R-CODOX-M/IVAC

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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For the Sponsor:		
Professor Jonathan Ledermann Director, UCL CTC	Allan Hackshaw Deputy Director	19/8/10

Please note: This trial protocol must not be applied to patients treated outside the R-CODOX-M/IVAC trial. CR UK and UCL Cancer Trials Centre (UCL CTC) can only ensure that approved trial investigators are provided with amendments to the protocol

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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.

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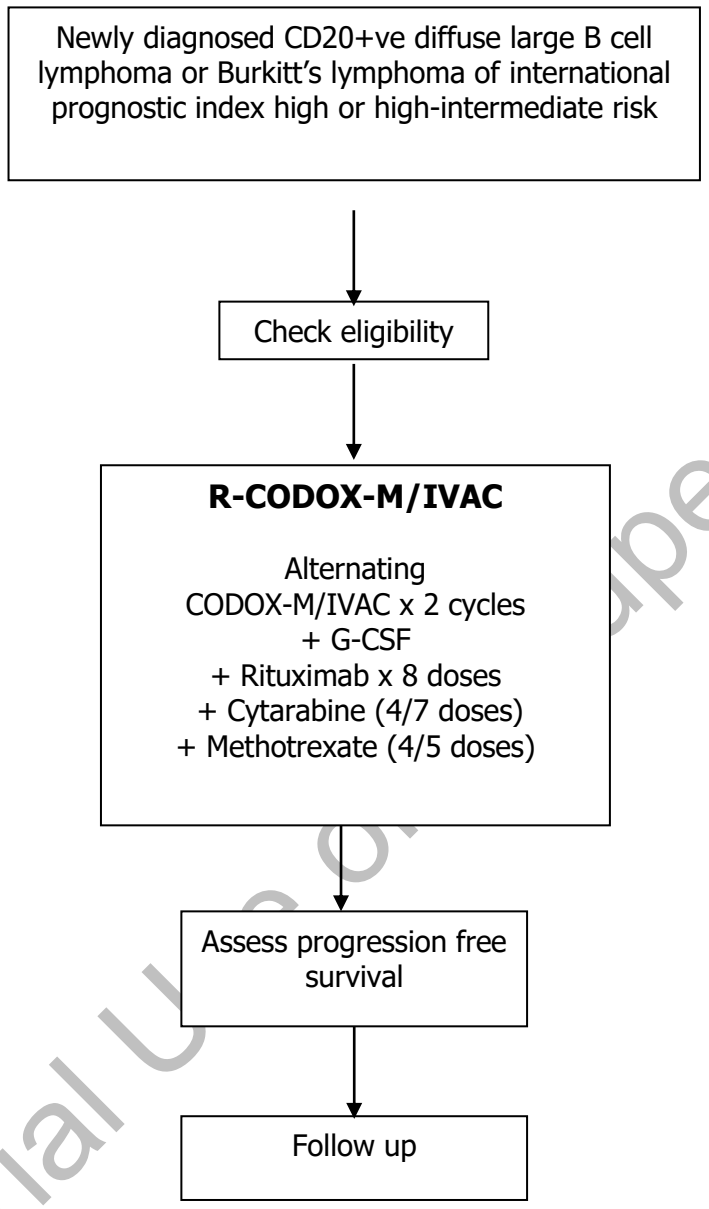
1.0: PROTOCOL SUMMARY

1.1 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
Start and end dates of study	Start date: May 2008 Patients will be recruited over 2-3 years and followed up 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 and all morphological variants 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 18-65yrs (consideration of individual patient's 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

1.2 Trial Outline

Figure 1



2.0: BACKGROUND

2.1 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]

2.2 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 7.3.

2.3 Rationale of the Study

2.3.1 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.

2.3.2 Rationale for Burkitt's 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.

2.4 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:

- Complete response rate (CR and Cru)

- Toxicity

2.5 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

3.0: SELECTION OF SITES/SITES INVESTIGATORS

3.1 Site Selection

In this protocol trial **"Site"** refers to the hospital or site where trial-related activities are actually conducted.

Sites must be able to comply with:

- Trial treatments, imaging, 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

3.2 Selection of Principal Investigator and other investigators at sites

Sites must have an appropriate Principal Investigator (PI) i.e. a health care professional authorised by the site, ethics committee and Competent Authority to lead and coordinate the work of the trial on behalf of the site. Other investigators at site wishing to participate in the trial must be trained and approved by the PI; all investigators will be required to sign a declaration of participation. This protocol involves intensive therapy, which should only be given in expert sites. Therefore, it is recommended that only sites with expertise in the management of chemotherapy for Acute Myeloid Leukaemia given with curative intent (BCSH level 2) take part in this trial.

3.3 Site Initiation and activation

3.3.1 Site initiation

Site initiation will be performed by teleconference

The following documentation must be in place prior to a site being opened to recruitment by UCL CTC trial team:

- Trial specific Declaration of Participation (identifying relevant local staff)
- All relevant institutional approvals (e.g. local NHS R&D permission)
- A signed Clinical Trial Site Agreement (CTSA) between the Sponsor and the relevant institution (usually a NHS Trust)

The PI, other delegated site investigators and all staff involved in the conduct of the trial at the site must be identified on the site delegation log held at site and copied to UCL CTC prior to site activation.

Sites must also have in place facilities for providing **24 hour medical advice** for trial patients.

3.3.2 Site activation

Once the trial team at UCL CTC have confirmed that all documentation is in place a site activation letter will be issued to the Principal Investigator, at which point the site may start to approach patients.

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
- Prompt notification and assessment of all adverse events

4.0: INFORMED CONSENT

Sites are responsible for assessing a patient's capability to give informed consent.
Sites are responsible for ensuring all patients have been given the current version of the patient information sheets, are fully informed about the trial and have confirmed their willingness to take part in the trial by signing a consent form. The PI or other delegated site investigators 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 detailed patient information sheets for the trial will be given to the patient. A minimum of twenty four hours must be allowed for the patient to consider and discuss participation in the trial. Written informed consent on the current version of the consent form for the trial must be obtained before any trial-specific procedures are conducted.

Site staffs are responsible for:

- checking that information on the consent forms are complete and legible
- checking that the patient has initialled all relevant sections and signed and dated the form
- Checking that an appropriate member of staff has countersigned and dated the consent forms 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. info given, consent signed etc.)
- Adding the patient trial number to all copies of the consent form to be filed in the medical notes and investigator site file

The original signed consent form and a copy must be stored at site (in the Investigator Site File and the patient's medical notes).
A further copy must be given to the patient

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 15.0 – withdrawal of patients).

5.0: SELECTION OF PATIENTS

5.1 Baseline Investigations

The following investigations are required to evaluate the suitability of patients for the trial and should be done 14 days prior to trial entry (except where specified):

a) Complete medical history.

b) Concomitant diseases and treatment.

c) Physical examination.

d) Vital signs.

e) WHO performance status (Appendix 5).

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. **This is mandatory for all patients aged 61 - 65 years inclusive, and the Left Ventricular Ejection Fraction (LVEF) should be normal according to local practice.**

i) Serology for HIV, HBV and HCV

j) Contrast enhanced CT scan of the neck, thorax, abdomen and pelvis*

k) Full blood count.

l) Serum electrolytes, urea and creatinine.

m) Creatinine clearance (measured either by 24 hour urinary collection or radio-isotope methods) measured no more than 72 hours before initial high dose methotrexate

n) Serum bilirubin, liver transaminases, alkaline phosphatase, albumin, total proteins, calcium, magnesium, phosphate level, uric acid

o) Serum lactate dehydrogenase (LDH) and β2 microglobulin.

p) Bone marrow biopsy*.

q) Cerebrospinal fluid examination if clinically indicated or lymphomatous involvement in peripheral blood, bone marrow, nasal/paranasal sinuses, orbit or testis.

For patients pre-treated with steroids, investigations should be performed before the steroid treatment (except for the echocardiogram or MUGA which can be done after).

All investigations should be within 14 days prior to entering trial.

***Scans and bone marrow biopsy should be performed within 28 days prior to entering trial.**

5.2 Screening Logs

A screening log should be maintained by the site and kept in the Investigator Site File. This should record each patient screened for the trial. The log should be sent to UCL CTC when requested with patient identifiers removed prior to sending.

The information collected will include:

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

5.3 Patient Eligibility

There will be no exception to the eligibility requirements at the time of registration. Queries in relation to the eligibility criteria should be addressed prior to faxing for registration. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria applies.

5.3.1 Inclusion criteria

a) Age 18-65 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, > 1 extranodal site and poor performance status – WHO performance status >/= 2. (See Appendix 4).

d) Disease stage II - IV

e) No previous chemotherapy, radiotherapy or other investigational drug for this indication **(although pre-treatment with steroids is acceptable)**

f) 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.

g) Serum creatinine < 150μmol/l, serum bilirubin < 35μmol/l and transaminases < 2.5× upper limit of institutional normal range unless attributed to lymphoma.

h) Normal MUGA or echocardiogram without areas of abnormal contractility and normal left ventricular ejection fraction (LVEF). (Only applicable if over 60 years of age, past history of diabetes, cardiac disease, hypertension or abnormal resting ECG).

i) No concurrent uncontrolled medical condition.

j) 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.

k) Life expectancy > 3 months.

l) Adequate contraceptive precautions for all patients of childbearing potential.

m) Written, informed consent.

5.3.2 Exclusion criteria

a) Disease stage I

b) T-cell lymphoma.

c) 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.

d) Past history of heart failure or uncontrolled angina pectoris.

e) Cardiac contra-indication to doxorubicin (abnormal contractility on echocardiography or nuclear medicine examination [MUGA]).

f) Neurological contra-indication to vincristine (e.g. pre-existing diabetic neuropathy).

g) Any other serious active disease.

h) General status that does not allow the administration of 2 cycles of CODOX-M/IVAC according to the investigator.

i) Positive serology for HIV, Hepatitis B or Hepatitis C

j) Medical or psychiatric conditions that compromise the patient's ability to give informed consent.

5.3.3 Pregnancy and Birth control

Female patients potentially able to bear children should have a negative pregnancy test prior to commencing the trial drugs, and agree to use an approved contraceptive method (IUD,

birth control pills or barrier device) during and for at least 1 year after the trial. All male patients should take adequate contraceptive precautions during and for at least 1 year after stopping treatment.

A woman of childbearing potential (WCBP) is a sexually mature woman (i.e. any female who has ever experienced menstrual bleeding) and who has not undergone a hysterectomy or who has not been postmenopausal for 24 consecutive months (i.e. who has had menses at any time in the preceding 24 consecutive months).

5.3.4 Long term infertility

- If produced at all, sperm or eggs may not be formed normally during treatment and one year after chemotherapy.

- Treatment will make most patients infertile; males and females over 30 years are likely to become infertile. Women younger than 30 years may retain their fertility. It is though likely they will experience an earlier menopause by 5-10 years.

Prior to commencing chemotherapy arrangements can be made for sperm storage.

6.0: TRIAL REGISTRATION PROCEDURES

6.1 Registration

Patient registration will be undertaken centrally at UCL CTC and this must be performed prior to commencement of any trial treatment.

Following baseline investigations (as detailed in section 5.1), confirmation of eligibility and consent of a patient at a site, the registration form must be fully completed and then faxed to UCL CTC. The faxed registration form will be used to confirm patient eligibility at UCL CTC.

A trial number will be assigned for the patient and details added to the form.
UCL CTC will fax confirmation of the patient's inclusion in the trial and their trial number to the main contact and pharmacy. Patient specific Case Report Forms (CRFs) will be sent to the main contact at site.

Registration telephone number:	+44 (0)20 7679 9860
Registration fax number:	+44 (0)20 7679 9861
Office hours:	09:00 to 17:00 Monday to Friday (UK Time)

Once a patient has been registered onto the trial they must be provided with a copy of their signed consent forms and patient information sheets.

6.2 Initial trial drug supply

Please see summary of drug supply arrangements for details of initial supply of Neulasta® (pegfilgrastim) for the trial.

Rituximab, cyclophosphamide, vincristine, doxorubicin, cytarabine, methotrexate, etoposide, ifosfamide and Mesna are to be supplied from Hospital Commercial Stock as detailed in the summary of drug supply arrangements.

7.0: TRIAL TREATMENT

7.1 Treatment Summary

For the purpose of this protocol, the IMPs are Rituximab, cyclophosphamide, vincristine, doxorubicin, cytarabine, methotrexate, etoposide and ifosfamide.

Pegylated Granulocyte colony-stimulating factor (G-CSF), pegfilgrastim (Neulasta®), is being supplied free by Amgen for this trial.

7. 2 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.

7.3 Summary Treatment Schedule

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

7.3.1 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 7.4
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 8) 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.

7.3.2 IVAC

The table below shows the ideal schedule for delivering IVAC. 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 7.3
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 suspected CNS disease* see section 6.7]	70mg	**INTRATHECAL**	
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 7.4
42	Rituximab	375 mg/m^2	IV	Infusion rate as per section 7.4

7.3.3 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.

7.3.4 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)

7.4 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°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.

7.5 Other medications

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

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

- Corsdyl 5ml qd mouthwash
- Acyclovir 200mg qd or 400mg bd
- Lansoprazole 30mg od (po)
- Metoclopramide 10mg tds for 3 days

7.6 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.

7.7 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 to be given below (ONLY THE FIRST TWO CYCLES).

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

7.8 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 ·g) 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.

7.9 Trial Treatment Details

7.9.1 Pharmacy responsibilities

Please see separate trial drug supply summary document and appendix 3 of the Clinical Trial Site Agreement.

7.9.2 Drug Accountability

Accountability for Rituximab, cyclophosphamide, vincristine, doxorubicin, cytarabine, methotrexate, etoposide, ifosfamide and Neulasta at participating sites is the responsibility of the Principal Investigator, who may delegate this responsibility to the local pharmacist, or other appropriately qualified personnel. The responsible person will ensure that the Rituximab, cyclophosphamide, vincristine, doxorubicin, cytarabine, methotrexate, etoposide, ifosfamide and Neulasta are used only in accordance with this protocol and that appropriate drug accountability records are maintained.

Neulasta® is supplied for R-CODOX-M/IVAC trial patients only and must not be used outside the context of this protocol.

The site pharmacy must maintain accountability records for each drug including receipt (where applicable), dispensing, returned medication, storage conditions and destruction of returned/unused medication. Template accountability forms will be supplied, however, sites are permitted to use their own drug accountability records as long as the same information is captured and are available to the Sponsor.

7.9.3 Toxicity and Dose Modification

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/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf

7.9.4 Haematological toxicity

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

7.9.5 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.

7.9.5.1 Hepatic Impairment

		% of full dose to be given
Cytarabine	Bilirubin (µmol/L)> 34	50%
	Escalate doses in subsequent cycles in the absence of toxicity	
Doxorubicin	Bilirubin (µmol/L) 20 – 51 51 – 85 > 85 If AST is 2-3 x ULN If AST is > 3 x ULN	 50% 25% Omit 75% 50%
Etoposide	If bilirubin (µmol/L) is 26-51 or AST is 60-180 If bilirubin (µmol/L) is > 51 or AST is > 180	50% Clinician's decision
Methotrexate	If bilirubin (µmol/L) < 52 and AST < 180 If bilirubin (µmol/L) is 53 – 84 or AST > 180 If bilirubin (µmol/L) is > 85	100% 75% Omit
Vincristine	If bilirubin (µmol/L) is 26 – 51 or AST/ALT is 60-180 If bilirubin (µmol/L) > 51 with normal AST/ALT If bilirubin (µmol/L) > 51 with AST/ALT > 180	50% 50% Omit
Cyclophosphamide	Dose reduction not necessary	
Ifosfamide	Clinician's decision	

7.9.5.2 Renal Impairment

		% of full dose to be given
Cytarabine	High dose (1-3g/m^2): CrCl (ml/min) > 60 > 45 < 35	 60% 50% omit
Doxorubicin	Severe impairment – clinical decision	
Etoposide	CrCl (ml/min 60 45 30 < 15	 85% 80% 75% 50%
	Subsequent doses should be based on clinical response	
Methotrexate	CrCl (ml/min) > 80 60 45 < 30	 100% 65% 50% omit
Vincristine	No dose reduction	
Cyclophosphamide	CrCL (ml/min) > 50 10-50 < 10	 100% 75% 50%
	Consider whether patient is being treated with high dose treatment	
Ifosfamide	CrCl (ml/min) > 60 40-59 < 40	 100% 70% Clinician's decision
	If creatinine is > 120 µmol/L, not recommended	

7.9.6 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. This needs to be confirmed in writing to UCL CTC.

7.9.7 Management after treatment withdrawal

If a patient withdraws consent or stops trial treatment for any reason e.g. toxicity or patient's decision then subsequent treatment will be at the discretion of the treating clinician.

8.0: ASSESSMENTS

8.1 Assessments time points

Information is required from patients at the following time points:

- Before each treatment cycle
- Within a month of the second IVAC cycle
- Follow Up

See also the trial investigation schedule (appendix 2).

8.2 Assessments during treatment

During treatment the patient should be seen before each cycle of treatment commences and the following investigations performed:

- Physical examination
- Laboratory tests including full blood count, serum electrolytes, urea, creatinine, bilirubin, liver transaminases, alkaline phosphatase, lactate dehydrogenase, albumin and total proteins.

- Toxicity and adverse event assessment.

8.3 Assessments on completion of trial treatment

Within one month of completing the trial treatment (after the second IVAC cycle), the patient should be seen and the following investigations performed:

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

8.4 Assessments during follow up

All patients will be followed up at the following time points:

- Monthly during the first 4 months, and 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
- Annually thereafter till death

A physical examination should be done at each follow up visit.

CT scans of the chest, abdomen and pelvis should be performed at month 4 and 1 year (month 12) after finishing treatment.

No routine blood tests are required as part of the trial.

If a patient fails to attend any visit then the site must make every effort to gain follow up information as requested. All efforts should be made by the Site to contact the patient's GP to assess their condition, if a patient fails to attend a clinic or cannot be followed up at site.

Patients will be followed up for five years in the first instance and then until death.

9.0: OUTCOME MEASURES

9.1 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.

9.2 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.

9.3 Toxicity

This will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v 3.0 (CTCAE)
http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf

10.0: 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:

10.1 Complete response (CR)

A complete response requires **all** of the following criteria 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 ($\leq$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 $\leq$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.

10.2 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).

10.3 Partial response (PR)

A partial response requires **all** of the following:

a) $\geq$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

10.4 Stable disease (SD)

Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.

10.5 Progressive disease (PD)

Progressive disease 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.

10.6 Relapsed disease (after CR, CRu)

Relapsed disease 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.

Summary of disease response evaluation

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

11.0: 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.

11.1 Completing Case Report Forms

All CRFs must be completed and signed by staff that 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 and a copy kept at site. All entries must be clear and legible. The use of abbreviations and acronyms must be avoided.

11.2 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 and a copy retained at site.

11.3 Missing Data

To avoid the need for unnecessary data queries CRFs must be checked at site to ensure there are no blank fields before sending to UCL CTC. When data is 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).

11.4 Data Queries

Data arriving at UCL CTC will be checked for completeness, accuracy and consistency. Queries on incomplete, inaccurate or inconsistent data will be sent to the CRF contact at site. When responding to a query, site staff should attach an amended copy of the case report form held at site and send to UCL CTC, keeping a copy at site. All amendments must be initialled and dated.

11.5 Timelines for data return

CRFs must be completed at site and returned to UCL CTC as soon as possible after patient visit and within a month of the patient being seen. Follow up CRFs should be returned to UCL CTC within 2 weeks of the follow up visit.

Sites who persistently do not return data within the required timelines may be suspended from recruiting further patients into the trial by UCL CTC.

12.0: PHARMACOVIGILANCE

12.1 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" andICH 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 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 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 (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 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 (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.

12.2 Reporting Procedures

12.2.1 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. 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 also section 12.2.2 (Serious Adverse Events (SAEs)).

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

Overdoses

All accidental or intentional overdoses, whether they result in an adverse event or not, must be recorded in the patient notes and CRFs. Overdoses resulting in an adverse event are classified as SAEs and must be reported to UCL CTC according to SAE reporting procedures. 'Other medically significant event' must be ticked as the classification of serious and the fact that an overdose has occurred must be clearly stated. See also section 12.2.2 (Serious Adverse Events (SAEs)).

Sites must inform UCL CTC immediately when an overdose has been identified. See also section 12.8 (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 v3.0 (CTCAE), available online at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf.

Severity

Severity of each adverse event must 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/protocolDevelopment/electronic_applications/docs/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

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 medications).

• **Possible**

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 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.

12.2.2 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 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. If the event is **not being reported within 1 business day** to UCL CTC, the circumstances that led to this must be detailed in the SAE Report to avoid unnecessary queries.

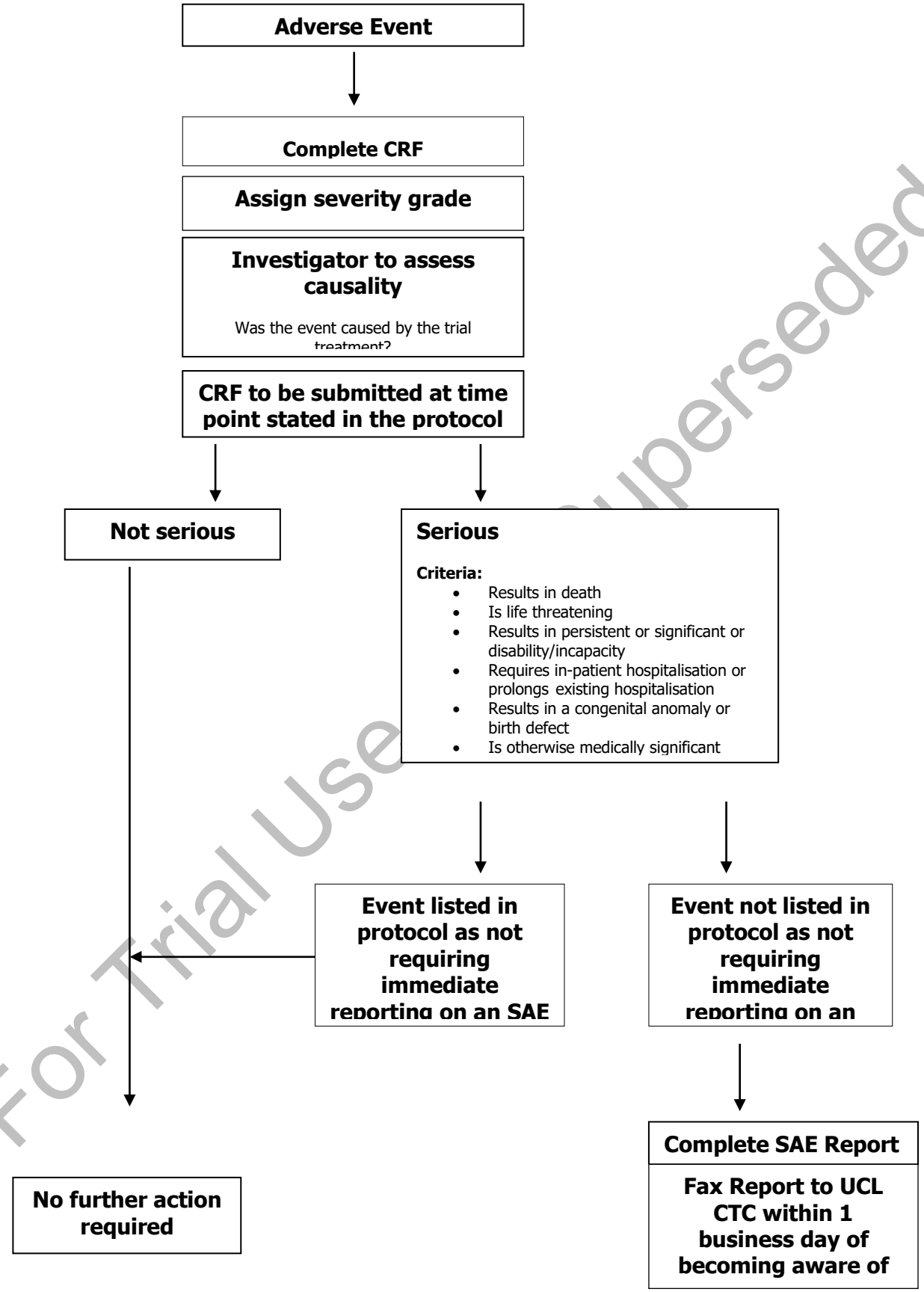
Events which do not require immediate reporting on an SAE report

The following events do not require immediate reporting on an SAE report for this trial, but must be reported on the relevant section of the CRF:

- disease progression
- disease related deaths

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

Adverse Event Reporting Flowchart



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 list of expected adverse events for the CODOX-M/IVAC regimen in appendix 9, the current SmPCs for Rituximab, cyclophosphamide, vincristine, doxorubicin, cytarabine, methotrexate, etoposide and ifosfamide.

The CI, or their delegate (e.g. a clinical member of the TMG), will be contacted 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.

UCL CTC will fax all individual serious adverse drug reactions related to the Trial Drug, Neulasta®, to Amgen within 1business day.

12.3 SUSARs

If the event is evaluated as a Suspected Unexpected Serious Adverse Reaction (SUSAR), UCL CTC will submit a report to the MHRA and the REC 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. In the case of conflicting evaluations of causal relationship by the site and UCL CTC/CI, both opinions will be reported.

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

12.4 Clinical Review

UCL CTC will provide safety information to the TMG and the IDMC 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 the REC.

12.5 Additional Safety Monitoring at UCL CTC

UCL CTC will also monitor safety data for any trial related events that are not considered related to the trial treatment regimen. Should any trial procedures appear to be resulting in adverse events, the Trial TMG will be contacted for their opinion. If it is declared necessary to review the conduct of the trial, UCL CTC will inform the MHRA and the REC as appropriate.

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

12.6 Pregnancy

If a patient or the partner of a male 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. Consent to report information regarding pregnancy outcomes must be obtained from the mother, if not a trial patient. The Pregnant Partner Information Sheet and Consent Form must be used for this purpose.

All pregnancies must be reported by faxing a completed Pregnancy Report within 1 business day of becoming aware of the pregnancy to the UCL CTC:
Fax: 020 7679 9861

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 **1 business day** 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. See section 12.2.2 (Serious Adverse Events (SAEs)) for details.

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

UCL CTC will submit a report to the MHRA and the REC should the pregnancy outcome meet the definition of a SUSAR. See section **12.3** (SUSARs) for details.

12.7 Annual Safety Reports

UCL CTC will submit Annual Safety Reports to the MHRA and the REC. This will commence one year from the date of CTA approval obtained for the trial. The final Annual Safety Report will be submitted in the year following trial closure. See section 16.1 (End of Trial) for details.

13.0: INCIDENT REPORTING AND SERIOUS BREACHES

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).

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

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.

Sites must have written procedures for notifying the sponsor of serious breaches (MHRA Guidance on the Notification of Serious Breaches, 2009).

UCL CTC will use an organisation's history of non-compliance to make decisions on future collaborations.

14.0: TRIAL MONITORING AND OVERSIGHT

Participating sites and Principal Investigators must agree to allow trial-related on-site monitoring, including 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 are asked to consent to their medical notes being reviewed by UCL CTC on the consent form.

14.1 Self-assessment monitoring

Participating sites will be requested to complete a self-assessment monitoring report periodically, at a frequency detailed in the trial monitoring plan. This report may include, but is not limited to, Investigator Site File and Pharmacy File document version checklists, recruitment status for consistency checks, reporting of adverse events and review of informed consent forms. Responses will be reviewed at UCL CTC to identify areas of non-compliance/fraud and to indicate training needs. Findings may trigger an on-site monitoring visit.

14.2 Central monitoring

Data stored at UCL CTC will be checked for missing or unusual values (range checks) and checked for consistency over time. If any problems are identified data queries will be issued to the site. Sites are required to resolve any queries and update the relevant CRF as required. All changes must be initialled and dated. The amended version must be sent to UCL CTC and a copy retained at site.

Sites will also be requested to submit screening logs and staff delegation logs to UCL CTC on request and these will be checked for consistency and completeness.

14.3 Non-Compliance/'for cause' on-site monitoring

Additional 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/GCP requirements. Sites will be sent a letter in advance outlining the reason(s) for the visit, 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 will likely occur.

14.4 Committees

14.4.1 Trial Management Group (TMG)

The TMG will include the Chief Investigator, clinicians and experts from relevant specialities and R-CODOX-M/IVAC trial staff from UCL CTC (see page 1). The TMG will be responsible for overseeing day to day issues arising from the trial. The group will meet regularly twice a year and will send updates to Principal Investigators (via newsletters) and to the NCRI Lymphoma Clinical Studies Group.

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

A charter, signed by the members of the TMG is in place for this trial.

14.4.2 Independent Trial Steering Committee (ITSC)

The role of the ITSC is to provide overall supervision of the trial and ensure that it is conducted in accordance with GCP and the Protocol. The ITSC 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 ITSC acts on behalf of the funder and Sponsor.

A charter, signed by the members of the ITSC is in place for this trial.

14.4.3 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 address any issues. The IDMC is advisory to the Trial Steering Committee (TSC) and can recommend premature closure of the trial to the TSC.

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. The interim analyses will be performed by a statistician at 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.

A charter, signed by the members of the IDMC is in place for this trial.

14.4.4 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 will ensure that all SAEs and SUSARs are appropriately reported to the regulatory authorities, the REC and Amgen. In addition expedited reports of all SUSARs will be reported promptly to all Principal Investigators.

15.0: 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
- Intolerable adverse effects as judged by the investigator or the patient
- Patients withdrawing consent to further trial treatment
- Recurrent grade 3 or 4 drug related toxicity despite dose modification as judged by the investigator
- Serious systemic allergic reaction to any of the trial drugs e.g. angio-oedema, anaphylaxis.

In these cases patients remain within the trial for the purposes of follow-up and data analysis. 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.

Withdrawal of Consent to Data Collection

If a patient explicitly states they do not wish to contribute further data to the trial their decision must be respected and recorded on the relevant CRF and UCL CTC notified in writing. In this event details should be recorded in the patient's hospital records, no further CRFs must be completed and no further data sent to UCL.

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 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.

16.0: TRIAL CLOSURE

16.1 End of Trial

For regulatory purposes the end of the trial will be 3 years after last patient has been recruited, at which point the 'declaration of end of trial' form will be submitted to participating regulatory authorities and ethical committees, as required. However, this will be followed by the non-interventional phase of long-term follow-up, which will continue indefinitely.

16.2 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 continue to be available for inspection by appropriate authorities upon request.

At any time, if a patient **explicitly** withdraws consent for **any** collected data to be used in the trial the data will be destroyed at site and at UCL CTC when notification is received from the site.

16.3 Early discontinuation of trial

The trial may be stopped before completion as an Urgent Safety Measure on the recommendation of the ITSC or IDMC (see section 14.1.2 ITSC and 14.1.3 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.

16.4 Withdrawal from trial participation by a site

Should a 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.

17.0: 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.

18.0: 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) as set out in Schedule 1 (Conditions and Principles of Good Clinical Practice and for the Protection of Clinical Trial Subjects) of the Medicines for Human Use (Clinical Trials) Regulations 2004 and the GCP Directive 2005/28/EC, as set out in SI 2006/1928
- the Human Rights Act 1998
- the Data Protection Act 1998
- the Freedom of Information Act 2000
- the Human Tissue Act 2004
- the Medicines Act 1968
- the 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)

18.1 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.

The trial has received a favourable opinion from the Hertfordshire 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.

18.2 Regulatory Approval

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

18.3 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.

18.4 Protocol Amendments

UCL CTC will be responsible for gaining ethical and regulatory approvals 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 as appropriate.

Site staff will be responsible for acknowledging receipt of documents and for gaining local Trust R&D acknowledgement for all amendments and approval for substantial amendments, and for providing UCL CTC with evidence of this.

18.5 Patient Confidentiality & Data Protection

Patient identifiable data, including initials, date of birth and NHS number will be required for the registration 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.

19.0: SPONSORSHIP AND INDEMNITY

19.1 Sponsor Details

Sponsor Name:	University College London
Address:	Gower Street London WC1E 6BT
Contact:	Senior Clinical Trials Manager or Divisional Manager
Postal Address:	Joint UCLH and UCL Biomedical Research Unit (1st floor, Maple House) Ground Floor, Rosenheim Wing 25 Grafton Way London WC1E 5DB

19.2 Indemnity

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 (i.e. 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.

20.0: FUNDING

The Leukaemia Research Fund (LRF) is supporting the central coordination of the trial through UCL CTC.

Pegylated G-CSF (Neulasta®) will be supplied **free of charge** by **Amgen Limited** to sites for Trial Subjects.

21.0: PUBLICATION POLICY

All publications and presentations relating to the trial will be authorised by the TMG. The first publication of the trial results will be in the name of the TMG, if this does not conflict with the journal's policy. The TMG will form the basis of the writing committee and advice on the nature of publications. If there are named authors, these should include the Chief Investigator, Trial Coordinator, and Statistician involved in the trial. Contributing site investigators in this trial will also be acknowledged. 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 CTC. Drug companies who have contributed towards the trial will be permitted to see the draft manuscripts and make comments at least 30 days prior to submission for publication. The Eudract number (2005-003479-19) or the clinicaltrials.gov number (NCT00974792) will be quoted in any publications resulting from this trial.

22.0: REFERENCES

1. Jaffe ES, Harris NL, Stein H et al: World Health Organization Classification of Tumours. Pathology & Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Jaffe ES, Harris NL, Stein H, Vardiman JW (ed) Lyon, IARC Press, 2001

2. Ferlay J, Bray F, Pisani P et al: GLOBOCAN 2000-Cancer Incidence, Mortality and Prevalence Worldwide, Version 1.0. 2001

3. Shipp M, Harrington D, Andersen J. A predictive model for aggressive non-Hodgkin's lymphoma. The international non-Hodgkin's lymphoma prognostic factors project 1993 New England Journal of Medicine, 329, 987-994

4. Pettengell R, Gurney H, Radford J, Deakin D, James R, Wilkinson P, Kane K, Bentley J, Crowther D. Granulocyte colony-stimulating factor to prevent dose-limiting neutropenia in non-Hodgkin's lymphoma: a randomized controlled trial. Blood. 1992 80, 1430-6.

5. Pfreundschuh M., Kloess M., Schmitz N., Glass B., Schmits R., Engert A., Rudolph C., Illiger J., Hossfield G., Loeffler M. 2 weekly CHOP (CHOP 14): The new standard regimen for patients with aggressive non-Hodgkin's lymphoma (NHL) > 60 years of age. Journal of Clinical Oncology 2002 13, 81

6. Wunderlich A. Practibility and acute haematological toxicity of 2 and 3 weekly CHOP and CHOEP chemotherapy for aggressive non-Hodgkin's lymphoma: results from the NHL-B trial of the German High Grade non-Hodgkin's lymphoma study group (DSHNHL) Annals of Oncology 2003, 14, p.881-893

7. Coiffer B. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large B-cell lymphoma. New England Journal of Medicine 2002 346, 235-242

8. Sehn L, Donaldson J, Chhanabhai M, Fitzgerald C, Gill K, Klasa R, Macpherson N, O'Reilly S, Spinelli J, Sutherland J, Wilson K, Gascoyne R, Connors J. Introduction of Combined CHOP Plus Rituximab Therapy Dramatically Improved Outcome of Diffuse Large B-Cell Lymphoma in British Columbia. Journal of Clinical Oncology, Vol 23, No 22 (August 1), 2005: pp. 5027-5033
9. Cuttica A, Zallio F, Ladetto M, Di Nicola M, Caracciolo D, Magni M, Marinone C, Dell'Aquila M, Rosace M, Pileri A, Boccadoro M, Gianni A, Tarella C. Patients with High-Risk Aggressive Lymphoma Treated with Frontline Intensive Chemotherapy and Autografting. Evidence of marked difference in outcomes between patients with age-adjusted international prognostic index scores 2 and 3. 2003 Cancer 98 983-992

10. Haioun C, Lepage E, Gisselbrecht C, Salles G, Coiffier B, Brice P, Bosly A, Morel P, Nouvel C, Tilly H, Lederlin P, Sebban C, Briere J, Gaulard P, Reyes F. Survival benefit of high-dose therapy in poor risk aggressive non-Hodgkin's lymphoma: Final analysis of the

prospective LNH87-2 protocol - by Groupe d'Etude des Lymphomes de l'Adulte study Journal of Clinical Oncology 2000, 18, 3025-3030

11. Milpied N, Deconinck E, Gaillard F, Delwail V, Foussard C, Berthou C, Remy Gressin R, Lucas V, Colombat P, Harousseau J. Initial Treatment of Aggressive Lymphoma with High-Dose Chemotherapy and Autologous Stem Cell Support. 2004, 350, 1287-1295

12. Magrath I, Adde M, Shad A. Adults and children with small non-cleaved cell lymphoma have a similar excellent outcome when treated with the same chemotherapy regimen. Journal of Clinical Oncology 1996, 14, 925-934

13. Mead G, Sydes M, Walewski J, Grigg A, Hatton C, Norbert P, Guarnaccia C, Lewis M, McKendrick J, Stenning S, Wright D. An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study. 2002 Annals of Oncology 13, 1264-1274

14. Davidson K, Devaney M, Tighe J, Roger S, Dunlop D, Mackie M, Thomas R, Johnson P. A pilot study of CODOX-M/IVAC in primary refractory or relapsed high-grade non-Hodgkin's lymphoma. A Scotland and Newcastle Lymphoma Group. 2003 Haematologica. 88, 1366-1371

15. Barrans SL, Carter I, Owen RG, Davies FE, Patmore RD, Haynes AP, Morgan GJ, Jack AS. Germinal centre phenotype and bcl-2 expression combined with the International Prognostic Index improves patient risk stratification in diffuse large B-cell lymphoma. Blood. (2002) Feb 15;99(4):1136-43

16. Barrans SL, O'Connor SJ, Evans PA, Davies FE, Owen RG, Haynes AP, Morgan GJ, Jack AS. Rearrangement of the BCL6 locus at 3q27 is an independent poor prognostic factor in nodal diffuse large B-cell lymphoma. Br J Haematol. (2002) May;117(2):322-32.

17. Barrans SL, Evans PA, O'Connor SJ, Owen RG, Morgan GJ, Jack AS. The t(14;18) is associated with germinal centre derived diffuse large B cell lymphoma and is a strong predictor of outcome. Clinical Cancer Research (2003) Jun;9(6):2133-9

18. Barrans SL, Fenton JAL, Banham A, Owen RG, Jack AS. Strong expression of FOXp1 identifies a distinct subset of diffuse large B-cell lymphoma patients with poor outcome. Blood, 1 November 2004, Vol. 104, No. 9, pp. 2933-2935

19. Glantz MJ, LaFollette S, Jaeckle KA, Shapiro W, Swinnen L, Rozental JR, Phuphanich S, Rogers LR, Gutheil JC, Batchelor T, Lyter D, Chamberlain M, Maria BL, Schiffer C, Bashir R, Thomas D, Cowens W, Howell SB. Randomized trial of a slow-release versus a standard formulation of cytarabine for the intrathecal treatment of lymphomatous meningitis. J Clin Oncol. 1999 Oct;17(10):3110-6

20. Van Besien K, Ha CS, Murphy S, McLaughlin P, Rodriguez A, Amin K, Forman A, Romaguera J, Hagemeister F, Younes A, Bachier C, Sarris A, Sobocinski KS, Cox JD, Cabanillas F. Risk factors, treatment, and outcome of central nervous system recurrence in adults with intermediate-grade and immunoblastic lymphoma. Blood. 1998 Feb 15;91(4):1178-84.

21. Hollender A, Kvaloy S, Nome O, Skovlund E, Lote K, and Holte H. Central nervous system involvement following diagnosis of non-Hodgkin's lymphoma: a risk model Ann Oncol 13: 1099-1107

22. Voog E, Morschhauser F, Solal-Celigny P. Neutropenia in patients treated with rituximab. N Engl J Med. 2003 Jun 26;348(26):2691-4

23. Chaiwatanatorn K, Lee N, Grigg A, Filshie R, Firkin F. Delayed-onset neutropenia associated with rituximab therapy. Br J Haematol. 2003 Jun;121(6):913-8

24. Cheson BD, Horning SJ, Coiffier B et al: Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 17:1244 1999

25. Mead GM, Barrans S, Qian W et al: A prospective clinicopathological study of dose modified CODOX-M/IVAC in patients with sporadic Burkitt lymphoma defined using cytogenetic and immunophenotypic criteria' Blood, 15 September 2008, Vol. 112, No. 6, pp. 2248-2260

26. Thomas et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer 2006; 106: 1569-1580

27. Moleti ML et al. CODOX-M/IVAC (NCI 89-C-41) in children and adolescents with Burkitt's leukemia/lymphoma and large B-cell lymphomas: A 15-year monocentric experience. Leukemia & lymphoma 2007; Vol. 48, No. 3, Pages 551-559

28. Mead GM et al. An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study. Annals of Oncology 2002; 13: 1264 - 1274

APPENDICES

Appendix 1: ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BD	'Bis Die' – twice daily
BL	Burkitt's Lymphoma
R-CHOP chemotherapy	Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone
CI	Chief Investigator
CNS	Central Nervous System
CR	Complete response
CRu	Complete Response undocumented/unconfirmed
CRF	Case Report Form
CT	Computerised Tomography
CTA	Clinical Trial Authorisation
CTAAC	Clinical Trials Advisory & Awards Committee
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
CTSA	Clinical Trial Site Agreement
CXR	Chest X-Ray
DFS	Disease Free Survival
DPA	Data Protection Act
DLBCL	Diffuse large B-Cell
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylene Diamine Tetra Acetate
EudraCT	European Clinical Trials Database
FBC	Full Blood Count
G-CSF	Granulocyte Colony Stimulating Factor
GELA	Groupe d'Etude des Lymphomes de l'Adulte
GFR	Glomerular Filtration Rate
GP	General Practitioner
HDT	High Dose Therapy
HGNHL	High Grade Non-Hodgkin's Lymphoma
HMDS	Haematological Malignancy Diagnostic Service
IB	Investigator Brochure
ICH GCP	International Conference of Harmonisation-Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IPI	International Prognostic index

ISRCTN	International Standard Randomised Controlled Trial Number
IT	Intrathecal
IUD	Intrauterine Device
IV	Intravenous
LDH	Lactate Dehydrogenase
LFT	Liver Function Tests
LRF	Leukaemia Research Fund
LVEF	Left Ventricular Ejection Fraction
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
MHRA	Medicines and Healthcare products Regulatory Agency
MUGA	Multi Gated Acquisition
NCRI	National Cancer Research Institute
NCRN	National Cancer Research Network
NHL	Non-Hodgkin's Lymphoma
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NRES	National Research Ethics Service
OS	Overall Survival
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PI	Principal Investigator
PO	By mouth
PR	Partial Response
R&D	Research & Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SD	Stable Disease
SmPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UCL CTC	CR UK and UCL Cancer Trials Centre
ULN	Upper Limit of Normal
WBC	White Blood Cells
WCBP	Woman of Child Bearing potential

Appendix 2: TRIAL INVESTIGATIONS SCHEDULE

	Pre-treatment screening (within 14 days)	before each treatment course					Follow-up visits:
		Cycle 1 CODOX-M	Cycle 1 IVAC	Cycle 2 CODOX-M	Cycle 2 IVAC	End of treatment	
Informed consent	×						
History	×						
Physical examination	×	x	x	x	x	x	x
Performance status	×						
Electro-cardiogram	×						
CT scan[a]	×					×	x[h]
Bone marrow biopsy	×					(×)[g]	
Serum biochemistry[b]	×	×	×	×	×	×	
Haematology[c]	×	×	×	×	×	×	
Echocardiogram[d]	×					(×)	
Cerebrospinal fluid examination[e]	×						
Central pathology review[f]	×						
CODOX-M		×		×			
IVAC			×		×		
Rituximab		×	×	×	×		
Toxicity assessment		x	x	x	x	x	
Adverse events		x	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 is to be performed only at baseline.

[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.
[h]Contrast enhanced CT scans of chest abdomen and pelvis to be done at 4 months and 1 year after finishing treatment.

Appendix 3: 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 (HMDS) in Leeds. Following registration, a letter will be sent from the Haematology Trials Group, UCL CTC to the local pathologist requesting that a representative histological tissue block or 15 unstained slides be provided for central review.

All histological material is to be sent directly to the HMDS at:

HAEMATOLOGICAL MALIGNANCY DIAGNOSTIC SERVICE
The Leeds Teaching Hospitals NHS Trust
St. James's University Hospital
Leeds, West Yorkshire
LS9 7TF

Samples should be identified by a combination of trial number, initials and date of birth, sent in a Jiffy bag or other suitable packaging. Tissue blocks will be returned to UCL CTC by HMDS as soon as practicable, which will then be forwarded to the local pathologist via the haematology trials group, UCL CTC after the review has been completed. The registering site will receive a copy of the review pathology report.

Slides, tissue microarrays and extracted nucleic acids will be retained in HMDS until the trial is complete. This material will then be transferred to an ethically approved tissue bank. Applications for access to stored material will be discussed with the trial management groups and the NCRI lymphoma group on a case by case basis

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 and Burkitt's lymphomas 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

j) DNA and RNA extraction

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.

Appendix 4: 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 5: 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 6: 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 7: 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 8: METHOTREXATEADMINISTRATION 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 x 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 x 10^{-8}M, or predicted to be below 5 x 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 x 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 x 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 9: EXPECTED ADVERSE EVENTS

AEs expected for Treatment regimens

Certain AEs are expected for the treatment regimen (see references 25, 27 and 28). The following AEs are commonly associated with the trial treatment regimen and will be considered expected for each of the trial drugs:

Fever
Infection
Infection with grade 3/4 neutrophils

Neutropenia
Febrile neutropenia
Thrombocytopenia
Leucopenia

Mucositis
Diarrhoea (grade 3)
Neuropathy (grade 3 motor & sensory)

AEs expected for individual IMPs

Where the event does not appear in the above list of expected AEs for the treatment regimen, the most recent SmPC for each of the IMPs will be checked.

Appendix 10: PROTOCOL VERSION HISTORY

Protocol:		**Amendments:**
Version no.	**Date**	**Summary of main changes from previous version.**
7.0	22.07.2010	Increase of patient inclusion maximum age from 60 to 65 years.
6.0	13.05.2009	Inclusion of Burkitt's Lymphoma patients
5.0	20.08.2008	Omission of Depocyte from the trial schedule
4.0	01.08.2007	Change from the aaIPI to IPI Additional information on prophylaxis
3.0	16.10.2006	Amendment of Depocyte administration in the IVAC cycles
1.2	06.06.2006	Amendment to PIS & consent form
1.1	19.12.2005	First Approved Protocol