

MULTI-CENTRE RESEARCH ETHICS COMMITTEES

APPLICATION FORM

For official MREC Use Only

MREC/ / /

For official MREC Use Only

INSTRUCTIONS: Please complete in type. Please place a circle around Yes/No options as appropriate. A version of this form is available on disc from the administrator of the MREC.

It is essential that this form is completed fully and sent with relevant enclosures. **You should not simply refer to the protocol but complete the form with the information requested.** Please refer to the accompanying Guidance Notes when completing the form and complete the checklist before sending. Where a question is not applicable it is important to make this clear and not to leave it blank. **It is important that the language used in this application is clear and understandable to lay members.** All abbreviations should be explained.

Applicant's Checklist

Please indicate if the following have been enclosed by underlining or placing a circle round Yes/No/Not applicable options.

Application Form (one copy only)	Yes	
Full protocol with reference details (six copies)	Yes	
Application Fee of £1000		Not applicable
Research subject consent form with version number and date	Yes	
Research subject information sheet with version number and date	Yes	
Advertisement for research subjects		Not applicable
GP/consultant information sheet or letter	Yes	
Interview schedules for research subjects		Not applicable
Letters of invitation to research subjects		Not applicable
Questionnaire* Finalised/Not yet finalised		Not applicable
Researchers brochure or data sheet for all drugs (six copies)	Yes	
Statement regarding compensation arrangements (one copy only)		Not applicable
Principal Researcher c.v. (one copy only)	Yes	
CTX/CTC/DDX (one copy only)	Yes	
Annexe A**	Yes	
Annexe B***	Yes	
Annexe C****	Yes	

* Please indicate whether or not this is the final version

** Required if the study involves the use of a new medicinal product or medical device, or the use of an existing product outside the terms of its product licence. Annexe A is attached to the Application Form.

*** Required if the study includes the use of ionising, radioactive substances or X-Rays. Annexe B is attached to the Application Form.

**** Information concerning local researchers should always be given where possible at this stage. Annexe C is attached to the Application Form. Please make additional copies as necessary.

1. Short title of project (including any version dates):

MRC CLL V Trial

Full title: **THE VALUE OF AUTOGRAFTING IN YOUNGER PATIENTS WITH
HIGH RISK CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL)
A RANDOMISED PHASE III INTERGROUP TRIAL**

2. Principal researcher (who will be responsible for dealing with the MREC)

Surname: **Milligan**

Forename: **Donald**

Title: **Dr**

Present appointment of applicant:

Consultant Haematologist and Senior Lecturer

Qualifications: **BSc, MBChB, MD, FRCP, FRCPath.**

Address: Department of Haematology
Birmingham Heartlands Hospital
Birmingham
B9 5SS

Tel: 0121 424 43699

Fax: 0121 766 7530

E-Mail: d.w.milligan@bham.ac.uk

3. Senior researcher at LEAD centre (if different from above)

Surname:

Forename:

Title:

Present appointment:

Qualifications:

4. Who is sponsoring the study?

Contact name: **Dr Graham Cadwallader**
graham.cadwallader@headoffice.mrc.ac.uk

**Medical Research Council,
20 Park Crescent,
London W1B 1AL**

**Tel: 020 7636 5422
Fax: 020 7436 6179**

5. Drug Company Reference Number **N/A**

6. Will researchers be paid for taking part in the study? *No*

If so, will BMA guidelines (*Manual II.47* - see Guidelines) be followed? *Yes* *No*

If not, why not?

7. Proposed start date and duration of the study September 2001

8. What other researchers are/do you intend to be involved in this project? (Details of researchers added subsequently must be notified to the MREC)

Please use the form attached at Annexe C

The MRC are sponsoring the UK component of a European trial run by the Chronic Leukaemia Working party of the EBMT. Within the UK the collaborators will comprise those who already participate in trials run by the Leukaemia in Adults Working Party of the MRC. Details of centres participating in the MRC CLL IV and CLL Autograft Pilot study are attached in Annexe C.

*This section must be completed fully. A copy of the protocol should be enclosed with the application form, but it is **not** sufficient to complete questions by referring to the protocol.*

9. Aims and objectives of project (*Approx. 250 words*)

Chronic lymphocytic leukaemia is generally a condition of older people commoner in men. It is classically staged using the Binet scheme A,B, C. Patients with stage B and C disease have median survivals of 3-8 years. About 10% of patients are aged less than 55 and 20% are less than 65. The outlook for these younger patients is the same as for older patients. Standard therapy is with oral alkylating agents (usually chlorambucil) with or without prednisolone or combination chemotherapy (eg. cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone). More recently the purine analogues have been shown to have good activity in CLL, but although they may extend remission duration there is no compelling data to show that life is extended. In the last 5-10 years studies in Europe and the USA of high-dose chemo(radiotherapy) with bone marrow or stem cell rescue have shown that prolonged periods of clinical and molecular remission can be achieved in CLL by this technique and that autografting is relatively safe with a transplant related mortality of approximately 5%. This collaborative European trial, sponsored in the UK by the MRC, is designed to establish whether autografting in CLL will:-

- Extend survival
- Extend disease free survival
- Improve quality of life

10. Scientific background of study (*Approx. 250 words*)

There are now a number of single arm studies, including the recently closed MRC CLL Pilot Study conducted by the applicants, which demonstrate that the use of bone marrow ablation with high-dose cyclophosphamide and total body irradiation followed by stem cell rescue with peripheral blood stem cells or marrow stem cells results in a complete clinical remission in all patients with achievement of molecular remission in 70-80%. It is not clear if purging the autologous graft of residual CLL cells is of value (the recent CLL Pilot Study could demonstrate no advantage for purging). Molecular remissions are almost never achieved using standard chemotherapy but it is not yet clear if this deepening of remission status will improve overall survival or quality of life. In addition this trial will closely monitor the molecular responses of patients

undergoing an autograft to establish the pattern of minimal residual disease post-transplant.

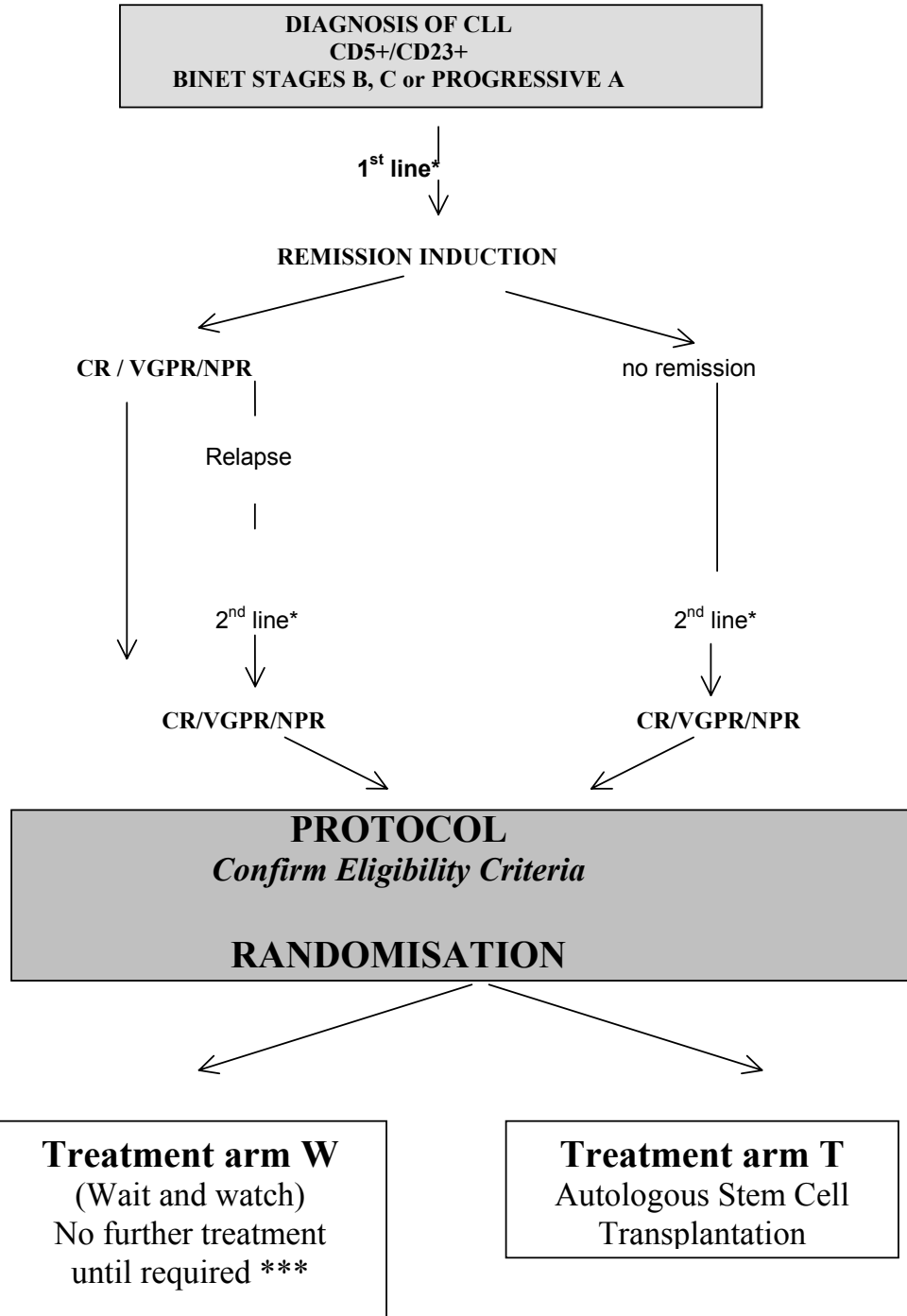
There is also some uncertainty about the best timing for those patients receiving an autograft – should it be after first response to initial therapy or subsequently? This question has been left to physician and patient choice but the randomisation will be stratified according to the timing of the transplant and the stage of disease.

In addition, although there might be some scientific validity in comparing autograft with no additional therapy, there was strong feeling across Europe that this would not be acceptable to patients and thus stem cells will be harvested from all patients after randomisation to be used for a late transplant in those not allocated an early autograft.

11. Brief outline of project (*Approx. 250 words*)

The trial is a randomised trial of high dose chemo-radiotherapy plus autologous stem cell rescue versus no further treatment conducted throughout Europe. The principal recruiting countries are likely to be the UK, Germany and France. Patients will be entered into the trial only after they have received chemotherapy which has resulted in the achievement of a “complete response”, “good partial response” or “nodular partial response” to standard induction chemotherapy. If patients fail to achieve a satisfactory response to frontline initial treatment they may be treated with a second-line schedule and will become eligible for entry if one of the above responses is obtained. The schema is shown below.

study design



* The treatment recommended before randomisation is agreed by each participant group (see section 6) although any therapy leading to CR, VGPR or NPR is acceptable

** Before any harvest is done

*** Harvest (PBPC and/or BM) is recommended

12. **Study design** (e.g. RCT, cohort, case control, epidemiological analysis)

Randomised clinical trial

13. Size of the study (including controls)

Will the study involve:

(a) **Human Subjects** *Yes*

i) **How many patients will be recruited?**

300

We anticipate (based on the earlier Pilot Study) that the UK will contribute approximately 125 patients to the overall trial.

ii) **How many controls will be recruited?**

0

iii) **What is the primary end point?**

1. overall survival
2. disease free survival

iv) **How was the size of the study determined?**

For patients having stage B, C or progressive A disease in the age group > 15 and ≤ 65 years, the progression-free survival (PFS) at 5 years after randomisation without further treatment can be expected to be approximately about 30 % at best. Applying autologous stem cell transplantation will hopefully lead to a PFS 5 years after randomisation of 50%. To detect a absolute difference of 20% using a two-sided significance level of 0.05 and a power of 0.90 requires 134 patients in each arm. So altogether about 270 patients have to be randomised.

v) **What is the statistical power of the study?**

90% chance of detecting a 20% improvement.

(b) **Patient Records** *No*

i) **How many records will be examined?**

ii) **How many control records will be examined?**

iii) **What is the primary end point?**

iv) **How was the size of the study determined?**

v) **What is the statistical power of the study?**

14. Scientific critique

Has the protocol been subject to scientific critique? If so, please give the following information:

If the critique formed part of the process of obtaining funding, please give the name and address of the funding organisation:

**Medical Research Council,
20 Park Crescent,
London W1B 1AL**

**Tel: 020 7636 5422
Fax: 020 7436 6179**

The Medical Research Council Board banded this proposal as alpha rating. The MRC Review included : CLL Working Group, Adult Leukaemia Working Party, Leukaemia Steering Committee, Molecular and Cellular Medicine Board and Health Services and Public Health Board.

If the critique took place as part of an internal process, please give brief details:

If no critique has taken place, please explain why, and offer justification for this:

If you are in possession of any referees' or other scientific critique reports relevant to your proposed research, please forward copies with your application form.

Referee reports enclosed

SECTION 3

Recruitment of subjects

15. How will the subjects in the study be:

i) **selected?**

All patients with a diagnosis of CLL fulfilling the entry criteria will be entered by the haematologist managing their care by telephoning the Clinical Trial Service Unit to randomise once consent has been obtained.

ii) **recruited?**

By the managing haematologist

iii) **what inclusion criteria will be used?**

- B CLL CD5+/CD23+,
 - Binet stage B and C, or progressive A (lymphocytosis $>30 \times 10^9/l$, haemoglobin $<10g/l$, lymphocyte doubling time < 12 months and diffuse infiltration of bone marrow) *provided they have reached:-*
 - Complete Remission (CR)
- or**
- Very Good Partial Remission (VGPR)
- or**
- Nodular Partial Remission (NPR) assessed by bone marrow biopsy after first or second line treatment
 - Written informed consent.

iv) what exclusion criteria will be used?

- Patients aged less than 18
- WHO Performance status > 2
- T CLL, NHL, Richter syndrome
- Rai stages 0-II, Binet stage A (stable)
- Known HIV seropositivity.
- Inadequate renal or liver function, i.e. creatinine and bilirubin >1.5 times the upper limit of normal
- Patients with severe heart failure, requiring diuretics or ejection fraction of less than 50%
- Patients with severe concomitant neurological or psychiatric disease
- Pregnancy /lactation
- Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.
- Patients will be excluded if an allograft is planned

Definitions

Complete Remission

Complete Remission (CR) is defined by a bone marrow containing < 30% lymphocytes (normal immunophenotype) and a cellularity of at least 20% with maturation of all cell lines (including an haemoglobin which should be >11 g/dl, a neutrophil count > $1.5 \times 10^9/l$ and platelets more than $100 \times 10^9/l$), and a blood lymphocytosis < $5 \times 10^9/l$.

Extramedullary leukemia, such as CNS involvement, leukaemic infiltration of the skin, hepatosplenomegaly or lymphadenopathy exceeding 1.5 cm dimension should not be present. All CR criteria, should be present at the time of randomisation.

Very Good Partial Remission (VGPR) or Nodular Partial Remission (NPR)

A VGPR is characterised by a bone marrow containing < 50% lymphocytes, with a blood lymphocytosis of < $5 \times 10^9/l$, haemoglobin >11 g/dl, platelets > $100 \times 10^9/l$, neutrophils > $1.5 \times 10^9/l$ and a decrease of lymph nodes by at least 50%.

A **NPR** is characterised by the same parameters than VGPR with nodular infiltration of lymphocytes in bone marrow assessed by bone marrow biopsy.

16. How will the control subjects group (if used) be: *(Type N/A if no controls)*

i) selected? N/A

ii) recruited?

iii) what inclusion criteria will be used?

iv) what exclusion criteria will be used?

17. Will there be payment to research subjects of any sort? *No*

If yes, how much per subject and for what?

18. Is *written* consent to be obtained?

Yes

If yes, please attach a copy of the consent form to be used.

If no written consent is to be obtained, please justify.

19. How long will the subject have to decide whether to take part in the study?

If less than 24 hours please justify.

28 days

20. Please attach a copy of the written information sheet or letter to be given to the subject.

MRC CLL5 Patient information sheet

Version 2, 26 Sept 2001

A Medical Research Council prospective randomised study to compare autologous stem cell transplant versus no further treatment in patients with high risk chronic lymphocytic leukaemia who have achieved a good response to treatment

Introduction

You are being asked to take part in a multi-centre randomised trial that is being conducted in many hospitals throughout the UK. It is run through the Medical Research Council and has been subject to ethical approval by your local hospital. This UK trial is part of a larger study taking place across Europe which is co-ordinated by the European Bone Marrow Transplant Group.

Before you decide whether or not 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.

Background

Chronic lymphocytic leukaemia (CLL) is the most common adult leukaemia in western countries. It is a disease that affects the blood, lymph glands and bone marrow. You have high risk CLL which means that your life expectancy is shorter than it is for people without CLL. You have had a good response to treatment, but chemotherapy only rarely makes all the biological signs of the disease disappear. The current standard is that no further treatment should be given now even though some of these signs may still be present. It is very likely that the disease will recur at some point and autologous stem cell transplantation (a transplant using cells from your own body rather than from a donor) is often given then, as it can lead to the disappearance of all biological signs of the disease. With an autologous transplant certain cells in your own blood (called stem cells) are collected. You are then given high doses of chemotherapy and radiotherapy to destroy the remaining traces of leukaemia in your body. This also damages your body's healthy cells, but the collected cells are transplanted back into your bone marrow to help it recover. Currently we do not know if it would

benefit more patients if autologous stem cell transplantation was given at the earlier stage that you are now at, rather than waiting until the CLL has progressed.

This trial is a comparison between no further treatment at present and an autologous stem cell transplant. Whether or not you receive a transplant will be selected by a process called randomisation. That is, it will not be chosen by you or your doctor but by a computer and it is like the toss of a coin. This is to prevent bias in the results of the trial. You have a fifty-fifty chance of being put in the autologous transplant group. We need about 300 patients with high risk CLL to participate in the trial for us to be able to tell reliably if autologous transplantation at this stage makes a difference to survival. Patients in the “no further treatment at present” group can still receive an autologous transplant at a later stage.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide to take part you will be asked to sign a consent form and given a copy of both it and this information sheet to keep. If you decide to take part you are still free to change your mind or withdraw at any time and without giving any reason. This will not affect the standard of treatment or care you receive. Your legal rights are not affected by giving your consent to take part in this study.

What does the trial involve for me?

If you agree to take part in this study you will be asked to have a clinical examination, blood tests, a chest x-ray, a heart function test and tests to see how well your CLL is being controlled (blood tests and a bone marrow biopsy).

You will then be randomised to either autologous transplantation or simple surveillance of the disease. After randomisation you will have a course of chemotherapy and we will remove stem cells from your blood (called harvesting) ready for use in an autologous transplant. This will be carried out even if you are put in the no further treatment group, for use if your disease progresses. In all cases your doctor will need to see you regularly to monitor your disease. A clinical examination, and blood tests will be done at each visit, which should be every 4 months in the first year and then every six months for the two following years. If you have a transplant then a bone marrow sample will also be needed every 4 months in the first year and then at six month intervals. Some of the blood and bone marrow samples will be used for medical research. You will also be asked to fill in a quality of life form at entry into the trial and at 4, 8, 12, 24, 36 and 48 months after this. It only takes a few minutes to complete and gives us valuable information about how your every day activities are affected by your disease and treatment.

	Randomisation	4 mths	8 mths	1 year	18 mths	2 years	30 mths	3 years	4 years
Blood test	Y	Y	Y	Y	Y	Y	Y	Y	Y
Bone marrow*	Y	Y*	Y*	Y*	Y*	Y*	Y*	Y*	Y*
Quality of life form	Y	Y	Y	Y		Y		Y	Y

* Bone marrow samples other than the first one are requested only from patients receiving transplant.

What are the possible side effects?

The chemotherapy that you have already received has some side effects. The most common effects are

- a reduction in white blood cells which can be accompanied by fever and may require an antibiotic treatment
- a reduction in red blood cells (anaemia) which can cause fatigue and may require blood transfusion
- a reduction in blood platelets which may cause bleeding and require transfusions of platelets

The other side effects that can occur are nausea, vomiting, sores and problems with sensitivity in the lower limbs. There is a high risk that you will temporarily lose your hair.

Autologous transplantation and the high dose chemo- and radiotherapy that precede it also have side effects similar to those listed above, most common is an increase in the risk of infection both during and after the procedure. Irritation to the lining of the mouth and gullet is common (mucositis) and lasts about 7 days. The transplant will only be carried out in centres experienced in this type of treatment. Normally the blood count will recover in 14 days and patients can expect to be in hospital about three weeks for the autograft procedure. There is also a risk that transplantation can lead to death. In CLL the risk could be as much as 10%.

After autologous transplantation there is a high risk of permanent sterility therefore men will be given the opportunity to have sperm frozen. At present there is no generally available method for freezing the eggs of women although it is sometimes possible to freeze embryos. Your doctor will discuss these issues with you. It is possible that if a woman is pregnant when given a transplant it will harm the unborn child. Pregnant women must not therefore take part in this study, nor should women who are breast feeding as this may also be harmful to the child. Women who are at risk of pregnancy may be asked to have a pregnancy test before taking part to exclude the possibility of pregnancy. Women who could become pregnant must use an effective contraceptive during the course of this study. Effective contraceptives include the pill, barrier methods (e.g. condoms), hormonal implants, contraceptive injections, intrauterine devices and sterilisation. Any woman who finds that she has become pregnant while taking part in the study should tell her research doctor immediately. Women of childbearing age who receive a transplant will usually find that their periods stop after the transplant and hormone replacement treatment will be given if indicated.

Will my taking part in this study be kept confidential?

Your general practitioner will be informed of your treatment with your permission. It may be necessary for your records to be inspected by regulatory bodies. All personal information which is collected about you during the course of the research will be kept strictly confidential and will not be seen by anyone not involved in the study. You will not be identified in any report or publication.

For further information please contact:

Dr Don Milligan on 0121 424 3699

or

Multi-Centre Research Ethics Committees Application Form - February 1998

MRC CLL 5 trial version 2 26 September 2001

Given as an example: each hospital will provide the corresponding local information

Thank you for considering taking part in this study.

Patient consent form

Study Title: MRC CLL5 - A Medical Research Council prospective randomised study to compare autologous stem cell transplant versus no further treatment in patients with high risk chronic lymphocytic leukaemia who have achieved a good response to treatment

	Yes	No
I have read the patient information sheet for this trial and have received a copy to keep.	<input type="checkbox"/>	<input type="checkbox"/>
I have been given the opportunity to ask questions about the trial and have received satisfactory answers to all of my questions.	<input type="checkbox"/>	<input type="checkbox"/>
I am aware 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.	<input type="checkbox"/>	<input type="checkbox"/>
I accept that some of the blood and bone marrow samples taken may be used for biomedical research.	<input type="checkbox"/>	<input type="checkbox"/>
I give permission for responsible individuals from the trial research team and regulatory authorities to review my medical records.	<input type="checkbox"/>	<input type="checkbox"/>
I understand that information which identifies me will be kept confidential to those concerned with my care and the trial research team.	<input type="checkbox"/>	<input type="checkbox"/>
I give permission for the anonymised information provided for the trial to be used in future medical research.	<input type="checkbox"/>	<input type="checkbox"/>
I agree to take part in the above study	<input type="checkbox"/>	<input type="checkbox"/>

Patient:

Name: Signature Date:
(Name In Block Letters)

Investigating doctor:

Name: Signature Date:
(Name In Block Letters)

Witness:

Name: Signature Date:
(Name In Block Letters)

Appendix VIII

SERIOUS ADVERSE EVENT REPORT FORM

In this trial it is important that *unexpected* serious adverse events are reported immediately to the principal investigators. **Serious adverse events** are those which are:-

- life threatening
- delay discharge from hospital
- associated with congenital abnormality

DESCRIPTION OF ADVERSE EVENT

SignatureDate

NamePosition

Please fax to :-

Dr D W Milligan fax 0121 766 7530

or

Professor D Catovsky fax 020 7351 6420

21. Have any special arrangements been made for subjects for whom English is not a first language? *Yes*

If yes, give details.

Patients whose first language is not English will not be excluded from taking part. In the UK hospital translators will be used to help explain the trial to patients whose first language is not English.

If no, please justify.

22. Will any of the subjects or controls be from one of the following vulnerable groups?

Children under 18 (16 in Scotland)	No
People with learning difficulties	No
Unconscious or severely ill	No
Other vulnerable groups e.g. mental illness, dementia	No

If yes, please specify and justify:

23. What special arrangements have been made to deal with the issues of consent for the subjects above? (Please see Guidelines.) N/A

-
24. **Does the study involve the use of a new medicinal product or medical device, or the use of an existing product outside the terms of its product licence?** *(Please see Guidelines.)* Yes

If yes, please complete Annexe A of the Application Form.

25. **Will any ionising or radioactive substances or X-Rays be administered?** Yes

(NB Please ensure information in Question 14 includes exclusion criteria with regard to ionising radiation if appropriate.)

If yes, please complete Annexe B of the Application Form.

26. **Please list those procedures in the study to which subjects will be exposed indicating those which will be part of normal care and those that will be additional (e.g. taking more samples than would otherwise be necessary). Please also indicate where treatment is withheld as a result of taking part in the project.**

The additional investigations which will be performed as part of the study are as follows:

- bone marrow aspirate and biopsy every 4 months for the first year post transplant and then 6 monthly thereafter until relapse or for 5 years, whichever is the less.

Investigations as part of normal care for this group of patients include:

- Regular blood tests (5-10 ml blood every 4-12 weeks)
 - Bone marrow aspirate and biopsy (at diagnosis, to determine remission and at relapse)
 - CXR
 - CT scan or abdominal ultrasound.
-

27. Are there any potential hazards?

Yes

If yes, please give details, and give the likelihood and details of precautions taken to meet them, and arrangements to deal with adverse events.

Autologous stem cell transplantation causes severe bone marrow failure for between 12-25 days together with mucositis, vomiting and diarrhoea. Patients are vulnerable to infections and haemorrhage during the period of marrow failure. Following blood count recovery patients are usually well but there may be an increased incidence of herpes zoster infection (shingles) which is common in patients with chronic lymphocytic leukaemia anyway. Patients will be treated in the UK only in BCSH Level 3 transplant centres experienced in dealing with the supportive care needs of this cohort of patients. Within the recent UK CLL Pilot study for the MRC there has been one transplant related death (1/57; 1.7%) and the latest EBMT results suggest that the current mortality for peripheral blood stem cell transplants is 5%. Patients will be warned to be vigilant about the symptoms of shingles and to report immediately for treatment should they occur.

28. Is this study likely to cause any discomfort or distress?

Yes

If yes, please give details and justify.

Chemotherapy can cause bone marrow failure with the consequent risks of infection and haemorrhage. The principal unpleasant complications of high-dose therapy are nausea, vomiting, mucositis (sore mouth, throat and gullet) and infection causing fever. The symptoms may last up to 14 days. The side effects are justifiable because there is good evidence that this treatment is associated with the achievement of molecular remission in the majority of patients and this may translate into an improved outlook.

29. What particular ethical problems or considerations do you consider to be important or difficult with the proposed study?

Ideally this trial would have examined autograft versus no autograft. This randomisation was deemed to be unacceptable to patients and the trial will now

compare early autograft with the possibility of a deferred autograft for those in arm W. This overcomes the principal potential problem of lack of equipoise between the arms. The loss of fertility is an important issue for younger patients and this will be fully discussed with those at risk. For the majority of patients with chronic lymphocytic leukaemia this will not be relevant since the median age of patients in the MRC Pilot was 50 and families were complete.

30. Will information be given to the patient's General Practitioner? *Yes*

Please note: permission should always be sought from research subjects before doing this.

If yes, please enclose an information sheet/letter for the GP.

If no, please justify:

31. If the study is on hospital patients, will consent of all consultants whose patients are involved in this research be sought? *Yes*

If no, please justify:

Product liability and consumer protection legislation make the supplier and producer (manufacturer) or any person changing the nature of a substance, e.g. by dilution, strictly liable for any harm resulting from a consumer's (subject or patient) use of a licensed product.

32. Have arrangements been made to provide indemnity and/or compensation in the event of a claim by, or on behalf of, a subject for non negligent harm?

(Please indicate N/A if not applicable)

N/A

If yes, please give details of compensation arrangements with this application.

For NHS-sponsored research, HSG(96)48 reference no. 2 refers.

The study will adhere to the 1998 MRC guidelines for Good Clinical Practice in clinical trials. The MRC accepts responsibility for its sponsorship. Hospital indemnity applies as all researchers are employees of NHS trusts undertaking research on NHS patients. Local management approval of the research constitutes acceptance of liability for negligence and must be obtained before the trial starts.

For pharmaceutical company sponsored research, the company should confirm that it will abide by the most recent ABPI guidelines (*Manual V.14.1.1*)

33. In cases of equipment or medical devices, have appropriate arrangements been made with the manufacturer to provide indemnity?

(Please indicate N/A if not applicable)

N/A

If yes, please give details and enclose a copy of the relevant correspondence with this application.

34. Will the study include the use of any of the following?

Audio/video recording

No

Observation of patients

No

If yes to either:

i) How are confidentiality and anonymity to be ensured?

ii) What arrangements have been made to obtain consent for these procedures?

35. Will medical records be examined by research worker(s) outside the employment of the NHS?

Yes

If yes, please see Guidelines.

Only anonymised data (initials and DOB) will be provided to the EBMT Data Centre however both the EBMT and the Medical Research Council reserve the right to inspect source data as part of audit and in cases of data inconsistency.

36. What steps will be taken to safeguard confidentiality of personal records?

The clinical records (hospital notes) will be safeguarded in the usual way. The Clinical Record Forms only identify patients by initials and trial number. Data held on computer at the EBMT Data Management Centre at Leiden and at the CTSU in Oxford will be carefully safeguarded and password protected.

37. What steps will be taken to safeguard the information relating to specimens and the specimens themselves?

The specimens will be labelled with patient name and trial number. Once analysis is carried out the data will be recorded by trial number and initial only to ensure anonymity. Information on research tests will not be available to clinicians during the trial.

PLEASE ENSURE THAT YOU COMPLETE THE CHECKLIST ON THE FRONT COVER OF THE APPLICATION FORM AND ENCLOSE ALL RELEVANT ADDITIONAL DOCUMENTS.

DECLARATION

The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

I understand it is my responsibility to obtain management approval where appropriate from the relevant NHS body before the project takes place.

I agree to supply interim and final reports on the pro forma provided, and to advise my sponsor, the MREC from which approval was granted for this proposal and any local researchers taking part in the project of any adverse or unexpected events that may occur during this project.

Signature of Principal Researcher:

Date:.....

This form is to be used if the study involves the use of a new medical product or medical device, or the use of an existing product outside the terms of its produce licence.

- i) **Is a pharmaceutical or other commercial company arranging this trial?** *No*
If no, has approval of the licensing authority been obtained by means of a DDX? *Yes*
- ii) **Does the drug(s) or device have a product licence(s) for the purpose for which it is to be used?** *Yes*
If yes, please attach data sheet or equivalent.
- iii) **Is any drug or medical device being supplied by a company with a Clinical Trial Certificate or Clinical Trial Exemption?** *No*
Please attach CTC, CTX, or DDX.
- iv) **Has a CTC, CTX or DDX been applied for but not yet received?** *No*
If so, the application can be made but a valid CTX must be provided to the MREC before the research can proceed
- v) **Details of drugs to be used** *(Please complete the table below for each drug making additional copies of this page as necessary)*

Approved Name(s):

Generic Name:

1. Fludarabine phosphate
2. Cyclophosphamide
3. Carmustine
4. Etoposide
5. Cytosine
6. Melphalan
7. Vincristine
8. Doxorubicin
9. Prednisolone
10. Dexamethasone
11. Lenograstim

Trade Name:

1. Fludara
2. Endoxana
3. BiCNU
4. Etoposide, Etopophos
5. Cytarabine, Cytosar

6. Alkeran
7. Oncovin
8. Adriamycin
9. Prednisolone, Precortisyl Forte, Prednesol
10. Granocyte
11. Dexamethasone,

<u>Drug</u>	<u>Strength</u>	<u>Dosage and Frequency</u>	<u>Route</u>	<u>Duration of Course</u>
fludarabine	50 mg vials	25 mg/m ² every 4 weeks	iv	5 days (3 days plus cyclophosphamide)
	10mg tabs	40 mg/m ² every 4 weeks	oral	5 days plus 5 days oral cyclophosphamide
		24 mg/m ² every 4 weeks	oral	
cyclophosphamide	200 and 500 mg vials	250mg/m ² every 4 weeks	iv	3 days (plus fludarabine)
	50mg tabs	150mg/m ² every 4 weeks	oral	5 days plus fludarabin
		2g/m ²	iv	one day (stem cell mobilisation)
		60mg/m ²	iv	one day (autograft conditioning)
Carmustine	100 mg vial	300 mg/m ²	iv	One day
Etoposide	100 mg vial	100 mg/m ² bd	iv	4 days
Cytosine	100 mg vial	200 mg/m ² bd	iv	4 days
Melphalan	50 mg vial	140 mg/m ²	iv	One day
Cyclophosphamide	200 and 500 mg vials	750 mg/m ² every 4 weeks	iv	One day
Doxorubicin	10 and 50 mg vials	50 mg/m ² every 4 weeks	iv	One day
Vincristine	1 ml and 2 ml vials	1.4 mg/m ² (max 2 mg) every 4 weeks	iv	One day
prednisolone	5mg and 25 mg tabs	100mg every 4 weeks	oral	5 days
Dexamethasone		24 mg	oral	10 days
Carmustine		60 mg/m ²	iv	1 day
Etoposide	100 mg vial	75 mg/m ²	iv	4 days
Cytosine	100 mg vial	200 mg/m ²	iv	4 days
Melphalan	50 mg vial	20 mg/m ²	iv	1 day
Lenograstim	105 and 263 microgram vial	150 mg/m ²	sc	8 days

- vi) **When Drugs not listed in the British National Formulary are being used, applicants should provide the following information on not more than 3 sides of A4 paper :**
- a) **What is the formulation, purity and source of the Drug ?**
 - b) **What are the pharmacological actions of the Drug - including those not relevant to the proposed therapeutic indications ?**

c) **Toxicology - including details of species, number of animals, doses, duration of treatment and route(s) of administration. Important findings should be summarised.**

d) **Clinical pharmacology in Man including :**

- Extent of Use in Man
- Dosage schedules used - dose, route, duration
- Side effects and their frequency
- Information on duration of action and mechanism of elimination, if known.

e) **Applicant's experience with this drug in man. Give brief information on previous studies, number and type of subjects and nature and incidence of side effects.**

vi) **Details of Medical Device**

vii) **If an electrical device, has the device been through acceptance and safety testing?**

Yes No

Give details:

This form is to be used if the study involves the use of additional ionising or radioactive substances or X-Rays.

a) **RADIOACTIVE SUBSTANCES**

i) **Details of substances to be administered** *(Please complete the table below)*

Investigation:

Radionuclide

Chemical form

<u>Quantity of radio-activity to be administered (MBq)</u>	<u>Route</u>	<u>Frequency</u>
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ii) **Estimated Effective Dose (Effective Dose Equivalent) (mSv):**
(Please supply source of reference or attach calculation)

iii) **Absorbed dose to organ or tissues concentrating radioactivity (mGy)**
(Specify dose and organ)
(Please supply source of reference or attach calculation)

Patients receiving an autograft will be treated with total body irradiation. This will be given in a schedule with which the Transplant Centre are familiar. The aim will be to deliver 10 Gy midline dose with lung shielding. Depending on the fractionation the dose may vary from 8 Gy to 14.4 Gy.

b) **X-RAYS**

i) **Details of radiographic procedures**

<u>Investigation</u>	<u>Organ(s)</u>	<u>Frequency</u>
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ii) **Estimated Effective Dose (Effective Dose Equivalent) (mSv):**
(Please supply source of reference or attach calculation)

OTHER RESEARCHERS INVOLVED IN THIS STUDY

Please provide the name and contact details of other researchers involved in this study. Please include your own name and centre if you are also a local researcher.

(Please copy and complete this page for each researcher. You must inform the MREC Administrator by means of a copy of this form as each new researcher is recruited.)

MREC Reference Number:**Name Professor D Catovsky****Contact Address:**

Academic Department of Haematology and Cytogenetics
Royal Marsden Hospital
Fulham Road
London
SW3 6JJ
Tel 020 7808 2880/2875
Fax 020 7351 6420
E mail d.catovsky@icr.ac.uk

Dr Sue Richards**Contact address:**

Clinical Trial Service Unit
Harkness Building
Radcliffe Infirmary
Oxford
OX2 6HE
Tel 01865 404863
Fax 01865 404849
e-mail Sue.Richards@ctsu.ox.ac.uk

Professor Gareth Morgan

Haematological Malignancy Diagnostic Service
Leeds General Infirmary
Leeds LS1 3EX
Tel 0113 243 2799
Fax 0113 233 3404
e-mail garethm@pathology.leeds.ac.uk

Dr Maggie Watson

Psychological Medicine Group
Royal Marsden Hospital
Downs Road
Sutton
Surrey
SM2 5PT
Tel 020 8642 6011
Fax 020 8661 6250
E mail maggie.watson@rmh.nthames.nhs.uk

Dr J A Child

Department of Haematology
The General Infirmary
Leeds
LS1 3EX
Tel 0113 392 6643
Fax 0113 392 6349
E Mail tonych@pathology.leeds.ac.uk

Please retain a blank copy of this form, complete it and send to the MREC Administrator whenever other local researchers become involved in the future.

SUPPLEMENTARY FORM FOR LOCAL ARRANGEMENTS

To be completed by the local researcher or principal researcher if appropriate (please see guidelines) once MREC approval has been obtained.

Please send this signed and completed form to the appropriate LREC administrator together with the **appropriate number** of copies of::

the MREC application form
the MREC letter of approval
the signed MREC response form.
the local researcher's c.v.
the consent form and information sheet

together with **one** copy of the protocol

If you require help with the address of your appropriate LREC please seek advice from the MREC Administrator.

1 MREC Reference Number:

2. Short title of project

3. Details of lead of local investigator:

Surname:

Forename:

Title:

Present Appointment:

Qualifications:

4. Please give an approximate figure for the number of trials/studies in which the principal researcher has been involved over the past year

5. Proposed start date and duration of project

6. Names, titles and qualifications of other local researchers working on this project

7. Location of project

8. Funding

Please give full details where applicable of:

- a) **Payment to subjects**

- b) **Payment to Trust/practice/research funds**

- c) **Personal payment or personal benefit to researcher**

Is payment:

- i) A block grant *Yes* *No*
- ii) Based on the number of research subjects recruited? *Yes* *No*

If yes, how much per patient:

- d) **Details of other benefits, e.g. equipment**

- e) **Will the costs incurred by the institution be covered by the payment?** *Yes* *No*

9. Local Recruitment of Subjects

- a) **How many subjects are being studied locally?**

- b) **Are any of these subjects involved in existing research or have been involved in any recent research in the last six months?** Yes No

If yes, please justify their use in this project

- c) **Will any of the subjects involved be in a dependent relationship with the researcher?** Yes No

If yes, please ensure you comply with local recruitment arrangements

- d) **Will any of the subjects involved be medical students?** Yes No

If yes, please obtain signed agreement of the Principal of the Medical School:

Signature of Principal of Medical School:

10. Local Safety Requirements

- a) **Are you going to administer radioisotopes?** Yes No

- i) **If yes, do you have an ARSAC certificate?** Yes No

- ii) **Have you informed the local radiation officer?** Yes No

Signature of Radiation Safety Officer:

- b) **If you are going to administer drugs what arrangements have you made to store, code and administer them?**

Signature of Hospital Pharmaceutical Officer:

- c) **Local emergency contact details:**

- d) **Local independent adviser details:**

DECLARATION

I have read and understood the MREC form and the supplementary form for LRECs, the protocol, guidelines and all documents pertaining to this research approved by the MREC that I now enclose. The information therein and above is accurate to the best of my knowledge and belief and I take full responsibility for it.

I understand it is my responsibility to obtain management approval where appropriate from the relevant NHS body before the project takes place.

I confirm that this research will comply with all relevant UK legislation, including the Data Protection Act and the Access to Medical Records Act.

I agree to supply interim and final reports to my LREC as required.

I agree to advise my sponsor, the LREC and MREC from which approval was granted for this proposal of any adverse or unexpected events that may occur during this project. I also agree to advise the LREC if this is withdrawn or not completed.

Signature of Local Investigator:

Date: