APPLICANT'S CHECKLIST

CTIMP (Clinical trial of an investigational medicinal product)

REC Ref:	08/MRE09/29	EudraCT No:	2007–003798–16
Short Title of Study:	AML 17		
CI Name:	Professor Alan Burnett		
Sponsor:	Cardiff University		

Please complete this checklist and send it with your application

- Send ONE copy of each document (except where stated)
- ALL accompanying documents must bear version numbers and dates (except where stated)
- When collating please do NOT staple documents as they will need to be photocopied.

Document	Enclosed?	Date	Version	Office use
Covering letter on headed paper	(•) Yes ( ) No	08/03/2008		
NHS REC Application Form, Parts A&B – AML 17	Mandatory	12/03/2008	5.4	
Site–Specific Information Form (for SSA)	( ) Yes (•) No			
Request form for authorisation from the MHRA (Annex 1 to ENTR/CT1) without enclosures – pending	Mandatory			
Research protocol (6 copies) – AML 17	Mandatory	01/03/2008	1	
Investigator's brochure (3 copies) – ATO	(•) Yes ( ) No	18/10/2004	8.1	
Investigator's brochure (3 copies) – Clofarabine	(•) Yes ( ) No	15/05/2007	3	
Investigator's brochure (3 copies) – Mylotarg	(•) Yes ( ) No	01/11/2006		
Investigator's brochure (3 copies) – CEP 701	(•) Yes ( ) No	25/05/2006	3	
Investigator's brochure (3 copies) – Everolimus	(•) Yes ( ) No	26/11/2007	edition 6	
Summary C.V. for Chief Investigator (CI) – Prof Burnett	Mandatory	10/10/2007		
Research participant information sheet (PIS) – patient information sheet 1 Trial overview	Mandatory	01/03/2008	1	
Research participant information sheet (PIS) – patient information sheet 2 Induction Randomisation for Non–APL Patients	(•) Yes ( ) No	01/03/2008	1	
Research participant information sheet (PIS) – patient information sheet 3 AIDA versus Chemo Free (Atra and Arsenic)	(•) Yes ( ) No	01/03/2008	1	
Research participant information sheet (PIS) – patient information sheet 4 Randomisation to FLT3 inhibitor	(•) Yes ( ) No	01/03/2008	1	
Research participant information sheet (PIS) – patient information sheet 5 high Risk Disease	(•) Yes ( ) No	01/03/2008	1	
Research participant information sheet (PIS) – Patient information sheet 6 Randomisation to mTOR inhibitor	(•) Yes ( ) No	01/03/2008	1	
Research participant information sheet (PIS) – Patient Information sheet 8 Residual disease	(•) Yes ( ) No	01/03/2008	1	

monitoring				
Research participant information sheet (PIS) – Patient/parent information sheet 1 trial overview	◉ Yes ○ No	01/03/2008	1	
Research participant information sheet (PIS) – Patient /Parent information sheet 2 induction Randomisation for Non–APL patients	◉ Yes ○ No	01/03/2008	1	
Research participant information sheet (PIS) – Patient/Parent information sheet 4 Randomisation to FLT3 inhibitor	◉ Yes ○ No	01/03/2008	1	
Research participant information sheet (PIS) – Patient /Parent Information sheet 5 high risk disease Treatments	◉ Yes ○ No	01/03/2008	1	
Research participant information sheet (PIS) – Patient/Parent Information sheet 6 randomisation to mTOR inhibitor	◉ Yes ○ No	01/03/2008	1	
Research participant information sheet (PIS) – Patient/Parent Information sheet 7a consolidation MACE–MidAC versus High Dose Ara–C	◉ Yes ○ No	01/03/2008	1	
Research participant information sheet (PIS) – Patient/Parent information sheet 9 Sample donation to Research	◉ Yes ○ No	01/03/2008	1	
Research participant consent form – Patient Consent Trial overview	Mandatory	01/03/2008	1	
Research participant consent form – patient consent sheet 2 Induction Randomisation for Non–APL Patients	◉ Yes ○ No	01/03/2008		
Research participant consent form – patient consent sheet 3 AIDA versus Chemo Free (Atra and Arsenic)	◉ Yes ○ No	01/03/2008		
Research participant consent form – patient consent sheet 4 Randomisation to FLT3 inhibitor	◉ Yes ○ No	01/03/2008		
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Research participant consent form – Patient consent sheet 6 Randomisation to mTOR inhibitor	◉ Yes ○ No	01/03/2008		
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Research participant consent form – Patient /Parent consent sheet 5 high risk disease Treatments	◉ Yes ○ No	01/03/2008		
Research participant consent form – Patient/Parent consent sheet 6 randomisation to	◉ Yes ○ No	01/03/2008		

mTOR inhibitor				
Research participant consent form – Patient/Parent information Sheet 7a consolidation MACE_MidAC Versusu high dose Ara–C	◉ Yes ○ No	01/03/2008		
Research participant consent form – Patient/Parent Consent sheet 9 Sample donation to Research	◉ Yes ○ No	01/03/2008		
Letters of invitation to participants	○ Yes ◉ No			
GP/Consultant information sheets or letters – GP Sheet 1	Mandatory	01/03/2008	1	
GP/Consultant information sheets or letters – GP Sheet 2	◉ Yes ○ No	01/03/2008	1	
GP/Consultant information sheets or letters – GP Sheet 3	◉ Yes ○ No	01/03/2008	1	
GP/Consultant information sheets or letters – GP Sheet 4	◉ Yes ○ No	01/03/2008	1	
GP/Consultant information sheets or letters – GP Sheet 5	◉ Yes ○ No	01/03/2008	1	
GP/Consultant information sheets or letters – GP Sheet 6	◉ Yes ○ No	01/03/2008	1	
GP/Consultant information sheets or letters – GP sheet 6a	◉ Yes ○ No	01/03/2008	1	
Evidence of insurance or indemnity (non–NHS sponsors only)	Mandatory			
Letter from sponsor	○ Yes ○ No			
Letter from statistician	○ Yes ◉ No			
Letter from funder	○ Yes ○ No			
Referees' or other scientific critique report	○ Yes ◉ No			
Summary, synopsis or diagram (flowchart) of protocol in non–technical language	○ Yes ◉ No			
Details of any Data Monitoring Committee	○ Yes ◉ No			
Sample diary card/patient card	○ Yes ◉ No			
Validated questionnaire – AML 17 Quality of Life	◉ Yes ○ No			
Non–validated questionnaire	○ Yes ◉ No			
Copies of advertisement material for research participants, e.g. posters, newspaper adverts, website. For video or audio cassettes, please also provide the printed script.	○ Yes ◉ No			

WELCOME TO THE NHS RESEARCH ETHICS COMMITTEE APPLICATION FORM

An application form specific to your project will be created from the answers you give to the following questions.

1. Is your project an audit or service evaluation?

○ Yes ◉ No

2. Select one research category from the list below:

◉ Clinical trials of investigational medicinal products
○ Clinical investigations or other studies of medical devices
○ Other clinical trial or clinical investigation
○ Research administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
○ Research involving qualitative methods only
○ Research limited to working with human tissue samples and/or data
○ Research tissue bank

If your work does not fit any of these categories, select the option below:

○ Other research

2a. Please answer the following questions:

Is this trial subject to advice from the Expert Advisory Group on Clinical Trials and the Commission on Human Medicine prior to authorisation from MHRA?	○ Yes	◉ No

2b . Please answer the following questions:

a) Does the study involve the use of any ionising radiation?	○ Yes	◉ No
b) Will you be taking new human tissue samples?	◉ Yes	○ No
c) Will you be using existing human tissue samples?	○ Yes	◉ No

3. Is your research confined to one site?

○ Yes ◉ No

4. Does your research involve work with prisoners?

○ Yes ◉ No

5. Do you plan to include in this research adults unable to consent for themselves through physical or mental incapacity?

○ Yes ◉ No

6. Is the study, or any part of the study, being undertaken as an educational project?

○ Yes ◉ No

NHS Research Ethics Committee NHS
Application form for a clinical trial of an investigational medicinal product

This form should be completed by the Chief Investigator, after reading the guidance notes. See glossary for clarification of different terms in the application form.

Short title and version number: (maximum 70 characters – this will be inserted as header on all forms)
AML 17

Name of NHS Research Ethics Committee to which application for ethical review is being made:
MREC for Wales

Project reference number from above REC: 08/MRE09/29
Submission date: 10/04/2008

PART A: Introduction

A1. Title of the research

Full title: AML 17: A Programme of Development for the Treatment of Younger Patients with Acute Myeloid Leukaemia and High Risk Myelodysplastic Syndrome

Key words: Acute Myeloid Leukaemia / High Risk MDS

A2. Chief Investigator

Title:	Professor
Forename/Initials:	Alan
Surname:	Burnett
Post:	Professor of Haematology
Qualifications:	MD, FRCP (Ed. LON. Glas), FRCPath, FMed SCi
Organisation:	Cardiff University
Work Address:	Department of Haematology School of Medicine, Heath Park, Cardiff
Post Code:	CF14 4XN
E–mail:	burnettak@cardiff.ac.uk
Telephone:	02920742375
Fax:	029 20744655
Mobile:	077780605236

A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application

A3. Proposed study dates and duration

Start date: 01/07/2008
End date: 01/07/2014
Duration: Years: 6 ; Months:

A4. Primary purpose of the research: *(Tick as appropriate)*

- ☐ Commercial product development and/or licensing
- ☑ Publicly funded trial or scientific investigation
- ☐ Educational qualification
- ☐ Establishing a database/data storage facility
- ☐ Other

A5. Type of medicinal trial:

- ☑ Clinical trial of a non−authorised investigational medicinal product
- ☑ Clinical trial of an authorised product for a new indication, i.e. not in the Summary of Product Characteristics, (SmPC)
- ☑ Clinical trial of an authorised medicinal product in new conditions of use (different from those in the SmPC, i.e. new target population, new dosage schemes, new administration route, etc.)
- ☐ Clinical trial of an authorised medicinal product used according to the SmPC
- ☐ Other

If Other, please specify:

A5a. Phase of medicinal trial: *(Tick one category only)*

- ○ Human pharmacology trial *with no evidence of potential benefit to the proposed participants* (Phase 1 or 1/2a)
- ○ Therapeutic exploratory trial in patients (Phase 2)
- ◉ Therapeutic confirmatory trial in patients (Phase 3)
- ○ Therapeutic use trial in patients (Phase 4)

Applicants must enclose a copy of the completed request for authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA). The application form is published as Annex 1 to the European Commission guideline ENTR/CT1 and can be obtained from the EudraCT website at http://eudract.emea.eu.int.

A6. Does this research require site−specific assessment (SSA)? (Advice can be found in the guidance notes on this topic.)

◉ Yes ○ No

If No, please justify:

If Yes, an application for SSA should be made for each research site on the Site−Specific Information Form and submitted to the relevant local Research Ethics Committee. Do not apply for SSA at sites other than the lead site until the main application has been booked for review and validated by the main Research Ethics Committee.

Management approval to proceed with the research will be required from the R&D office for each NHS care organisation in which research procedures are undertaken. This applies whether or not the research is exempt from SSA. R&D applications in England, Wales and Scotland should be made using the Site−Specific Information Form.

PART A: Section 1

A7. What is the principal research question/objective? *(Must be in language comprehensible to a lay person.)*

1. For patients with the Acute Promyelocytic (APL), subtype, to compare the standard All transretinoic acid(ATRA) plus Idarubicin versus Arsenic Trioxide (Trisenox) plus retinoic acid (equivalence study), with primary endpoints, Q o L and markers of economic differences.
2. For non APL patients:
i. to compare ADE (Ara–C/Daunorubicin/Etoposide) vs ADE + Mylotarg 3mgs vs ADE 6mgs vs DA +Mylotarg 3mgs vs DA + Mylotarg 6mgs in induction.
ii. to compare chemotherapy vs chemotherapy + the FLT–3 inhibitor CEP–701 in patients who have a FLT–3 mutation.
iii. in high risk patients (defined in protocol appendix 6) to compare initially standard arm FLTA–Ida[Fludarabine/Ara–C/G–CSF/Idarubicin] versus Daunorubicin + Clofarabine.
iv. in patients who are not FLT–3 mutations, not CBF leukaemia, not high risk, to compare chemotherapy versus chemotherapy + mTOR inhibitor.
v. for consolidation chemotherapy in adults to compare 1 (MACE:Amsacrine/Ara–C/Etoposide) versus 2 (MACE + MidAc:– Mitoxantrone/Ara–C) courses (equivalence study). For children (<16 years) to compare MACE + MidAc versus 2 courses of high dose Ara–C.
vi. To assess the clinical value to minimal residual disease monitoring by randomising patients to be monitored versus not to be monitored.

A8. What are the secondary research questions/objectives? *(If applicable, must be in language comprehensible to a lay person.)*

- In APL randomisations survival and relapse are secondary endpoints.
- In non–APL
- Correlation of response with in vitro evidence of FLT–3 or mTOR inhibitory activity.
- Characterisation of molecular characteristics ie mutation screening and gene expression array.
- Correlation of cytogenetic and molecular characteristics with outcome.
- Storage of excess diagnostic material for future haematological research.
- Identification and validation of markers of minimal residual disease.

A9. What is the scientific justification for the research? What is the background? Why is this an area of importance? *(Must be in language comprehensible to a lay person.)*

Although UK trials produce the best results in the world in this age group, half of all patients die. Much knowledge is emerging about the molecular and biological features of the disease (eg expression of CD33/variation in response based on cytogenetic abnormalities/presence of molecular mutations) make it no longer viable for patients to receive a “one size fits all” treatment approach. We have already, been the first shown that the immunoconjugate Mylotarg significantly improves overall survival – the first observation of antibody directed chemotherapy in cancer – without increasing side effects. So we now wish to examine a higher (6mg) dose. The molecular knowledge tells us that small molecules can in lab studies counteract some of the effects of some of the mutations found in leukaemia cells. Some patients do very badly on current therapy (20% survival), and have done so for several years. We aim to explore novel chemotherapy agents in this group. We have some retrospective evidence that 3 treatment courses in total, may be just asgood as the standard 4 courses, so we aim to compare treatment with 3 versus 4 courses. All of these questions are completely unique to this trial. Although complicated, the design is similar to our present trial which has record recruitment suggesting that both investigators and patients are confident in undertaking. We are the only group in the world with the capacity to recruit sufficient patients to achieve the trial objectives. We expect participation from Denmark, Australia New Zealand and possibly Finland.

A10–1. Give a full summary of the purpose, design and methodology of the planned research, including a brief explanation of the theoretical framework that informs it. It should be clear exactly what will happen to the research participant, how many times and in what order.

This section must be completed in language comprehensible to the lay person. It must also be self–standing as it will be replicated in any applications for site–specific assessment on the Site–Specific Information Form. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.

1. All interventions are randomised, open label and the analysis will include all who enter the randomisation on an intent – to – treat basis.
2. At diagnosis patients will be identified by the local Haematologist (155 sites) and the diagnosis and treatment options discussed in the normal way. The option of the AML17 trial will be raised and the patient will be given the PIS 1 which gives an overview of the trial. They will be invited to enter. If the data from the lab indicates that the patient has the APL subtype (15% of patients) the different treatment required for this subtype will be explained and they will be offered entry to the trial comparison for this subgroup (PIS 3). Patients who do not have APL will be offered induction treatment and given PIS number 2. At this point patients will be asked to consent to excess material collected at diagnosis or subsequent assessments to be stored for future research.
3. After completion of course 1 chemotherapy reference labs will inform investigators if the diagnostic sample has a FLT – 3 mutation. Patients with a mutation will be offered entry to continue chemotherapy with or without a novel FLT – 3 inhibitor CEP – 701. PIS 4 will be used. Note that the randomisation characteristics will give a 2 out of 3 chance of receiving the inhibitor.
4. When the patient has recovered from course 1, more prognostic information will be available on the other patients. If the chromosome analysis indicates a Core Binding Factor (CBF) subtype with a favourable prognosis the patient will proceed to the second treatment course. If the patient has a high risk score, which suggests a poor response to current chemotherapy. They will then be offered the high risk comparison using PIS 5, with the aim of going to stem cell transplantation.
The remaining patients (about 30% of all patients) who do not have a FLT – 3 mutation, or a CBF leukaemia, or a high risk score, will be offered the planed chemotherapy ± a weekly infusion (12 weeks) of the mTOR inhibitor.
5. All patients who are not high risk who complete the first two treatment courses will then be eligible to enter the comparison of 1 versus 2 courses of consolidation. If they have already been allocated to receive a FLT – 3 or mTOR inhibitor, they will continue to take it.
6. At diagnosis patients will be asked to consent to excess material (blood and bone marrow) which is collected at the time of routine disease assessments, to be stored for future research in leukaemia. In the initial part of the trial reference labs will be developing methods of minimal residual disease detection using this material. This will include immunophenotypic and molecular analysis. This information will not be fed back to investigators during this phase. An aspect of this development is to correlate the lab level that predicts relapse. When this developmental phase is complete – and the time required depends on the marker used – we will then enter the assessment of clinical value.
The rationale is that the expensive technology may have a high chance of predicting relapse a few weeks before it actually happens, but we do not know the clinical value of knowing that. In other words is it better to give more treatment at this point rather than dealing with the relapse if/when it happens? If the latter therapeutic is just as valuable monitoring is not needed. The trial aims to answer this by inviting patients to be randomised to be monitored or not to be monitored using PIS 9.
Trial Flow Diagram
An individual patient with APL has 1 randomisation. A non – APL patient has a maximum of 3 randomisations (diagnosis/risk based after course 1/consolidation) later they may be invited into the monitory randomisation which will take place around the time of diagnosis or within 1 month of entry.

A10–2. In which parts of the research have patients, members of the public or service users been involved?

- [x] As user–researchers
- [x] As members of a research project group
- [x] As advisor to a project
- [x] As members of a departmental or other wider research strategy group
- [ ] None of the above

Please provide brief details if applicable:

Trial Design extensively discussed in trial group. Presented at annual meeting of > 300 investigators. Presented to NCRI committee for lay input. Reviewed by international reviewers (MRC – can be supplied)

reviewed by MRC Trial Steering committee.

A10–3. Could the research lead to the development of a new product/process or the generation of intellectual property?

○ Yes ◉ No ○ Not sure

A11. Will any intervention or procedure, which would normally be considered a part of routine care, be withheld from the research participants?

○ Yes ◉ No

A12. Give details of any clinical intervention(s) or procedure(s) to be received by research participants over and above those which would normally be considered a part of routine clinical care. *(These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material.)*

Additional Intervention	**Average number per participant**		**Average time taken** (mins/hours/days)	**Details of additional intervention or procedure, who will undertake it, and what training they have received.**
	Routine Care	Research		
Biopsy material	3–4	2–3	30 mins	Research – some patients may have 2 – 3 extra bone marrow in first 2 years. Treatment team may be asked to take up to 3 extra bone marrows for MRD monitoring over the first 18 months.
Venepuncture	>12	3	2 mins	Blood Sample taken for research – a 10mls extra sample will be taken as required when a routine blood sample is being taken

A13. Give details of any non–clinical research–related intervention(s) or procedure(s). *(These include interviews, non–clinical observations and use of questionnaires.)*

Additional Intervention	**Average number per participant**	**Average time taken** (mins/hours/days)	**Details of additional intervention or procedure, who will undertake it, and what training they have received.**
Other Questionnaire	4	30 mins	A Principle endpoint in APL comparison, also X 2 in the monitoring randomisation.

A14. Will individual or group interviews/questionnaires discuss any topics or issues that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could take place during the study (e.g. during interviews/group discussions, or use of screening tests for drugs)?

○ Yes ◉ No

The Information Sheet should make it clear under what circumstances action may be taken

A15. What is the expected total duration of participation in the study for each participant?

Treatment should be completed in 6 months. Patients are followed up for life in "routine care" enviroment.

A16. What are the potential adverse effects, risks or hazards for research participants either from giving or withholding medications, devices, ionising radiation, or from other interventions (including non−clinical)?

All chemotherapy and investigational agents represent a risk of side effects. With Mylotarg this is not adding any in our experience of > 900 recipients. The addition of FLT−3 inhibitor can cause nausea, the mTor inhibitor can cause skin rash, nausea and hypocholesterolaemia.

A17. What is the potential for pain, discomfort, distress, inconvenience or changes to lifestyle for research participants?

the treatment of leukaemia (outside the trial) causes distress, discomfort, life risk, inconvenience and major change in lifestyle. It is not anticipated that any of the interventions should increase this.

A18. What is the potential for benefit to research participants?

i) no cohort of entrants to MRC AML trials for the last 30 years have done worse than the historical patients.
ii) the trial may increase the average survival rate. The trial tests in APL and consolidation may show less chemotherapy is just as effective

A19. What is the potential for adverse effects, risks or hazards, pain, discomfort, distress, or inconvenience to the researchers themselves? *(if any)*

None

A20. How will potential participants in the study be (i) identified, (ii) approached and (iii) recruited?
Give details for cases and controls separately if appropriate:

Patients are identified by routine practice in local hospitals. They will come under the care of a haematologist who will discuss the trial as a treatment option.

A21. Where research participants will be recruited via advertisement, give specific details.

☑ Not Applicable

If applicable, enclose a copy of the advertisement/radio script/website/video for television (with a version number and date).

A22. What are the principal inclusion criteria? *(Please justify)*

Patients are eligible for the AML17 trial if:
— They have one of the forms of acute myeloid leukaemia as defined by the WHO Classification (Appendix A) — this can be any type of de novo or secondary AML or high risk Myelodysplastic Syndrome (defined as >10% bone marrow blasts).
— Adult patients with acute promyelocytic leukaemia (APL) are eligible and should be entered into the randomisations specifically for APL (see Section 19).
— They are considered suitable for intensive chemotherapy.
— They should normally be under the age of 60, but patients over this age are eligible if intensive therapy is considered a suitable option.
– Patients must have liver function tests within twice the upper limit of the normal local range to eligible for the Mylotarg randomisation.
— They have given written informed consent.

A23. What are the principal exclusion criteria? *(Please justify)*

Patients are not eligible for the AML17 trial if:
— They have previously received cytotoxic chemotherapy for AML. [Hydroxycarbamide, or similar low–dose therapy, to control the white count prior to initiation of intensive therapy is not an exclusion.]
— They are in blast transformation of chronic myeloid leukaemia (CML).
— They have a concurrent active malignancy.
— They are pregnant or lactating

A24. Will the participants be from any of the following groups? *(Tick as appropriate)*

- [x] Children under 16
- [ ] Adults with learning disabilities
- [ ] Adults who are unconscious or very severely ill
- [ ] Adults who have a terminal illness
- [ ] Adults in emergency situations
- [ ] Adults with mental illness (particularly if detained under Mental Health Legislation)
- [ ] Adults with dementia
- [ ] Prisoners
- [ ] Young Offenders
- [ ] Adults in Scotland who are unable to consent for themselves
- [ ] Healthy Volunteers
- [ ] Those who could be considered to have a particularly dependent relationship with the investigator, e.g. those in care homes, medical students
- [ ] Other vulnerable groups

Justify their inclusion.

AML is a potentially fatal disease, in children and adults 4% die and improvement is required. children have been involved in unified national protocols for the last 20 years.

- [ ] No participants from any of the above groups

A25. Will any research participants be recruited who are involved in existing research or have recently been involved in any research prior to recruitment?

○ Yes ◉ No ○ Not Known

If Yes, give details and justify their inclusion. If Not Known, what steps will you take to find out?

A26. Will informed consent be obtained from the research participants?

◉ Yes ○ No

If Yes, give details of who will take consent and how it will be done. Give details of any particular steps to provide information (in addition to a written information sheet) e.g. videos, interactive material.

If participants are to be recruited from any of the potentially vulnerable groups listed in A24, give details of extra steps taken to assure their protection. Describe any arrangements to be made for obtaining consent from a legal representative.

If consent is not to be obtained, please explain why not.

Patients will be given written and verbal information and asked to give written consent by the local PI or his delegated colleague – as explained in A10

Copies of the written information and all other explanatory material should accompany this application.

A27. Will a signed record of consent be obtained?

◉ Yes ○ No

If Yes, attach a copy of the information sheet to be used, with a version number and date.

A28. How long will the participant have to decide whether to take part in the research?

Treatment may have to start immediately. Normally 24 – 48 hours

A29. What arrangements have been made for participants who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? *(e.g. translation, use of interpreters etc.)*

Each site will be responsible for preparation of PIS and consents in the language most suitable for the patients, and to mprovide interpreters as required.

A30. What arrangements are in place to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

Regular newsletters are sent to PI's and research nurses. The trial has a web–site and this is regularly interacted with the research team.

Question(s) 30–1 disabled.

A31. Does this study have or require approval of the Patient Information Advisory Group (PIAG) or other bodies with a similar remit?*(see the guidance notes)*

○ Yes ◉ No

A32a. Will the research participants' General Practitioner (and/or any other health professional responsible for their care) be informed that they are taking part in the study?

◉ Yes ○ No

If Yes, enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

A32b. Will permission be sought from the research participants to inform their GP or other health professional before this is done?

◉ Yes ○ No

If No to either question, explain why not

It should be made clear in the patient information sheet if the research participant's GP/health professional will be informed.

A33. Will individual research participants receive any payments for taking part in this research?

○ Yes ◉ No

A34. Will individual research participants receive *reimbursement of expenses* or any other *incentives or benefits* for taking part in this research?

○ Yes ◉ No

A35. Insurance/indemnity to meet potential legal liabilities

Note: References in this question to NHS indemnity schemes include equivalent schemes provided by Health and Personal Social Services (HPSS) in Northern Ireland.

A35–1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the *sponsor(s)* for harm to participants arising from the *management of the research*?

Note: Where a NHS organisation has agreed to act as the sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, describe the arrangements and provide evidence.

◉ NHS indemnity scheme will apply
○ Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A35–2. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the *sponsor(s) or employer(s)* for harm to participants arising from the *design of the research*?

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), describe the arrangements and provide evidence.

◉ NHS indemnity scheme will apply to all protocol authors
○ Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A35–3. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of *investigators/collaborators* and, where applicable, *Site Management Organisations*, arising from harm to participants in the *conduct of the research*?

Note: Where the participants are NHS patients, indemnity is provided through NHS schemes or through professional indemnity. Indicate if this applies to the whole of the study (there is no need to provide documentary evidence). Where non–NHS sites are to be included in the research, including private practices, describe the arrangements which will be made at these sites and provide evidence.

◉ All participants will be recruited at NHS sites and NHS indemnity scheme or professional indemnity will apply
○ Research includes non–NHS sites (give details of insurance/indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A36. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

○ Yes ◉ No

If Yes, give details of the compensation policy:

Please enclose a copy of relevant documents.

A37. How is it intended the results of the study will be reported and disseminated? *(Tick as appropriate)*

- [x] Peer reviewed scientific journals
- [ ] Internal report
- [x] Conference presentation
- [ ] Other publication
- [ ] Submission to regulatory authorities
- [ ] Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- [x] Written feedback to research participants
- [x] Presentation to participants or relevant community groups
- [ ] Other/none e.g. Cochrane Review, University Library

A38. How will the results of research be made available to research participants and communities from which they are drawn?

Local PI receives required feedback in acedemic activities. They are each sent a copy of the published manuscript. Information to participants should flow from PI.

A39. Will the research involve any of the following activities at any stage (including identification of potential research participants)? *(Tick as appropriate)*

- [x] Examination of medical records by those outside the NHS, or within the NHS by those who would not normally have access
- [ ] Electronic transfer by magnetic or optical media, e–mail or computer networks
- [x] Sharing of data with other organisations
- [ ] Export of data outside the European Union
- [ ] Use of personal addresses, postcodes, faxes, e–mails or telephone numbers
- [ ] Publication of direct quotations from respondents
- [ ] Publication of data that might allow identification of individuals
- [ ] Use of audio/visual recording devices
- [x] Storage of personal data on any of the following:
  - [ ] Manual files including X–rays
  - [x] NHS computers
  - [ ] Home or other personal computers
  - [x] University computers
  - [ ] Private company computers
  - [ ] Laptop computers

Further details:

the sponsor may wish to conduct limited source verification/ audit and may choose to contract this out. Anonymised data only will be used for eg lab studies/cochrane reviews etc. The sponsor will have contracts for data management with NHS and university sites.

A40. What measures have been put in place to ensure confidentiality of personal data? Give details of whether any encryption or other anonymisation procedures have been used and at what stage:

Patients will enter the trial by means of a telephone call, or entry using a secure website address, both functions devolved to the trials office. At this point patient demographics (including initials and date of birth) will be given, and the patient will be allocated a unique trial number. This trial number, initials and date of birth will be the only identifier used for attaching subsequent data including any tissue as agreed in the consent forms, in the event a patient does not consent to the use of their initials and date of birth being used they will be identified by their trial number only . Patient initials are collected to facilitate flagging of patients with ONS for complete ascertainment of mortlaity. Data are all stored in a secure SQL Server database with full password protection.

A41. Where will the analysis of the data from the study take place and by whom will it be undertaken?

The data will be analysed in Cardiff by the trial statistians, (Dr Hills assisted by Prof Wheatley).

A42. Who will have control of and act as the custodian for the data generated by the study?

The sponsor will deligate duties to the Wales Cancer trials unit. Adverse Event documentation/management will be run from the Cancer Trials Unit, University Hospital of Wales, Cardiff.

A43. Who will have access to research participants' or potential research participants' health records or other personal information? *Where access is by individuals outside the normal clinical team, justify and say whether consent will be sought.*

Only the trial team or individuals appointed by the sponsor.

A44. For how long will data from the study be stored?

15 Years Months

Give details of where they will be stored, who will have access and the custodial arrangements for the data:

Computer database will be maintained by the Wales Cancer Trials Unit but will remain the "property" of Cardiff University.

A45–1. How has the scientific quality of the research been assessed? *(Tick as appropriate)*

- [x] Independent external review
- [x] Review within a company
- [x] Review within a multi–centre research group
- [x] Review within the Chief Investigator's institution or host organisation
- [x] Review within the research team
- [ ] Review by educational supervisor
- [ ] Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:

A45–2. How have the statistical aspects of the research been reviewed? *(Tick as appropriate)*

- [x] Review by independent statistician commissioned by funder or sponsor
- [x] Other review by independent statistician
- [x] Review by company statistician
- [x] Review by a statistician within the Chief Investigator's institution
- [x] Review by a statistician within the research team or multi–centre group
- [ ] Review by educational supervisor
- [ ] Other review by individual with relevant statistical expertise

In all cases give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

Title: Forename/Initials: Surname:

Department:
Institution:
Work Address:

Postcode:
Telephone:
Fax:
Mobile:
E–mail:

Please enclose a copy of any available comments or reports from a statistician.

Question(s) 46–47 disabled.

A48. What is the primary outcome measure for the study?

The main endpoints for each comparison will be:
— Complete remission (CR) achievement and reasons for failure (for induction questions).
— Duration of remission, relapse rates and deaths in first CR.
— Overall survival.
– Toxicity, both haematological and non–haematological
– Quality of life
— Supportive care requirements (and other aspects of health economics).

A49. What are the secondary outcome measures? *(if any)*

— The relevance of the molecular and immunophenotypic detection of minimal residual disease
— The relevance of the presence of a cytogenetic abnormality in the bone marrow of patients in morphological remission.
— To correlate the blood level of anti–FLT3 activity and the extent of dephosphorylation of the FLT3 receptor with response for patients allocated to receive FLT3 inhibition therapy
— To assess the level of plasma mTOR activity in relation to clinical outcome.
— Store excess diagnostic material for future research.

A50. How many participants will be recruited?
If there is more than one group, state how many participants will be recruited in each group. For international studies, say how many participants will be recruited in the UK and in total.

2500–3000 (approximated 150 from non UK sites)

A51. How was the number of participants decided upon?

There are approximately 700 cases of AML under the age of 60 diagnosed each year in the British Isles, of whom about 15% have the APL sub–type. It is hoped that the majority of suitable patients will be entered into the trial. Indeed, recruitment to AML15 has typically run at around 650 patients per annum, so that over the course of the recruitment period it should be possible to randomise at least 300 APL patients and 2700 non–APL patients.
For the APL randomisation, it is anticipated that a similar number of patients will be recruited from both the NCRI and GIMEMA networks, giving a total of 600 patients for analysis. Outcomes are typically very good for this group of patients, so 600 patients would only be sufficient to consider around a 7.5% difference in five–year survival (85% v 92.5%), representing a halving in mortality rates between the two groups. Thus, while this will remain a secondary objective in this section of the trial, the study will, as in AML15, use quality of life and resource usage as primary endpoints. With 600 patients it is possible to detect, with 80% power at $p<0.05$, a small–to–moderate difference of 0.25 standard deviations, and would have 90% power to detect a standardised difference of 0.27. Interim data from AML15 indicate that the standard deviation of the EORTC–QLQ30 global score is approximately 20 points, indicating that the trial will be powered to detect a 5 to 6 point difference in quality of life. The use of repeated measures modelling for the quality of life outcomes should increase the power to detect smaller differences.
With 2700 patients entering the non–APL induction randomisation, there are likely to be some who will not be eligible for the 5–way randomisation, because of liver function tests. However, it is likely that approximately 2300 patients will enter this randomisation, meaning that 1400 patients will contribute to a comparison of ADE + GO 3mg v DA +GO 3mg. This will give 80% power to detect a 10% difference in overall survival at 5 years between the two experimental arms and ADE, allowing for multiple testing by setting significance at $p=0.025$. These results will be meta–analysed with the accumulating data from AML15, where the same randomisation took place. The analysis of the mylotarg dose question will depend on whether there is any interaction between chemotherapy regimen and mylotarg (whether the effect of mylotarg differs between ADE and DA chemotherapy). Assuming no interaction, the mylotarg dose question will have recruited some 1800 patients, giving 90% power to detect improvements in 5–year survival from 45% to 52.5% between the two Mylotarg doses. Interaction will be tested here using standard techniques.

If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.

A52. Will participants be allocated to groups at random?

(●) Yes ( ) No

If yes, give details of the intended method of randomisation:

Computer generated;stratified randomisation The randomisations — and subsidiary data analyses — will be stratified by age (0 – 14, 15 – 29, 30 – 39, 40 – 49, 50 – 59, 60+), performance status, and type of disease (de novo/secondary AML). Consolidation randomisations will also be stratified by initial allocation and by risk group, and comparisons of mylotarg dose will be stratified by chemotherapy allocated. All analyses will assume that there may be some quantitative differences in the size of any treatment effects in these different strata, but that there is unlikely to be any qualitative difference (i.e. harm in one group, benefit in another).

A53. Describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

Interim analyses of the main endpoints will be supplied periodically, in strict confidence, to the MRC Leukaemia Data Monitoring and Ethics Committee (DMEC). In the light of these interim analyses, the DMEC will advise the chairman of the Trial Steering Committee if, in their view, one or more of randomised comparisons in the trial have provided proof beyond reasonable doubt* that for all, or for some, types of patient one treatment is clearly indicated or clearly contraindicated.
The main analyses will be performed using standard contingency table and log−rank methods based on the intention to treat — i.e. all patients believed to be eligible at the time of randomisation will be included in the analysis, irrespective of protocol compliance, early death, etc. The randomisations — and subsidiary data analyses — will be stratified by age (0−14, 15−29, 30−39, 40−49, 50−59, 60+), performance status, and type of disease (de novo/secondary AML). Consolidation randomisations will also be stratified by initial allocation and by risk group, and comparisons of mylotarg dose will be stratified by chemotherapy allocated. All
analyses will assume that there may be some quantitative differences in the size of any treatment effects in these different strata, but that there is unlikely to be any qualitative difference (i.e. harm in one group, benefit in another).

A54. Where will the research take place? *(Tick as appropriate)*

- [x] UK
- [x] Other states in European Union
- [ ] Other countries in European Economic Area
- [x] Other

If Other, give details:

Australia and New Zealand

A55. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK, the European Union or the European Economic Area?

○ Yes ◉ No

A56. In how many and what type of host organisations (NHS or other) in the UK is it intended the proposed study will take place?

Indicate the type of organisation by ticking the box and give approximate numbers if known:

	Number of organisations
☑ Acute teaching NHS Trusts	150
☑ Acute NHS Trusts	150
☐ NHS Primary Care Trusts or Local Health Boards in Wales	
☐ NHS Trusts providing mental healthcare	
☐ NHS Health Boards in Scotland	
☐ HPSS Trusts in Northern Ireland	
☐ GP Practices	
☐ NHS Care Trusts	
☐ Social care organisations	
☐ Prisons	
☑ Independent hospitals	2–3
☐ Educational establishments	
☐ Independent research units	
☐ Other (give details)	

Other:

A57. What arrangements are in place for monitoring and auditing the conduct of the research?

A pharmacovigilance officer will phone the research sites weekly for up to 4 weeks after each IMP is given. Investigators provide written agreement to record adverse events using standard documentationfor the trial. The DEMC will review data x 2 per annum and advise the TSC.

A57a. Will a data monitoring committee be convened?

◉ Yes ○ No

If Yes, details of membership of the data monitoring committee (DMC), its standard operating procedures and summaries of reports of interim analyses to the DMC must be forwarded to the NHS Research Ethics Committee which gives a favourable opinion of the study.

What are the criteria for electively stopping the trial or other research prematurely?

no set citerai. Experiences MRC DEMC (chair Prof Gordon Murray) reviews data including adverse events twice a year or more if required.

A58. Has external funding for the research been secured?

(•) Yes ( ) No

If Yes, give details of funding organisation(s) and amount secured and duration:

Organisation:	Cancer Research UK
Address:	P.O. Box 123, Lincoln's Inn Fields, London
Post Code:	WC2A 3PX
UK contact:	Nicola Keat
Telephone:	020 7121 6699
Fax:	020 7121 6700
Mobile:	
E–mail:	
Amount (£):	750,000 Duration: Months

A59. Has the funder of the research agreed to act as sponsor as set out in the Research Governance Framework?

( ) Yes (•) No

Has the employer of the Chief Investigator agreed to act as sponsor of the research?

(•) Yes ( ) No

Lead sponsor *(must be completed in all cases)*

Name of organisation which will act as the lead sponsor for the research:

Cardiff University

Status:

( ) NHS or HPSS care organisation (•) Academic ( ) Pharmaceutical industry ( ) Medical device industry ( ) Other

If Other, please specify:

Address:	34–36 Newport Road Cardiff
Post Code:	CF23 ODE
Telephone:	02920879274
Fax:	
Mobile:	
E–mail:	daviesKP@Cardiff.ac.uk

Sponsor's UK contact point for correspondence with the main REC *(must be completed in all cases)*

Title: Dr	Forename/Initials: K	Surname: Pittard−Davies

Work Address: 34−36 Newport Road
Cardiff
Post Code: CF23 ODE
Telephone: 02920879274
Fax:
Mobile:
E−mail: daviesKP@Cardiff.ac.uk

Co−sponsors

Are there any co−sponsors for this research?

○ Yes ◉ No

Legal representative* of the sponsor in the EU for the purpose of this trial *(if applicable)*

Title:	Forename/Initials:	Surname:

Work Address:
Post Code:
Telephone:
Fax:
Mobile:
E−mail:

** A legal representative must be appointed for a clinical trial of an investigational medicinal product if the sponsor is not established within the European Economic Area (EEA) (see article 19 of Directive 2001/20/EC). If this applies, enclose evidence that the legal representative is established within the EEA and has accepted the role of legal representative.*

A60. Has any responsibility for the research been delegated to a subcontractor?

(•) Yes ( ) No

If Yes, give details including:
Name of research contract organisation/site management organisation, and summary of delegated responsibility

Data Management/website maintenance, Wales Cancer Trials Unit.
Labelling and QP release of IMP's (trisenox, CEP−701, Mylotarg, M−Tor to St Mary's Pharmaceutical Unit Cardiff

A61. Will individual *researchers* receive any personal payment over and above normal salary for undertaking this research?

( ) Yes (•) No

A62. Will individual *researchers* receive any other benefits or incentives for taking part in this research?

( ) Yes (•) No

A63. Will the host organisation or the researcher's department(s) or institution(s) receive any payment or benefits in excess of the costs of undertaking the research?

( ) Yes (•) No

A64. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share−holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

( ) Yes (•) No

A65. Research reference numbers: *(give any relevant references for your study):*

Applicant's/organisation's own reference number, e.g. R&D (if available):	
Sponsor's/protocol number:	372−07
Funder's reference number:	
International Standard Randomised Controlled Trial Number (ISRCTN):	55675535
ClinicalTrials.gov Identifier (NCT number):	
European Clinical Trials Database (EudraCT) number:	2007−003798−16
Project website:	

A66. Other key investigators/collaborators *(all grant co−applicants or protocol co−authors should be listed)*

Title: Dr Forename/Initials: D Surname: Milligan

Post:	Consultant Haematologist
Qualifications:	MB, FRCPath
Organisation:	Department of Haematology
Work Address:	Birmingham Heartlands Hospital Birmingham
Postcode:	B9 5SS
Telephone:	0121 424 3699
Fax:	0121 766 7530
Mobile:	
E−mail:	d.w.milligan@bham.ac.uk

Title: Dr Forename/Initials: M Surname: Dennis

Post:	Consultant Haematologist
Qualifications:	MB, FRCPath
Organisation:	Department of Haematology
Work Address:	Christie's Hospital Wilsmlow Rd Manchester
Postcode:	M20 4BX
Telephone:	0161 446 8420
Fax:	0161 446 3940
Mobile:	
E−mail:	mike.dennis@christie−tr.nwest.nhs.uk

Title: Dr Forename/Initials: D Surname: Bowen

Post:	Consultant Haematologist
Qualifications:	MRCP (UK), MD, FRCPath
Organisation:	The Leeds Teaching Hospitals NHS Trust
Work Address:	The Leeds General Infirmary, D Floor Br Great George Street Leeds
Postcode:	LS1 3EX
Telephone:	0113 3925153
Fax:	0113 3923766
Mobile:	

E−mail: david.bowen@leedsth.nhs.uk

Title: Dr Forename/Initials: Ann Surname: Hunter

Post: Consultant Haematologist
Qualifications: MD, MRCP, MRCPath
Organisation: Department of Haematology
Work Address: Leicester Royal Infirmary
Infirmary Square
Leicester
Postcode: LE1 5WH
Telephone: 0116 258 6602
Fax: 0116 258 5093
Mobile:
E−mail: ann.hunter@uhl−tr.nhs.uk

Title: Dr Forename/Initials: R Surname: Clarke

Post: Consultant Haematologist
Qualifications: MA, MD, FRCP, FRCPath
Organisation: Department of Haematology
Work Address: Royal Liverpool Hospital
Duncan Building, Prescott St
PO Box 147, Liverpool
Postcode: L69 3BX
Telephone: 0151 706344
Fax: 0151 706810
Mobile:
E−mail:

Title: Dr Forename/Initials: Jenny Surname: Craig

Post: Consultant Haematologist
Qualifications: MBChB, MD, FRCP(Edin), FRCPath
Organisation: Cambridge University Hospitals NHS Foundation Trust
Work Address: Department of Haematology, Box 234
Addenbrooke's Hospital
Hills Road, Cambridge
Postcode: CB2 2QQ
Telephone: 01223 596289
Fax: 01223 216407
Mobile:
E−mail: jenny.craig@addenbrookes.nhs.uk

Title: Dr Forename/Initials: MF Surname: McMullin

Post: Consultant Haematologist
Qualifications: MD MRCPath
Organisation: Belfast City Hospital
Work Address: Lisburn Road

	Belfast
Postcode:	BT9 7AB
Telephone:	028 90263903
Fax:	028 90263897
Mobile:	
E−mail:	m.mcmullin@queens.ac.uk

Title: Dr Forename/Initials: WJ Surname: Kell

Post:	Consultant Haematologist
Qualifications:	MD, MRCPI, MRCPath, MA
Organisation:	Department of Haematology
Work Address:	University Hospital of Wales
	Heath Park
	Cardiff
Postcode:	CF14 4XN
Telephone:	02920 746427
Fax:	029 20 744655
Mobile:	
E−mail:	Jonathan.Kell@cardiffandvale.wales.nhs.uk

Title: Dr Forename/Initials: Panos Surname: Kottaridis

Post:	Consultant Haematologist
Qualifications:	
Organisation:	The Royal Free NHS Trust
Work Address:	Department of Haematology
	Pond Street
	London
Postcode:	NW3 2QG
Telephone:	002 7794 0500 x 199
Fax:	020 7830 2092
Mobile:	
E−mail:	panagiotis.kottaridis@royalfree.nhs.uk

Title: Prof Forename/Initials: N Surname: Russell

Post:	Professor of Haematology
Qualifications:	MB,ChB, MRCP, MRCPath
Organisation:	Department of Haematology
Work Address:	City Hospital
	Hucknell Road
	Nottingham
Postcode:	NG5 1PB
Telephone:	01159 627708
Fax:	01159 627742
Mobile:	
E−mail:	nigel.russell@nottingham.ac.uk

Title: Dr Forename/Initials: P Surname: Vyas

Post:	Honorary consultant Haematologist
Qualifications:	MB, FRCPath
Organisation:	Department of Haematology
Work Address:	University of Oxford John Radcliffe Hospital Oxford
Postcode:	OX3 9DS
Telephone:	01865 310825
Fax:	
Mobile:	
E−mail:	paresh.vyas@imm.ox.ac.uk

Title: Dr Forename/Initials: B Surname: Gibson

Post:	consultant Haematologist
Qualifications:	MB, FRCPath
Organisation:	Royal Hospital for Sick Children
Work Address:	Yorkhill Glasgow
Postcode:	G3 8SJ
Telephone:	0141 201 0675
Fax:	0141 201 0857
Mobile:	
E−mail:	brenda.gibson@yorkhill.scot.nhs.uk

A67. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

Not applicable

PART A: Summary of Ethical Issues

A68. What are the main ethical issues with the research?

Summarise the main issues from the participant's point of view, and say how you propose to address them.

Leukaemia is a fatal disease. PIs are specifically trained in the care of such patients. The protocol fits into conventional clinical practice. There are a number of IMP's involved although Mylotarg has been recently given European approval and we have already treated several hundred patients (AML 15 trial), we have an enhanced telephone monitoring system already in place for picking up early signals in IMP use.
We don't see an ethical problem in relation to not divulging the MRD data during the development phase or indeed the intention to randomise, to monitor, or not to monitor in view of the fact that there is no known benefit of treating MRD other than morphological relapse.

Indicate any issues on which you would welcome advice from the ethics committee.

Question(s) 69–71 disabled.

PART B: Section 1 – List of proposed research sites

List below all research sites you plan to include in this study. The name of the site is normally the name of the acute NHS Trust, GP practice or other organisation responsible for the care of research participants. In some cases it may be an individual unit, private practice or a consortium – see the guidance notes.

Principal Investigators at other sites should apply to the relevant local Research Ethics Committee for site–specific assessment (SSA) using the Site–Specific Information Form. Applications for SSA may be made in parallel with the main application for ethical review (once the main REC has validated the application), or following issue of a favourable ethical opinion. Approval for each site will be issued to you by the main REC following SSA.

1. Name of the research site:

University Hospital of Wales

Principal Investigator for the study at this site:

Title: Prof Forename/Initials: AK Surname: Burnett

Post: Head of Department
Work Address: Department of Haematology
Cardiff University School of Medicine
Cardiff
Postcode: CF14 4XN

2. Name of the research site:

Birmingham Heartlands Hospital

Principal Investigator for the study at this site:

Title: Dr Forename/Initials: Donald Surname: Milligan

Post: Consultant Haematologist
Work Address: Department of Haematology
Birmingham Heartlands Hospital
Bordesley Green East
Postcode: B9 5SS

3. Name of the research site:

Leeds Teaching Hospitals NHS Trust

Principal Investigator for the study at this site:

Title: Dr Forename/Initials: D Surname: Bowen

Post: Consultant Haematologist
Work Address: D Floor, Brotherton Wing
Leeds General Infirmary
Great George Street, Leeds
Postcode: LS1 3EX

4. Name of the research site:

Christie's Hospital

Principal Investigator for the study at this site:

Title: Dr. Forename/Initials: M Surname: Dennis

Post: Consultant Haematologist
Work Address: Adult Leukaemia Unit
Christie Hospital, Wilmslow Road
Withington
Postcode: M20 4BX

5. Name of the research site:

Nottingham City Hospital

Principal Investigator for the study at this site:

Title: Prof Forename/Initials: N Surname: Russell

Post: Professor of Haematology
Work Address: City Hospital
Hucknell Road
Nottingham
Postcode: NG5 1PB

6. Name of the research site:

University Hopital of Leicester

Principal Investigator for the study at this site:

Title: Dr Forename/Initials: Ann Surname: Hunter

Post: Consultant Haematologist
Work Address: c/o Research Office
Leicester General Hospital
Postcode: LE5 4PW

7. Name of the research site:

Royal Liverpool Hospital

Principal Investigator for the study at this site:

Title: Prof Forename/Initials: Surname: Clark

Post: Professor of Haematology
Work Address: Prescot Street
Liverpool
Postcode: L7 8XP

8. Name of the research site:

Royal Free NHS Trust

Principal Investigator for the study at this site:

Title: Dr Forename/Initials: Panos Surname: Kottaridis

Post: Consultant Haematologist
Work Address: Department of Haematology
Pond Street
London
Postcode: NW3 2QG

9. Name of the research site:

Belfast City Hospital

Principal Investigator for the study at this site:

Title: Dr Forename/Initials: MF Surname: McMullin

Post: Consultant Haematologist
Work Address: Lisburn Road
Belfast
Postcode: BT9 7AB

10. Name of the research site:

John Radcliffe Hospital

Principal Investigator for the study at this site:

Title: Dr Forename/Initials: P Surname: Vyas

Post: Honorary Consultant Haematologist
Work Address: University of Oxford
John Radcliffe Hospital
Oxford
Postcode: OX3 9DS

11. Name of the research site:

Royal hospital for sick Children

Principal Investigator for the study at this site:

Title: Dr Forename/Initials: B Surname: Gibson

Post: Consultant Haematologist
Work Address: Royal hospital for sick Children,
Yorkhill
Glasgow
Postcode: G3 8SJ

PART B: Section 5 – Use of newly obtained human biological materials

1. What types of human tissue or other biological material will be included in the study?

Bone Marrow and peripheral blood

2. Who will collect the samples?

Investigators at local site

3. Will the samples be: *(Tick as appropriate)*

☑ Obtained primarily for research purposes?
☑ Surplus (i.e. left over from tissue taken in the course of normal clinical care for diagnostic or therapeutic purposes)?

4. Will informed consent be obtained from donors for use of the samples:

In this research?

◉ Yes ○ No

In future research?

◉ Yes ○ No

5. Will the samples be stored:

In fully anonymised form? *(link to donor broken)*

◉ Yes ○ No

In linked anonymised form? *(linked to donor but donor not identifiable to researchers)*

◉ Yes ○ No

If Yes, say who will have access to the code and personal information about the donor.

The cross reference Trial number, date of birth and initials will only be connectible with the master database, we see no circumstances where patient identifications will be needed.

In a form in which the donor could be identifiable to researchers?

○ Yes ◉ No

If Yes, please justify:

6. What types of test or analysis will be carried out on the samples?

1. Mutation detection / gene expression signatures
2. Immunophenotyping
3. Blood levels of activity (FLT–3 mTOR inhibiter)

7. Will the research involve the analysis of human DNA in the samples?

(●) Yes ( ) No

8. Is it possible that the research could produce findings of clinical significance for individuals? *(May include relatives as well as donors)*

( ) Yes (●) No

9. If so, will arrangements be made to notify the individuals concerned?

( ) Yes ( ) No (●) Not applicable

If No, please justify. If Yes, say what arrangements will be made and give details of the support or counselling service.

10. Give details of where the samples will be stored, who will have access and the custodial arrangements.

Diagnostic samples sent to one of the four reference immunophenotyping labs who will receive follow–up (Bristol, london, Birmingham, Cardiff). molecular screening (london–UCL, Cardiff). Cardiff University will have ultimate responsibility for stored material which will be in London UCL or Cardiff.

11. What will happen to the samples at the end of the research?

( ) Destruction

(●) Transfer to research tissue bank
(If the bank is in England, Wales or Northern Ireland a licence from the Human Tissue Authority will be required to store the tissue for possible further research.)

( ) Storage by research team pending ethical approval for use in another project
(Unless the researcher holds a licence from the Human Tissue Authority, a further application for ethical review should be submitted before the end of this project.)

( ) Storage by research team as part of a new research tissue bank
(The bank will require a licence from the Human Tissue Authority. A separate application for ethical review of the tissue bank may also be submitted.)

( ) Not yet known

Please give further details of the proposed arrangements:

Both the Department of Haematology at UCL in London or the university department in Cardiff have HTA licences to store.

PART B: Section 8 – Declarations

Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.
2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.
3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application of which the main REC has given a favourable opinion and any conditions set out by the main REC in giving its favourable opinion.
4. I undertake to seek an ethical opinion from the main REC before implementing substantial amendments to the protocol or to the terms of the full application of which the main REC has given a favourable opinion.
5. I undertake to submit annual progress reports setting out the progress of the research.
6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer.
7. I understand that research records/data may be subject to inspection for audit purposes if required in future.
8. I understand that personal data about me as a researcher in this application will be held by the relevant RECs and their operational managers and that this will be managed according to the principles established in the Data Protection Act.
9. I understand that the information contained in this application, any supporting documentation and all correspondence with NHS Research Ethics Committees or their operational managers relating to the application:

   – Will be held by the main REC until at least 3 years after the end of the study.

   – May be disclosed to the operational managers or the appointing body for the REC in order to check that the application has been processed correctly or to investigate any complaint.

   – May be seen by auditors appointed by the National Research Ethics Service to undertake accreditation of the REC.

   – Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.

10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.

Optional – please tick as appropriate:

☐ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

Signature: .....

Print Name: Alan K Burnett

Date: (dd/mm/yyyy)

Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co−sponsors by a representative of the sponsor nominated to take the lead for the REC application.

I confirm that: *(tick as appropriate)*

☐ This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

☐ An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.*

☐ Any necessary indemnity or insurance arrangements, as described in question A35, will be in place before this research starts.

☐ Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

☐ Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

☐ The duties of sponsors set out in the NHS Research Governance Framework for Health and Social Care will be undertaken in relation to this research.**

☐ The statutory responsibilities of sponsors set out in the Medicines for Human Use (Clinical Trials) Regulations 2004 will be undertaken in relation to this trial.

* Not applicable to student research (except doctoral research).
** Not applicable to research outside the scope of the Research Governance Framework.

Signature: .....

Print Name:

Post:

Organisation:

Date: (dd/mm/yyyy)