alkaline phosphatise and lactate dehydrogenase.

Common

Splenomegaly
Pain
Injection site pain
Chest pain (non cardiac)
Headache
Arthralgia
Myalgia
Back, limb, musculo-skeletal and neck pain

Rare
Interstitial pneumonia
Pulmonary Oedema
Pulmonary infiltrates and fibrosis
Respiratory failure or Adult Respiratory Distress Syndrome – may be fatal
Thrombocytopenia
Leukocytosis

Very rare
Sweets syndrome
Cutaneous vasculitis

APPENDIX 7: TRIAL MANAGEMENT GROUP

Andrew McMillan	Nottingham City Hospital
Russell Patmore	Hull Royal Infirmary
Cathy Burton	HMDS, Leeds General Infirmary
Andrew Jack	Leeds General Infirmary
David Linch	University College Hospital, London
David Cunningham	Royal Marsden Hospital Sutton, Surrey.

Staff at Lymphoma team, UCL CTC, London

Wendi Qian
Paul Smith

Data Monitoring Committee

Howie Scarffe	Lister Hospital, Stevenage
Rob Glynne-Jones	Mount Vernon Hospital, London
Robin Prescott	Edinburgh Medical School