MRC CTU

LY10

A Clinicopathological Study In Burkitt's And Burkitt-Like Non-Hodgkin's Lymphoma

A study sponsored by the Cancer Research UK, developed on behalf of the NCRI (formerly UKCCCR) Lymphoma Group

Co-ordinated by:
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Protocol Version 1.1

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ADMINISTRATION

This protocol is intended to describe a Cancer Research UK funded trial in the treatment of lymphoma, and to provide information about procedures for entering patients. The protocol is not intended for use as an aide-memoire or guide to the treatment of other patients. Amendments may be necessary; these will be circulated to known participants in the study, but centres entering patients for the first time are advised to contact the MRC Clinical Trials Unit to confirm the details of the protocol in their possession.

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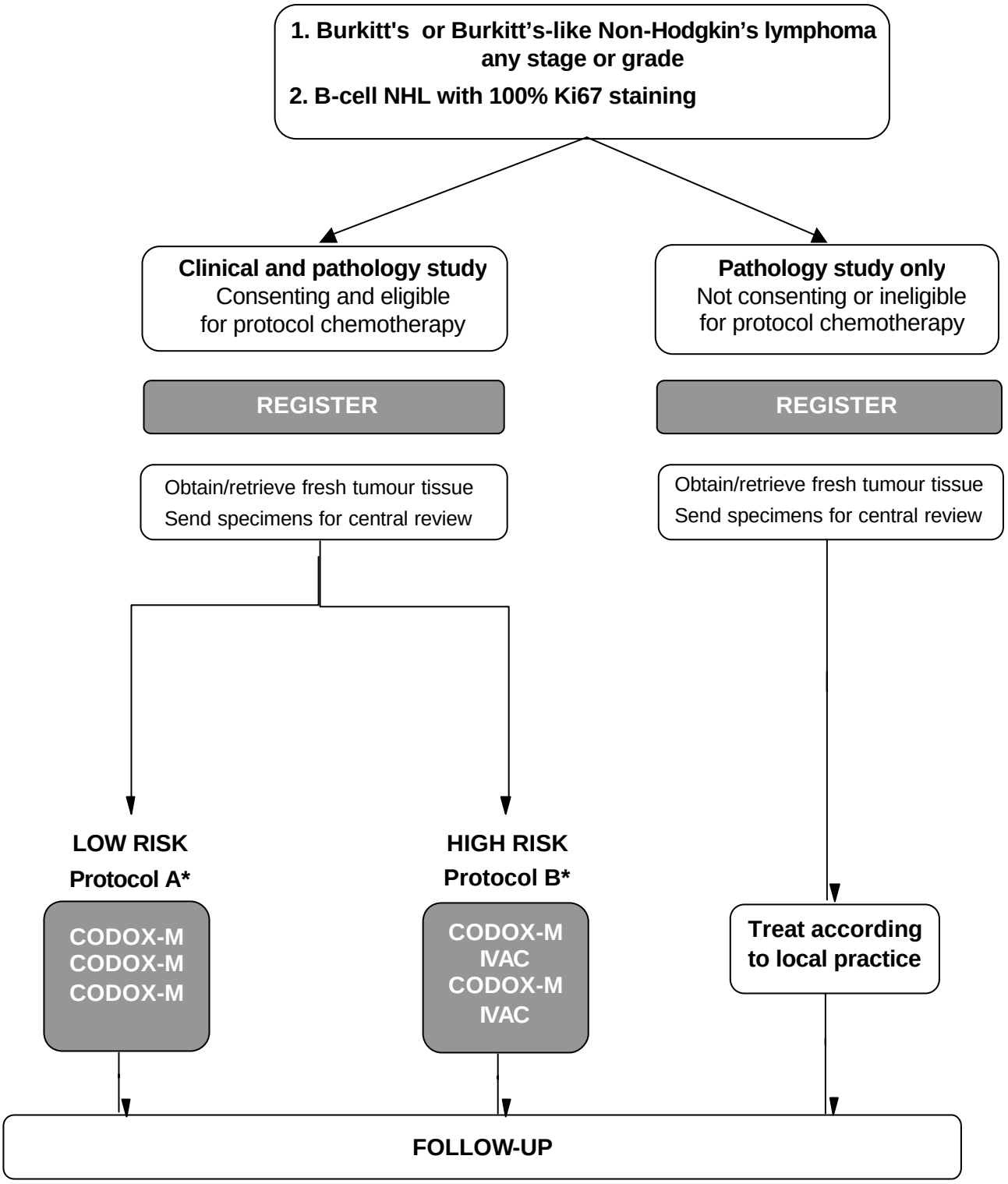

***N.B. CODOX-M and IVAC doses have been modified throughout when compared with the UKLG LY06 (methotrexate dose has been decreased) and CODOX-M and IVAC are further modified for patients over 65 years.**

1. INTRODUCTION

Clinical aspects of Burkitt's Lymphoma

Burkitt's lymphoma (BL) is a rare form of B cell Non-Hodgkin's Lymphoma (NHL) which occurs most commonly in children and young adults.[1] This condition occurs in three settings:

(a) endemic BL occurs characteristically as a jaw tumour in African children in the malarial zone

(b) HIV related BL occurs as one of the commonest neoplasms to develop in this immunosuppressed patient population and

(c) sporadic BL occurs as a rare explosive tumour of early adult life well described in the Western world

Whilst BL is reasonably well defined pathologically by a c-myc translocation associated with the presence of a t(8:14), t(2:8) or t(8:22) translocation, an allied condition, Burkitt's-like lymphoma has been a source of considerable controversy (*vide infra*).[1]

In the West, Burkitt's lymphoma commonly arises at extranodal sites e.g., the ileocaecal region, oropharynx or stomach and is a rapidly progressive neoplasm which commonly involves other organ sites, in particular the bone marrow and central nervous system (CNS). Untreated, survival is measurable in days or weeks, and it is widely accepted that combination chemotherapy should be urgently commenced with full precautions against the anticipated complication of acute tumour lysis. Intensive chemotherapy is necessary, together with CNS prophylaxis, and cure is possible in a high proportion of cases.

The clinical literature with regards to the treatment of Burkitt's lymphoma is confusing because of changes in pathological classification. Many cases in early studies were managed in a group denoted diffuse small non-cleaved lymphoma (Working Formulation classification)[2] which comprised patients with true BL mixed with less well defined patients with Burkitt-like lymphoma (and probably a variety of other entities). In practice it is not possible to compare these series with more modern series in which BL has been more clearly defined.

What is quite clear is that these lymphomas are potentially curable. Early experience with standard four drug regimens (e.g. COMP: cyclophosphamide, vincristine, methotrexate and prednisolone)[3] - was disappointing, particularly in patients with Ann Arbor stage IV disease or those with a high LDH level. In recent years, predominantly lead by a positive paediatric experience, brief high dose regimens have been used, incorporating high doses of intravenous methotrexate and cytosine arabinoside, supplemented by intrathecal therapy. Irradiation has found almost no role in the management of these neoplasms - and is it currently accepted that high dose therapy with stem cell support is largely unnecessary as a component of primary therapy. [4]

Therefore currently brief, intense, chemotherapy is regarded as the treatment of choice for BL. Multiple paediatric regimens (e.g. the LMB protocols from France),[5-7] protocols derived by the BFM Group (Germany),[8,9] and HI-COM,[10] Hyper-CVAD[11] and National Cancer Institute protocol 89-C-41 (all from the United States)[12] have adequately demonstrated the curability of this disease. These protocols have predominantly been used in children and young adults and experience in older patients (>60 years) is anecdotal, though a recent report emphasised the markedly increased toxicity of the treatment programme in these cases together with much poorer treatment outcome.[11] Burkitt's lymphoma is well described as involving (or arising in) the bone marrow and it has been suggested this distribution of disease occurs in a slightly older population, though this has been relatively ill-validated in the literature. In addition, it is not unusual for patients with BL to present in a moribund state or to be of an advanced age or medically unfit. Such patients are not included in the relatively intensive treatment protocols currently described and are thereby poorly represented in the literature.

In 1995, the UK Lymphoma Group, sponsored by the Cancer Research Campaign began an international study designed to confirm the efficacy of NCI protocol 89-C-41.[13] Between 1995 and 1999 86 patients with BL were entered into this protocol. These patients were derived from 5 nations across the world and represented the largest series of adult patients with this condition yet described. The patient population was split into two - a low risk group comprising 26% of the patients and a high-risk group comprising 74% of the patients. Results were excellent - patients in the two groups have an estimated 1-year progression-free survival, respectively, of 91% (95%CI 80-99) and 60% (95%CI 48-73) which would be expected to translate into long term survival. The treatment was however extremely toxic and 4 toxic deaths resulted. The high doses of methotrexate used in this study - 6.7g/m² by 24-hour infusion - was considered a particular problem and is larger than that used in comparable paediatric studies. This study did not aim to recruit leukaemic BL or Burkitt-like lymphoma and was not inclusive in the sense that all patients were fit to receive this extremely intensive treatment at the time of trial registration.

Pathology of Burkitt and Burkitt-like lymphoma

The last two decades have seen enormous changes in the pathological classification of lymphoma. Whilst the classical pathological features of Burkitt's lymphoma (BL) as originally described have remain unchanged [1,14,15] those of the allied condition, variously known as Burkitt-like lymphoma (BLL) (or atypical Burkitt's lymphoma) have been a source of confusion and controversy, as has the relationship of this condition to the rarer BL.[16-19] The clinical literature in this areas can, at best be described as confusing. Burkitt-like NHL is described as having intermediate morphology between BL and diffuse large B cell NHL.[1,17] However its further definition clinically, immunophenotypically or on chromosomal analyses remains to be defined.

The REAL classification[16] separated BL from Burkitt-like NHL on the basis of morphology, putative immunophenotype and genetic features, however when expert pathologists were invited to sub-classify a thousand cases of NHL using the REAL criteria the entity of Burkitt-like NHL (comprising 2% of cases) proved the least reproducible of all NHL sub-types.[17]

In the last few months the REAL classification has been slightly modified into the World Health Organisation Classification of Neoplastic disease of Hematopoetic and Lymphoid Tissues.[1] It is quite clear from the report of this classification that controversy has continued to surround the classification of BL and Burkitt-like lymphoma. Pathologists propose that these entities be separated and that Burkitt-like lymphoma should become a sub-type of diffuse large B cell NHL. However the clinicians disagreed and suggested it should be a sub-type of BL with comparable proliferation fraction (≥99%) and genetic features, but different morphology.

BL is characterised by c-myc translocation associated with the presence of t(8:14), t(2:8) or t(8:22). The deregulation of c-myc results in very high rates of self-proliferation and apoptosis. The immunophenotype of BL suggests it is a germinal centre derived tumour with IgM+ IgD- (in most cases), CD10+, CD38+ and CD23-. A few cases show immunoglobulin class switching and IgG expression. The immunoglobulin genes show evidence of somatic hypermutation.[20-22] Unfortunately, the t(8:14) translocation is not specific to a diagnosis of BL as recent studies have shown that this can occur in diffuse large B-cell lymphoma and follicular lymphoma which have no other features of BL and may not have an aggressive clinical course.[23-25] In a proportion of adult patients with BL additional chromosomal translocations, usually the t(14:18) may be present in addition to c-myc rearrangements.[25-28] It is not clear whether the presence of these translocations correlates with bcl-2 expression. In some of these patients there may be a previous history of follicular lymphoma or other lymphoma. Others present with apparently de-novo BL. There is some recent evidence that suggests that these are exceptionally malignant tumours with a very short median survival despite intensive treatment.[18] This emphasises the need to define BL in terms of morphology, phenotyping and cytogenetics. At present there are no published clinical trials of adult Burkitt's

lymphoma which used these criteria to define their study group. There are certainly no studies in which Burkitt-like lymphoma has been effectively pathologically, let alone clinically, defined.

Pathological Diagnosis of Burkitt's Lymphoma

There are thus a number of unresolved problems with both the definition of non-endemic Burkitt's lymphoma and the practical aspects of diagnosis. It is one of the aims of this study to address some of these areas of difficulty.

Patients with Burkitt's lymphoma may present with a rapidly growing tumour mass or with bone marrow replacement and leukaemia. In the past the condition has been defined in terms of cellular morphology. However, in biopsy specimens the relevant morphological features are highly susceptible to the effects of tissue fixation making this one of the least reproducible diagnoses by expert haematopathologists. In blood and bone marrow specimens it is clear that FAB L3 morphology can occur in non-Burkitt's diffuse large B-cell lymphomas and precursor B-cell acute lymphoblastic leukaemia.

In the WHO classification of haematological malignancies the presence of a c-myc rearrangement is proposed as the gold standard for the diagnosis of Burkitt's lymphoma and the term Burkitt-like lymphoma is used to describe cases where this is not associated with the typical morphological features. It remains unclear whether the translocation alone is sufficient to identify B-cell lymphomas with the very aggressive clinical behaviour associated with Burkitt's lymphoma. An important practical problem is that it will not be possible to demonstrate the presence of the translocation in most cases before therapy must be commenced in this group of patients. To address this problem it has been suggested that a cell cycle fraction of 100%, defined by Ki67 expression, is a surrogate marker for the presence of c-myc rearrangements. This feature is certainly present in lymphomas with a c-myc translocation but there is little data on the number of tumours without a t(8;14) that have very high cell cycle fractions.

A number of other immunophenotypic features have been associated with Burkitt's lymphoma. These include strong expression of sIgM, CD10 and possibly absence of bcl-6 expression, but at present the evidence is contradictory and there is no consensus on a characteristic immunophenotype in Burkitt's and Burkitt like lymphomas. The extent of correlation between this immunophenotype, Burkitt's type morphology and c-myc rearrangements remains unclear and will be investigated in the course of this study.

Whatever definition is used, it is clear that non-endemic Burkitt's lymphoma in adults may occur as a *de novo* tumour or arise by transformation of a follicular lymphoma. Complex karyotypes, especially the presence t(8;14) and t(14;18) may be found even where there is no documented history of an underlying indolent lymphoma and there is some evidence to suggest that this is a very poor prognostic feature.

Given these difficulties it is important that the initial entry criteria for this study should be simple and reproducible across a large number of laboratories. It is proposed that the primary criteria for entry to the study should be B-cell lymphomas with 100% Ki67 expression and/or presentation with marrow replacement/leukaemia. It is recognised that this will include a slightly broader range of patients that would conventionally be regarded as having Burkitt's lymphoma. Using these criteria should help to maximise recruitment by reducing dependence on subjective morphological criteria and will facilitate understanding of the relationship between immunophenotype, cell cycle fraction and cytogenetics.

2. STUDY OUTLINE

Eligible patients who are considered fit for protocol chemotherapy will be asked to give their consent:

(a) for tumour tissue to be reviewed centrally
(b) to be treated according to the protocol regimens
(c) to allow data on their treatment and progress to be recorded

Consenting patients will be registered and will contribute both to the pathology study and the clinical study.

Eligible patients who are unfit, or non-consenting, for protocol chemotherapy but who are willing for their tissue to be reviewed and basic data to be recorded (i.e. they consent to parts a and c above), should also be registered, and will contribute only to the pathological study.

3. STUDY OBJECTIVES

Pathological

- To describe BL and the related Burkitt-like lymphoma in terms of morphology, phenotype and cytogenetics, using, where possible, fresh tumour tissue.
- To determine whether cytogenetic and molecular changes are associated with, or predictable from, the immunophenotype of the tumour cells or patient characteristics such as age, in particular to examine the relationship of t(14:18) to bcl-2 expression.
- To determine whether the presence of specific cytogenetic and molecular changes (in particular the presence of t(14:18) in addition to the t(8:14)) is associated with an adverse outcome (progression-free and overall survival) using this treatment.

Clinical

- To assess the activity of CODOX-M/IVAC using a lower dose of methotrexate (compared to the UKLG LY06 Trial) of 3g/m² in a phase II study in adult sporadic BL and Burkitt-like lymphoma.
- To further assess the activity of these regimens in patients with leukaemic BL and, by modifying chemotherapy doses, to include older patients often excluded from clinical trials.

A number of patients with BL fail to enter clinical trials as they are very sick at diagnosis or have pre-existing illness. This study will aim to include all pathologically eligible patients in participating centres in order to provide a clearer overall picture of this disease, whether or not they undergo protocol chemotherapy.

4. ELIGIBILITY

4.1 Pathology Study

I. Pathology (See Appendix A): Diffuse B-cell lymphoma in nodal or extranodal site, CD20+ CD79+ with 100% expression of Ki67 (MIB1) in all of the tumour cells

or

Bone marrow replacement/leukaemia consisting of mature B-cell lymphoma showing sIg+, CD19+, CD34-, Tdt-

4.2 Clinical Study

I. Pathology as in section 4.1
II. Age at least 16 years
III. Patient's mental and physical status must be sufficient to withstand the treatment described
IV. Maximum of 1 cycle of pre-induction chemotherapy - see Section 7.2
V. All patients should be HIV negative
VI. No previous chemotherapy or radiotherapy treatment (other than pre-induction chemotherapy - see Section 7.2)
VII. No other disease or previous malignancy likely to interfere with the protocol treatments or comparisons
VIII. Written informed consent

5. PRE-REGISTRATION INVESTIGATIONS

Patients will be assessed **urgently** because of the fulminant nature of this disease. Patients will be staged according to the Ann Arbor system and an IPI score will be calculated (See section 6).

Where possible fresh tissue will be obtained (e.g. Trucut biopsy) for preparation of imprints and cytogenetics (use local laboratories).

Staging investigations must be performed prior to registration and will always include:

I. Patient's WHO performance status (Appendix B)
II. Ann Arbor stage and IPI score
III. FBC, film, ESR
IV. Biochemical profile (blood urea, creatinine, electrolytes including calcium and magnesium, phosphate level and LFT's)
V. LDH level
VI. Uric acid
VII. Immunoglobulin levels and serum protein electrophoresis
VIII. FSH, LH levels
IX. HIV antibody testing
X. Creatinine clearance (measured either by 24 hour urinary collection or radio-isotope methods) measured no more than 72 hours before initial high dose methotrexate
XI. Chest x-ray
XII. CT scan of chest, abdomen and pelvis (plus head scan, if any clinical suggestion of CNS disease). MR scans of head/axial skeleton as indicated
XIII. Bone scan (when clinically indicated by presence of bone pain or increased alkaline phosphatase)
XIV. Bone marrow trephine and aspirate with cytogenetics
XV. CSF examination for cytology, protein, glucose (to be followed on day one of protocol treatment by instillation of intrathecal cytarabine)

Optional investigations

Sperm count/banking may be offered to male patients.

6. REGISTRATION

Centres must send a copy of their LREC's approval letter to the MRC Clinical Trials Unit (CTU) before registering their first patient.

Patients planned for the pathology study only

These patients should be registered as soon as possible after diagnosis, and pathology specimens sent for review immediately afterwards (see Appendix A).

Patients planned for the pathology and clinical studies

Please register **all** patients prior to starting CODOX-M chemotherapy, or exceptionally up to 7 days after starting CODOX-M if treatment must be started immediately and timing (weekends/public holidays for example) prevent prior registration. Later registrations will not be accepted. Please send pathology specimens for review as soon as possible (see Appendix A).

Complete a registration form, then telephone the MRC Clinical Trials Unit, London between 09h00 and 17h00, Monday to Friday.

Telephone:	**020 7670 4777**

NOTE: Once a patient has been registered that patient remains in the study irrespective of treatment given, and full documentation and follow-up will be required.

7. PREPARATION FOR PROTOCOL THERAPY

Note: patients who are ineligible for or decline participation in the clinical study should be prepared and treated accordingly to normal clinical practice.

7.1 Initial preparation (See Appendix C and D)

i. At presentation, patients will 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.

ii. Allopurinol starts immediately at a dose of 10mg/kg/day in 3 divided doses. This can be reduced, 3 days after the start of induction therapy to 5mg/kg/day, and stopped after 2 weeks.

iii. Hydration will also be commenced immediately at a rate of 4.5 litres per m^2 or as close to this figure as tolerated. Sodium content should be at least 75 mmol/l (equivalent: ½ normal saline / 5% dextrose). Frusemide should be used as needed to ensure that output is consistent with intake.

iv. Potassium should not be added to IV solutions prior to, or during, the first few days of therapy unless potassium drops below 3.0 mmol/L.

v. Sodium bicarbonate should be added to IV solutions in the presence of an elevated uric acid level (normally 50-100 mmol of bicarbonate per litre of fluid will be administered). Urine pH should be kept at 7.0 or above.

All bicarbonate should be removed from IV solutions as soon as plasma uric acid is within the normal range or serum bicarbonate >30 mmol/l and/or immediately prior to the commencement of chemotherapy.

vi. Intensive post chemotherapy biochemical monitoring is mandatory in patients with bulky disease and should be considered in all patients during the first 3-5 days of treatment. Serum electrolytes, creatinine, calcium and phosphorus may need to be measured up to every 4-6 hours in patients with bulky disease.

7.2 Pre-induction chemotherapy

In a proportion of patients with Burkitt's Lymphoma the diagnosis will not initially be clear, and therapy with CHOP or a related regimen will have been initiated. Such patients remain eligible for the CODOX-M protocol provided that:

I. **no more than one cycle** of this treatment has been used

II. Patient now meets the eligibility criteria in Section 4.2

III. Patient is registered in accordance with Section 7

IV. It is recommended that CODOX-M be commenced as soon as possible – generally between days 14–21 if full dose CHOP is given, or earlier for reduced dose regimens

Occasionally, patients present with fulminant BL sometimes associated with acute renal failure. If the patient is considered unfit to receive CODOX-M, then an initial treatment using either 50% CHOP (full dose vincristine and prednisolone) or COP (cyclophosphamide 300mg/m^2 IV, vincristine 2mg IV, prednisolone 60mg po daily for 5 days) is permissible with CODOX-M commencing on day 8. This treatment should, however, rarely be necessary.

8. RISK GROUPS

The treatment protocol for all patients in the clinical study will be based on the following factors:

1. Risk group: Low risk vs High risk
2. Age: 65 years and under vs greater than 65 years

Low Risk

All patients treated with this protocol must fall into the IPI low risk group i.e. they must have **at least 3** of the factors identified below:-

(a) Normal LDH level
(b) WHO performance status 0-1
(c) Ann Arbor stage I-II
(d) Number of extra-nodal sites (e.g. bone marrow, GI tract, CNS) ≤1

High Risk

All remaining patients are high risk. They should have **2 or more** of the following features:

(a) Raised LDH level
(b) WHO performance status 2-4
(c) Ann Arbor stage III-IV
(d) Number of extra nodal sites >1

Age

N.B Patients in both risk groups will receive modified chemotherapy if aged greater than 65 years.

9. TREATMENT PROTOCOLS

NB: Prescribing and administration of intrathecal drugs

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. In particular please note that these guidelines require there to be written proof that any intravenous cytotoxic drugs for the named patient for that day have been administered ***before*** *intrathecal drugs can be issued (this is relevant to Day 1 of CODOX-M).*

In addition, intrathecal chemotherapy must only be administered ***within normal working hours*** *under normal circumstances. This has implications on the timings of the administration of IT chemotherapy specified in this section of the protocol. Listed below are recommendations on how to change the timing of the administration of IT chemotherapy in order to keep with the above guidelines.*

Where a CODOX-M cycle starts on either a Thursday or a Friday, the day 3 IT Cytarabine is due during the weekend centres should:

- Start on a Thursday, but give the day 3 IT Cytarabine 2 days late
- Start on a Friday, but give the day 3 IT Cytarabine a day late

Where IVAC starts on a Tuesday or a Wednesday, the day 5 IT Methotrexate is due during the weekend centres should:

- Start on a Tuesday but give day 5 IT Methotrexate 2 days late
- Start on a Wednesday but give day 5 IT Methotrexate a day late

Please contact the clinical co-ordinator for advice if this raises concerns about the timing of chemotherapy for any patient under your care.

Protocol A: Low Risk

Patients will receive a total of 3 cycles of CODOX-M with dose dependent on patient age.

9A.1: CODOX-M for patients aged £65 years

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

Day	Drug	Dose	Method	Time
1	Cyclophosphamide Vincristine Doxorubicin **Cytarabine**	800mg/m^2 1.5mg/m^2 (max 2mg) 40mg/m^2 **70mg**	IV IV IV **IT**	
2-5	Cyclophosphamide	200mg/m^2	IV	Daily
3	**Cytarabine**	**70mg**	**IT**	
8	Vincristine	1.5mg/m^2	IV	
10	Methotrexate[?]	300mg/m^2 2700mg/m^2	IV IV	1 hour Given over next 23 hours
11	Leucovorin[? †]	15mg/m^2 15mg/m^2 15mg/m^2	IV IV IV	At hour 36 Every 3 hrs between 36-48 Then every 6 hrs until methotrexate level is >1.0x10^{-7} M
13	G-CSF	5µg/kg (1 ampoule)	SC	Daily until granulocyte count >1x10^9/l then discontinue
15	**Methotrexate**	**12mg**	**IT**	
16	Leucovorin	15mg	PO	24 hrs after IT methotrexate
Commence next cycle on the day that the unsupported absolute granulocyte count is >1.0x10^9/l, with an unsupported platelet count of >75x10^9/l.				

[? ?] **Methotrexate:** Methotrexate (see Appendix E) 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/meter^2. Commence methotrexate regardless of blood counts. Stop infusion at hour 24 regardless of dose given.

[?†] **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.

9A.2: CODOX-M for patients aged > 65 years

3 cycles of CODOX-M will be given as shown in the table below (Note: the reduced day10 intravenous methotrexate dose for this group of patients):

Day	Drug	Dose	Method	Time
1	Cyclophosphamide Vincristine Doxorubicin **Cytarabine**	800mg/m^2 1.5mg/m^2 (max 2mg) 40mg/m^2 **70mg**	IV IV IV **IT**	
2-5	Cyclophosphamide	200mg/m^2	IV	Daily
3	**Cytarabine**	**70mg**	**IT**	
8	Vincristine	1.5mg/m^2	IV	
10	Methotrexate[?]	100mg/m^2 900mg/m^2	IV IV	1 hour Given over next 23 hours
11	Leucovorin[? †]	15mg/m^2 15mg/m^2 15mg/m^2	IV IV IV	At hour 36 Every 3 hrs between 36-48 Then every 6 hrs until methotrexate level is >1.0x10^{-7} M
13	G-CSF	5µg/kg (1 ampoule)	SC	Daily until granulocyte count >1x10^9/l then discontinue
15	**Methotrexate**	**12mg**	**IT**	
16	Leucovorin	15mg	PO	24 hrs after IT methotrexate
Commence next cycle on the day that the unsupported absolute granulocyte count is >1.0x10^9/l, with an unsupported platelet count of >75x10^9/l.				

[?] [?] **Methotrexate:** Methotrexate (see Appendix E) 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/meter^2. Commence methotrexate regardless of blood counts. Stop infusion at hour 24 regardless of dose given.

† **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.

DOSE MODIFICATIONS

There will be no dosage modifications based on the degree or duration of myelosuppression. In the presence of motor weakness or severe sensory symptoms, discuss reducing or withholding vincristine with the principal investigator.

Protocol B: High Risk

Treatment will consist of alternating cycles of regimens CODOX-M and IVAC, for a total of 4 cycles given in the following sequence: CODOX-M, IVAC, CODOX-M, IVAC. Details on CODOX-M are shown under Protocol A in Tables 9A.1 (p12) and 9A.2 (p 13) and Appendix E.

9B.1: IVAC for patients aged £65 years

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.				
1-5	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**	**IT**	
6	Leucovorin	15mg	PO	24 hours after IT methotrexate
7	G-CSF	5µg/kg	SC	Daily until granulocyte count > 1.0x10^9/L
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.				

9B.2: IVAC for patients aged > 65 years

Note: a reduced dose of ifosfamide and cytarabine is used for this group of patients.

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.				
1-5	Etoposide	60mg/m^2 (in 500ml of N.saline or 5% dextrose)	IV	Daily over 1 hour
	Ifosfamide	1g/m^2	IV	Daily over 1 hour
	Mesna	200mg/m^2 (mixed with ifosfamide)	IV	Over 1 hour
		Then 200mg/m^2	IV	4 hourly x 2
1 & 2	Cytarabine	1g/m^2	IV	Over 3 hours, 12 hourly total of 4 doses
5	**Methotrexate**	**12mg**	**IT**	
6	Leucovorin	15mg	PO	24 hours after IT methotrexate
7	G-CSF	5μg/kg	SC	Daily until granulocyte count > 1.0x10^9/L
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.				

DOSE MODIFICATIONS

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

10. OTHER TREATMENT ISSUES

10.1 Management of Patients with CNS Disease at Diagnosis

Radiotherapy

There is no evidence that radiotherapy is beneficial in the treatment of meningeal disease. Because several neurotoxic drugs (methotrexate, cytarabine and 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.

The dose of radiation and treatment fields will be decided upon by the radiotherapist, taking into account individual circumstances. Wherever possible, a dose not in excess of 30 Gy will be administered.

In the presence of CNS disease, systemic therapy will be unchanged but an Ommaya reservoir or lumbar access devise (LAD) may be placed at the discretion of the investigator though this should rarely be needed (please discuss with the Clinical Co-ordinator). If Ommaya is used chemotherapy will be delivered according to the schedule shown below.

Ommaya Reservoir

This should rarely be needed (see note above). If indicated it will be inserted at the earliest time point, usually during the third week, during marrow recovery (granulocytes over 500 required). If a reservoir is not placed, chemotherapy will be given intrathecally according to the same schedule. Doses for intrathecal and intraventricular therapy differ and are given overleaf.

Intrathecal/Intraventricular Therapy

For patients with CNS disease, intensified intrathecal treatment is given to all patients for THE FIRST TWO CYCLES ONLY, regardless of age. These drugs may be given either intrathecally **or** intraventricularly via an Ommaya Reservoir. The schedule of drug delivery will differ from Tables 9A.1 and 9B.1 as follows:-

Cycle	Day	Drug	Intrathecal Dose	Intraventricular Dose (Ommaya Reservoir)
1	1, 3, 5	Cytarabine	70mg	15mg
CODOX-M	15, 17	Methotrexate	12mg	2mg
	16, 18	Leucovorin	12 mg oral, 24 hrs after each lumbar puncture	
2	7, 9	Cytarabine	70mg	15mg
IVAC	15, 17	Methotrexate	12mg	2mg
	16, 18	Leucovorin	12 mg oral, 24 hrs after each lumbar puncture	

Intrathecal/intraventricular therapy for cycles 3 and 4 will be given according to the schedule for High Risk patients without CNS disease (Table 9A.1 and 9B.1).

10.2 Management of Isolated CNS Relapse

Patients who develop isolated CNS recurrence, documented by malignant CSF pleocytosis or cranial nerve palsies or both, at any time after the first cycle of therapy, should be treated exactly as patients with CNS disease at diagnosis with the exception that whole brain irradiation will be given to a total dose of 30 Gy over 3 weeks.

This difference in approach is based upon the fact that patients who relapse in the CNS will have already been exposed to intrathecal drugs as part of their prophylactic therapy, so that additional measures are essential, even though the specific value of radiation in this situation is not documented. Four cycles of systemic therapy should be delivered from the time of the relapse.

10.3 Management of Testicular Involvement at Diagnosis

Patients with testicular disease at diagnosis should always be discussed with the principal investigator.

10.3 Recording of toxicty

Toxicity will be reported and graded according to the latest CTC criteria (see appendix I)

11. ASSESSMENT OF RESPONSE

3-4 weeks following final chemotherapy administration all patients will be systematically re-evaluated to assess response using the standard criteria.[29] As necrotic/fibrotic masses occasionally will persist at the end of chemotherapy, the primary endpoint of this study will be progression free survival. It is not recommended that further therapy is given in the absence of documented disease progression.

Re-evaluation Investigations

I. Full history and physical examination
II. FBC
III. Biochemical profile
IV. LDH level
V. Chest x-ray
VI. Chest, abdominal and pelvic CT scan ± MR scans. Repeat radiology of all sites found to be abnormal pre-chemotherapy
VII. Bone marrow trephine + aspirate (with cytogenetics), if abnormal pre-chemotherapy.
VIII. Examination of the CSF, if abnormal pre-chemotherapy

12. FOLLOW-UP

Following re-evaluation, patients will be seen at monthly intervals for 4 months, then 2 monthly until 1 year after starting chemotherapy. Thereafter, follow-up will be 3 monthly in year 2, 4 monthly in year 3, 6 monthly in year 4 and thereafter annually.

Investigations at follow-up

I. FBC, LDH at each visit

II. Chest x-ray at alternate visits only

III. Follow up CT scan at discretion of clinician (mandatory if residual mass is seen at first post-chemotherapy scan)

IV. Bone marrow trephine and aspirate if abnormal at presentation

V. Bone scan, if abnormal pre-treatment this should be repeated at three month post treatment visit

VI. FSH/LH levels annually; sperm count at discretion of clinicians at 2 years

13. FORM COMPLETION

Complete a **Registration form** then phone the CTU, once the patient has been registered complete a **Pre-Chemotherapy form** and a **Local Pathology form**. An appropriate **Treatment form** will need to be completed at the end of each chemotherapy cycle, and a **Response form** 3-4 weeks after final treatment. For patients on the pathology study a summary **Treatment/Response** should be completed in place of the Treatment forms and Response forms. A completed **Follow-Up form** will be required 6-monthly for 2 years and annually thereafter.

14. ENDPOINTS

The primary endpoint will be progression-free survival, with clinical progression and death as the events. On suspicion of progression (e.g. new of enlarging masses), patients should be re-evaluated according to normal procedures to confirm relapse. Survival time, including death from any cause, will also be investigated. For both endpoints, the event-free times will be dated from the start of chemotherapy.

15. STATISTICAL CONSIDERATIONS

The study has been powered with respect to the principal clinical and pathological hypotheses, to enable reasonably accurate estimation of the progression-free survival rate amongst those patients undergoing protocol chemotherapy, and to examine the prognostic value of specific cytogenetic features.

Pathological study

Sample Size: We aim to register **at least 120 patients**. This will enable differences in the 1 year progression-free survival rate between groups of patients (in particular those with and without t(14;18)), of approximately 25% (e.g. from 55% to 80%) to be detected with approximately 80% power at a 5% significance level. All registered patients would contribute to the analysis of differences in PFS between different groups of patients whether or not they go on to get protocol chemotherapy.

Analysis plan: The initial analyses will be descriptive, with simple estimates of frequency of the various mutations, with 95% confidence intervals. Key examples include, what proportion of patients have t(14;18) in addition to t(8;14)? Presence of a cell cycle fraction of 100% is a key requirement for this study, but what proportion of these patients have c-myc rearrangements?

The ability of the immunophenotype of the tumour cells and/or the clinical characteristics, to predict the presence of cytogenetic or molecular abnormalities will be addressed by presenting appropriate measures of association or comparison between the various factors, for example we would summarise the age distribution of patients with and without t(14,18).

Finally, the association between the various factors and outcome will be presented through Kaplan Meier event-free curves for the various groups, which would be compared using the logrank test, for example the progression-free survival rates of patients with both t(8,14) and t(14,18) will be compared with those for patients with t(8,14) alone.

Clinical study

Sample Size: A minimum of 100 patients who are planned to receive protocol chemotherapy will be entered. It is anticipated that the ratio of low to high risk will be approximately 1:3. Progression-free survival (PFS) at 1 year is expected to be approximately 70% in the group undergoing protocol therapy, and with 100 patients the PFS would be estimated with a standard error of <5% (and hence the 95% CI would extend from approximately 60%-80%). In the previous LY06 trial, approximately one quarter of patients registered were "low risk" and the remainder "high risk". The low risk group had a 1-year PFS of 83%; if a similar rate is seen here this would be estimated with a standard error of approximately 7.5%. The 1-year PFS amongst the high risk patients was 65%; again on the assumption of a similar rate here, the 1-year PFS would be estimated with a standard error of approximately 5.5%.

Analysis plan: With respect to the analysis of the clinical study, our main endpoint is (PFS) and we will therefore present survival curves and estimates for the following groups

- An intention to treat progression-free survival analysis of all patients consenting to protocol chemotherapy (irrespective of risk group and age)
- An intention to treat progression-free survival analysis of all patients consenting to protocol treatment according to risk group (high vs low) irrespective of age
- An intention to treat analysis of all patients consenting to protocol treatment according to age group (above and below 65) irrespective of risk group
- Exploratory analyses of other potential prognostic factors (e.g. IPI score) will also be carried out in a similar manner

Anticipated accrual rate

LY06 recruited 88 patients over approximately 3-4 years. The expanded eligibility criteria for this trial should increase the number available by approximately 20%, and so the higher numbers required here should be achievable over a similar timeframe.

16. ETHICAL CONSIDERATIONS

This study will have Multi-centre Research Ethics Committee (MREC) approval. Copies of the approval letter will be circulated to participants. Before entering patients into the study, clinicians must ensure that the protocol has additionally received clearance from their Local Research Ethics Committee (LREC). The patient's consent to participate in the study should be obtained for all cases, after a full explanation has been given of the treatment.

The right of a patient to refuse to participate without giving reasons must be respected. After the patient has entered the study the clinician must remain free to give alternative treatment to that specified in the protocol at any stage if it is felt to be in the patient's best interests. The reason for giving such alternative treatment must be recorded and the patient should remain in the study for the purposes of follow-up and data analysis. Similarly, the patient must remain free to withdraw at any time from protocol treatment without giving reasons and without prejudicing further treatment.

17. PUBLICATION

The data from the participating centres will be analysed together and published as soon as possible. All participating clinicians will be identified in addition to the principal investigator, Reference Pathologist, Statistician and Trial Manager. Individual clinicians must not publish either data concerning their patients which are directly relevant to the questions posed by the study, or interim analyses of the collective data, until such time as the main results of the study have been published.

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APPENDIX A: PATHOLOGICAL DIAGNOSIS AND REVIEW.

Primary Diagnosis

? **Tissue Specimens**

It is highly desirable that all specimens should be sent unfixed to the laboratory. When unfixed tissue is available the following procedure is recommended:-

1. 8-10 air dried imprints should be made and stored for future use
2. Where local facilities are available a sample of tissue should be sent for cytogenetic analysis
3. 1-2mm sliced should be fixed in 10% formalin for 24hrs and processed for routine histology

When a biopsy is received in fixative it should be examined and if necessary sliced and fixed for 24 hrs in 10% formalin.

Morphological examination and immunohistochemistry should be carried out according to local protocols but must include MIB1 (Ki67).

? **Bone Marrow Specimens**

A bone marrow aspirate and trephine biopsy must be carried out for all cases. The following procedure should be followed even where the diagnosis has been made on a previous tissue biopsy.

1. 8 fresh bone marrow aspirate smears should be made and stored
2. A sample of bone marrow should be sent for cytogenetic analysis
3. Marker studies should be performed by flow cytometry according to local protocols. The minimum requirement include:-
   (a) Demonstration of a B-cell phenotype including clonal sIg and CD10
   (b) Exclusion of a precursor lymphoblastic leukaemia by absence of Tdt

   Burkitt's lymphoma cells undergo rapid apoptosis *ex vivo* and prompt handing of these specimens is essential
4. The trephine biopsy should be processed locally

Central Review

Central review of pathological material will be carried out by the Haematological Malignancy Diagnostic Service, Leeds Teaching Hospitals NHS Trust.

The local pathologist should ensure that the following are sent promptly to the reference pathology review centre for all patients entered in the study:-

1. Unstained imprint and fresh bone marrow smears. This material will be used for FISH studies to demonstrate the t(8;14) and t(14;18)
2. Paraffin blocks from tissue and trephine biopsies. A standard panel of marker studies will be carried out and the morphological features reviewed. Where no imprints are available isolated nuclei will be prepared from the blocks for FISH studies. However, this is less efficient than FISH carried out on imprints or fresh smears. These blocks will be returned as soon as possible
3. Copies of immunophenotyping studies carried out by flow cytometry
4. Copies of cytogenetic reports when available. The reference pathology review centre should be notified of cases where a cytogenetics report is pending

The results of these investigations will be reported to the referring centre, but they should not influence treatment.

APPENDIX B: WHO PERFORMANCE STATUS

Grade	Performance Status
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out 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 of only 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 C: PREVENTION OF ACUTE TUMOUR LYSIS SYNDROME

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

1. 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.

2. TREATMENT

Hyperkalaemia

Hyperkalaemia should be managed by correcting acidosis if present, decreasing K+ intake, increasing urinary excretion by establishing a saline diuresis if possible, and removing potassium by exchange resin administration, either by mouth or by enema.

Frequently, when such measures are necessary, other biochemical changes are present which together may necessitate hemodialysis.

Renal failure

In the presence of renal failure prior to treatment, renal ultrasound or CT scanning is indicated to exclude obstructive uropathy. This should be relieved by ureteric stents or temporary insertion of nephrostomy tubes.

APPENDIX D: 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.

In patients with extensive Burkitt's or Burkitt-like NHL, 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, hence **alkalinisation of the urine is normally stopped prior to chemotherapy.** 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 E: METHOTREXATE ADMINISTRATION AND UROPROTECTION

ADMINISTRATION

24-hour collections for creatinine clearance will be carried out and glomlerular 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, and significant changes brought to the attention of the attending physician.

The duration of the infusion **must not exceed 24 hours, regardless of the total dose administered up to that point.**

METHOTREXATE LEVELS

Serum methotrexate levels should be obtained as follows:

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

Leucovorin rescue is commenced at hour 36 from the start, i.e. 12 hours from the end of the infusion. This will be administered intravenously at a dose of 15mg/m^2. Thereafter, Leucovorin is given IV or PO every 6 hours until the methotrexate level is below 5 x 10^{-8}M, or predicted to be below 5 x 10^{-8}M.

Normally, during the first cycle a complete methotrexate disappearance curve will be obtained and the patient not discharged until the methotrexate level is below 5 x 10^{-8}M.

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

APPENDIX F: PATIENT INFORMATION SHEET (CLINICAL AND PATHOLOGICAL STUDY)

(HOSPITAL HEADED PAPER)

Version 5, February 2002

Study Title: A Cancer Research UK study of patients with Burkitt's and Burkitt-like non-Hodgkin's lymphoma

You are being invited to take part in a research study. Before you decide *whether to take part* it is important for you to 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. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Consumers for Ethics in Research (CERES) publish a leaflet entitled 'Medical Research and you'. This leaflet gives more information about medical research and looks at some questions you may want to ask. A copy may be obtained from CERES, PO Box 1365, London N16 0BW.

A summary of the principles of clinical trials can be found on the Cancer Research UK's patient website (www.cancerhelp.org.uk). There is also an independent patient advisory group called CancerBACUP who 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).

Thank you for reading this.

What is the purpose of the study?

Burkitt's and Burkitt-like lymphomas are very rare forms of non-Hodgkin's lymphoma which usually occur in young adults. These cancers are highly curable with intensive chemotherapy. A recent Cancer Research Campaign study, in which many hospitals worldwide treated patients with the same chemotherapy drug combinations, confirmed that a combination called "CODOX-M" with, in some patients, additional drugs called "IVAC", was extremely effective, but also associated with quite severe, mainly short-term, side effects. In this study we wish to build on the results of the previous study in two ways. Firstly, we want to find out if we can reduce the amount we give of the most toxic drug (methotrexate) while maintaining the very high cure rates. We also want to include a broader range of patients, including those aged over 60 who are often excluded from clinical trials, with drug doses tailored accordingly. These aspects we will refer to as the "clinical study". Secondly, as it can be difficult to diagnose this particular form of lymphoma, an important part of this study is to investigate tumour specimens, which are routinely collected, using new techniques. From this we hope to learn more about the characteristic features of this disease, and whether these features can be used to identify groups of patients with a better or worse than average chance of cure. This will help us decide whether some groups of patients should be treated differently in future. This aspect we will refer to as the "pathology sub-study".

Why have I been chosen?

You have been chosen to enter this study as the local Pathologist at your hospital has made a diagnosis of Burkitt's or Burkitt-like lymphoma on a biopsy specimen. This study aims to include a minimum of 120 patients from the UK and abroad.

Do I have to take part?

It is up to you to decide whether or not to take part, and it is possible for you to agree to take part in the clinical study, but not the pathology sub-study if you wish. If you do 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 and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

Whether or not you take part in this study the treatment you receive will be very similar. Involvement in the study will not involve any extra visits or time in hospital, therefore your expenses in travelling from home to the hospital will not be reimbursed.

Routinely, patients with suspected Burkitt's lymphoma will have a small sample of tissue removed under a local anaesthetic – this is known as a needle biopsy. This is used to determine which features of Burkitt's lymphoma are present, and ensure that the treatment you will receive is appropriate. If this has not been done already, it will be done before you start your treatment.

All patients involved in this study will receive intensive treatment with a combination of chemotherapy drugs called CODOX-M. Patients with more advanced disease will also receive courses of some additional drugs known as IVAC chemotherapy. More detailed information on these treatments will be provided to you. Data on the treatment you receive and your progress will be reported in confidence to the trial organisers, the Medical Research Council Clinical Trials Unit, who will put this together with data from all the other patients in the study, without identifying anyone individually.

With your permission, we would like to send some of the tumour sample collected routinely by your hospital to be examined by an expert pathologist at the Haematological Malignancy Diagnostic service, based in Leeds (this is the "pathology sub-study"). As part of this study, he is using new techniques to examine tumour cells in more detail. This will not affect your treatment in any way (and you will not benefit financially), but by collecting similar information on lots of patients we may be able to identify features which allow us to predict more accurately how patients will respond to different treatments in the future. The tumour sample would be anonymised, but would be identified by a numerical code so that when, and only when, the pathologist's report on the sample is sent to the study organisers (the Medical Research Council Clinical Trials Unit) they will be able to link the pathology details to details of your treatment and progress.

We would also like to ask your permission for the sample to be stored in Leeds for possible use in future projects relating to the diagnosis and treatment of Burkitt's lymphoma, as new techniques become available. These may be carried out by researchers other than those in Leeds and at the Medical Research Council. No one involved with this study would benefit financially if this were to happen. All further research using stored samples will require approval from an appropriate Research Ethics Committee. You may, if you wish, decline permission for the tissue sample to be used in other studies. In this case the tumour tissue would be returned to your hospital pathology department once this study is complete.

What do I have to do?

Standard treatment for Burkitt's lymphoma is quite intensive and virtually all patients will require a period of time in hospital with, occasionally, a need for continuous admission for 2-3 months. The treatment you will receive will temporary 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. The treatment is complex but will be discussed with you individually.

CODOX-M with or without IVAC is a standard intensive treatment for Burkitt's lymphoma or Burkitt-like lymphoma. Most of this treatment is given intravenously (i.e. into a vein). In addition however you will need to receive intrathecal treatment (that is treatment given via lumbar puncture into the spine). This latter treatment is required as Burkitt's lymphoma commonly spreads to the fluid surrounding the brain and spinal cord (cerebro-spinal fluid) and treatment with intravenous chemotherapy is ineffective at controlling lymphoma at these sites.

What is the drug or procedure that is being tested?

All the drugs included in CODOX-M/IVAC are standard chemotherapy drugs which are widely used in patients with non-Hodgkin's lymphoma. The individual drugs used are called cyclophosphamide, vincristine, doxorubicin, methotrexate, cytarabine and leucovorin (CODOX-M) and additionally etoposide and ifosfamide for those who receive IVAC chemotherapy. You will also receive a drug called G-CSF which helps maintain the production of white blood cells. In this study, we will extend the range of patients usually considered for this type of treatment, including older patients, but will modify the drug dosages accordingly. In addition, all patients entering this study will receive a lower dose of the drug methotrexate than is routinely used. We hope that by doing this, we will reduce the most severe toxicities without lessening the effectiveness of the treatment.

What are the alternatives for diagnosis or treatment?

Burkitt's lymphoma is a very aggressive condition and intensive chemotherapy would always be the treatment of choice, giving the maximum chance of cure. As CODOX-M/IVAC is standard treatment in the UK for Burkitt's lymphoma, many patients would receive this treatment even if not taking part in a clinical trial. However some of the drugs, in particular the methotrexate, may be given at different doses. Although the treatment to be given in this trial is only slightly different, it is important that any changes to standard treatment are carefully evaluated in large groups of patients to make sure that any reduction in toxicity is not offset by lower cure rates.

What are the side effects of any treatment received when taking part?

The side effects of treatment with CODOX-M/IVAC are those common to many chemotherapy drugs, but they occur more often as the treatment is given at higher dose and over a shorter period of time. All patients will lose their hair in the short term. Normal regrowth of hair always occurs once treatment is completed and, as noted above, all patients will develop low red cell counts requiring blood transfusion, low white cell counts often associated with infection requiring intravenous antibiotics and low platelet counts, sometimes requiring platelet transfusion. Additional common side effects are tiredness, a sore mouth related to the treatment and tingling in the fingers and toes. More details will be provided of this by your Doctor and nursing staff. Once chemotherapy is completed virtually all these side effects completely disappear.

What are the possible disadvantages and risks of taking part?

Although Burkitt's lymphoma and Burkitt-like lymphoma are both very rapidly progressive cancers which, untreated, usually cause death within a period of weeks, drug treatment like that recommended in this study results in cure in a high proportion of patients. It is therefore strongly recommended, whether or not you take part in this study. To achieve these high cure rates, we have to give very intensive chemotherapy, which does have side effects as

described above; however you will be monitored closely throughout your treatment so that any side effects can be treated promptly.

We hope that reducing the amount of the drug methotrexate will reduce the side effects of treatment for all patients without reducing its effectiveness. However, until the trial is complete we will not know for sure, and it is possible that it may not be as effective in preventing recurrence for some patients as the standard, higher doses. Any patient who has a recurrence of their disease would normally have further chemotherapy and – though again we cannot be sure - we would anticipate that the overall chances of cure should be unchanged.

It is likely that if the treatment is given to a pregnant woman it will harm the unborn child. Pregnant women must therefore not take part in this study and it is possible we would ask you to have a pregnancy test before taking part to exclude this possibility. Women who could become pregnant must use an effective contraceptive during the course of this study as should male patients as it is possible that the treatment may interfere with the normal functioning of the female egg or male sperm.

What are the possible benefits of taking part?

It is expected that receiving treatment with CODOX-M/IVAC will cure a substantial proportion of patients with these forms of lymphoma. We hope that the slightly modified treatment given in this trial will enable patients in this trial, and in the future, to receive effective, but less toxic treatment than before.

Accurate diagnosis of this disease is extremely important and currently Pathologists have difficulty in agreeing how they should be diagnosed precisely. The pathology part of the study will not benefit you directly as it will not affect your treatment, but we hope it will benefit future patients with this condition by giving them better information on their chances of cure, and in helping to decide the most appropriate treatment.

What if new information becomes available?

In the event that new treatment for Burkitt's and Burkitt-like lymphoma becomes available which is of advantage to you this will of course be shared with you. If a new form of therapy would be beneficial to you then this will be discussed with you and it would be possible for you to withdraw from the present study. If you chose to continue, you may be asked to sign an updated consent form.

What happens when the research study stops?

CODOX-M/IVAC would be regarded as standard therapy for Burkitt's lymphoma and this treatment will continue in many Centres in the UK. However, should this trial show that high cure rates can be maintained with lower drug doses, this is likely to change standard practice in future.

What if something goes wrong?

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 complaints mechanisms should be available to you. If you are harmed by taking part in this research project, there are no special compensation arrangements. 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.

Will my taking part in this study be kept confidential?

If you consent to taking part in a research study such as this one, relevant aspects of your medical records will be sent, in confidence, to the Medical Research Council Clinical Trials Unit (MRC CTU). They are registered under the data protection act to hold patient information in secure storage, to be accessed only by appropriate staff involved with this study. Once registered in the study, the MRC CTU will give your doctor an identification number which uniquely identifies you, so that your full name need not be kept on the main study database. Similarly, with your agreement, some small pathology specimens will be sent to the Department of Pathology in Leeds. Your name and address will be removed from such specimens so that you will not be identifiable other than to the MRC CTU, and all information from the study will be kept strictly confidential. No individual patients will be identified when the results of the study are published. Your General Practitioner will however be informed of your participation in the study.

What will happen to the results of the research study?

Approximately one to two years after the study has been completed (it is anticipated this will take at least 3-4 years) the results will be published in a recognised medical journal. The results will be available to you at this time as will a copy of the published results if you would like this. You will not be identified in any report or publication.

Who is organising and funding the research?

The administrative and pathology part of this research are funded by the charity "Cancer Research UK" working in conjunction with the Medical Research Council Clinical Trials Unit and the Department of Pathology at Leeds General Infirmary. Your clinical care will be paid for by the usual National Health Service mechanism. Your doctor will not be paid for including you in the study.

Who has reviewed the study?

The study has been reviewed by Cancer Research UK as part of the process of obtaining funding. Prior to this, the study was discussed and approved by the National Cancer Research Institute lymphoma group (formally the UK Coordinating Committee on Cancer Research lymphoma group). A Multi-centre Research Ethics Committee will have approved this study, as will the Local Research Ethics Committee for your hospital.

Contact for further information

Should you have worries or concerns about your treatment or condition we recommend that you contact:.....

who can be contacted on telephone no: .....

Can we thank you for considering taking part in this study.

APPENDIX F: PATIENT CONSENT FORM - CLINICAL AND PATHOLOGICAL STUDY

February 2002 Version 5

A Cancer Research UK study of patients with Burkitt's and Burkitt-like non-Hodgkin's lymphoma

Section 1: Clinical study **Please initial each box in this section to participate in this study**

Please initial each box

☐ I have had the opportunity to read and keep the Patient Information Sheet dated February 2002 (version 5) for the above study and have had the opportunity to ask questions.

☐ I understand that my participation is voluntary, and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

☐ I understand that sections of my medical notes may be looked at by members of the research team, where it is relevant to my taking part in research, and that this information will be kept confidential.

☐ I understand that information about me will be sent by my Doctor to be stored and analysed on a central database by the Medical Research Council Clinical Trials Unit. No information will be seen by anyone not directly involved with the study and that I will not be identified directly in any publications or presentations regarding the study.

☐ Given this information, I give my consent to participate in the study.

_____	_____	_____
Name of patient	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Section 2: Pathology sub-study – optional. Please indicate yes or no to the following two statements

	Yes	**No**
I agree that samples of my tumour may be stored in a central database and that additional tests may be performed on them for the purpose of this study. I understand that allowing the sample to be used is voluntary, and will not affect the treatment I receive.	☐	☐
I agree that the sample can be stored at the Haematological Malignancy Diagnostic Service in Leeds (custodian Dr Jack) for possible use in future projects relating to the diagnosis and treatment of lymphoma. I understand that some of these projects may be carried out by researchers other than those involved with the current study. The samples will be stored in an anonymised form and I shall not be identified.	☐	☐

_____	_____	_____
Name of patient	Date	Signature
_____	_____	_____
Researcher	Date	Signature

APPENDIX G: PATIENT INFORMATION SHEET

(PATHOLOGY STUDY ONLY)

(HOSPITAL HEADED PAPER)

Version 5 February 2002

Study Title: A Cancer Research UK study of patients with Burkitt's and Burkitt-like non-Hodgkin's lymphoma

You are being invited to allow information collected about you by your Doctor to be used as part of a research study. Before you decide *whether to take part* it is important for you to understand why the research is being done. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Consumers for Ethics in Research (CERES) publish a leaflet entitled 'Medical Research and you'. This leaflet gives more information about medical research and looks at some questions you may want to ask. A copy may be obtained from CERES, PO Box 1365, London N16 0BW.

Thank you for reading this.

What is the purpose of the study?
Burkitt's and Burkitt-like lymphomas are very rare forms of non-Hodgkin's lymphoma which usually occur in young adults. Because of their rarity, it can be difficult to diagnose this particular form of lymphoma.

The aim of this study is to investigate tumour specimens, which are routinely collected, using new techniques. From this we hope to learn more about the characteristic features of this disease, and whether these features can be used to identify groups of patients with a better or worse than average chance of cure. This will help us decide whether some groups of patients should be treated differently in future.

Why have I been chosen?
You have been chosen to enter this study as the local Pathologist at your hospital has made a diagnosis of Burkitt's or Burkitt-like lymphoma on a biopsy specimen. This study aims to include a minimum of 120 patients from the UK and abroad.

Do I have to take part?
It is up to you to decide whether or not to take part. The treatment you will receive and your standard of care will not be affected. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. If you decide to take part you are still free to change your mind at any time, without giving a reason.

What will happen to me if I take part?
Your involvement in the study will not involve any extra visits or time in hospital, and will not affect your treatment in any way, therefore your expenses in travelling to and from hospital will not be reimbursed.

Routinely, patients with suspected Burkitt's lymphoma will have a small sample of tissue removed under a local anaesthetic – this is known as a needle biopsy. This is used to determine which features of Burkitt's lymphoma are present, and ensure that the treatment you will receive is appropriate. If this has not been done already, it will be done before you start your treatment.

With your permission, we would like to send some of the tumour sample collected routinely by your hospital to be examined by an expert pathologist at the Haematological Malignancy Diagnostic service, based in Leeds. As part of this study, he is using new techniques to examine tumour cells in more detail. This will not affect your treatment in any way (and you will not benefit financially), but by collecting similar information on lots of patients we may be able to identify features which allow us to predict more accurately how patients will respond to different treatments in the future. To do this, we will also need to send details of your treatment and progress, in confidence, to the organisers of the study, the Medical Research Council Clinical Trials Unit. The tumour sample would be anonymised, but would be identified by a numerical code so that when, and only when, the pathologist's report on the sample is sent to the study organisers they will be able to link the pathology details to details of your treatment and progress.

We would also like to ask your permission for the sample to be stored in Leeds by the study pathologist, Dr Jack, for possible use in future projects relating to the diagnosis and treatment of Burkitt's lymphoma, as new techniques become available. These may be carried out by researchers other than those in Leeds and at the Medical Research Council, who are coordinating this study. No one involved with this study would benefit financially if this were to happen. All further research using stored samples will require approval from an appropriate Research Ethics Committee. You may, if you wish, decline permission for the tissue sample to be used in other studies. In this case the tumour tissue would be returned to your hospital pathology department once this study is complete.

What do I have to do?

Nothing - the study uses routine information collected by your Doctor on your progress together with analysis of a sample of your tumour. Participation in this study will not affect your treatment, and therefore will not directly benefit you. However, we hope it will benefit future patients with this condition by giving them better information on their chances of cure, and helping to decide on the most appropriate type of treatment.

Will my taking part in this study be kept confidential?

If you consent to taking part in a research study such as this one, relevant details from your medical records will be sent, in confidence, to the Medical Research Council Clinical Trials Unit (MRC CTU). They are registered under the Data Protection Act to hold patient information in secure storage, to be accessed only by appropriate staff involved with this study. Once registered in the study, the MRC CTU will give your doctor an identification number which uniquely identifies you, so that your full name need not be kept on the main study database. Similarly, with your agreement, some small pathology specimens will be sent to the Department of Pathology in Leeds. Your name and address will be removed from such specimens so that you will not be identifiable other than to the MRC CTU, and all information from the study will be kept strictly confidential. No individual patients will be identified when the results of the study are published. Your General Practitioner will however be informed of your participation in the study.

Who is organising and funding the research?

The study is funded by the charity "Cancer Research UK" working in conjunction with the Medical Research Council Clinical Trials Unit and the Department of Pathology at Leeds General Infirmary. Your clinical care will be paid for by the usual National Health Service mechanism. Your doctor will not be paid for including you in the trial.

Who has reviewed the study?

The study has been reviewed by Cancer Research UK as part of the process of obtaining funding. Prior to this, the study was discussed and approved by the National Cancer Research Institute lymphoma group.

Contact for further information

Should you have worries or concerns about your treatment or condition we recommend that you contact:.....
who can be contacted on telephone no: .....

Thank you for considering taking part in this study.

APPENDIX G: PATIENT CONSENT FORM (PATHOLOGY STUDY ONLY)

Version 5 February 2002

A Cancer Research UK study of patients with Burkitt's and Burkitt-like non-Hodgkin's lymphoma

Section 1: Please initial each box in this section to participate in this study

☐ I have had the opportunity to read and keep the Patient Information Sheet dated February 2002 (version 5) for the above study and have had the opportunity to ask questions.

☐ I understand that my participation is voluntary, and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

☐ I understand that sections of my medical notes may be looked at by members of the research team, where it is relevant to my taking part in research, and that this information will be kept confidential.

☐ I understand that information about me will be sent by my Doctor to be stored and analysed on a central database by the Medical Research Council Clinical Trials Unit. No information will be seen by anyone not directly involved with the study and that I will not be identified directly in any publications or presentations regarding the study.

☐ I agree that samples of my tumour may be stored in a central database and that additional tests will be performed on them for the purpose of this study. I understand that allowing the sample to be used is voluntary, and will not affect the treatment I receive.

☐ Given this information, I give my consent to participate in the study.

_____	_____	_____
Name of patient	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Section 2: Optional consent to central tissue storage for future research.

Please answer yes or no to the following statement	Yes	No
I agree that the sample can be stored at the Haematological Malignancy Diagnostic Service in Leeds (custodian Dr Jack) for possible use in future projects relating to the diagnosis and treatment of lymphoma. I understand that some of these projects may be carried out by researchers other than those involved with the current study. The samples will be stored in an anonymised form and I shall not be identified.	☐	☐

_____	_____	_____
Name of patient	Date	Signature
_____	_____	_____
Researcher	Date	

APPENDIX H: GP LETTER

May 2001, Version 1

Dear Dr ……..

A clinicopathological study in Burkitt and Burkitt-Like Non-Hodgkin's Lymphoma (LY10)

Your Patient:…….

(D.O.B.: …./…./….)

has recently been found to have Non-Hodgkin's Lymphoma, for which combination chemotherapy has been recommended. They have kindly agreed to take part in a phase II study that uses the standard treatment CODOX-M / CODOX-M/IVAC (delete as appropriate).

You will be kept up to date with your patient's progress but if you have any concerns or questions regarding this study please contact the responsible physician:

Dr …….. at ……. Hospital

Tel: …….. at any time.

APPENDIX I: TOXICITY GRADES

Explanatory Notes

1. Toxicities are grouped into the following categories based on body system:

Allergy	Hepatic
Blood/bone marrow	Infection
Cancer-related symptoms	Metabolic
Cardiovascular	Neurologic
Coagulation	Ocular
Dentition (teeth)	Osseous (bone)
Endocrine	Other
Flu-like symptoms	Pulmonary
Gastrointestinal	Skin
Genitourinary	Weight

2. Protocols requiring detailed hyposensitivity reaction reporting will include a Hypersensitivity Reaction Module.

3. Categories are listed alphabetically, with toxicity variables (eg: dysrhythmia, nausea, dizziness) listed alphabetically within each category.

4. Toxicity codes are composed of a 2-character "prefix" based on toxicity category, and a 3-character "description" based on variable name. For example:(cardiovascular) dysrhythmia = CD DYS, (gastrointestinal) nausea = GI NAU, (neurologic) dizziness = NE DIZ

5. Some conventions: H = hyper (or high) (eg: CD HBP = hypertension)
   L = hypo (or low) (eg: MT LCA = hypocalcemia)

6. Codes are usually derived from the first 3 letters of the toxicity variable (eg: nausea = GI NAU). Exceptions to this rule have been made in the following cases:

   - where the first 3 letters are not particularly helpful or descriptive (eg: mouth dryness has been coded GI DRY instead of GI MOU)

   - where the first 3 letters are potentially confusing (eg: flushing, facial has been coded SK FAC instead of SK FLU)

   - where a "common" 3 letter abbreviation already exists (eg: hemoglobin has been coded BL HGB instead of BL HEM)

7. For toxicities which do not have an existing code, but do fit into an existing toxicity category, use "other" variable in the appropriate toxicity category (eg: code pathologic fracture OSSEOUS OTHER (OS OTH). For toxicities which do not have existing codes, and do NOT fit into existing categories, code OTHER OTHER (OT OTH).

8. Please note that ONLY the codes listed in the criteria may be used. Data managers should not "create" new toxicity codes. If a new toxicity is identified which doesn't have an existing code or doesn't fit an existing category, use OTHER and OTHER OTHER variables as outlined above. If you're unsure how to code a particular toxicity, please record toxicity type only on the form. A coding decision will then be made at the CTU.

NCIC CTG EXPANDED COMMON TOXICITY CRITERIA						REVISED: 94-DEC-21
	GRADE	0	1	2	3	4
ALLERGY						
AL LER	Allergy	None	Transient rash, fever <38°C, 100.4°F	Urticaria, fever = 38°C, 100.4°F, mild bronchospasm	Serum sickness, bronchspasm, req parenteral mode	Anaphylaxis
		Fever felt to be caused by drug allergy should be coded as ALLERGY (AL LER). Non-allergic drug fever (eg: as from biologies) should be coded under FLU-LIKE SYMPTOMS (FL FEV). If fever is due to infection, code INFECTION only (IN FEC or IN NEU). NB: Protocols requiring detailed reporting of hypersensitivity reactions, will include a Hypersensitivity Reaction module.				
AL OTH	Other*	None	Mild	Moderate	Severe	life threatening
BLOOD/BONE MARROW (SI UNITS)						
BL WBC	White Blood Count (WBC)	≥4.0 10^9 /L	3.0-3.9	2.0-2.9	1.0-1.9	<1.0
BL PLT	Platelets	WNL 10^9/L	75.0 normal	50.0-74.9	25.0-49.9	<25.0
BL HGB	Hemoglobin (Hgb)	WNL g/L	100 normal	80-99	65-79	<65
BL GRA	Granulocytes (ie. neuts + bands)	≥2.0 10^9/L	1.5-1.9	1.0-1.4	0.5-0.9	<0.5
BL LYM	Lymphocytes	≥2.0 10^9/L	1.5-1.9	1.0-1.4	0.5-0.9	<0.5
BL HEM	Hemorrhage resulting from thrombocytopenia (clinical)	None	Mild, no transfusion (inc bruise/hematoma, petechiae)	Gross, 1 - 2 units transfusion per episode	Gross, 3 - 4 units transfusion per episode	Massive, >4 units transfusion per episode
BL OTH	Other*	None	Mild	Moderate	Severe	Life threatening
CANCER RELATED SYMPTOMS						
CA DEA	Death from malignant disease within 30 days of treatment* (grd=5)	-		-	-	-
CA PAI	Cancer pain*	None	Pain, but no treatment req	Pain controlled with non-opioids	Pain controlled with opioids	Uncontrollable pain
CA SEC	Second malignancy*	None	-	-	Present	-
CA OTH	Other*	None	Mild	Moderate	Severe	life threatening
CARDIOVASCULAR						
CD ART	Arterial* (non myocardial)	None	-	-	Transient events (eg: transient ischemic attack)	Permanent event (eg: cerebral vascular accident)
CD VEN	Venous*	None	Superficial (excl IV site reaction-code SK LTO)	Deep vein thrombosis not req anticoagulant therapy	Deep vein thrombosis req anticoagulant therapy	Pulmonary embolism
CD DYS	Dysrhythmias	None	Asymptomatic, transient, req no therapy	Recurrent or persistent, no therapy req	Req trt	Req monitoring, or hypotension, or ventricular tachycardia, or fibrillation
CD EDE	Oedema* (eg: peripheral oedema)	None	1+ or dependent in evening only	2+ or dependent throughout day	3+	4+, generalised anasarca
CD FUN	Function	None	Asymptomatic, decline of resting ejection fraction of ≥10% but < 20% of baseline value	Asymptomatic, decline of resting ejection fraction by >20% of baseline value	Mild CHF, responsive to therapy	Severe or refractory CHF
CD HBP	Hypertension	None or no change	Asymptomatic, transient increase by >20mm Hg (D) or to >150/100 if previously WNL. No trt req	Recurrent or persistent increase by >20mm Hg (D) or to >150/100 if previously WNL. No trt req	Req therapy	Hypertensive crisis
CD LBP	Hypotension	None or no change	Changes req no therapy (incl transient orthostatic hypotension)	Req fluid replacement or other therapy but not hospitalisation	Req therapy & hospitalisation: resolves within 48hrs of stopping agent	Req therapy & hospitalisation for >48hrs after stopping agent

NCIC CTG EXPANDED COMMON TOXICITY CRITERIA						REVISED: 94-DEC-21
	GRADE	**0**	**1**	**2**	**3**	**4**
CD ISC	Ischemia (myocardial)	None	Non-specific T wave flattening	Asymptomatic, ST & T wave changes suggesting ischemia	Angina without evidence for infarction	Acute myocardial infarction
CD PAI	Pain (chest)*	None	Pain, but no treatment req	Pain controlled with non-opioids	Pain controlled with opioids	Uncontrollable pain
CD PER	Pericardial	None	Asymptomatic, effusion, no intervention req	Pericarditis (rub, chest pain, ECG changes)	symptomatic effusion; drainage req	Tamponade, drainage urgently req: or constrictive pericarditis req surgery
CD TAC	Sinus tachycardia*	None	Mild	Moderate	Severe	life threatening
CD OTH	Other*	None	Mild	Moderate	Severe	life threatening
	COAGULATION					
CG FIB	Fibrinogen	WNL	0.99-0.75 x N	0.74-0.50 x N	0.49-0.25 x N	≤0.24 x N
CG PT	Prothrombin time	WNL	1.01-1.25 x N	1.26-1.50 x N	1.51-2.00 x N	>2.00 x N
CG PTT	Partial thromboplastin time	WNL	1.01-1.66 x N	1.67-2.33 x N	2.34-3.00 x N	>3.00 x N
CG OTH	Other*	None	Mild	Moderate	Severe	Life threatening
	DENTITION (TEETH)					
DE DEC	Tooth decay*	None	Mild	Moderate	Severe	-
DE PAI	Toothache*	None	Pain, but no treatment req	Pain controlled with non-oploids	Pain controlled with opoids	Uncontrollable pain
DE OTH	Other*	None	Mild	Moderate	Severe	Life threatening
	ENDOCRINE*					
EN AME	Amenorrhea	None	Irregular menses	≥3 months	-	-
EN CUS	Cushingoid	Normal	Mild	Pronounced	-	-
EN FLA	Hot flashes	None	Mild or<1/day	Moderate & ≥1/day	Frequent & interferes with normal function	-
EN GYN	Gynecomastia	Normal	Mild	Pronounced or painful	-	-
EN IMP	Impotence/Libido	Normal	Decrease in normal function	-	Absence of function	-
EN OTH	Other	None	Mild	Moderate	Severe	Life threatening
	FLU-LIKE SYMPTOMS					
FL FEV	Fever in absence of infection* (incl drug fever)	None	37.1-38.0°C 98.7-100.4°F	38.1-40.0°C 100.5-104.0°F	>40.0°C >104.0°F for <24hrs	>40.0°C (104.0°F) for >24hrs or fever accompanied by hypotension
		Fever felt to be caused by drug allergy should be coded as ALLERGY (AL LER). Non-allergic drug fever (eg: as from biologics) should be coded under FLU-LIKE SYMPTOMS (FL FEV). If fever is due to infection, code INFECTION only (IN FEC or IN NEU).				
FL HAY	Hayfever* (incl sneezing, nasal stuffiness, post-nasal drip	None	Mild	Moderate	Severe	-
FL JOI	Arthralgia* (joint pain)	None	Mild	Moderate	Severe	-
FL LET	Lethargy* (fatigue, malaise)	None	Mild, or fall of 1 level in performance status	Moderate, or fall of 2 levels in perf. status	Severe, or fall of 3 levels in perf. Status	-
FL MYA	Myalgia* (muscle ache)	None	Mild	Moderate	Severe	-
FL RIG	Rigors/Chills* (gr 3 incl cyanosis)	None	Mild	Moderate	Severe	-
FL SWE	Sweating* (diaphoresis)	None	Mild	Moderate	Severe	-
FL OTH	Other*	None	Mild	Moderate	Severe	Life threatening

NCIC CTG EXPANDED COMMON TOXICITY CRITERIA					REVISED: 94-DEC-21
GRADE	0	1	2	3	4
GASTROINTESTINAL					
GI ANO Anorexia*	None	Mild	Moderate	Severe	Dehydration
GI APP Appetite increased*	None	Mild	Moderate	-	-
GI ASC Ascites (non-malignant)*	None	Mild	Moderate	Severe	Life threatening
GI DIA Diarrhea	None	Increase of 2-3 stools/day; or mild increase in loose watery colostomy output compared to pre-trt	Increase of 4-6 stools/day, or nocturnal stools; or moderate increase in loose watery colostomy output compared to pre-trt	Increase of 7-9 stools/day, or incontinence, malabsorption; or severe increase in loose watery colostomy output compared to pre-trt	Increase of ≥10 stools/day, or grossly bloody diarrhea; or grossly bloody colostomy output or loose watery colostomy output req parenteral support; dehydration
GI DPH Esophagitis/ dysphagia/ odynophagia* (incl recall reaction)	None	Dys, or odyn, not req trt, or painless ulcers on esophagoscopy	Dys. or odyn. req trt	Dys. or odyn. Lasting >14 days despite trt	Dys, or odyn. with 10% loss of body wt, dehydration, hosp. Req
GI DRY Mouth, nose dryness*	None	Mild	Moderate	Severe	-
GI FIS Fistula (intestinal, esophageal, rectal)*	None	-	-	Req intervention	Req operation
GI GAS Flatulence*	None	Mild	Moderate	Severe	-
GI HEA Heartburn* (incl dyspepsia)	None	Mild	Moderate	Severe	-
GI HEM Gastrointestinal bleeding*	None	Mild, no transfusion	Gross, 1-2 units transfusion per episode	Gross, 3-4 units transfusion per episode	Massive, >4 units transfusion per episode
	Bleeding resulting from thrombocytopenia should be coded under BL HEM, not GI				
GI NAU Nausea	None	Able to eat reasonable intake	Intake significantly decreased but can eat	No significant intake	-
GI OBS Small bowel obstruction*	None	-	Intermittent, no intervention	Req intervention	Req operation
GI PAI Gastrointestinal pain/cramping* (incl rectal pain)	None	Pain, but no treatment req	Pain controlled with non-opioids	Pain controlled with opioids	Uncontrollable pain
GI PRO Proctitis (rectal)	None	Perianal itch, hemorrhoids	Tenesmus or ulcerations relieved with therapy, and fissure	Tenesmus or ulcerations or other symptoms not relieved with therapy	Mucosal necrosis with hemorrhage or other life threatening proctitis
GI STO Stomatitis/oral	None	Painless ulcers, erythema, or mild soreness	Painful erythema, oedema, or ulcers but can eat	Painful erythema, oedema, or ulcers, and cannot eat	Mucosal necrosis and/or req parenteral or enteral support, dehydration
GI TAS Taste, sense of altered*	None	Mild	Moderate	Severe	-
GI ULC Gastritis/ulcer*	None	Antacid	Req vigorous medical management or non-surgical trt	Uncontrolled by medical management; req surgey for GI ulceration	Perforation or bleeding
GI VOM Vomiting	None	1 episode in 24hrs	2-5 episodes in 24hrs	6-10 episodes in 24hrs	>10 episodes in 24hrs or req parenteral support, dehydration
GI OTH Other*	None	Mild	Moderate	Severe	life threatening

NCIC CTG EXPANDED COMMON TOXICITY CRITERIA						REVISED: 94-DEC-21
	GRADE	**0**	**1**	**2**	**3**	**4**
			GENITOURINARY			
GU BLA	Bladder changes*	None	Light epithclial atrophy, or minor telangiectasia	Generalised telangiectasia	Severe generalised telangiectasia (often with petechlae) or reduction in bladder capacity (<15ml)	Necrosis, or contracted bladder (capacity <100ml), or fibrosis
GU CRE	Creatinine	WNL	<1.5 x N	1.5-3.0 x N	3.1-6.0 x N	>6.0 x N
GU CYS	Cystitis* (non-bacterial)	None	Mild symptoms req no intervention	Symptoms relieved completely with therapy	Symptoms not relieved despite therapy	severe (life threatening) cystitis
		Urinary tract infection should be coded under infection, not GU				
GU FIS	Fistula* (vaginal, vesicovaginal)	None	-	-	Req intervention	Req operation
GU FRE	Frequency*	None	Freq of urination or nocturia twice pre-trt habit	Freq of urination or nocturia <hourly	Freq with urgency and nocturia ≥hourly	-
GU HEM	Hematuria, bleeding per vagina	Neg	Micro only	Gross, no clots	Gross + clots	Req transfusion
		Bleeding resulting from thrombocytopenia should be coded under BL HEM, not GU				
GU INC	Incontinence*	None	Mild	Moderate	Severe	-
GU OBS	Ureteral obstruction*	None	Unilateral, no surgery	Bilateral, no surgery req	Not complete bilateral, but stents, nephrostomy tubes or surgery req	Complete bilateral obstruction
GU PAI	Genito-urinary pain (eg: dysuria, dysmenorrhea, dyspareunia)	None	Pain, but no treatment req	Pain controlled with non-opioids	Pain controlled with opioids	Uncontrollable pain
GU PRT	Proteinuria	no change	1+ or <0.3g% or <3g/L	2-3+ or 0.3-1.0g% or 3-10g/L	4+ or >1.0g% or >10g/L	Nephrotic syndrome
GU VAG	Vaginitis* (+/- vaginal discharge) (non-infectious)	None	Mild, no trt req	Moderate, relieved with trt	Severe, not relieved with trt	Life threatening
GU OTH	Other*	None	Mild	Moderate	Severe	Life threatening
			HEPATIC			
HP ALK	Alk Phos or 5' nucleotidase	WNL	≤ 2.5 x N	2.6-5.0 x N	5.1-20.0 x N	>20.0 x N
HP ALT	Transaminase SGPT (ALT)	WNL	≤ 2.5 x N	2.6-5.0 x N	5.1-20.0 x N	>20.0 x N
HP AST	Transaminase SGOT (AST)	WNL	≤ 2.5 x N	2.6-5.0 x N	5.1-20.0 x N	>20.0 x N
HP BIL	Bilirubin	WNL	-	<1.5 x N	1.5-3.0 x N	>3.0 x N
HP CLI	Liver (clinical)	No change from baseline	-	-	Precoma	Hepatic coma
HP LDH	LDH*	WNL	≤2.5 x N	2.6-5.0 x N	5.1-20.0 x N	>20.0 x N
HP OTH	Other*	None	Mild	Moderate	Severe	life threatening
		Viral Hepatitis should be coded as infection rather than liver toxicity				
			INFECTION			
IN FEC	Infection	None	Mild, no active trt	Moderate, localised infect req active trt	Severe, systemic infect req parenteral trt, specify site	Life threatening sepsis, specify site
IN NEU	Febrile neutropenia* Absolute gran. count <1.0 x 10°/L, fever >38.5°C treated with (or ought to have been treated with) IV antibiotics	None	-	-	Present	-
		Fever felt to be caused by drug allergy should be coded as ALLERGY (AL LER). Non-allergic drug fever (eg: as from biologies) should be coded under FLU-LIKE SYMPTOMS (FL FEV). If fever is due to infection, code INFECTION only (IN FEC or IN NEU				

NCIC CTG EXPANDED COMMON TOXICITY CRITERIA						REVISED: 94-DEC-21
	GRADE	0	1	2	3	4
METABOLIC (SI UNITS)						
MT AMY	Amylase	WNL	<1.5 x N	1.5-2.0 x N	2.1-5.0 x N	>5.1 x N
MT HCA	Hypercalcemia	<2.64 mmol/L	2.64-2.88	2.89-3.12	3.13-3.37	>3.37
MT LCA	Hypocalcemia	>2.10 mmol/L	2.10-1.93	1.92-1.74	1.73-1.51	≤1.50
MT HGL	Hyperglycemia	<6.44 mmol/L	6.44-8.90	8.91-13.8	13.9-27.8	>27.8 or ketoacidosis
MT LGL	Hypoglycemia	>3.55 mmol/L	3.03-3.55	2.19-3.02	1.66-2.18	<1.66
MT LKA	Hypokalemia*	no change or >3.5 mmol/L	3.1-3.5	2.6-3.0	2.1-2.5	≤2.0
MT LMA	Hypomagnesemia	>0.70 mmol/L	0.70-0.58	0.57-0.38	0.37-0.30	≤0.29
MT LNA	Hyponatremia*	no change or >135 mmol/L	131-135	126-130	121-125	≤120
MT OTH	Other*	None	Mild	Moderate	Severe	Life threatening
NEUROLOGIC						
NE CER	Cerebellar	None	Slight incoordination, dysdiadochokinesis	Intention tremor, dysmetria, slurred speech, nystagmus	Locomotor ataxia	Cerebellar necrosis
NE CON	Constipation	None or no change	Mild	Moderate	Severe, obstipation	Ileus >96hrs
NE COR	Cortical (incl drowsiness)	None	mild somnolence	Moderate somnolence	Severe somnolence, confusion, disorientation, hallucinations	Coma, seizures, toxic psychosis
NE DIZ	Dizziness* (incl light headedness)	None	Mild	Moderate	Severe (incl fainting)	-
NE EXT	Extrapyramidal / Involuntary movement*	None	Mild agitation (incl restlessness)	Moderate agitation	Tonicollia, oculogyric crisis, severe agitation	-
NE HED	Headache	None	Mild	Moderate or severe but transient	Unrelenting and severe	-
NE HER	Altered hearing	None or no change	Asymptomatic, hearing changes on audiometry only	Tinnitus, symptomatic hearing changes not req hearing aid or trt	Hearing changes interfering with function but correctable with hearing aid or trt	Hearing changes or deafness not correctable
NE INS	Insomnia*	None	Mild	Moderate	Severe	-
NE MOO	Mood	No change	Mild anxiety or depression	Moderate anxiety or depression	Severe anxiety or depression	Suicidal ideation
NE MOT	Motor	None or no change	Subjective weakness; no objective findings	Mild objective weakness without significant impairment of function	Objective weakness with impairment of function	Paralysis
NE PAI	Neurologic pain* (eg: jaw pain)	None	Pain, but no treatment req	Pain controlled with non-opioids	Pain controlled with opioids	Uncontrollable pain
NE PER change*	Personality	No change	Change, not disruptive to pt or family	Disruptive to pt or family	Harmful to others or self	Psychosis
NE SEN	Sensory	None or no change	Mild paresthesias, loss of deep tendon reflexes (incl tingling)	Mild or moderate objective sensory loss; moderate paresthesias	sensory loss or paresthesias that interfere with function	-
NE VIS	Vision	None or no change	Blurred vision	-	symptomatic subtotal loss of vision	Blindness
NE OTH	Other*	None	Mild	Moderate	Severe	Life threatening

NCIC CTG EXPANDED COMMON TOXICITY CRITERIA						REVISED: 94-DEC-21
	GRADE	**0**	**1**	**2**	**3**	**4**
			OCULAR			
OC CAT	Cataract*	None	Mild	Moderate	Severe	-
OC CJN	Conjunctivitis/ Keratitis	None	Erythema or chemosis not req steroids or antibiotics	Req trt with steroids or antibiotics	Corneal ulceration or visible opacification	-
OC DRY	Dry eye	Normal	Mild	Req artificial tears	Severe	Req enucleation
OC GLA	Glaucoma	No change	-	-	Yes	-
OC PAI	Eye pain*	None	Pain, but no treatment req	Pain controlled with non-opioids	pain controlled with opioids	Uncontrollable pain
OC TEA	Tearing* (watery eyes)	None	Mild	Moderate	Severe	-
OC OTH	Other	None	Mild	Moderate	Severe	Life threatening
			OSSEOUS (BONE)			
OS PAI	Bone pain*	None	Pain, but no treatment req	Pain controlled with non-opioids	Pain controlled with opioids	Uncontrollable pain
OS OTH	Other* (eg: avascular necrosis)	None	Mild	Moderate	Severe	Life threatening
			OTHER			
OT OTH	Other	None	Mild	Moderate	Severe	Life threatening
		For toxicities which do not have an existing code, but do fit into an existing toxicity category, use 'other' variable in the appropriate toxicity category. Only toxicities which do not fit into existing categories should be coded OTHER OTHER (OT OTH).				
			PULMONARY			
PU CMD	Carbon Monoxide Diffusion Capacity (DLCO)*	>90% of pretreatment value	decrease to 76-90% of pre-trt	Decrease to 51-75% of pre trt	Decrease to 26-50% of pre-trt	Decrease to ≤25% of pre-trt
PU COU	Cough*	None	Mild	Moderate	Severe	-
PU EDE	Pulmonary Oedema*	None	-	Out-pat management	In-pat management	Req intubation
PU EFF	Pleural effusion* (non-malignant)	None	Mild	Moderate	Severe	Life threatening
PU FIB	Pulmonary fibrosis*	Normal	Radiographic changes, no symptoms	-	Changes with symptoms	-
PU HEM	Hemoptysis*	None	Mild, no transfusion	Gross, 1-2 units transfusion per episode	Gross, 3-4 units transfusion per episode	Massive, >4 units transfusion per episode
		Bleeding resulting from thrombocytopenia should be coded under BL HEM, not PU				
PU HIC	Hiccoughs*	None	Mild	Moderate	Severe	-
PU PAI	Pulmonary pain*	None	Pain, but no treatment req	Pain controlled with non-opioids	Pain controlled with opioids	Uncontrollable pain
PU PNE	Pneumonitis* (non-infectious)	Normal	Radiographic changes, symptoms do not req steroids	Steroids req	Oxygen req	Req assisted ventilation
PU SOB	Shortness of breath (SOB) (incl wheezing)	None or no change	Asymptomatic, with abnormallity in PFT's	Dyspnea on significant exertion	Dyspnea at normal level of activity, apnea without cyanosis	Dyspnea at rest, apnea with cyanosis
PU VOI	Voice changes* (incl hoarseness, loss of voice)	None	Mild	Moderate	Severe	-
PU OTH	Other*	None	Mild	Moderate	Severe	Life threatening
		Pneumonia is considered infection and not graded as pulmonary toxicity unless felt to be resultant from pulmonary changes directly induced by treatment				

NCIC CTG EXPANDED COMMON TOXICITY CRITERIA						REVISED: 94-DEC-21
	GRADE	0	1	2	3	4
SKIN						
SK ALO	Alopecia	No loss	Mild hair loss	Pronounced or total head hair loss	Total body hair loss	-
SK CHA	skin changes* (eg: photosensitivity)	None	Localised pigmentation changes	Generalised pigmentation changes or atrophy	Subcut fibrosis or localised shallow ulceration	Generalised ulcerations or necrosis
SK DES	Desquamation*	None	Dry desquamation	Moist desquamation	Confluent moist desquamation	-
SK DRY	Dry skin*	None	Mild	Moderate	Severe	-
SK FAC	Flushing* (eg: facial)	None	Mild	Moderate	Severe	-
SK HEM	Bruising/bleeding	None	Mild, no transfusion	Gross, 1-2 units transfusion per episode	Gross, 3-4 units transfusion per episode	Massive, >4 units transfusion per episode
		Bleeding resulting from thrombocytopenia should be coded under BL HEM, not SK				
SK LTO	Local Toxicity (reaction at IV site)	None	Pain	Pain and swelling, with inflammation or phlebitis	Ulceration	Plastic surgery indicated
SK NAI	Nail changes*	None	Mild	Moderate	Severe	-
SK PAI	Skin pain* (incl scalp pain)	None	Pain, but no treatment req	Pain controlled with non-opioids	Pain controlled with opioids	Uncontrollable pain
SK RAS	Rash/Itch* (not due to allergy) (incl recall reaction)	None or no change	Scattered macular or papular eruption or erythema that is asymptomatic	Scattered macular or papular eruption or erythema with pruritus or other associated symptoms	Generalised symptomatic macular, papular, or vesicular eruption	Exfoliative dermatitis or ulcerating dermatitis
SK OTH	Other*	None	Mild	Moderate	Severe	Life threatening
WEIGHT						
WT GAI	Weight Gain	< 5.0%	5.0-9.9%	10.0-19.9%	≥ 20.0%	-
WT LOS	Weight Loss	< 5.0%	5.0-9.9%	10.0-19.9%	≥ 20.0%	-

Any toxicity which causes death should be given Grade 5

* Denotes NCIC specific criteria.

APPENDIX J: ANN ARBOR STAGING CLASSIFICATION

Stage I

Involvement of a single lymph node region (I) or localised involvement of a single extralymphatic organ or site (IE).

Stage II

Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localised involvement of a single associated extralymphatic organ or site and its regional nodes with or without other lymph node regions on the same side of the diaphragm (IIE). NOTE: The number of lymph node regions involved may be indicated by a subscript (e.g., II3)

Stage III

Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localised involvement of an extralymphatic organ or site (IIIE) or by involvement of the spleen (IIIS), or both (IIISE).

Stage IV

Disseminated (multifocal) involvement of one or more extralymphatic organs with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (non-regional) nodal involvement.

Ann Arbor Staging Criteria (AJCC, Manual for Staging Cancer, 5th Ed., 1997)

APPENDIX K: FORMS

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A Clinicopathological study in Burkitt's and Burkitt-like Non Hodgkin's Lymphoma

LY10/1

REGISTRATION FORM

Use block capitals when completing the form

Please complete before registration and return top copy to:
LY10 Trial, MRC Clinical Trials Unit, 222 Euston Road, London NW1 2DA

First name:

Surname

Date of Birth: dd / mm / yyyy

Sex:
1 = Male
2 = Female

Consultant:

Hospital:

Hospital number:

Pathologist:

Pathology number:

ELIGIBILITY FOR STUDY

Note: tick box **1a** for patients entering the **clinical and pathological study** or tick box **1b** for patients entering the **pathological study** only.

Eligibility for clinical and pathological study

1a ☐ Please confirm that ALL eligibility criteria have been fulfilled by ticking the box

1. Local confirmed diagnosis of Burkitt's lymphoma, Burkitt-like NHL, Burkitt's Leukaemia or B-cell NHL with 100% Ki67 staining
2. Age 16+ years
3. HIV negative
4. No previous radiotherapy or chemotherapy (other than pre-induction chemotherapy)
5. Maximum of 1 cycle of pre-induction chemotherapy
6. Register within 7 days of starting the first CODOX-M cycle
7. Written informed consent obtained

Eligibility for Pathological study only

1b ☐ Please confirm that ALL eligibility criteria have been fulfilled by ticking the box

1. Local confirmed diagnosis of Burkitt's lymphoma, Burkitt-like NHL, Burkitt's Leukaemia or B-cell NHL with 100% Ki67 staining
2. HIV negative
3. Written informed consent obtained

DIAGNOSTIC CRITERIA

2 dd / mm / yyyy **Date of diagnostic biopsy**

3 **LDH**
1 = Normal
2 = Raised

4 **WHO performance status**
See appendix B for full classification
0 = Normal activity
1 = Restricted in strenuous activity
2 = Self care, but unable to work
3 = Only limited self care
4 = Completely disabled

5 **Ann Arbor stage**
See appendix J for full classification
1 = I
2 = II
3 = III
4 = IV

6 **Number of extra nodal sites of disease**
1 = 0 or 1
2 = >1

PATIENT'S RISK GROUP

Please use the scoring system below to calculate the patient's risk group

☐ 0 = Normal LDH level
1 = Raised LDH level

☐ 0 = WHO performance status 0-1
1 = WHO performance status 2-4

☐ 0 = Ann Arbor stage I-II
1 = Ann Arbor stage III-IV

☐ 0 = Number of extra nodal sites 0 or 1
1 = Number of extra nodal sites > 1

☐ **Total**

1 Low Risk

3 **2 High Risk**

TO REGISTER PLEASE TELEPHONE THE MRC CLINICAL TRIALS UNIT (020 7670 4777)

N.B. dose reductions apply for patients over 65 years

7 ☐ **1** = Protocol A: low risk - protocol
(if patient aged >65 see protocol 13)
2 = Protocol B: high risk - protocol
(if patient aged >65 see protocol 14)
3 = Pathology study and follow-up only

Trial number

Date of registration dd / mm / yyyy

Signed _____ **Date** _____

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LY10/2

ON-STUDY FORM

Use block capitals when completing the form

Please complete before registration and return top copy to:
LY10 Trial, MRC Clinical Trials Unit, 222 Euston Road, London NW1 2DA

Patient initials: _____ **Trial number** _____

Hospital: _____ **Date of Birth:** dd / mm / yyyy

Hospital number: _____

EXTRA NODAL SITES OF DISEASE

(code 0 = Not involved, 1 = Involved or 2 = Primary)

1 **Ileocaecal**
2 **Stomach**
3 **Waldeyer's ring**
4 **Central nervous system**
5 **Other, specify** _____

6 **Marrow** If bone marrow is involved specify the percentage of aspirate involved
7 _____ . _____ **% Aspirate involved**
8 _____ **x 10^9/l Absolute circulating lymphoma cell count**

CENTRAL NERVOUS SYSTEM

(code 0 = Not involved, 1 = Involved or 9 = Not done)

9 **Intra-cerebral**
10 **Cranial Nerve Palsy**
11 **Extradural**
12 **Positive CSF**
13 **Other, specify** _____

OTHER DETAILS

14 _____ **cm Height of patient**
15 **B - Symptoms**
0 = No
1 = Yes

STAGING INVESTIGATIONS

(code 0 = Not involved, 1 = Involved or 9 = Not done)

16 **Chest X-Ray**
17 **Ultrasound abdomen/pelvis**
18 **CT scan chest**
19 **CT scan abdomen/pelvis**
20 **Other, specify** _____

BIOCHEMICAL PROFILE

21 _____ **g/l Albumin**
22 _____ **IU/l LDH**

Normal range for LDH

23 _____ **IU/l LDH Higher Limit**

PRE-INDUCTION CHEMOTHERAPY

24 **Was pre-induction chemotherapy given?**
0 = No
1 = CHOP, specify percentage dose given
2 = COP
3 = Other, specify _____

25 dd / mm / yyyy **Date pre-induction chemotherapy started**

26 _____ . _____ **% Dose**

Signed _____ **Date** _____

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LY10/3

TREATMENT FORM

Use block capitals when completing the form

Please complete AFTER EVERY CYCLE of protocol treatment and return top copy to:
LY10 Trial, MRC Clinical Trials Unit, 222 Euston Road, London NW1 2DA

Patient initials: ______ **Trial number** ______

Hospital: ______ **Date of Birth:** __ / __ / ____ (dd / mm / yyyy)

Hospital number: ______

1 __ / __ / ____ (dd / mm / yyyy) **Date cycle started**

3 ☐ **Cycle number**

2 ☐ **Chemotherapy cycle given**
1 = CODOX-M
2 = IVAC
3 = Other, specify ______

4 ___ . _ **kg Weight**

Complete either CODOX-M or IVAC with total dose of drug given

CODOX-M

5 ____ . _ **mg Cyclophosphamide**
6 _ . _ **mg Vincristine**
7 ___ . _ **mg Doxorubicin**
8 ___ **mg Cytarabine (IT)**
9 ____ . _ **mg Methotrexate (IV)**
10 __ **mg Methotrexate (IT)**
11 ____ . _ **mg Leucovorin (IV)**
12 __ **mg Leucovorin (PO)**

Other, specify ______

IVAC

13 ___ . _ **mg Etoposide**
14 __ . _ **g Ifosfamide**
15 _____ . _ **mg Mesna**
16 __ . _ **g Cytarabine (IV)**
17 __ **mg Methotrexate (IT)**
18 __ **mg Leucovorin (PO)**

Other, specify ______

FULL BLOOD COUNTS ON DAY 1 OF THE CYCLE

19 __ / __ / ____ (dd / mm / yyyy) **Date of bloods**

20 ___ **g/l Haemoglobin**
21 __ . _ **x 10^9/l Total WBC**
22 __ . _ **x 10^9/l Neutrophils**
23 __ . _ **x 10^9/l Lymphocytes**
24 ___ **x 10^9/l Platelets**

25 ☐ **Major reason for dose reduction**
0 = No dose reduction
1 = Leucopenia
2 = Thrombocytopenia
3 = Mucositis
4 = Neutropenic fever
5 = Other, specify ______

26 ____ . _ **mg G-CSF (Total dose)**

27 ☐ **Type of G-CSF used**
1 = Lenograstim
2 = Filgrastim

WORST TOXICITY
(Please use NCIC CTG grades in Appendix I of the protocol, 9 = not assessed)

28 ☐ **WBC (BL WBC)**
29 ☐ **Neutropenic fever (IN NEU)**
30 ☐ **Neutrophil count (BL GRA)**
31 ☐ **Platelets (BL PLT)**
32 ☐ **Other, specify** ______
33 ☐ **Mucositis (GI STO)**
34 ☐ **Diarrhoea (GI DIA)**
35 ☐ **Cardiac function (CD FUN)**
36 ☐ **Conjunctivitis (OC CJN)**
37 ☐ **Neuropathy, sensory (NE SEN)**
38 ☐ **Neuropathy, motor (NE MOT)**
39 ☐ **Renal function (GU CRE)**

Signed ______ **Date** ______

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LY10/4

RESPONSE FORM

Use block capitals when completing the form

Please complete 3 to 4 weeks post treatment and return top copy to:
LY10 Trial, MRC Clinical Trials Unit, 222 Euston Road, London NW1 2DA

Patient initials: ______ **Trial number** ______

Hospital: ______ **Date of Birth:** __ / __ / ____ (dd / mm / yyyy)

Hospital number: ______

POST CHEMOTHERAPY ASSESSMENT

1 __ / __ / ____ (dd / mm / yyyy) **Date of assessment**

2 ☐ **Number of cycles of protocol chemotherapy given**

3 ☐ **Reason for terminating protocol chemotherapy**
1 = Protocol treatment completed
2 = Disease progression
3 = Excessive toxicity, specify ______
4 = Patient choice
5 = Death - complete death form
6 = Other, specify ______

4 ☐ **Overall response**
1 = Complete response
2 = Partial response
3 = No response
4 = Progressive disease, if yes give the date __ / __ / ____ (dd / mm / yyyy) **Date of first progression**

RADIOTHERAPY

5 ☐ **Was radiotherapy given?**
0 = No
1 = Yes, (if yes complete all this section)

Specify radiotherapy fields

6 ______

7 __ . _ **Gy Total dose**

8 __ **Number of fractions given**

9 __ / __ / ____ (dd / mm / yyyy) **Date radiotherapy started**

10 __ / __ / ____ (dd / mm / yyyy) **Date radiotherapy finished**

Signed ______ **Date** ______

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LY10/5

TREATMENT/RESPONSE FORM
FOR PATHOLOGICAL STUDY ONLY

Use block capitals when completing the form

Please complete 3 to 4 weeks post treatment for patients on the **PATHOLOGICAL STUDY ONLY** and return top copy to:
LY10 Trial, MRC Clinical Trials Unit, 222 Euston Road, London NW1 2DA

Patient initials: |_|_|_|_|_|

Trial number [ ][ ][ ][ ]

Hospital: |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|

Date of Birth: [ ][ ] / [ ][ ] / [ ][ ][ ][ ]
dd mm yyyy

Hospital number: |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|

CHEMOTHERAPY

1 [ ] **Did the patient receive any chemotherapy?**
0 = No
1 = Yes

2 [ ][ ] / [ ][ ] / [ ][ ][ ][ ] **Date chemotherapy started**
dd mm yyyy

3 [ ][ ] / [ ][ ] / [ ][ ][ ][ ] **Date chemotherapy finished**
dd mm yyyy

What chemotherapy was given?

4 |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|

5 [ ] **Number of chemotherapy cycles given**

6 [ ] **Reason for terminating chemotherapy**
1 = Protocol treatment completed
2 = Disease progression
3 = Excessive toxicity, specify |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|
4 = Patient choice
5 = Death - complete death form
6 = Other, specify |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|

RADIOTHERAPY

7 [ ] **Was radiotherapy given?**
0 = No
1 = Yes, (if yes complete all this section)

Specify radiotherapy fields

8 |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|

9 [ ][ ] . [ ] **Gy Total dose**

10 [ ][ ] **Number of fractions given**

11 [ ][ ] / [ ][ ] / [ ][ ][ ][ ] **Date radiotherapy started**
dd mm yyyy

12 [ ][ ] / [ ][ ] / [ ][ ][ ][ ] **Date radiotherapy finished**
dd mm yyyy

RESPONSE

13 [ ] **Overall response**
1 = Complete response
2 = Partial response
3 = No response
4 = Progressive disease, if yes give the date [ ][ ] / [ ][ ] / [ ][ ][ ][ ] **Date of first progression**
dd mm yyyy

Signed ______________________ **Date** ______________________

8287584462

CANCER RESEARCH UK

A Clinicopathological study in Burkitt's and Burkitt-like Non Hodgkin's Lymphoma

LY10/6

FOLLOW-UP FORM

Use block capitals when completing the form

Please complete after all re-evaluation time points as specified in the protocol (Section 12) and return top copy to:
LY10 Trial, MRC Clinical Trials Unit, 222 Euston Road, London NW1 2DA

Patient initials: __________ **Trial number** ______

Hospital: __________ **Date of Birth:** __ / __ / ____ (dd / mm / yyyy)

Hospital number: __________

Section A

1 __ / __ / ____ (dd / mm / yyyy) **Date of assessment**

2 ☐ **Current status**
1 = Alive, disease free
2 = Alive, residual lesions present (stable, non-progressing)
3 = Alive, progressive disease
4 = Died

3 ☐ **WHO performance status**
See appendix B for full classification

Section B

RELAPSE/PROGRESSION

4 ☐ **Has the patient progressed since last follow-up?**
0 = No (if no go to section C)
1 = Yes

5 __ / __ / ____ (dd / mm / yyyy) **Date of progression since last assessment**

SITE OF PROGRESSION
(Code as 0 = No and 1 = Yes)

6 ☐ **Nodal disease**

7 ☐ **Marrow**

8 ☐ **Other, specify** __________

9 ☐ **Central nervous system**
0 = No
1 = CSF
2 = Brain
3 = Extradural
4 = Cranial nerve

Section C

TOXICITY
(Please use NCIC CTG grades and codes in Appendix I of the protocol)

	Grade	CTG code	
10	☐	☐☐☐☐☐	**Neurologic**
11	☐	☐☐☐☐☐	**Cardiovascular**
12	☐	☐☐☐☐☐	**Other, specify** __________

13 ☐ **Has the patient become pregnant or caused a pregnancy since the last recorded follow-up visit?**
0 = No
1 = Yes

Section D

14 ☐ **Has the patient received any treatment since last follow-up?**
0 = No
1 = Yes

16 __ / __ / ____ (dd / mm / yyyy) **Date treatment started**

17 __ / __ / ____ (dd / mm / yyyy) **Date treatment finished**

15 ☐ **Treatment since last assessment**
1 = Palliative
2 = Radiotherapy
3 = Chemotherapy
4 = Chemotherapy and allogeneic transplant
5 = Chemotherapy and stem cell transplant
6 = Other, specify __________

Specify chemotherapy (for 3–5) __________

Signed __________ **Date** __________

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LY10/7

CANCER RESEARCH UK

LOCAL PATHOLOGY FORM

Use block capitals when completing the form

This form is to be completed by the local pathologist

The top copy (yellow) should be returned to:
LY10 Trial, MRC Clinical Trials Unit, 222 Euston Road, London NW1 2DA

The second copy (pink) should be sent with the samples to:
Haematological Malignancy Diagnostic Service, General Infirmary, Leeds, LS1 3EX

Patient initials: |_|_|_|_|_|

Trial number [ ][ ][ ][ ]

Hospital: |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|

Date of Birth: [ ][ ] / [ ][ ] / [ ][ ][ ][ ] (dd / mm / yyyy)

Hospital number: |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|

1 **Pathologist:** |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|

2 **(a)** [ ][ ] / [ ][ ] / [ ][ ][ ][ ] (dd / mm / yyyy) **Date of specimen (a)** |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_| **Lab No.**

3 **(b)** [ ][ ] / [ ][ ] / [ ][ ][ ][ ] (dd / mm / yyyy) **Date of specimen (b)** |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_| **Lab No.**

FRESH TISSUE

4 [ ] **What fresh tissue was obtained?**
1 = Lymph node
2 = Bone marrow
3 = Lymph node & bone marrow
4 = Other, specify |_|_|_|_|_|_|_|_|_|_|_|_|_|_|

Where is the fresh tissue stored?

8 |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|

5 [ ] **What samples are being sent for central review?**
1 = Lymph node
2 = Bone marrow
3 = Lymph node & bone marrow
4 = Other, specify |_|_|_|_|_|_|_|_|_|_|_|_|_|_|

9 [ ] **How is the fresh tissue stored?**
1 = Frozen tissue blocks
2 = Frozen cell suspension
3 = Extracted DNA
4 = Extracted RNA

SITE OF BIOPSY

6 [ ] **Bone marrow (aspirate and trephine)**
0 = No
1 = Yes

10 [ ] **Lymph node**
0 = No
1 = Yes

7 [ ] **Other**
0 = No
1 = Yes, specify |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|

RESULTS - PLEASE SEND COPIES OF THE FLOW CYTOMETRY AND CYTOGENETICS DATA

11 [ ] **Flow cytometry phenotype**
9 = Not done
1 = Yes, specify |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|

17 [ ][ ][ ] . [ ] **% Ki67(tissue)**

12 [ ] **Cytogenetics**
9 = Not done
1 = Yes, specify |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|

Which lab did the cytogenetics?

13 |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|

14 |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_| **Cytogenetics reference number**

HISTOLOGY FIXATION

15 [ ][ ][ ] **days, Time in fixative**

16 [ ] **Type of fixative used?**
1 = 10% Neutral buffered formalin
2 = 10% Non-buffered formalin
3 = Other, specify |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|

DIAGNOSIS

18 [ ] **1 = Burkitt's Lymphoma**
2 = Burkitt-like Non-Hodgkin's Lymphoma
3 = Burkitt's Leukaemia
4 = B-cell NHL with 100% Ki67 staining

Signed ____________________ **Date** ____________________

3860633852

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LY10/8

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DEATH FORM

Use block capitals when completing the form

This form should be completed after the patient's death and return top copy to:
LY10 Trial, MRC Clinical Trials Unit, 222 Euston Road, London NW1 2DA

Patient initials:

Trial number

Hospital:

Date of Birth: dd / mm / yyyy

Hospital number:

1 dd / mm / yyyy **Date of death**

2 **Major cause of death**
1 = Disease related

2 = Treatment related, specify

3 = Coincidental disease, specify

3 **Secondary cause of death**
1 = Disease related

2 = Treatment related, specify

3 = Coincidental disease, specify

4 **Post-mortem performed?**
0 = No
1 = Yes

5 **Place of death**
1 = Home
2 = Hospital
3 = Hospice
4 = Other, specify

Signed **Date**