R-CODOX-M/IVAC for DLBCL

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 (International Prognostic Index High or High-Intermediate Risk)

Version number	5.0
Date	20.08.2008
Approved by Chief Investigator	Dr. Andrew McMillan
Date approved	

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

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Section 1: R-CODOX-M/IVAC TRIAL WORKING GROUP

Queries should be directed to an appropriate member of the Trial Working Group:

Chief Investigator:

Dr. Andrew McMillan
Department of Haematology
Nottingham City Hospital
Hucknell Road
Nottingham NG5 1PB
Tel: 01159 242152
Fax: 01159 242153
amcmillan@ncht.trent.nhs.uk

Trial Coordinators:

Dr. Cathy Burton
HMDS
1st Floor, The Algernon Firth Building
Institute of Pathology, St George's Road
Leeds General Infirmary Site
Leeds, LS1 3EX

Dr. Russell Patmore
Department of Haematology
Hull Royal Infirmary
Anlaby Road
Hull HU3 2JZ
Tel: 01482 328541
Fax: 01482 674196
Russell.Patmore@hey.nhs.uk

Statistician:

Dr Wendi Qian
MRC Clinical Trials Unit
222 Euston Road
London NW1 2DA
Tel: 020 7670 4705
Fax: 020 7679 8061
wendi.qian@ctu.mrc.ac.uk

Trial Coordinator:

Mr Paul Smith
Lymphoma Trials Office
CRUK and UCL Cancer Trials Centre
90 Tottenham Court Road
London
W1T 4TJ
Tel: 020 7679 9860
Fax: 020 7679 9861
p.smith@ctc.ucl.ac.uk

Data Management:

Lymphoma Trials Office
CRUK and UCL Cancer Trials Centre
90 Tottenham Court Road
London
W1T 4TJ
Tel: 020 7679 9860
Fax: 020 7679 9861
r-codox-mivac@ctc.ucl.ac.uk

Central Pathology Review:

Dr Andrew Jack
Haematological Malignancy Diagnostic Service
1st Floor
Algernon Firth Building
Institute of Pathology
St. George's Road
Leeds General Infirmary Site
Leeds LS1 3EX
Tel: 0113 392 2415
Fax: 0113 392 6286
a.s.jack@leeds.ac.uk

In the event of a medical emergency contact:

Dr. Andrew McMillan

The protocol may be revised periodically. If so participating centres will be informed. New centres are advised to check with the Lymphoma Trials Office that they have the current version of the protocol.

Section 2: STUDY SYNOPSIS

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

Section 3: BACKGROUND

Disease Background

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

Study Drugs Background

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

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

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

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

Excellent results with complete response rates of 86-95% have been reported using CODOX-M/IVAC in Burkitt Lymphoma (BL).[12,13] In the study by Magrath, event free survival was 92% at 2 years. These results were confirmed by Mead whose study involving BL and Burkitt- like DLBCL patients, showed event free survival of 65% and overall survival of 73% at 2 years. BL has also been successfully treated with CODOX-M/IVAC in the preceding NCRI trial of CODOX-M/IVAC in Burkitt and Burkitt-like NHL with proliferation index of 100% (LY10 trial – personal communication). 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 therapywill be administered 8 times in standard risk patients or 12times in high risk patients (proven CNS disease at diagnosis) according to the schedule in 6.2.

3.1 RATIONALE OF THE STUDY

Complete response rate for patients with diffuse large B cell lymphoma with IPI high-intermediate and high risk is xx% and xx% 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 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.

3.2 STUDY OBJECTIVES

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

Does the combination of Rituximab and CODOX-M/IVAC improve the complete response rate in patients with newly diagnosed diffuse large B cell lymphoma of international prognostic index high or high-intermediate risk?

Primary Outcome Measure:

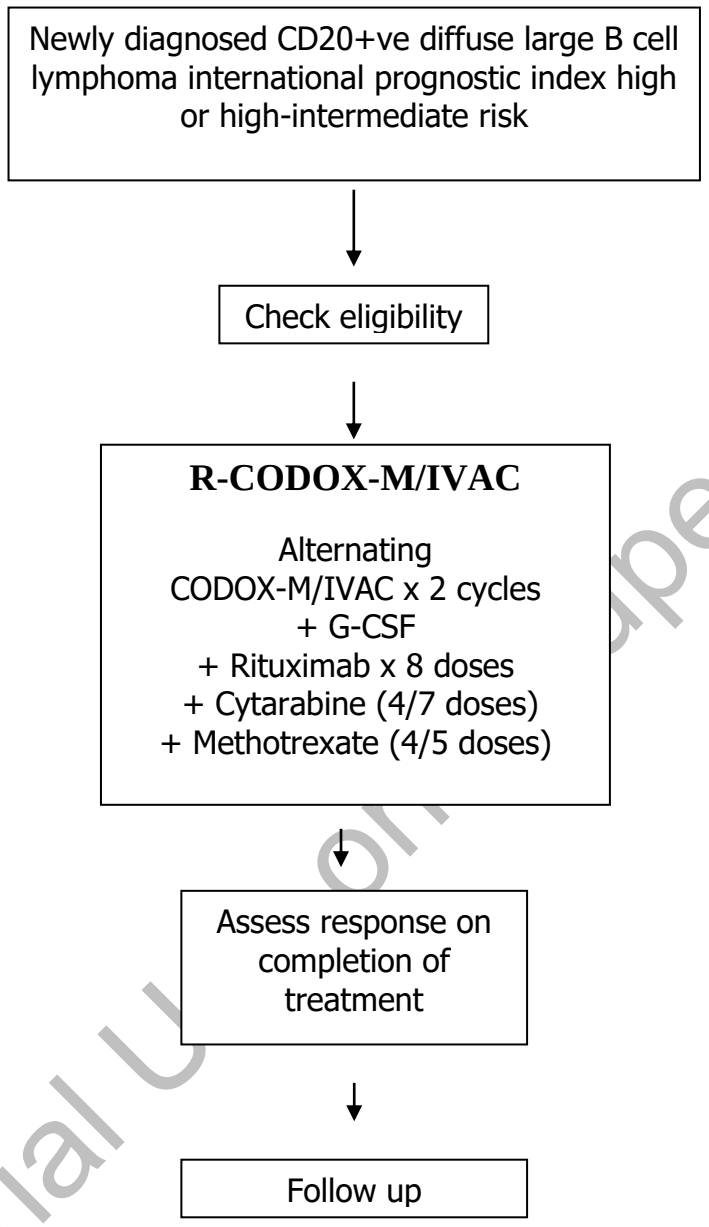
Complete response rate (CR and CRu)

Secondary Outcome Measure:

(1) Toxicity

(2) Progression free survival

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



Section 4: CENTRE SELECTION

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

Before the first patient is registered from each centre it will be ensured Local Research Ethics Committee (LREC) approval has been obtained.

4.1 DISEASE EVALUATION

Baseline investigations

a) Complete medical history.
b) Concomitant diseases and treatment.
c) Physical examination.
d) Vital signs.
e) WHO performance status (Appendix 2).
f) Electrocardiogram.
g) Echocardiogram or nuclear medicine scan (MUGA) should be performed if past history of diabetes, cardiac disease, hypertension or abnormal resting ECG.
h) Contrast enhanced CT scan of the neck, thorax, abdomen and pelvis
i) Full blood count.
j) Serum electrolytes, urea and creatinine,
k) Creatinine clearance (measured either by 24 hour urinary collection or radio-isotope methods) measured no more than 72 hours before initial high dose methotrexate
l) Serum bilirubin, liver transaminases, alkaline phosphatase, albumin, total proteins, calcium, magnesium, phosphate level, uric acid
m) Serum lactate dehydrogenase (LDH) and β2 microglobulin.
n) Bone marrow biopsy.
o) Cerebrospinal fluid examination if clinically indicated or lymphomatous involvement in peripheral blood, bone marrow, nasal/paranasal sinuses, orbit or testis.

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

4.2 ELIGIBILITY CRITERIA

4.2.1 Inclusion criteria

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

4.2.2 Exclusion criteria

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

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

Section 5: TRIAL REGISTRATION

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

To enter

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

Fax number 020 7679 9861

Between 09.00 and 17.00 Monday to Friday

Section 6: TREATMENT REGIMEN

Drug supply

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

6.1 Initial preparation

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

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

6.2 CODOX-M/IVAC

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

6.2.1 CODOX-M

CODOX-M will be given as shown in the table below:

Day	Drug	Dose	Method	Time
1	Rituximab	375 mg/m^2	IV	Infusion rate as per section 6.4
1	Cyclophosphamide Vincristine Doxorubicin	800mg/m^2 1.5mg/m^2 (max 2mg) 40mg/m^2	IV IV IV	
1	Cytarabine	70mg	**INTRATHECAL**	
2-5	Cyclophosphamide	200mg/m^2	IV	Daily
3	Cytarabine	70mg	**INTRATHECAL**	
5	Cytarabine [HIGH RISK ONLY 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 [HIGH RISK ONLY 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.				

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

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

6.2.2 IVAC

IVAC will be given as shown in the table below:

Day	Drug	Dose	Method	Time
Start day 1 of IVAC on the first day after CODOX-M that the unsupported absolute granulocyte count is >1.0x10^9/l, with an unsupported platelet count of >75x10^9/l.				
1	Rituximab	375 mg/m^2	IV	Infusion rate as per section 6.4
1-5	Etoposide	60mg/m^2 (in 500ml of N.saline or 5% dextrose)	IV	Daily over 1 hour
	Ifosfamide	1.5g/m^2	IV	Daily over 1 hour
	Mesna	300mg/m^2 (mixed with ifosfamide)	IV	Over 1 hour
		Then 300mg/m^2	IV	4 hourly x 2
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 [HIGH RISK ONLY see section 6.7]	70mg	**INTRATHECAL**	
9	Cytarabine [HIGH RISK ONLY 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.				

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

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

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

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

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

6.3.2 Growth factor support

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

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

6.4 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^{o}C)

b) Chills
c) Mucosal swelling
d) Bronchospasm
e) Hypotension (drop in blood pressure by 30mmHg)

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

6.5 Other medications

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

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

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

6.6 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.

6.7 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[21,22]. Patients with IPI High or High-Intermediate risk are therefore considered to be at greater risk of CNS disease than DLBCL patients as a whole, so in this study these patients 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 patients without CNS disease will receive 4 doses of Cytarabineand 4 doses of 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 patients with CNS disease will receive a total of 7doses of Cytarabine and 5 doses of Methotrexate**

Additional doses given below

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

6.8 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 μg) should be given until neutrophils > 1.0 x 10^9/l for more than 1 day).

Section 7: STUDY SCHEDULE

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

[a]Contrast enhanced CT scan of thorax, abdomen and pelvis (neck if indicated) should be carried out within 28 days of registration and one month after the end of treatment.

[b]Serum chemistry to include sodium, potassium, urea, creatinine, bilirubin, alanine transferase, alkaline phosphatase, lactate dehydrogenase, albumin and total proteins. Serum β2 microglobulin to be performed at baseline only.

[c]Full blood count to include haemoglobin, white blood cell, absolute neutrophil count and platelet.

[d]Echocardiogram or MUGA should be performed if past history of diabetes, cardiac disease or hypertension or abnormal resting ECG. Patients must have an acceptable left ventricular ejection fraction (LVEF) ≥50%. A repeat echocardiogram/MUGA should be considered at the end of treatment if performed initially and same assessment method should be used.

[e]Cerebrospinal fluid examination if clinically indicated or lymphomatous involvement in bone marrow, peripheral blood, orbit, nasal/paranasal sinuses and testis.

[f]Diagnostic histological material to be forwarded for central pathology review. However, results from central review do not need to be available before commencing treatment.
[g]Bone marrow biopsy to be repeated at the end of treatment if initially involved.

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

Section 8: TOXICITY AND DOSE MODIFICATIONS

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

8.1 Haematological toxicity

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

8.2 Non-haematological toxicity

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

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

Section 9: CENTRAL PATHOLOGY REVIEW

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

All histological material is to be sent to:

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

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

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

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

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

Section 10: DISEASE EVALUATION ON TREATMENT

Before each treatment course

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

Within one month after the second IVAC cycle

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

10.1 Follow Up

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

10.2 Treatment Withdrawal Criteria

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

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

Section 11: RESPONSE EVALUATION

Response will be assessed in accordance with the International Workshop Standardised Response Criteria for Non-Hodgkin's Lymphoma.[23]

Response criteria will be determined as follow:

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

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

Complete response, undocumented/unconfirmed (CRu):

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

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

Partial response (PR) requires all of the following:

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

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

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

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

Response Assessment

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

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

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

Section 12: OUTCOME MEASURES

Response Assessment

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

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

Toxicity

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

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.

Section 13: STATISTICAL CONSIDERATIONS

Intake

The overall response rate to standard chemotherapy (R-CHOP) for DLBCL is 76%[7]. The trial aims to detect an improvement in complete response rate of 10%, that is, to about 85%, with 5% significance level and 90% power. This will require a total of 139 patients. It is anticipated that 60-70 patients will be entered per year, so recruitment should occur over a 2-3 year period. Recruitment will be organised via the Lymphoma Trials Office.

Analysis plan

Analyses will be performed on an intention-to-treat basis. Complete response rate and toxicity will be based on patients who received some protocol treatment at least. Overall response rate will be assessed with 95% confidence interval. The incidence of toxicity will be presented. Progression-free survival analysis will be performed on an intention-to-treatment basis using the Kaplan-Meier approach[26].

Section 14: INTERIM ANALYSES AND DATA MONITORING

14.1.1 Independent Data Monitoring Committee (IDMC)

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

14.1.2 Trial Steering Committee (TSC)

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

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

14.2 SAFETY REPORTING

Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the indication under investigation that is not recorded elsewhere in the CRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

It is the responsibility of the investigator to document all AEs that occur during the study. AEs will be elicited by asking the patient a non-leading question, for example, "Have you experienced any new or changed symptoms since we last asked/since your last visit?" AEs should be reported on the appropriate page of the CRF.

Information about each of the study drugs including known associated toxicities can be found under Appendix 9

The Medicines for Human Use (Clinical Trials) Regulations 2004 provides the definitions given in table below:

Terms and definitions for adverse events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response in a subject to an investigational medicinal product, which is related to any dose administered to that subject.
Unexpected Adverse Reaction (UAR)	An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in: • The SPC for that product (for products with a marketing authorisation) • The Investigator's Brochure (IB) relating to the trial in question (for any other investigational product)
Serious Adverse Event (SAE) **Serious Adverse Reaction (SAR)** **Suspected Unexpected Serious Adverse Reaction (SUSAR)**	Respectively, any adverse event, adverse reaction or unexpected adverse reaction that: • results in death • is life-threatening* • requires hospitalisation or prolongation of existing hospitalisation** • results in persistent or significant disability or incapacity • consists of a congenital anomaly or birth defect • other important medical event(s)***

* The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

** Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

*** Other events that may not result in death, are not life threatening, or do not require hospitalisation may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above (excluding new cancers or result of overdose).

Assessment of Severity

Adverse event severity is defined according to the NCI-CTCAE, Version 3.0

If any AE occurs that does not appear in the NCI-CTCAE, the investigator will assign the severity as according to the table below

Assessment of Adverse Event Severity

Grade 1	Mild	An AE that is easily tolerated by the patient causes minimal discomfort and does not interfere with everyday activities.
Grade 2	Moderate	An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.
Grade 3	Severe	An AE that prevents normal everyday activities; treatment or other intervention usually needed.
Grade 4	Life-threatening or disabling	
Grade 5	Death	

If there is a change in severity of an AE, it must be recorded as a separate event.

Assessment of Causality

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the study drug. Causality should be assessed using the categories presented in the table below

Assessment of Adverse Event Causality

1	UNRELATED	Clinical event with an incompatible time relationship to study drug administration, and that could be explained by underlying disease or other drugs or chemicals.
2	UNLIKELY	Clinical event whose time relationship to study drug administration makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals.
3	POSSIBLE	Clinical event with a reasonable time relationship to study drug administration, but that could also be explained by concurrent disease or other drugs or chemicals.
4	PROBABLE	Clinical event with a reasonable time relationship to study drug administration, and is unlikely to be attributed to concurrent disease or other drugs or chemicals.
5	VERY LIKELY/ CERTAIN	Clinical event with plausible time relationship to study drug administration, and that cannot be explained by concurrent disease or other drugs or chemicals.

Drug-related adverse events are defined as those considered by the investigator to have a possible, probable or very likely/certain relationship to the study drug.

Follow-up of Adverse Events

All investigators should follow up patients with AEs until the event is resolved or until, in the opinion of the investigator, the event is stabilised or determined to be chronic. Details of AE resolution must be documented in the CRF.

Any significant changes in AEs should be reported post study. No time limit applies.

Patients should be followed up for 30 days after receiving the last dose of study drug and any AEs that occur during this time should be reported according to the procedures outlined above.

Documentation and Reporting of Adverse Events

AEs should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant CRF pages. The following data should be documented for each AE:

- Description of the symptom event;
- Severity;
- Action taken;
- Causal relationship;

Serious Adverse Events (SAE)

Any SAE must be reported by the investigator if it occurs during the clinical study or within 30 days of receiving the study drug, whether or not the SAE is considered to be related to the study drug. An SAE report consists of the SAE form, the AE form and the concomitant medication form. The investigator should not wait to receive additional information to document fully the event before notification of a SAE, though additional information may be requested. Where applicable,

information from relevant laboratory results, hospital case records and autopsy reports should be obtained.

Instances of death, congenital abnormality or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigator at any time after cessation of study drug administration and linked by the investigator to this study, should be reported to the Lymphoma Trials Office on 020 7679 9860 and by fax 020 7679 9861.

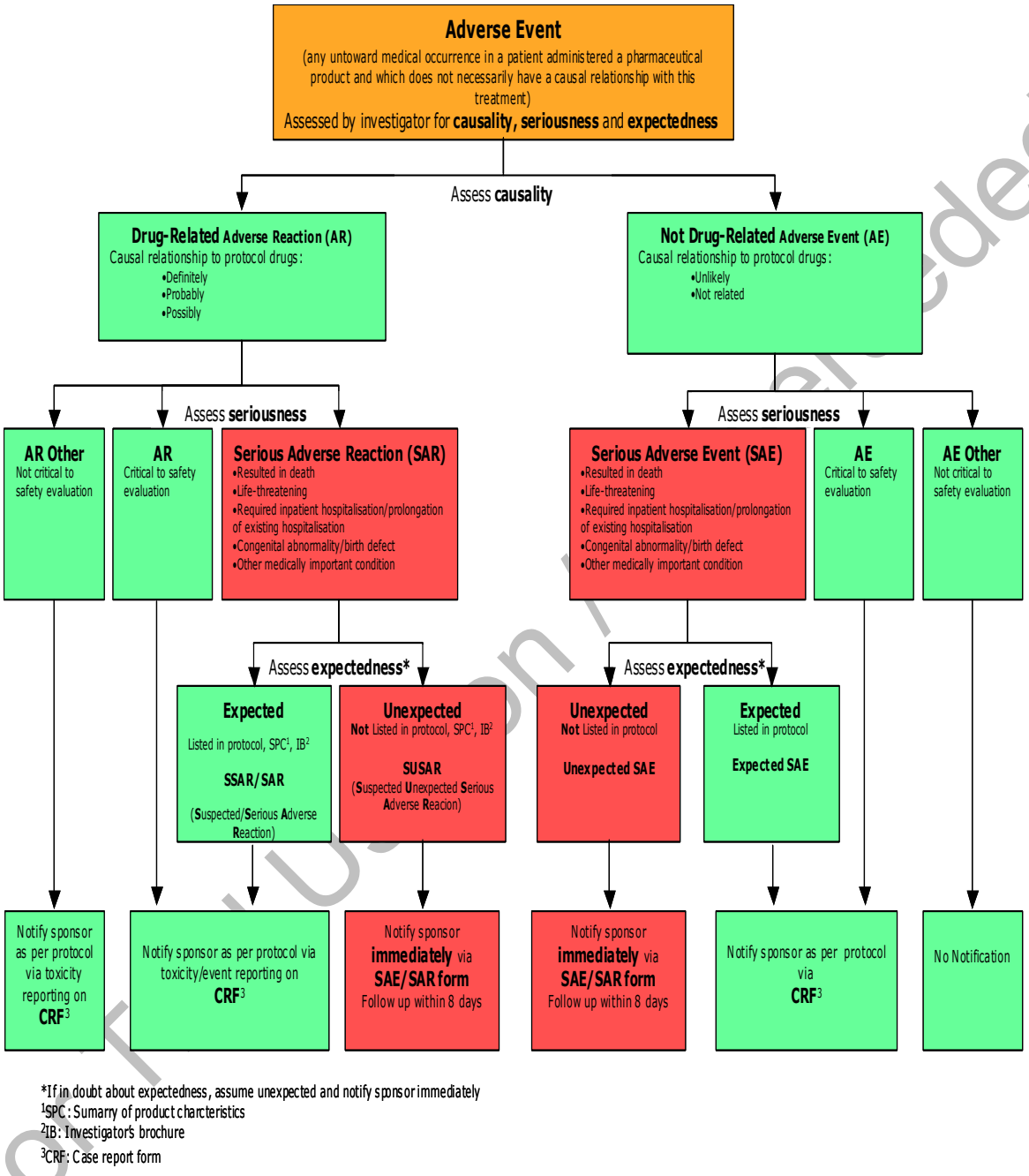
In addition, medical and scientific judgement is required to decide if prompt notification is required in situations other than those defined for SAEs above, i.e. any event that the investigator regards as serious that did not strictly meet the criteria above but may have jeopardised the patient or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the study drug.

Unexpected Adverse Reactions

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of a study drug at any dose that is not consistent with the applicable product information (e.g. the protocol, investigator's brochure, previous clinical and nonclinical studies).

All **suspected unexpected serious adverse reactions (SUSARs)** will be the subject of expedited reporting. The sponsor shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and MREC within 7 days after knowledge by the sponsor of such a case and that relevant follow up information is communicated within an additional 8 days. All other SUSARs will be reported to the relevant competent authorities and IEC within 15 days after knowledge by the sponsor of such a case.

Flow chart of assessing and notifying LTO of adverse events



*If in doubt about expectedness, assume unexpected and notify sponsor immediately
[1]SPC: Sumarry of product charcteristics
[2]IB: Investigator's brochure
[3]CRF: Case report form

14.3 ETHICAL CONSIDERATIONS

14.3.1 Ethical conduct of the study

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

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

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

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

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

14.3.2 Informed consent

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

14.3.3 Indemnity & Compensation

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

Negligent harm: Where studies are carried out in a hospital, the hospital continues to have a duty of care to a patient being treated within the hospital, whether or not the patient is participating in this trial. UCL does not accept liability for a breach in the hospital's duty of care, or negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not.

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APPENDIX 1:
INTERNATIONAL PROGNOSTIC INDEX

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

- Age greater than 60 years
- Stage III or IV disease
- Elevated serum LDH
- ECOG/Zubrod performance status of 2, 3, or 4
- More than 1 extranodal site

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

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

APPENDIX 2 WHO PERFORMANCE STATUS

0 Able to carry out all normal activity without restriction

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

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

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

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

APPENDIX 3 PREVENTION OF ACUTE TUMOUR LYSIS SYNDROME

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

Prophylaxis

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

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

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

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

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

   Please note that rasburicase should not be given to patients with G6PD deficiency

APPENDIX 4 OTHER TREATMENT ISSUES

Renal Problems

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

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

Hyperkalaemia

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

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

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

Elevated blood urea and creatinine

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

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

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

Hyperphosphataemia and Hypocalcaemia

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

Appendix 5 METHOTREXATE ADMINISTRATION AND UROPROTECTION

Administration

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

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

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

Methotrexate Levels

Serum methotrexate levels should be obtained as follows:

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

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

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

APPENDIX 6 PATIENT INFORMATION SHEET

Patient Trial Number | | | |

PATIENT INFORMATION SHEET

Version Number 5.0
Date 20.08.2008

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) of International Prognostic Index (IPI) High or High-Intermediate Risk (MREC reference 05/Q0201/81)

Study acronym: R-CODOX-M/IVAC for DLBCL

PATIENT INFORMATION SHEET

You have been invited to take part in a research study. Before you decide if you would like to take part, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP, if you wish. If you decide to enter the study your GP will be made aware of this. Ask us if there is anything that is not clear or if you would like more information.
CancerBACUP is also an independent patient advisory group which can provide information on all aspects of cancer care (freephone 0808 800 1234; address 3 Bath Place, Rivington Street, London EC2A 3DR; website (www.cancerbacup.org). The Lymphoma Association also publish leaflets for patients with lymphoma. A summary of the principles of clinical trials can be found on the Cancer Research UK's patient website (**www.cancerhelp.org.uk**).

What is the purpose of the study?

You have a condition called non-Hodgkin's lymphoma. In particular, you have a subtype of non-Hodgkin's lymphoma called diffuse large B cell non-Hodgkin's lymphoma. This is a cancer of the lymphatic system which extends throughout the body. This means the cancer may be present in more than one part of your body. This is an aggressive cancer but is curable with intensive chemotherapy. We are developing a new intensive treatment programme for patients who have disease like yours. This programme involves a combination of standard chemotherapy drugs (CODOX-M/IVAC) and a drug called rituximab.

CODOX-M/IVAC is a combination of chemotherapy drugs that are active in lymphoma. It consists of the following medicines: cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide and ifosfamide. Rituximab is a form of antibody whose action is directed against a protein present on the

surface of lymphoma cells. Rituximab has been shown in previous clinical trials to be effective in diffuse large B-cell lymphoma. We would like to find out whether giving CODOX-M/IVAC with rituximab, which is a more intensive treatment will induce a better response rate and increase your lifespan. If you agree to take part, you will be treated with 2 cycles of CODOX-M/IVAC chemotherapy and 8 doses of rituximab. In total, 150 patients like you will take part in the study.

Why have I been chosen?

You have a new diagnosis of aggressive diffuse large B-cell lymphoma and therefore you are suitable for this study. We are asking whether you would like to participate in this study.

Do I have to take part?

Your participation in this trial is entirely voluntary. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time without giving a reason. A decision to withdraw or a decision not to take part will not affect the standard of the care you receive.

What will happen to me during the study?

If you are willing to participate in the clinical trial, your doctor will assess you to ensure you are suitable to take part. This would include full medical details, physical examination, blood tests and tumour assessment (CT scan, chest X-ray and bone marrow biopsy). Blood samples will be taken before and during every treatment. The amount of blood taken at each occasion will not exceed a tablespoon in volume. **All these investigations are done routinely whether you decide to participate in the study or not.**

You will receive chemotherapy drugs (CODOX-M/IVAC) and rituximab. This treatment is quite intensive and all patients will require a period of time in hospital for each course of chemotherapy, i.e. 4 admissions, for the administration of the 2 courses of CODOX-M and 2 courses of IVAC. In total it will take about 16 weeks to give this treatment. It is likely you will be in hospital for a 2-week period every 2 weeks, i.e. 2 weeks in hospital, 2 weeks out of hospital for 16 weeks. On rare occasions continuous admission for 2-3 months will be required.

The treatment you receive will temporarily impair the ability of your bone marrow to produce blood cells and, depending upon your clinical condition, you may require blood transfusions, intravenous antibiotics or platelet transfusions, all given directly into a vein in you arm. The chemotherapy drugs cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide, ifosfamide and rituximab are also given into a vein in your arm. In addition you will need to receive intrathecal treatment (that is chemotherapy treatment given via a needle into the fluid around the spine). This will occur on a minimum of 8 occasions if you receive full protocol treatment or on a

maximum of 12 occasions if there is evidence of lymphoma in the brain or central nervous system This will be required as treatment with intravenous chemotherapy is ineffective at controlling lymphoma in the brain or central nervous system.

You will also receive an injection called granulocyte colony stimulating factor (G-CSF) to boost your white blood cells to help us give the treatment on time. This is given underneath your skin either on your stomach, on your arm or on your thigh during every cycle.

We shall repeat your CT scan at the end of treatment to assess the response of your lymphoma and at 4 months and 1 year after finishing treatment. At the end of treatment, a bone marrow biopsy will also be repeated (if involved at diagnosis). You will then be seen regularly in the clinic. Clinic visits with physical examination will occur at 1-4, 6, 8 10, 12, 15, 18, 21, 24, 28, 32, 36 months after completion of R-CODOX-M/IVAC, then 6 monthly for 1 year then annually for life.

Your tissue biopsy will be reviewed by a pathologist in another hospital to confirm the diagnosis. Additional tests for biological risk factors will be performed, although these results will not alter the treatment you receive. In addition, and with your permission, a small fragment of the lymphoma tissue that was taken to make your diagnosis will be stored. This may be used in future research studies. This material will be linked to the data collected during your participation in the study through your unique trial number. No other personal data will be held. We shall seek a separate ethics approval before any use of this material for future studies. This tissue is needed for research to improve the treatment of lymphoma in the future. **The donation of this tissue sample is entirely voluntary. You can decide not to consent to this part of the trial and still be eligible for the remainder of the trial.**

What do I have to do?

There are no particular lifestyle restrictions necessary. CODOX-M/IVAC chemotherapy and rituximab can affect egg and sperm production and therefore effective contraception should be used during and for 12 months after the last dose of treatment.

Are there any side effects associated with these treatments?

CODOX-M/IVAC chemotherapy is extremely effective, but can be associated with quite severe, mainly short-term, side effects. For this reason you will be required to be an inpatient during and after the administration of chemotherapy. There are both general side effects of chemotherapy and those specifically related to R-CODOX-M/IVAC as listed below.

After chemotherapy, possible general side-effects include:

1) Sore mouth – you will be given a mouthwash in an attempt to prevent this.

2) Diarrhoea – this is usually mild, but if it is persistent tablets will be provided to help relieve this.
3) Nausea and vomiting – this is usually controlled with anti-sickness drugs.
4) Lowering of the blood count - this usually does not cause symptoms but it does increase the risk of infection, bruising and bleeding. This is one of the reasons why you need to be in hospital and sometimes blood and platelet transfusions are necessary. It is likely you will require intravenous antibiotics
5) Loss of head and body hair – the hair usually grows back shortly after the chemotherapy is stopped.
6) Numbness or tingling sensation in hands and feet only. This is usually temporary but occasionally can be permanent.
7) Damage to heart, lungs, liver and kidneys can occur with the chemotherapy. This will be carefully monitored during treatment and measures initiated as appropriate.

Specific possible side effects of the drugs in CODOX-M/IVAC include:

Cyclophosphamide, Ifosfamide – bleeding from the bladder
Doxorubicin - palpitations, weakening of the heart musculature
Vincristine – nerve damage including tingling in hands and feet, constipation
Etoposide – liver damage if impaired liver function

There is also an increased risk of developing thromboembolism (blood clots) due to both the lymphoma and the chemotherapy. You should contact your doctor promptly if you develop swollen or painful legs (especially if only in one leg) or if you develop shortness of breath, chest pain or cough up blood. If you did develop a blood clot, this would be treated with injections to thin your blood.

After rituximab:
Mild and temporary side effects often occur during the first treatment. These include fever, chills, headache, tiredness, aching muscles and joints, itching, redness of skin, nausea and mild drop in blood pressure. Most of these disappear upon temporary slowing or discontinuation of the treatment or after the administration of paracetamol and/or anti-allergic medication.
Serious effects have occurred 1–2 hours after infusion of rituximab due to a severe allergic reaction characterised by marked shortness of breath. You are therefore monitored very closely during the infusion and a slower rate of infusion given if necessary.

GCSF:
You may experience some pain in your bones as the GCSF stimulates the bone marrow.

If any of these symptoms are severe, then the dose of your chemotherapy will be reduced. In exceptional circumstances, your doctor may decide to permanently discontinue treatment and this will be discussed with you.

During treatment and for one year after chemotherapy, your sperm or eggs may not be formed normally, if they are produced at all. You

or your partner should use effective contraception during this period. You should share this information with your partner as birth defects can occur in any pregnancies during this period.

This treatment will make most patients infertile. All males and females over 30 years are likely to become infertile. Prior to commencing chemotherapy arrangements can be made for sperm storage. Women younger than 30 years may retain their fertility. It is though likely they will experience an earlier menopause by 5-10 years.

What are the possible benefits of taking part?

We hope that the treatments will help you. However, this cannot be guaranteed. The information we get from this study may help us to improve the future treatment of patients like you with diffuse large B cell non-Hodgkin's lymphoma.

What if something goes wrong?

Every care will be taken in the course of this study. However if you are harmed by taking part in this research project, University College London (UCL), as sponsor, will provide non-negligent compensation. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaint mechanisms are available to you. Information regarding cancer, clinical trials and treatment is available through the CancerHelp UK website, www.cancerhelp.org.uk CancerBACUP and the Lymphoma Association also publish leaflets for patients with lymphoma.
What if new information becomes available?

If new information about diffuse large B cell non-Hodgkin's lymphoma and/or its treatment becomes available, then this will be shared with you by your doctor.

Will information about me in this study be kept confidential?

All information which is collected about you during the course of this study will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed, so you cannot be identified from it. We may need to obtain information from the Office of National Statistics. This is only necessary if you are lost to follow up for some reason, eg if you move away. We are only able to obtain the details of your GP and information on whether you are still alive. We will not be able to obtain more detailed information about you.

Who is sponsoring and organising the research?

This study is organised on behalf of the National Cancer Research Institute and is co-ordinated by the Lymphoma Trials Office.

What will happen to the results of the study?
Results will be analysed by the Lymphoma Trials Office. They will be presented at national and international haematological and oncological meetings and published in associated journals. Results will be published collectively so it will not be possible to identify individuals.

What if I do not wish to take part or change my mind?

The study is voluntary so that you should not feel under any pressure to enter. If you decide to take part you are free to withdraw at any time. In either case, you do not have to give a reason for your decision and this will not prejudice your future medical care. If you decide not to participate in the study, then your doctor will discuss other options with you.

There is no facility for payment of clinicians or patients or travel expenses.

If you do decide to take part in this research study, you will be asked to sign a consent form. You have 7 days to decide. Should you have any further queries regarding this study or about any of the treatments described above:

Please contact _____
Name and Title

APPENDIX 7 PATIENT CONSENT FORM - PART I

Patient Trial Number | | | |

PATIENT CONSENT FORM - PART I
Version 5.0
Date 20.08.2008

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) of International Prognostic Index (IPI) High or High-Intermediate Risk (MREC reference 05/Q0201/81)

PATIENT CONSENT FORM PART I* (please read carefully)

Name of Researcher: _____

	Please initial
I confirm that I have read and understand the information dated 20.08.2008 (version 5.0) for the above study and have had an opportunity to ask questions.	
I understand that my participation in this study is voluntary and that I am free to withdraw at any time without giving a reason, without my medical care or legal rights being affected.	
I understand that sections of my medical notes may be looked at by responsible individuals involved in this research or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	
I understand that samples of tissue taken will be reviewed by a pathologist in another hospital and that additional tests for biological risk factors will be performed	
I agree to take part in the above study.	

OPTIONAL

I agree for my GP to be informed	
I agree for information to be obtained from the Office of National Statistics	

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Name of Researcher	Date	Signature

* Three copies required: one each for the patient, researcher and hospital case notes

Patient Trial Number | | | |

PATIENT CONSENT FORM - PART II

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) of International Prognostic Index (IPI) High or High-Intermediate Risk (MREC reference 05/Q0201/81)

PATIENT CONSENT FORM PART II* (please read carefully)

Name of Researcher: _____

Please initial

VOLUNTARY DONATION OF TISSUE SAMPLE

I understand a small, anonymised fragment of the lymphoma tissue will be stored for future studies. I understand that this will be linked to the trial data through the unique trial number and no other personal data will be held. I understand separate ethics approval will be sought before the use of this material for future studies.	

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Name of Researcher	Date	Signature

* Three copies required: one each for the patient, researcher and hospital case notes

APPENDIX 8 GP LETTER
GP LETTER

Dear Dr

Patient Name & DOB
Patient Address

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) of International Prognostic Index (IPI) High or High-Intermediate Risk

Version No:4.0
Date:

Your patient has newly diagnosed, poor prognosis diffuse large B cell lymphoma. He/she has agreed to participate in a study evaluating combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide and ifosfamide together with rituximab (an anti-CD20 monoclonal antibody) to see if this improves outcome for this disease.

The potential general side effects of chemotherapy are:
1. Bone marrow suppression (anaemia, neutropenia and thrombocytopenia)
2. Nausea and vomiting
3. Stomatitis
4. Alopecia
5. Diarrhoea
6. Numbness and parathesiae
7. Cardiac, pulmonary, hepatic or renal impairment
8. Blood clots

Specific possible side effects of CODOX-M/IVAC chemotherapy are:

Cyclophosphamide, Ifosfamide – bleeding from the bladder
Doxorubicin - palpitations, weakening of the heart musculature
Vincristine – nerve damage including tingling in hands and feet, constipation
Etoposide – liver damage if impaired liver function

After rituximab:
Mild and temporary side effects occur during the first treatment. These include fever, chills, headache, tiredness, aching muscles and joints, itching redness of skin, nausea and mild drop in blood pressure. Most of these disappear upon temporary slowing or discontinuation of the treatment or after the administration of paracetamol and/or anti-allergic medication.

During treatment and for one year after chemotherapy, gametes may not be formed normally, if they are produced at all. The patient or their partner should use effective contraception during this period. The patient is aware that it is necessary to share this information with their partner as birth defects can occur in any pregnancies during this period.

The treatment will make most patients infertile. All males and females over 30 years are likely to become infertile. Prior to commencing chemotherapy arrangements can be made for sperm storage. Women younger than 30 years may retain their fertility. It is though likely they will experience an earlier menopause by 5-10 years.

Your patient will be monitored closely for all side effects and dose adjustments and additional medications given as appropriate. The treatment is given with curative intent for up to 6 months.

Should your patient run into any problems with this treatment, I would be grateful if you could communicate these to (designated person_____) or the out of hours equivalent at the (hospital name_____) on (phone no._____). We will keep you closely informed of the patient's progress, and if you should require any further information, please do not hesitate to enquire.

Yours sincerely,

APPENDIX 9 EXPECTED TOXICITIES

General toxicity associated with chemotherapy:

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

Specific side effects of chemotherapy:

Cyclophosphamide, Ifosfamide – bleeding from the bladder

Doxorubicin - palpitations, weakening of the heart musculature

Vincristine – nerve damage including tingling in hands and feet, constipation

Etoposide – liver damage if impaired liver function

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

Side effects of Rituximab

Mild and temporary side effects can occur during the first treatment. These include fever, chills, headache, tiredness, aching muscles and joints, itching, redness of skin, nausea and mild drop in blood pressure. Most of these disappear upon temporary slowing or discontinuation of the treatment or after the administration of paracetamol and/or anti-allergic medication. The first infusion of Rituximab will be monitored closely so action can be taken as required.
Fatalities following severe cytokine release syndrome characterised by severe shortness of breath and associated with features of tumour lysis syndrome have occurred 1–2 hours after infusion of rituximab. Patients with a high tumour burden as well as those with pulmonary insufficiency or infiltration are at increased risk and should be monitored very closely (and a slower rate of infusion considered).

Side effects of GCSF

GCSF may cause some bony pain.

APPENDIX 10 TRIAL MANAGEMENT GROUP

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

Staff at Lymphoma Trials Office, London

Wendi Qian
Paul Smith

Data Monitoring Committee

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

APPENDIX 11 DECLARATION OF HELSINKI

Policy

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in

accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.[1]

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.[2]

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

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[1] **Note of clarification on paragraph 29 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

[2] **Note of clarification on paragraph 30 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

9.10.2004