R-CHOP 14 vs 21

A phase III multicentre randomised clinical trial comparing rituximab with CHOP given every 14 days and rituximab with CHOP given every 21 days for the treatment of patients with newly diagnosed diffuse large B cell non-Hodgkin's lymphoma

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Signature	
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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-CHOP 14 vs. 21 TRIAL WORKING GROUP

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Prof. David Cunningham (details as above)

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

Section 2: STUDY SYNOPSIS

Study Title	A phase III multicentre randomised clinical trial comparing rituximab with CHOP given every 14 days and rituximab with CHOP given every 21 days for the treatment of patients with newly diagnosed diffuse large B cell non-Hodgkin's lymphoma
Short study title	R-CHOP 14 vs. 21
Start and end dates of study	Start date: June 2004 Patients will be recruited over 4 years and followed until death
Primary Objectives	To evaluate the improvement in overall survival of rituximab combined with CHOP given every 14 days (R-CHOP 14) in comparison to rituximab with CHOP given every 21 days (R-CHOP 21)
Primary endpoint	Overall survival
Clinical Phase	Phase III
Study design	A multicentre randomised trial comparing R-CHOP 14 given for 6 cycles with R-CHOP 21 given for 8 cycles in patients with newly diagnosed CD20 positive diffuse large B cell lymphoma, bulky stage IA to IV and no cardiac contra-indication to doxorubicin
Number of patients	1080 patients, 540 in each arm. Registration to continue until 200 patients are recruited in the PET sub-study
Inclusion criteria	• Patients with histological diagnosis of diffuse large B-cell lymphoma according to the World Health Organisation classification whatever the subtype. The B-cell nature of the proliferation must have been verified by the positivity with an anti-CD20 antibody before randomisation • Aged 18 or above • Not previously treated • Bulky stage IA to IV • WHO performance status 0, 1 and 2 • Patients who have signed an informed consent form
Current Control treatment	R-CHOP 21 (cycle repeats every 21 days for 6 cycles) + Rituximab given for 2 further cycles. Rituximab: 375mg/m^2 iv day 1 Cyclophosphamide: 750mg/m^2 iv day 1 Doxorubicin: 50mg/m^2 iv day 1 Vincristine: 1.4mg/m^2 iv day 1 Prednisolone: 40mg/m^2 po days 1 to 5
Experimental treatment	R-CHOP 14 (cycle repeats every 14 days for 6 cycles) Rituximab: 375mg/m^2 iv day 1 Cyclophosphamide: 750mg/m^2 iv day 1 Doxorubicin: 50mg/m^2 iv day 1 Vincristine: 2mg iv day 1 Prednisolone: 100 mg po days 1 to 5 Lenograstim: 263-368μg once daily sc days 4-12
Treatment duration	16 weeks in experimental treatment, 24 weeks in control treatment

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.[1] Diffuse large B cell NHL (DLBCL) is the most frequently occurring NHL, constituting approximately 31% of all NHL.[2]

Study Drugs Background

CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) given every 21 days (CHOP-21) has been considered as standard care for all patients with DLBCL. In order to improve cytotoxic delivery without compromising benefit, second and third generation multiagent chemotherapy regimens have been developed, but have not produced any survival advantage over CHOP.[3,4]

However, the results from two recent studies have challenged the role of CHOP-21 as the standard of care for patients with DLBCL. A French study organised by Groupe d'Etude des Lymphomes de l'Adulte (GELA) investigated the addition of rituximab to CHOP (R-CHOP)[5] whereas the German High Grade Non-Hodgkin's Lymphoma Study Group investigated dose intensified CHOP by recycling CHOP at standard doses every 14 days with granulocyte colony stimulating factor (GCSF) support (CHOP 14).[6]

Rituximab is a chimeric anti-CD20 antibody containing human IgG lambda and kappa constant regions with murine variable regions. It is used for treatment of patients with relapsed or refractory indolent and follicular CD20 positive B cell lymphoma. A dose of 375mg/m^2 rituximab given weekly for 4 weeks is now considered standard dose and schedule for indolent lymphoma. Response rate is between 40-60% with a median duration of response of 6-8 months.[8,9] More importantly, even patients who have been pre-treated extensively with cytotoxic drugs, those who relapse after myeloablative chemotherapy and those with bulky disease can respond. Rituximab and CHOP chemotherapy have non-overlapping toxic effects with some evidence of *in vitro* synergy in terms of efficacy. This combination has been tested in chemotherapy-naïve and previously treated patients. A response rate of 94% has been reported in aggressive NHL.[9]

In the GELA study, in newly diagnosed DLBCL, 399 patients aged 60 to 80 years old were randomly assigned to receive eight cycles of CHOP every 21 days (197 patients) or eight cycles of CHOP plus rituximab (202 patients). CHOP and rituximab are associated with significantly better complete response rate (76% vs. 63%; p=0.005), event-free survival (p<0.001) and overall survival (p=0.007) compared to CHOP alone. Although patients with low and high International Prognostic Index (IPI)[10] appeared to benefit from the addition of rituximab to CHOP in this trial, patients with low IPI appeared to benefit more. No significant increase in adverse effects was seen with the addition of rituximab.[5] A recent update on this trial with a median follow-up of 3 years showed 3 year event-free survival of 53% and 35% for R-CHOP and CHOP respectively (p=0.00008) and 3-year overall survival of 62% and 51% for R-CHOP and CHOP respectively (p=0.008).[11] NICE has recently approved

the use of rituximab in combination with CHOP for all newly diagnosed patients with DLBCL stage II-IV[12].

Another strategy to improve on the results of CHOP in aggressive NHL is through enhancing the intensity of chemotherapy. One approach to achieve this is to shorten the treatment intervals in an effective regimen. In the German NHL-B2 study of elderly patients, full CHOP-21 doses of cytotoxic drugs are given at 14-day therapy interval with GCSF support. This is known as CHOP-14. Patients were randomly assigned to CHOP-21 (n=152) or CHOP-14 (n=153). The dose intensities for both cyclophosphamide and doxorubicin were 93%. Complete remission rate was significantly better for CHOP-14 compared to CHOP-21 (77% vs. 63.2%; p=0.009). This effect was particularly pronounced for patients with elevated lactate dehydrogenase (LDH) (70.4% vs. 48.6%). Time to treatment failure and overall survival was significantly prolonged with CHOP-14 (p=0.05 and p=0.04 respectively).[6] However, only 21% of patients in this trial had high IPI (age adjusted IPI 2 and 3) as compared to 60% of patients in the GELA study.

More recently, the US Intergroup study reported their results on 632 patients with newly diagnosed DLBCL randomising firstly to CHOP-21 or R-CHOP 21 and secondly to rituximab maintenance or not.[13] However, unlike the GELA study where rituximab was given on the same day as CHOP chemotherapy, rituximab was given on days -7, -3 and two days before cycles 3, 5 and 7 in the US Intergroup study. There was no difference in objective response rates (77% R-CHOP vs. 76% CHOP). Induction R-CHOP (followed by rituximab maintenance or observation) significantly prolonged time-to-treatment failure (TTF p=0.025). Rituximab maintenance also significantly prolonged TTF in responders (p=0.01), but this advantage appeared to be limited to patients induced with CHOP alone. No statistically significant differences in overall survival have been observed with a median follow-up of 2.7 years.

With the results seen in the GELA study and the German study, it is probable that the addition of rituximab to CHOP-14 may improve results further. In addition, there is no biological reason to suggest that the benefit of adding rituximab to CHOP is confined to the elderly. One reason for proposing benefits of rituximab and CHOP-14 may be additive is that the benefit of CHOP-14 was particularly pronounced in patients with a raised LDH (surrogate for proliferation fraction), whereas the largest benefit of rituximab in the GELA study was in patients with a low IPI (normal LDH). In this current study CHOP-21 with rituximab is used as the reference arm to test the hypothesis that CHOP-14 with rituximab would improve the overall survival over CHOP-21 with rituximab.

3.1 RATIONALE OF THE STUDY

The addition of rituximab to standard CHOP given every 21 days (CHOP-21) has recently been shown to prolong event-free and overall survival in patients with diffuse large B cell lymphoma. CHOP given every 14 days (CHOP-14) with GCSF support has also been shown recently to prolong time to treatment failure and overall survival compared to CHOP-21. The addition of rituximab to CHOP-14 may provide synergistic effect, thereby improving survival in these patients. The GELA study compared CHOP and R-CHOP every 21 days over 8 cycles. The German NHL-B2 study compared CHOP-21 with CHOP-14 over 6 cycles. For this reason patients will receive 6 cycles of CHOP if randomised to the R-CHOP 14 group and 8 cycles of CHOP if randomised to the R-CHOP 21 group. The rationale for this is to compare the two best arms of the above trials. During the registration phase, All patients will receive 6 cycles of CHOP and 8 cycles of Rituximab on a 21 day cycle.

If the PET sub-study (*'Blinded evaluation of prognostic value of FDG-PET after 2 cycles of chemotherapy in Diffuse Large B-cell Non-Hodgkin's Lymphoma*') has not reached its target recruitment at the end of the randomisation phase., then patients will continue to be registered (in the regisatration phase) until the target of 200 patients has been reached.

3.2 STUDY OBJECTIVES

This randomised, multicentre phase III study will test this hypothesis:

Does the combination of rituximab and CHOP-14 improve the survival in patients with newly diagnosed diffuse large B cell lymphoma in comparison to those receiving rituximab and CHOP-21?

Primary Outcome Measure:

Overall survival

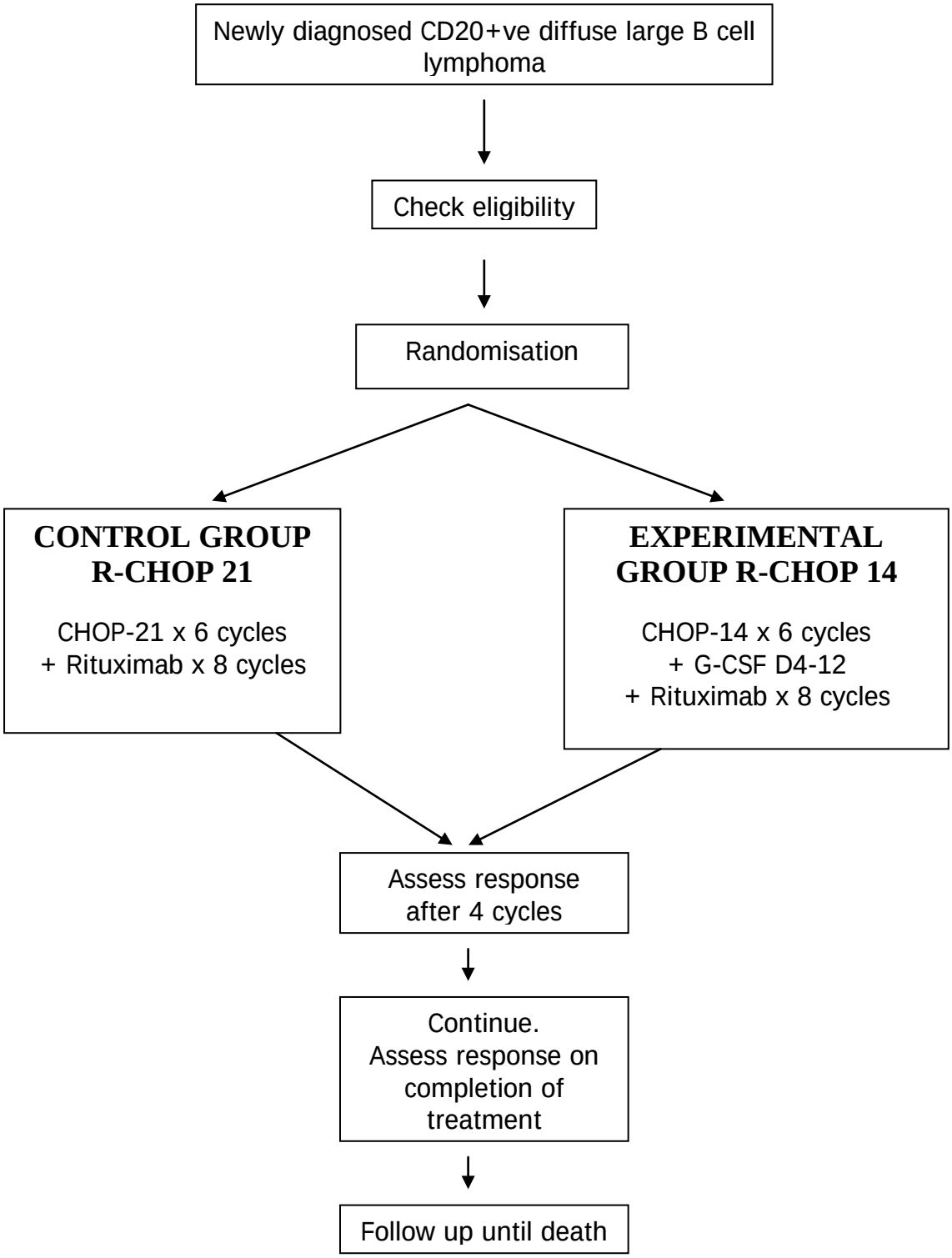
Secondary Outcome Measure:

(1) Failure free survival

(2) Toxicity up to and including 30 days from date of last treatment

(3) Complete response rates

3.3 Figure 1: R-CHOP 14 vs. 21 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. A launch meeting will be arranged prior to the trial opening for recruitment.

- **Before the first patient is registered from each centre it will be ensured Local Research Ethics Committee (LREC), R&D, MHRA approval and a signed CTSA 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 patient is aged over 70, known diabetic over the age of 65, has a past history of cardiac disease or hypertension or abnormal resting ECG.
h) Contrast enhanced CT scan of the neck, thorax, abdomen and pelvis (to be performed within 35 days prior to randomisation)
i) Full blood count.
j) Serum electrolytes, urea and creatinine.
k) Serum bilirubin, liver transaminases, alkaline phosphatase, albumin and total proteins.
l) Serum lactate dehydrogenase and β2 microglobulin.
m) Bone marrow biopsy.
n) 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 randomisation

4.2 ELIGIBILITY CRITERIA

4.2.1 Inclusion criteria

a) Age ≥ 18 years.
b) Histologically proven diffuse large B cell non-Hodgkin's lymphoma (DLBCL) according to the current World Health Organisation classification[14] including all morphological variants. 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) No previous chemotherapy, radiotherapy or other investigational drug for this indication.
d) Bulky stage IA (defined as lymph node or lymph node mass greater than 10cm in diameter), stage IB, stage II, stage III and IV.
e) WHO performance status 0-2 (Appendix 2).
f) Adequate bone marrow function with platelets > $100x10^9$/l; neutrophils > $1.5x10^9$/l at the time of study entry unless attributed to bone marrow infiltration by lymphoma.
g) Serum creatinine < 150μmol/l, serum bilirubin < 35μmol/l and transaminases < 2.5× upper limit of institutional normal range unless attributed to lymphoma.
h) Normal MUGA or echocardiogram without any areas of abnormal contractility. Patients must have an acceptable left ventricular ejection fraction (LVEF) ≥50%. (only applicable if aged over 70, known diabetic over 65, past history of cardiac disease or hypertension or abnormal resting ECG).
i) No concurrent uncontrolled medical condition.
j) No active malignant disease other than basal or squamous cell carcinoma of the skin or carcinoma in situ of the uterine cervix in the last 10 years.
k) Life expectancy > 3 months.
l) Adequate contraceptive precautions for all patients of childbearing potential
m) Written, informed consent.

4.2.2 Exclusion criteria

a) T-cell lymphoma or transformed follicular lymphoma.
b) Previous history of treated or non-treated indolent lymphoma. However, patients not previously diagnosed who have a diffuse 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) Central nervous system, meningeal involvement or cord compression by the lymphoma
e) Cardiac contra-indication to doxorubicin (abnormal contractility on echocardiography or nuclear medicine examination [MUGA]).
f) Neurological contra-indication to vincristine (e.g. pre-existing diabetic neuropathy).
g) Any other serious active disease.
h) General status that does not allow the administration of 8 courses of CHOP according to the investigator.
i) Positive serology for HIV, Hepatitis B or Hepatitis C
j) Medical or psychiatric conditions that compromise the patient's ability to give informed consent.

Section 5: RANDOMISATION AND REGISTRATION

5.1 Randomisation (All patients to be randomized until Lymphoma Trials Office informs sites that 1080 patients are recruited. After this point patients are to be registered (see 5.2)

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

To randomise

- Completed randomisation and baseline assessment forms should be faxed to

Fax number 020 7679 9861

Between 09.00 and 17.00 Monday to Friday

- Randomisation will be stratified by: a) LDH level, b) WHO performance status (Appendix 2), c) age and d) treatment centre.
- Patients will be randomised to one of two groups in a 1:1 ratio

R-CHOP 21: CHOP for 8 cycles and rituximab for 8 cycles given every 21 days
R-CHOP 14: CHOP for 6 cycles and rituximab for 8 cycles given every 14 days

The result of the randomisation will be faxed, phoned or e-mailed to the clinician entering the patient.

5.2 Registration

- Each patient must be given a patient information sheet and provide written, informed consent, witnessed and signed by the researcher.
- The registration and baseline assessment forms must be completed.
- Only patients fulfilling all eligibility criteria should be registered

ANY queries should be addressed directly to the Haematology Trials Group before registration. Tel. No. 020 7679 9860

- Only patients able to be entered onto the PET sub-study should be entered

To register

- Completed baseline assessment forms should be faxed to

Fax number 020 7679 9861
Between 09.00 and 17.00 Monday to Friday

Patients will be initially registered into the control arm (R-CHOP 21). This may change dependent upon the results of the randomised part of the trial. See below:

1) If R-CHOP 21 is found to be superior: Patients will continue being registered on R-CHOP 21
2) If R-CHOP 14 is found to be superior: Patients will be registered on R-CHOP 14
3) Neither arm is deemed superior: Centres will have the choice between R-CHOP 21 and R-CHOP 14

You will be informed of the above by the Haematology Trials Group

Section 6: TREATMENT REGIMENS

Treatment should start within 14 days of randomisation.

Treatment Schedules

This randomised controlled trial is unblinded for the chemotherapy agents because of different timings of administration among treatment arms.

6.1 R-CHOP 21: CHOP-21 × 6 cycles and rituximab × 8 cycles

Drug	Dose	Route of administration	Day 1	Day 2	Day 3	Day 4	Day 5
Cyclosphosphamide	**750 mg/m^2**	IV	X				
Doxorubicin	**50mg/m^2**	IV	X				
Vincristine*	**1.4mg/m^2**	IV	X				
Prednisolone	**40mg/m^2**	PO	X	X	X	X	X
Rituximab	**375mg/m^2**	IV	X				

* Note maximum dose of vincristine is 2mg

Patients will be treated with R-CHOP every 21 days (1 cycle) for a total of 6 cycles.

After 6 cycles of R-CHOP-21, two additional infusions of rituximab at a dose of 375mg/m2 each will be given three weeks apart. This is to ensure equal number of rituximab infusions is given in both arms of the study.

PLEASE NOTE: during the registration phase of the trial, **ALL PATIENTS** will be treated using the R-CHOP 21 regimen.

6.2 R-CHOP 14: CHOP-14 × 6 cycles and rituximab × 8 cycles

Drug	Dose	Route of administration	Day 1	Day 2	Day 3	Day 4	Day 5
Cyclosphosphamide	**750 mg/m^2**	IV	X				
Doxorubicin	**50mg/m^2**	IV	X				
Vincristine	**2mg**	IV	X				
Prednisolone	**100mg**	PO	X	X	X	X	X
Rituximab	**375mg/m^2**	IV	X				

Patients will be treated every 14 days (1 cycle) for a total of 6 cycles.

After 6 cycles of R-CHOP-14, two additional infusions of rituximab at a dose of 375mg/m^2 each will be given two weeks apart. This is to ensure equal number of rituximab infusions is given in both arms of the study.

6.2.1 Pre-requisites for the continuation of R-CHOP 14

a) Patient has passed the leucocyte and platelet nadir
b) Neutrophil count>1.5 x 10^9/l on day 15 after discontinuation of GCSF
c) Platelet count >80 × 10^9/l on day 15
d) No active infection
e) No serious organ or other toxicity

If the threshold counts (shown on the previous page) for neutrophils and platelets on day 15 are not achieved, the commencement of the next cycle will be initially postponed for 3 days. If the threshold counts are still not achieved by this time, the next chemotherapy cycles should be postponed for a further 3-4 days. During these periods, administration of GCSF is to be continued. If a postponement exceeding 1 week is required, dose reduction will be necessary to allow treatment to continue (see section 8).

6.2.2 Growth factor support for R-CHOP 14

Lenograstim 263μg/day s.c. if body surface area ≤1.8m^2 days 4-12 and Lenograstim 368μg/day s.c. if body surface area >1.8m^2 days 4-12

6.3 Administration of Rituximab in both treatment arms

- Rituximab 375mg/m^2 is given as an intravenous infusion ***after*** the administration of prednisolone and before the other cytotoxic drugs listed above. 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. If the first administration of rituximab was well tolerated, the rate of infusion can start at 100mg/hour and be increased by 50mg/hour every half an hour up to 400mg/hour for the following administrations.

- **Alternatively if the first administration of rituximab was well tolerated, 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.**

- 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.

Other medications to be prescribed with regimen:

- Allopurinol 300mg od po (during first cycle only)
- Co-trimoxazole 480mg bd po (Mon, Wed and Fri) to treatment end plus 2 weeks.

6.4 Other medications in both treatment arms

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

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

6.5 Radiotherapy

Following treatment with rituximab and CHOP, the use of radiotherapy to initial bulk disease or residual disease is left to individual investigator's discretion.

6.6 Central Nervous System (CNS) Prophylaxis

Patients with lymphomatous involvement in bone marrow, peripheral blood, nasal/paranasal sinuses, orbit and testis are considered to have high risk for CNS disease. They should receive prophylactic intrathecal methotrexate at 12.5mg for the first three cycles. **Intrathecal methotrexate should be given in accordance with local guidelines, once the intravenous cytotoxic drugs have been given.**

Section 7: STUDY SCHEDULES

7.1 R-CHOP 21: CHOP-21 × 6 cycles and rituximab × 8 cycles

	Pre-treatment screening (-2 to 0 weeks)	On treatment								End of treatment
		Cycle 1 Week 1	Cycle 2 Week 4	Cycle 3 Week 7	Cycle 4 Week 10	Cycle 5 Week 13	Cycle 6 Week 16	Cycle 7 Week 19	Cycle 8 Week 22	Week 26
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]	×									
CHOP		×	×	×	×	×	×			
Rituximab		×	×	×	×	×	×	×	×	
Toxicity assessment		x	x	x	x	x	x	x	x	
Adverse events		x	x	x	x	x	x	x	x	

[a]Contrast enhanced CT scan of thorax, abdomen and pelvis (neck if indicated) should be carried out within 28 days of randomisation, **BEFORE** the 5th cycle of treatment 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 for if the patient is aged over 70, known diabetic over the age of 65, have a past history of 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 3-monthly during the first year, 6-monthly during the second year and annually, thereafter. CT scan of chest, abdomen and pelvis at 3 months and 1 year after finishing treatment. No routine blood tests are recommended.

7.2 R-CHOP 14: CHOP-14 × 6 cycles and rituximab × 8 cycles

	Pre-treatment screening (-2 to 0 weeks)	On treatment								End of treatment
		Cycle 1 Week 1	Cycle 2 Week 3	Cycle 3 Week 5	Cycle 4 Week 7	Cycle 5 Week 9	Cycle 6 Week 11	Cycle 7 Week 13	Cycle 8 Week 15	Week 19
GCSF (days 4-12)		×	×	×	×	×	×			
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]	×									
CHOP		×	×	×	×	×	×			
Rituximab		×	×	×	×	×	×	×	×	
Toxicity assessment		x	x	x	x	x	x	x	x	
Adverse events		x	x	x	x	x	x	x	x	

[a]Contrast enhanced CT scan of thorax, abdomen and pelvis (neck if indicated) should be carried out within 28 days of randomisation, **BEFORE** the 5th cycle of treatment 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 for patients aged over 70, known diabetic over the age of 65, have a past history of 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.
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Follow-up: Clinic visit with physical examination 3-monthly during the first year, 6-monthly during the second year and annually, thereafter. CT scan of chest, abdomen and pelvis at 3 months and 1 year after finishing treatment. No routine blood tests are recommended.

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.

R-CHOP 21

8.1 Haematological toxicity

8.1.1 Neutropenia

Problem	Solution
Neutrophils $<1.5\times10^9$/l on day treatment due	Delay cycle one or two weeks. If count has not recovered after 14 days, CHOP will be stopped
Grade 4 neutropenia or any febrile neutropenia following any cycle of CHOP	All subsequent cycles of CHOP given with G-CSF support (lenograstim 263μg once daily on days 5-12)
Grade 4 neutropenia leading to infection despite G-CSF support	Reduce dose of cyclophosphamide and doxorubicin by 50% for all subsequent cycles
Grade 4 neutropenia recurs despite 50% dose reduction in cyclophosphamide and doxorubicin	**Stop CHOP**

- Rituximab dose will not be modified with neutropenia but, if CHOP is discontinued, rituximab will be discontinued too.

8.1.2 Thrombocytopenia

Problem	Solution
Platelets $<100\times10^9$/l on day treatment due	Delay cycle one or two weeks. If count has not recovered after 14 days CHOP will be stopped
Grade 3 or 4 thrombocytopenia following any cycle of CHOP	Reduce dose of cyclophosphamide and doxorubicin by 50% for all subsequent cycles
Grade 3 or 4 thrombocytopenia recurs despite 50% dose reduction in cyclophosphamide and doxorubicin	**Stop CHOP**

- Rituximab dose will not be modified with thrombocytopenia but, if CHOP is discontinued, rituximab will be discontinued too. (as above)

R-CHOP 14

8.2 Haematological toxicity

8.2.1 Neutropenia

Problem	Solution
Neutrophils $<1.5\times10^9$/l on day treatment due	Delay cycle by 3 days. If neutrophil count is still below 1.5×10^9/l, delay for further 3-4 days. GCSF should be continued.
After one week of postponement of therapy neutrophil count is still below 1.5×10^9/l	Further treatment should be delayed with checks of blood counts every 3 days until neutrophils are above 1.5×10^9/l. The next cycle should be given at a reduced dose as outlined in the dose adjustment table below.

Dose Adjustment

	Cyclophosphamide	Doxorubicin	Vincristine	Prednisolone
Postponement of therapy by 0-7 days	No reduction	No reduction	No reduction	No reduction
Postponement of therapy by 8-14 days	25% dose reduction	25% dose reduction	No reduction	No reduction
Postponement of therapy by >14 days	50% dose reduction	50% dose reduction	No reduction	No reduction

8.2.2 Thrombocytopenia

Problem	Solution
Platelets $<80\times10^9$/l on day treatment due	Delay cycle by 3 days. If platelet count is still below 80×10^9/l, delay for further 3-4 days.
After one week of postponement of therapy platelet count is still below 80×10^9/l	Further treatment should be delayed with checks of blood counts every 3 days until platelets are above 80×10^9/l. The next cycle should be given at a reduced dose as outlined in the dose adjustment table below.

Dose Adjustment

	Cyclophosphamide	Doxorubicin	Vincristine	Prednisolone
Postponement of therapy by 0-7 days	No reduction	No reduction	No reduction	No reduction
Postponement of therapy by 8-14 days	25% dose reduction	25% dose reduction	No reduction	No reduction
Postponement of therapy by >14 days	50% dose reduction	50% dose reduction	No reduction	No reduction

In addition, dose reduction of individual medications can be considered if other toxicities such as neuropathy or severe mucositis occur.

If possible, administration of rituximab should be synchronised with chemotherapy. In the rare instances in which rituximab may have already been administered for the new cycle, but postponement of chemotherapy is necessary for unforeseen reasons, the next dose of rituximab should be postponed accordingly, i.e. given with chemotherapy cycle.

In cases of intolerable toxicity attributable to CHOP, rituximab can be continued.

8.3 Non-haematological toxicity for both groups

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 CHOP, 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.

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 and t(14,18) translocation, evaluated by interphase fluorescence *in situ* hybridisation (FISH) mutational analysis. The presence of abnormalities of p53 will be assessed using a combination of interphase FISH and immunohistochemistry.

   It is now recognised that immunohistochemistry is not reproducible enough to accurately distinguish germinal centre and non-germinal centre type DLBCL in the clinical setting, and that gene expression profiling is the gold standard in this regard. Gene expression based classification of DLBCL using the Illumina DASL assay is now in routine use in Haematological Malignancy Diagnostic Service and this will be performed in cases where there is sufficient quality and quantity of RNA available for analysis and the results will be compared to the definition of GC/non-GC that was made using the Hans criteria at the time of pathology review.

   It is also emerging that the pathogenesis of DLBCL is defined by somatic mutations of a defined set of genes. The newer technologies that allow assessment of these abnormalities, that weren't available at the time of the clinical analysis, are now in use in Haematological Malignancy Diagnostic Service.

   In samples where there is sufficient tissue remaining in the block, DNA will be extracted and next generation sequencing will be performed to determine the incidence of such mutations. The genes that will be investigated for mutations have recently been reported to be significant in DLBCL and include (but not limited to) *MYD88, CARD11, A20, EZH2, CREBBP & TP53*, and this data will be correlated with cell of origin (using gene expression profiling), treatment arm and clinical outcome."

Following randomisation, 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:

Haematology Trials Group
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 randomising centre will receive a copy of the review pathology report.

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.

After 4 cycles

a) CT scan of chest, abdomen and pelvis (+ neck, if indicated).

One month after the final dose of protocol treatment (i.e after the 8th cycle of Rituximab in R-CHOP 21)

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 3, 6, 9, 12, 18 and 24 months after completion of CHOP, then annually.

b) CT scan of chest, abdomen and pelvis at 3 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.[15]

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	≥ 50%	≥ 50%	Irrelevant

	liver/spleen	decrease	decrease	
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

Overall survival

This will be measured from date of randomisation to date of death from any cause; surviving patients will be censored at date last known to be alive.

Failure free survival

This will be measured from date of randomisation to date of first appearance of disease progression, relapse, death from any cause; patients alive without progression or relapse will be censored at date last known to be alive.

Toxicity

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

Response Assessment

CT scan of thorax, abdomen and pelvis (+ neck if clinically indicated) both before cycle 5 and one month after the end of treatment.

Section 13: STATISTICAL CONSIDERATIONS

Intake

It is anticipated that the 2-year survival rate of patients in the R-CHOP 21 group will be about 70%. The trial aims to detect an improvement in 2-year survival in the R-CHOP14 group of about 8%, that is, to about 78%, with 5% significance level and 90% power (two-sided). This will require a total of 330 events (deaths). To observe this required number of events, it is planned to have 1,080 patients (540 in each group) randomised over a 3-year period and a further 1-year follow-up after the last patient being entered.

Analysis plan

Analyses will be performed on an intention-to-treat basis except for toxicity for which patients will be required to have received at least one cycle of chemotherapy to be included for analysis. The standard log-rank test[16] will be applied to time-to-event outcome analyses along with plots of Kaplan-Meier curves.[17] The $\chi 2$ test or Mann-Whitney test will be implemented in the comparisons on categorical outcomes. The known prognostic factors for this group of patients including age, tumour stage, WHO performance status, LDH level, BCL-2 expression and histological categorisation as a germinal cell tumour or otherwise will be considered in a Cox multiple regression analysis to try to identify prognostic groups. Analysis of the effect of cell proliferation, as measured by MIB1 (> 90% versus the rest), on response, progression free survival and overall survival will also be undertaken.

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. Initial data will be reviewed 12 months from commencement of the trial. 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. The interim analyses will be performed by a statistician at the Haematology Trials Group 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 4 for IDMC members).

14.1.2 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial and to ensure that the trial is conducted in accordance with the International Conference on

Harmonisation Good Clinical Practice (ICH GCP). This independent committee will review the recommendations from the IDMC. On consideration of this information, the TSC will decide on continuing or stopping the trial, or modifying its protocol. The TSC is to be appointed.

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

Section 15: SAFETY REPORTING

15.1 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.

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

Table 1: 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).

15.2 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 table 2.

Table 2: 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.

15.3 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 table 3.

Table 3: 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.

Action Taken

The investigator will describe the action taken in the appropriate section of the CRF, as follows:

- None;
- Study drug stopped;
- Study drug delayed;

- Study drug dose reduction;
- Concomitant medication;
- Other, specify.

15.4 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.

15.5 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 toxicity page of the Treatment CRF. This will document severity of AE and causal relationship.

15.6 Serious Adverse Events (SAE)

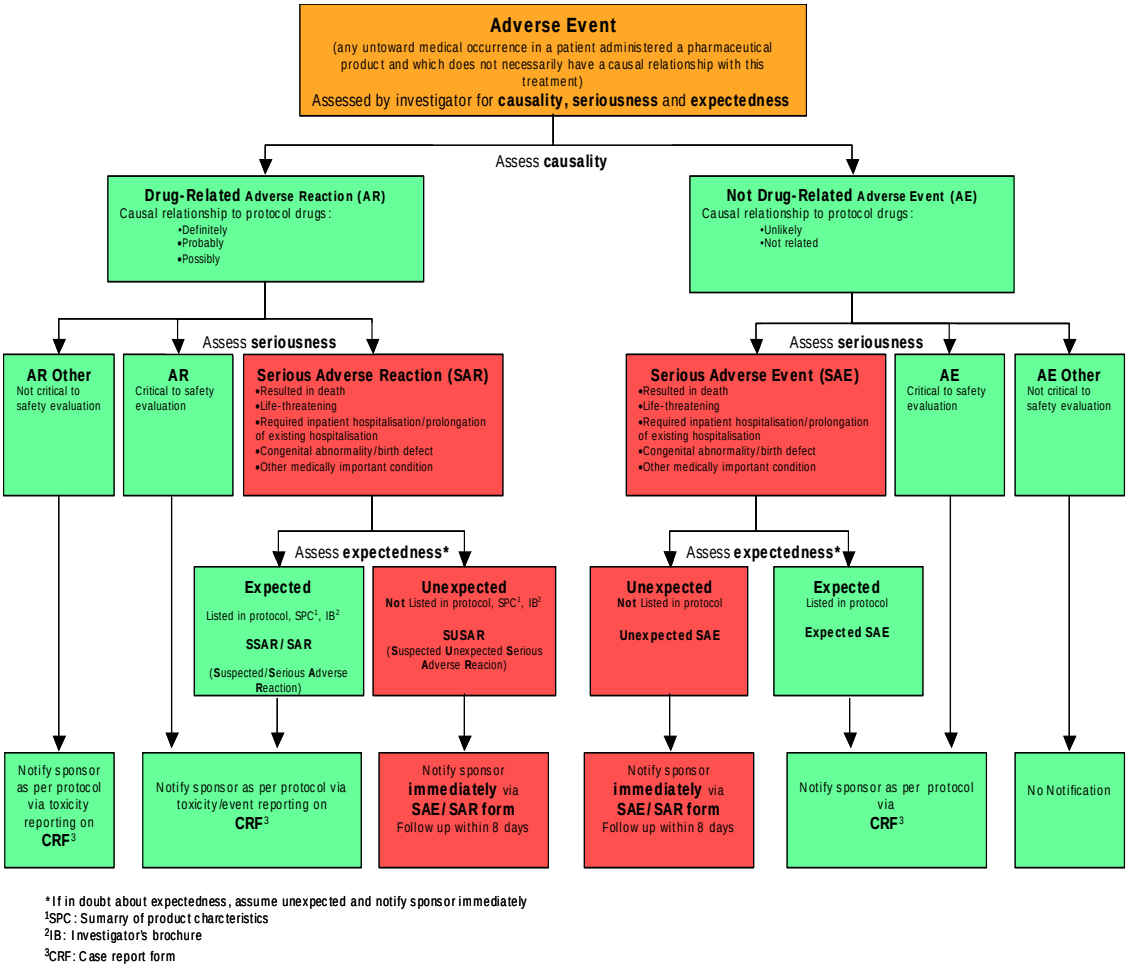
Any SAE must be reported by the investigator if it occurs during the clinical study or within 30 days of receiving the study drug, whether or not the SAE is considered to be related to the study drug. An SAE report consists of the SAE form, the AE form and the concomitant medication form. The investigator 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.

15.7 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.

Figure 2: Flow chart of assessing and notifying HTG 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

16.0 ETHICAL CONSIDERATIONS

16.1 Ethical conduct of the study

This study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) and Scotland (2000)) and the EU Directive. The study protocol will be given approval by the MREC before patients are entered. Participants will only be allowed to enter the study provided they have given written informed consent. Subjects will be informed that they have the right to withdraw from the study at any stage without prejudice or without having to give reason.
This study may be terminated at the request of the Chief Investigator after discussion with the IDMC or TSC, or the independent Research Ethics Committee(s) if, during the course of the study, any concerns about safety emerge. The Chief Investigator will update the ethics committee of any new information related to the study as appropriate.

16.2 Informed consent

Written informed consent should be obtained from each patient, in accordance with regulatory requirements, GCP and the Declaration of Helsinki. The subject will have the exact nature of the study explained to them in writing and verbally, including the known side-effects which they might expect and the risks. They will be advised that they are free to withdraw from the study or study treatment at any time without obligation. The consent form will also request permission for personnel involved in the research, including members of the Lymphoma 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 NHS Information Centre.

17 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

The risk factors used in calculating the International Prognostic Index (IPI)[10] are shown below. Give one point for each criteria met:

a) Age >60 years

b) Tumour stage III or IV

c) WHO performance status $\geq$ 2 (see Appendix 2)

d) Serum LDH greater than upper limit of local normal range

e) More than one extranodal sites of disease

Patients are then assigned to one of four risk groups on the basis of their number of presenting risk factors:

Low risk:	0 or 1
Low intermediate risk:	2
High intermediate risk:	3
High risk:	4 or 5

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: EXPECTED TOXICITIES

General toxicity associated with chemotherapy:

1) Sore mouth
2) Diarrhoea, constipation, 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.
4) Loss of hair -the hair usually grows back shortly after the chemotherapy is stopped.
5) Numbness or tingling sensation
6) Reduced reproductive function
7) Thromboembolic events
8) Tiredness or lethargy
9) Skin and nail changes
10) Changes in liver function

Specific side effects of chemotherapy:

Cyclophosphamide – bleeding from the bladder. Lung damage. Secondary cancer.

Doxorubicin - palpitations, weakening of the heart musculature. Eye irritation.

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

Prednisolone- indigestion, peptic ulceration, acute pancreatitis, muscle weakness, high blood sugar, mood disturbance and cataracts

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 4: TRIAL MANAGEMENT GROUP

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Ian Chau	Royal Marsden Hospital, London
Andrew Jack	Leeds General Infirmary
David Linch	University College Hospital, London
Kirit Ardeshna	Mount Vernon Hospital, London
Andrew McMillan	Nottingham City Hospital
Russell Patmore	Hull Royal Infirmary
Paul Fields	Guys and St. Thomas' Hospital, London
Andy Webb	Brighton Hospital
David Edwards	Glan Clywd Hospital, North Wales
Iain Singer	Glasgow Royal Infirmary
Linda Evans	Weston Park Hospital, Sheffield
Cathy Burton	Leeds General Infirmary
George Mikhaeel	Guys and St Thomas' Hospital, London

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Wendi Qian
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Howie Scarffe	Lister Hospital, Stevenage
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Robin Prescott	Edinburgh Medical School