

**MEDICAL RESEARCH COUNCIL
WORKING PARTY ON LEUKAEMIA IN CHILDREN
UK NATIONAL RANDOMISED TRIAL FOR CHILDREN AND YOUNG
ADULTS WITH ACUTE LYMPHOBLASTIC LEUKAEMIA (ALL)**

**UKALL 2003
Version 7**

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Version 2: December 2003 (Administrative changes)
Version 3: April 2004 (Administrative changes)
Version 4: February 2006 (summary of changes page 6)
Version 5: August 2007 (summary of changes page 5)
Version 6: June 2008 (summary of changes page 4)
Version 7: August 2009 (summary of changes page 3)

**Sponsor: University of Sheffield
Reference Number 103727**

UKALL 2003

The most recent version of this Protocol including the flow diagrams can be downloaded from: www.ctsu.ox.ac.uk/projects/leuk/ukall2003

This national prospective randomised trial for childhood lymphoblastic leukaemia is testing whether MRD-based risk stratification allows delivery of optimal therapy with minimal toxicity. This document is intended to describe the study and to provide information about procedures for entering patients. The Council does not intend the protocol to be used as an aide-memoire or guide to treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary and these will be circulated to regional representatives. Centres entering patients for the first time are advised to contact the Clinical Trial Service Unit, Oxford, to confirm the correctness of the protocol.

Before entering patients into the trial, clinicians must ensure that the trial protocol has received clearance from their local research ethical committee and research office.

Clinicians must read the whole protocol before starting treatment and to contact one of the co-ordinators if there are any doubts or queries about the protocol.

Risks of intrathecal therapy

All medical staff involved in the care of patients with leukaemia **MUST** be aware that the **inadvertent** administration of vincristine by the **intrathecal** route is invariably **FATAL**. **Vincristine should NOT BE AVAILABLE when an intrathecal needle is *in situ*.** This protocol has been written to provide separation of intrathecal methotrexate administration from intravenous vincristine administration in time. An additional precaution is that the two drugs should not be administered in the same place.

It is appreciated that not all centres will be able to administer the drugs in the suggested order within a given week, and therefore local factors may determine an alternative scheme. The single most crucial element in avoiding errors is the appropriate education and training of all personnel involved in the administration of chemotherapy.

UKALL 2003 Version 7

Summary of Changes

Treatment flow diagrams are unchanged (Use single DI flow diagrams for low risk patients).

1. Closure of low risk randomisation. MRD low risk patients to henceforth receive a single delayed intensification. Pages 8, 23 -26
2. Extension of recruitment to high risk randomisation to August 2010. Page 23
3. MRD low risk re-defined to include patients who are MRD Positive $< 5 \times 10^{-5}$ at day 29. Patients will be categorised as low risk on a day 29 result alone without the need for a repeat level at week 11. Pages 23 – 31.
4. Change of recommendations for patients with CNS disease at presentation (CNS3). They should no longer receive cranial radiotherapy. In addition to receiving extra intra-thecal chemotherapy during induction, they should transfer to Regimen C if they have a slow early response or are MRD high risk at day 29. Page 27.
5. Routine central morphology review will cease from 1 October 2009 due to lack of funding. From that point on, slides for central review should be sent to Professor Vora from patients with CNS disease at presentation or those considered to be non-remitters at day 29. Page 32.
6. Information sheets and consent forms updated with new version number and date.

UKALL 2003 Version 6**Summary of Changes**

Treatment flow diagrams are unchanged.

1. **DOWN PATIENTS, URGENT SAFETY MEASURE.**
Due to persistent high treatment related mortality, Down syndrome patients will no longer be eligible for the trial randomisations but instead receive reduced intensity treatment. The mortality data, rationale for and details of treatment changes are described at pages 76 -77. Additional changes to reflect this amendment on pages 6, 23 and 24.
2. Revised recommendations for transplantation of patients with iAMP21 (previously known as AML1 amplification) – page 27.
3. Definition of what constitutes trial IMPs clarified after advice from Dr Elaine Godfrey, MHRA – pages 11 and 66.
4. Minor changes:
 - a) Information sheets and Consent forms:
 - Removed from protocol text
 - Additional information about sample banking in PISs
 - Version number and date updated to be consistent with protocol.
 - Minor other changes to reflect above amendments.
 - b) Contact details for Bristol MRD laboratory updated (Page 97)

UKALL 2003 Version 5**Summary of Changes****Trial Randomisations not affected and treatment flow diagrams are unchanged.**

1. Revised recommendations for treatment of specific sub-groups:
 - t(17;19) (*E2A-HLF*) – page 26
 - Patients 1 – 2 years of age with CNS disease at presentation (CNS 3) – page 25
 - Based on results of recent international study, definition of hypodiploidy changed from less than or equal to 44 chromosomes to less than 44 chromosomes. (pages 5, 6, 22 and 133)

3. Asparaginase study – changes to sample requirements – Pages 18, 32 and Appendix Q, page 115.

3. Supportive care recommendations for Downs syndrome patients. Page 75.

4. Appendix B, page 65 – drug information. Changes to improve compliance with EU clinical trials directive.

5. Addition of EUDRACT number - page 1.

- 6 **Upper age limit of eligibility increased to 25th birthday – pages 6, 21, 22 and 131,133 and 136.**

- 7 Documents specifying the standards required of laboratories providing molecular MRD results for the trial.added to appendix N, page92.

- 7 Minor changes:
 - a) Information sheets and Consent forms:
 - Version number and date updated to be consistent with protocol.
 - Minor other changes to reflect above amendments.
 - b) QOL study – 18 -25 section and contact details added, page 126.
 - e) Contact details for co-ordinators updated (Page 11)

**Version 4
Summary of Changes**

1. Revised recommendations for treatment of specific sub-groups:
 - Amplified RUNX1 (AML1) – page 25
 - Testicular disease at diagnosis – page 24
 - Obese patients – page 62
2. Changes to CNS directed therapy:
 - Day 1 IT Ara-C changed to IT MTX – pages 35, 44 and 54 + flow sheets 1, 8 and 15.
 - Recommendations on management of traumatic and CNS 2 taps – page 24
 - Instructions on formulating IT MTX and post-LP care. – page 24
3. **6-thioguanine (6TG) was found to increase remission deaths compared to 6-Mercaptopurine (6MP) in ALL97 and there are continuing problems with 6-TG related VOD during Delayed Intensification courses in this trial. Therefore 6MP replaces 6TG in the Delayed Intensification courses. Pages 32, 38, 40, 48, 50, 58 and 60; flow sheets 4, 6 11, 13, 18 and 20**
3. Recommendations for management of encephalopathy due to IT MTX – page 76.
4. Changes to SAE reporting to improve compliance with GCP guidelines – page 80. Note **NEW!** SAE reporting form, please use for reporting SAEs from now.
5. Addition of sponsor's name - page 1.
6. **Upper age limit for entry to trial increased to 20th birthday – pages 4, 5, 21 and 129.**
7. Statistics update – page 19.
8. Change of trial co-ordinators; Dr Goulden replaces Professor Hann, addition of co-ordinators for young adult patients – page 10.
9. Guidance on use of Erwinase – pages 5, 6 and 74.
10. Caution on use of chemotherapy in women of child bearing potential – page 64.
11. Minor changes:
 - a) Information sheets and Consent forms:
 - Age for consent changed to >16 years throughout UK on patient consent form.
 - Version number and date updated to be consistent with protocol.
 - Minor other changes to reflect above amendments.
 - b) CTSU new address – page 10
 - d) Asparaginase study, sample collection details and contacts list added, page 115

The trial randomisations are not affected by these amendments.

ENTRY FLOWCHART AND INITIAL TREATMENT ALLOCATION

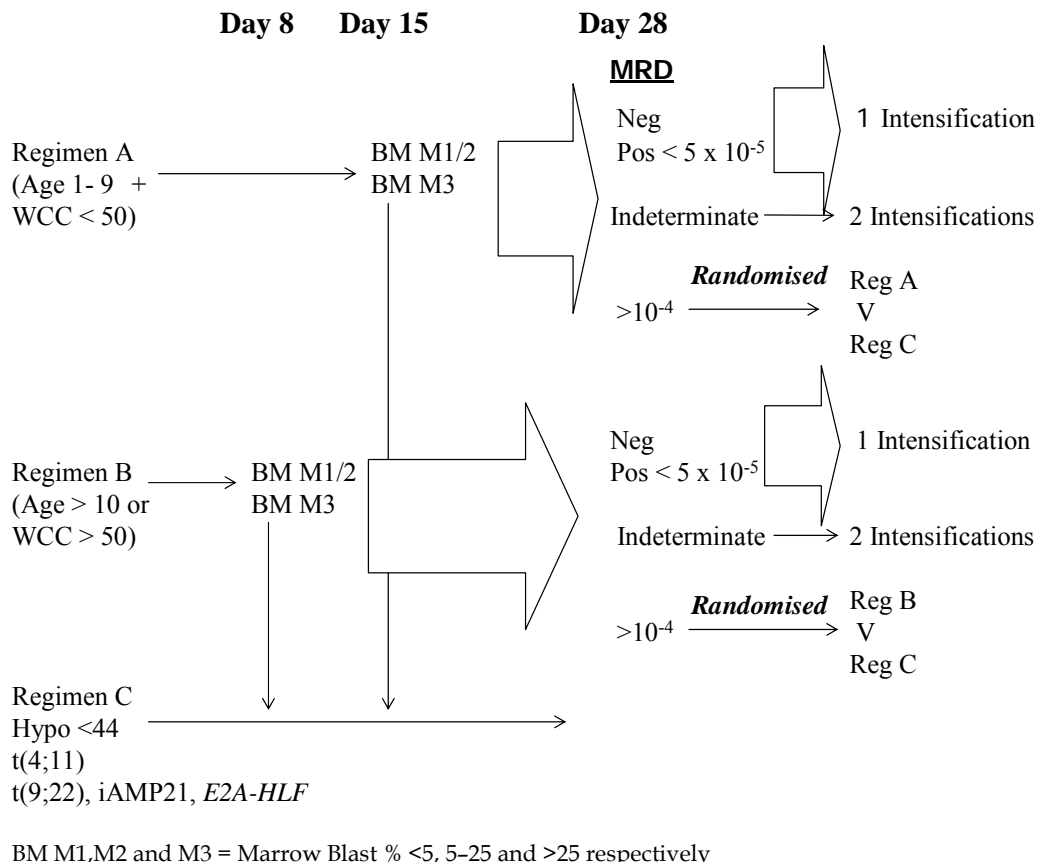
(See also pages 76 – 77 for guidance on treatment of Downs patients)

At diagnosis:

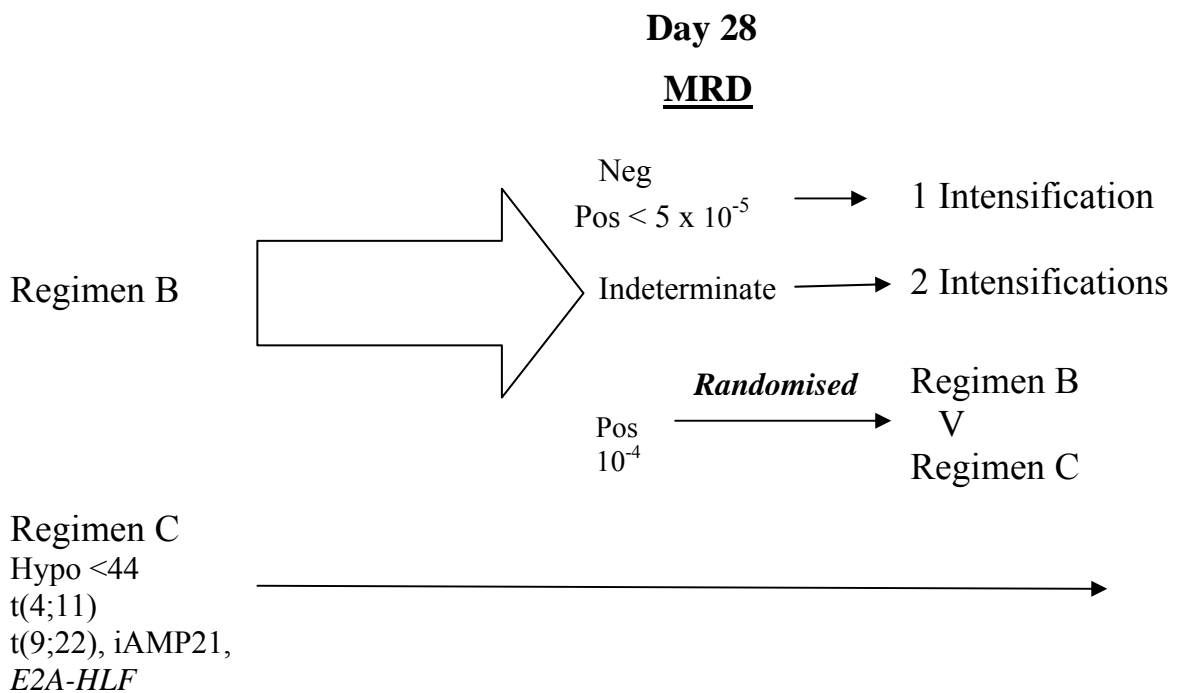
Under 12 months?	→	yes	Interfant trial
↓ no			
B-ALL ?	→	yes	UKCCSG protocol
↓ no			
BCR-ABL?	→	yes	REGIMEN C
↓ no			
MLL rearrangement ?	→	yes	REGIMEN C
↓ no			
Hypodiploid < 44 chromosomes ?	→	yes	REGIMEN C
↓ no			
AML1 amplification?	→	yes	REGIMEN C
↓ no			
≥ 10 years ?	→	yes	REGIMEN B
↓ no			
WBC ≥50x10 ⁹ /l ?	→	yes	REGIMEN B
↓ no			
REGIMEN A			
<u>Marrow morphology at day 8/15</u>			
If on regimen B, aged 1 -15 years: >25% blasts (M3) at day 8?	→	yes	transfer to Regimen C
If on regimen A: >25% blasts (M3) at day 15?	→	yes	transfer to Regimen C
Regimens A or B < 25% blasts (M1 or M2) at day 8/15?	→	yes	continue on Regimen to day 28
Regimen B ≥ 16 years?	→	yes	continue on Regimen B regardless of day 8/15 result
<u>At day 28</u>			
Regimens A or B >5% but <25% blasts (M2)	→	yes	transfer to Regimen C
> 25% blasts (M3)	→	yes	OFF PROTOCOL
<5% blasts (M1)	→	yes	MRD high risk randomisation

TREATMENT AND RANDOMISATION ALGORITHM

Age < 16 years



16th birthday – 25th birthday



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ETHICAL CONSIDERATIONS

The Scottish Multi-Centre Research Ethics Committee has approved this protocol. Patient and parent information sheets approved by the Scottish MREC are in Appendix. All participating centres must notify their local ethics committees before patients are entered into this trial. A statement of MRC policy on ethical considerations in the study of cancer therapy including the question of informed consent is available from the Cancer Therapy Committee Secretariat, MRC Head Office, 20, Park Crescent, London W1N 4AL, and may be used to accompany applications to the local ethical committee. The right of a patient and or parents/guardians to refuse to participate in or withdraw from the allocated treatment without giving reasons must be respected. The clinician must remain free to give alternative treatment to that specified in the protocol at any stage if he/she feels it to be in the patient's best interest. The reasons for doing so should be recorded and the patient will need to remain in the study for the purposes of follow-up and data analysis according to the treatment option to which he/she has been allocated.

NOTES FOR MHRA

- UKALL 2003 was conceived (2001), designed (2002) and opened (October 2003) prior to the EU Directive on clinical trials being brought into law.
- It is testing whether treatment for children with Acute Lymphoblastic Leukaemia (ALL) can be tailored according to the risk of relapse defined by a sensitive test for early response called MRD. Children are allocated to high and low risk groups according to their MRD response after a month's treatment. Those in the high risk group are randomised to treatment intensification, whilst those in the low risk group are randomised to treatment reduction. It opened in October 2003 and has so far accrued 800 patients from the UK and Ireland.
- The combination chemotherapy regimens contained within the trial protocol have been rigorously tested in a previous UK trial, as well as in Germany and USA, and found to be as effective and safe as any other treatment regimens for this condition.
- All the drugs, bar Pegylated Asparaginase (Oncospar, see below), Mercaptopurine 10 mg tablets, and special formulations of Mercaptopurine and Methotrexate solutions, contained within this protocol have a UK licence for treatment of acute lymphoblastic leukaemia.
- Pegylated Asparaginase, Oncospar, has a German but not a UK licence. There is no alternative for Asparaginase. There are multiple formulations made by several different manufacturers. Historically the most commonly used in the UK, Erwinase, went out of production in the late nineties and has only recently come on the market again.
- We applied for DDXs for Oncospar and Medac E.Coli Asparaginase (unpegylated formulation of Oncospar) when the trial opened, and these were rolled over into CTAs (MF 8000/12172, MF 8000/12713) in May 2004.
- The experimental aspect of the trial, therefore, is not the treatment regimens or any particular drug within them, but a method for tailoring these "standard" treatments to risk groups defined in a novel fashion.
- Therefore, the only drugs categorised as IMPs (and which are covered by the CTAs) in the protocol are Oncospar, Mercaptopurine 10 mg tablets and the special formulations of Mercaptopurine and Methotrexate solutions. **ALL OTHER DRUGS AND THE COMBINATIONS IN WHICH THEY ARE USED WITHIN THE TREATMENT REGIMENS ARE STANDARD THERAPY FOR ALL AND ARE THEREFORE NOT DEFINED AS IMPs.**
- We have defined SUSARs (see Appendix I) as serious adverse reactions NOT due to:
 - a. complications of bone marrow failure (infection, bleeding and anaemia)
 - b. drug side effects described in Appendices B and E
 - c. drug side effects described in the SpCs of individual drugs
- Death due to the above complications or side effects is unfortunately expected in a small minority of patients and will NOT be considered a SUSAR unless there are excess numbers compared to previous trials or those seen in comparable trials elsewhere.
- The trial is monitored by an independent, MRC appointed, Leukaemia Data Monitoring and Ethics Committee which reviews the results of the trial randomisations as well as toxicity data annually.

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1 SYNOPSIS

Title:

A randomised trial to evaluate whether treatment can be reduced without compromising efficacy in a low risk group of patients defined by a molecular minimal residual disease (MRD) technique; and to evaluate whether further post-remission intensification can improve outcome for a MRD-defined high risk group.

Brief Rationale:

Around 85% of all children with ALL are now cured. However, historically around 50% were cured with much less intensive treatment and the attendant reduction in risks incurred by such therapy. On the other hand, still around 15% of patients will experience a recurrence of their leukaemia, necessitating further often highly toxic treatment. Until now it has not been possible to gauge with accuracy which patients will fall into these low and high risk categories. Recent developments in molecular techniques for assessing minimal residual disease in the bone marrow once a patient is in remission by standard morphological criteria provides such a tool. It may therefore be possible to refine treatment so that it is more or less intensive, based on MRD defined criteria

Trial Summary

The study will carry forward stratifications and treatment allocation based on age, presenting WCC, and treatment response at day 8 & 15 of induction. In addition, eligible patients will be stratified and entered into treatment intensification and reduction randomisations according to their MRD status at the end-of-induction and week 11. Those in the MRD low risk group will be randomised between one and two Delayed Intensifications, while those in the MRD high risk group will be randomised to receive standard therapy (Regimens A or B) versus Regimen C (Augmented intensity schedule) of ALL 97/99/01. Blood Asparaginase antibodies and Asparaginase pharmacokinetic studies will be measured at defined time-points on treatment in a limited number of patients. Quality of Life will be assessed using a measure that is brief, has adequate psychometric properties and with parallel versions available for both parents and children (PedsQL cancer module, Varni 2002). The burden of care on the family will also be explored using a brief, focussed questionnaire. These measures will be given to the families at five time points: diagnosis (retrospective 'pre' diagnosis baseline), at week four, at the start of maintenance chemotherapy (following completion of all intensification), at the end of treatment and one year following the end of treatment. The measure will take no more than 5 minutes to complete and will be administered in the outpatient clinic.

Trial conduct:

This trial will be conducted according to the Declaration of Helsinki (<http://www.wma.net/e/policy/pdf/17c.pdf>) and the principles of Good Clinical Practice (<http://www.emea.eu.int/pdfs/ich/013595en.pdf>).

2. FULL RATIONALE:

What is the problem to be addressed?

Despite significant improvements in outcome over the last three decades, around 25% of children with Acute Lymphoblastic Leukaemia (ALL) relapse after first-line treatment and require salvage therapy which is toxic, expensive and often unsuccessful. On the other hand,

around 50% of patients are probably over-treated at present since this proportion was cured by less intensive therapy in UKALL VIII. Precise identification of these prognostic sub-groups would allow intensity of therapy to be adapted to the risk of relapse. Compared with conventional criteria such as age, gender and WCC, monitoring for the presence of sub-microscopic levels of leukaemia (Minimal Residual Disease, MRD) in patients in morphological complete remission is a more sensitive and specific indicator of relapse risk. Techniques to measure MRD are now well established and validated, and this large national prospective randomised study will test whether MRD-based risk stratification allows delivery of optimal therapy with minimal toxicity. Asparaginase is an important component of ALL treatment regimens. There is conflicting evidence on the degree to which silent sensitisation to Asparaginase influences treatment efficacy. We will assess the frequency of sensitisation and its impact on the efficacy of asparaginase therapy by screening for neutralising antibodies and pharmacokinetic monitoring of Asparaginase activity. Lastly, we will measure the Quality of Life impact of the different treatment arms on the patients and their families.

What are the principal research questions to be addressed?

Randomised:

1. Can treatment be reduced without compromising efficacy in a MRD-defined low risk group?
2. Does further post-remission intensification improve outcome for a MRD-defined high risk group?

Non-randomised:

1. What is the frequency of sensitisation to asparaginase and its impact on efficacy of second exposure to the drug (Appendix Q)?
2. To Measure the Quality of Life impact of the different treatment arms on the children and their families.

Why is a trial needed now?

This is an opportune time to conduct a study centred on Minimal Residual Disease (MRD) monitoring. Developments in technologies to assess MRD have reached a stage where quality assured results can be turned-round rapidly enough for use in support of treatment decisions. This gives us an opportunity to test whether adjustment of treatment according to MRD allows improvement of cure rates for high risk patients and reduction of treatment for those at low risk of relapse. These will form the principal research questions in this study proposal. The recently closed MRC UK childhood ALL study 97/99/01 was a randomised trial testing the efficacy and toxicity of dexamethasone and thioguanine compared to prednisolone and mercaptopurine respectively. On the Data Monitoring Committee's advice, this trial closed to accrual in June 2002. The decision was based on an interim analysis showing significantly fewer CNS and systemic relapses amongst Dexamethasone recipients and increased risk of Veno-Occlusive Disease (VOD) of the liver in thioguanine recipients. Preliminary results of CCG 1922¹ (1995 – 1999) and CCG 1952², which tested the same two interventions, concord with these result. Analysis of the cumulative data from ALL97/99/01 and CCG studies is planned.

MRC UK childhood ALL studies.

Over the last 30 years, a network of clinicians supported by the MRC have realised an excellent accrual to national childhood ALL studies such that the most recent trial, MRC

UKALL97/99/01, recruited >90% of all new cases in the UK. In addition to addressing important questions relating to the biology and treatment of childhood ALL within randomised studies, the network has overseen, and been primarily responsible for, standardisation of therapy and uniformity of outcomes across the UK^{3;4}. Recent studies have addressed both treatment efficacy and toxicity questions. UKALL X (1985 – 1992, none vs 1 vs 2 intensification courses) & XI (1992 – 1997, 2 vs 3 intensification courses) tested the benefit of post-remission intensification therapy. The cumulative effect of three post-remission intensification courses was a 20% improvement in 5 year EFS^{5;6}. The benefits of intensification therapy have been confirmed by a worldwide meta-analysis⁷. UKALL XI also tested and found that intensive intrathecal chemotherapy is as effective as cranial radiotherapy in preventing CNS relapses in the vast majority of patients⁸, and this has been confirmed by a meta-analysis which included 13,000 patients⁹. In addition, UKALL XI reduced anthracycline exposure and associated risk of cardiac toxicity. However, patients in the 3 intensifications arm of UKALL XI, despite showing an 8% EFS advantage over the 2 intensification arm in that study, achieved approximately the same EFS (68%) as the 2 intensification arm in UKALL X. This lack of improvement in overall EFS between the two studies may have been due to omission of anthracyclines from induction in UKALL XI, and resulted in a shortfall of 5-10% in EFS for UK patients compared to patients treated in the US and Germany during this period, although overall survival was equivalent. Pharmacokinetic studies indicated that, at equivalent unit dosage, the potency of Erwinia-derived asparaginase used in the UK until March 2001 was less than of the E Coli-derived product used in the US and Germany. Therefore, changes to asparaginase dosage and frequency were introduced just over a year into the then current study (ALL97, 1997 – 2002). Also, in recognition of the EFS disadvantage for UK patients, the MRC childhood leukaemia working party approved adoption of the then current US CCG protocols in November 1999. Risk stratification based on age, presenting WCC and early response to therapy were important components of these protocols and were adapted into the modified protocol ALL97/99. Preliminary analysis suggests that these changes have resulted in an improved EFS (78% at 3 years) equivalent to that in the US and Germany. Fortunately, the interventions being tested in ALL 97 were not affected by these modifications, and ALL97/99 continued accruing patients to the original randomisations until June 2002.

Risk Stratification

Although treatment stratification based on conventional criteria was introduced in ALL97/99, risk groups identified by these variables are relatively non-specific. For example, a high-risk group with a 5 year EFS of around 50% defined by age, gender and presenting WCC identifies only 20% of patients destined for relapse, with the majority of relapses still arising out of the remaining, apparently, low risk patients. Similarly, although slow early response, measured as slow clearance of blood or marrow blasts after a week or two of induction therapy, is associated with a relatively high risk of relapse, over 60% of relapses arise from the group with a rapid response. Assessment of MRD, appears to offer a very sensitive and specific means of distinguishing between patients who will and will not relapse. Refinement of risk stratification based on measurement of MRD is being adopted by both the German BFM and US COG groups. BFM 2000, their current trial, is testing MRD based treatment stratification and has now accrued nearly 800 patients. It provides both a role model and a test of the feasibility of performing such a trial.

Minimal Residual Disease

Several large studies have reported on the sensitivity and specificity of positive and negative MRD results at different time points during treatment and on different protocols

(BFM90¹⁰ and EORTC¹¹). These studies have revealed that the positive and negative predictive value of a particular MRD result depends on the sensitivity of the technique used to measure it, the time point at which it is measured, and the treatment received by the patient before and after the point of assessment. Despite differences in these variables amongst published studies, there is sufficient consensus in the results relating to certain clinical end-points to derive some general conclusions from them. Firstly, patients who become MRD negative for 2 clonal markers by the end of induction (EOI) have a <5% risk of relapse. Secondly, patients who have significant levels of MRD at the EOI have a 30-40% relapse risk. Preliminary data from patients treated on the unmodified ALL97 protocol confirm these results, particularly in regard to the proportions of MRD positive and negative patients at the end of a 3-drug induction schedule (*Goulden et al, personal communication*). The relapse risk associated with MRD status is also consistent with that cited above. However, current post-remission therapy is significantly different from that received by these patients and these results are being confirmed in patients treated on the CCG-adopted treatment schedules.

Treatment Reduction

Fifty-percent of patients treated on UKALLVIII were cured by a regimen without post-remission intensification therapy. Therefore, these 50% are over-treated by current protocols which contain two post-remission intensification courses. Since the 40 - 50% of patients who clear MRD rapidly by the end of consolidation have a >95% chance of cure, there must be substantial overlap between this MRD Low-Risk (MRD LR) group and the group of patients who can be cured without post-remission intensification. A treatment reduction randomisation (one vs two intensifications) is therefore planned for MRD LR patients

Treatment Intensification

Patients with substantial MRD (MRD High Risk) at the end of induction sub-divide into two groups on follow-up. In around 70% of these patients (40% of all patients) the MRD level falls below 1:1000 by week 12⁶. This group have a 30% relapse risk and, as in BFM 2000, we believe they should be the subjects for a trial of further intensification of therapy. The remaining 30% (10% of all patients) have persistent MRD >1:1000 at post-induction follow-up, and an associated 50-60% risk of relapse. The optimal therapy for this MRD very high risk (VHR) group is uncertain. We believe this MRD VHR group, along with VHR patients defined by chromosome abnormalities such as t(9;22), near-haploidy and t(4;11), should be the subject of an international trial of innovative treatment. In the interim, we intend including them with MRD IR patients in the intensification randomisation.

UK MRD Laboratory Network

At an early stage of trial planning, we recognised that there was no laboratory capability in the UK for providing quality assured and rapid turn around MRD results. Much effort has been directed in the last 24 months to creating a laboratory infrastructure capable of supporting the MRD aspect of this study. A network of five laboratories across the UK has been shaped into a virtual single laboratory co-ordinated by clinical and scientific leads based at Bristol Children's Hospital. The network works to common standard operating procedures and participates in national and European External Quality Assurance schemes. It has received financial support from the Leukaemia Research Fund to establish a fully validated technique for MRD monitoring using the TaqMan instrument for RQ-PCR of antigen receptor gene rearrangements. Having established this technique, the laboratories have undertaken a retrospective study of 80 B-cell precursor patients treated on the CCG-modified treatment regimens of ALL97/99. Results of this study are summarised below. At the time of writing of the protocol, the network is running prospective laboratory and clinical pilot

studies. The Leukaemia Research Fund has extended its support of the laboratory network for a further 3 years.

Results of Retrospective pilot MRD study

Samples from 100 patients treated on the CCG-modified ALL 97/99 treatment regimens between September 1999 and October 2000 were studied for MRD using the RQ-PCR technique described above. So far, results are available for 80 Precursor B-ALL patients. At day 29 (end-of-induction), around 50% of patients have MRD at a level of greater than one cell in 10^4 . However, there are fewer MRD negative patients than expected (only 20% compared to expected 40% from BFM 95 and 2000). The likely reason for this finding is the UK 3 drug Regimen A induction and absence of prednisone pre-phase. Around 30% of the Regimen A patients have low positive results ($<10^{-4}$). The clinical outcome of this group is uncertain. We cannot assume that they have the same low relapse risk as the true negatives, nor that the relapse risk is as high as for the $> 1 \times 10^{-4}$ positive patients. Further results on the remaining 40 cases, including those with T-ALL, and clinical outcome data will be available by April 2004. Based on these results, we have decided to measure MRD at week 11 in patients with a negative or low positive ($<10^{-4}$) results at day 28 and, of these, enter those who are negative week 11 into the treatment reduction randomisation.

Justification for the use of Pegylated Asparaginase (Oncaspar)

Leukaemic cells are unable to synthesize asparagine due to a lack of asparagine synthetase and are dependent on an exogenous source of asparagine for survival. Rapid depletion of asparagine which results from treatment with the enzyme L-asparaginase kills the leukaemic cells. Normal cells, however, are less affected by the rapid depletion due to their ability to synthesize asparagine. This is an approach to therapy based on a specific metabolic defect in some leukaemic cells which do not produce asparagine synthetase.

The native forms of the enzyme derived from *E.coli* (used in ALL 97/99)) and *Erwinia chrysanthemi* are highly immunogenic. Immunoglobulin G anti-asparaginase antibodies are frequently produced resulting in either overt hypersensitivity reactions after repeated exposure and/or 'silent' antibodies producing inhibition of enzyme activity and reduced asparagine depletion. Such antibody production is reported in 60 – 70% of patients and, by inhibiting enzyme activity, affects the extent and duration of asparagine depletion with a resultant influence on lymphoblast cytotoxicity. Pegylated asparaginase (a conjugate of monomethoxypoly ethylene glycol and native *E. coli* Asparaginase) has a significantly longer half life of 5.73 days, an A.U.C. of 10.2 I.u/ml (0.14 I.u/ml for native *E. Coli*), at a dose of 1000u/m^2 and a slower clearance of 14 – 16 days depending on route of administration, even in heavily pre-treated patients.

The production of antibodies is reported to be less with this conjugate product, and hence there should be less overt hypersensitivity and less "silent" inactivation. Patients will therefore more likely derive the benefit of treatment with asparaginase by using this agent since there will be less concern about anaphylaxis, which is often a reason for stopping the use of asparaginase; and there will be fewer patients with "silent inactivation", a situation where although asparaginase is being administered it is being inactivated without overt hypersensitivity. An additional benefit is the reduction in the number of injections necessary from 9 in induction to two and from 6 in intensification phases to one.

Long-term studies, in animals, of carcinogenesis have not been performed with Oncaspar; nor have studies been performed on impairment of fertility. Oncaspar did not exhibit a mutagenic effect when tested against *Salmonella typhimurium* strains in the Ames assay.

Animal reproduction studies have not been conducted with Oncaspar and it is not known whether it can cause fetal harm when administered to a pregnant woman, or if it can affect reproductive capacity. However, studies of long-term survivors of treatment for a variety of childhood cancers, including patients with ALL treated with a variety of other types of asparaginase do not suggest that there is any teratogenic effect as a consequence of the chemotherapy.

Asparaginase Study

Aims

- (i) Development of a rapid high throughput assay to accurately detect AEP expression at diagnosis in blast cells, bone marrow and peripheral blood plasma.
- (ii) Correlation of AEP levels with asparaginase levels and the formation of anti-asparaginase antibodies.
- (iii) Identify antigenic epitopes responsible for formation of antibodies to asparaginase.

Quality of life Study

Whilst event free and overall survival are paramount, the quality of life (QoL) of the child and family during therapy is also very important and until now this has not been formally evaluated. It is proposed that this study will assess quality of life of the children treated within the ALL 2003 trial and in particular compare the impact of the different treatment regimens on QoL. It will also aim to describe changes in QoL throughout treatment and up to 12 months after its completion. A summary of the methodology is provided in answer to Q 3.11 below.

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3. STATISTICAL CONSIDERATIONS

What are the planned trial interventions?

1. MRD Low Risk Group (negative or positive $< 10^{-4}$ at d29) randomised between two delayed intensifications and one delayed intensification. **Randomisation closed August 2009.**
2. MRD High Risk Group (positive $>10^{-4}$ at d29) randomised between current standard therapy and Regimen C of ALL 97/99/01.
3. MRD Indeterminate Group. Included in this group will be patients for whom a clinically relevant MRD result is not available. This group will continue on current standard therapy with two delayed intensifications.

What are the proposed practical arrangements for allocating participants to trial groups?

Allocation obtained by telephone call to central trials unit. Randomisation, by computer programme, stratified by MRD result, balanced on gender, age (<10,10+), and WBCx $10^9/l$ at diagnosis (<50,50+) by method of minimisation.

What are the proposed methods for protecting against other sources of bias?

All analyses will be intention to treatment. Blinding is not possible, but primary end points are survival and event-free survival and therefore not prone to ascertainment bias. Events are clearly defined as death or relapse requiring major extra treatment.

What are the proposed outcome measures?

Primary:

Event Free Survival (EFS) (relapse or death) and Survival

Secondary:

Remission rate, bone marrow relapse, non-bone marrow relapse

Acute and late toxicity

Days in hospital

Quality of Life

What is the proposed sample size?

Total accrual over 6 years will be 2500 patients. **See version 6 for original sample size calculations and below for revised calculations.**

Accrual update August 2009

MRD High Risk randomisation

Power calculations for the MRD high risk randomisation at the planning stage of UKALL 2003 were predicated on results of a retrospective MRD study in patients treated on ALL 97/99 referred to above. The expectation from that study was that 50% of patients would fall into the MRD high risk category and carry a 30% risk of relapse. Non-randomised changes in therapy have resulted in the MRD high risk group being both smaller (around 30%) and having a better outcome (17% actuarial risk of relapse at 5 years) in UKALL 2003 than expected based on our ALL97/99 results. Only 19 of 346 randomised MRD high risk patients had relapsed at last review in January 2009. Whilst being excellent news for patients, this improvement in overall outcomes has resulted in under-accrual to the high risk randomisation. We have tried various means of increasing recruitment including increasing the age of entry to 25 years (older patients are more likely to be high risk) and resolving obstacles to the uptake of randomisation by physicians and patients. Unfortunately, although

randomisation rates have improved with time, the rise has not been sufficient to make up the shortfall created by the improved overall efficacy of treatment. **In view of this under-accrual, on the recommendation of the Data Monitoring Committee and Leukaemia Trials Steering Committee, the high risk randomisation will continue to accrue patients till August 2010.** We anticipate that 450 patients will be entered into the high risk randomisation by August 2010 against the original expectation of 660. Revised power calculations based on 450 patients randomised, with an 80% EFS in the standard treatment arm, yields an 84% chance of detecting a 10% improvement in EFS to 90% in the intensification arm (82% allowing for 10% drop out).

MRD Low Risk Randomisation

A slight broadening of the molecular definition of MRD low risk and inclusion of day 29 low positive patients who become negative at week 11 has resulted in a higher (around 50%) than expected (30%) proportion of patients being classified as MRD low risk. The proportion of eligible patients being randomised is also better than the high risk group, such that accrual to this randomisation is fast approaching target levels. **This randomisation was closed in August 2009 after accruing the target number of patients (450 against a target of 400)). At that point, the 5 year relapse risk for low risk patients was < 5% and, based on the recently released results of US and German trials, the trial investigators recommended that low risk patients should receive a single delayed intensification. At the same time, the definition of MRD low risk was changed in two respects. Firstly, the low risk group would also include patients with MRD < 10⁻⁴ at day 29 regardless of the level at week 11 as their outcome is very similar to that of MRD negative patients. Secondly, as there is only a very small risk of the MRD level increasing between day 29 and week 11, patients will be defined as low risk on a day 29 result alone.**

What is the planned recruitment rate?

Recent recruitment into the current childhood ALL trial through the MRC childhood leukaemia network has been 360 patients per annum, with over 90% of these randomised. This network is still functioning and has approved the trial. Recruitment should continue for 6 years.

What is the likely rate of loss to follow-up?

Attrition and loss of follow-up from MRC Childhood Leukaemia Trials has been historically very low (<1%).

Planned analyses

Log rank survival analyses of EFS and of survival, by randomised allocation. Secondary analyses will include log rank analysis of relapse free survival, and of bone marrow and non-bone marrow relapses separately; overall remission rate and acute toxicities as proportions. Outcomes of subgroups according to MRD status at post-induction time-points and other biological variables (gene expression etc) will be analysed. Results will be considered hypothesis-generating only.

What is the proposed frequency of analyses?

Primary analyses will be once a year after 4 years of recruitment, at which time those recruited in the first year will have at least 3 years follow-up. Toxicity will be monitored at least annually.

4. ELIGIBILITY AND INITIAL RISK STRATIFICATION (Flow diagram page 4):

UKALL 2003 is open to all patients from age 1 (the first birthday) to 25th birthday with ALL diagnosed using standard criteria, except the following:

1. Infants less than a year old should be entered onto the relevant Interfant ALL study.
2. Patients with B-ALL (Burkitt-like, t(8;14), L3 morphology, SMIg positive). Patients with this disease should be treated on a suitable protocol for this condition, such as the UKCCSG B cell NHL/ALL trial.
3. Patients with Philadelphia-positive ALL (t(9;22) or BCR/ABL positive) will start induction therapy on this protocol but transfer to the European Intergroup Protocol (children) or UKALL XII (young adults) on completion of induction.
4. Informed consent from parents and or patients must be obtained before starting treatment.
5. The treating hospital should have appropriate national and local ethical approval for the conduct of this trial.

Initially, eligible patients will be stratified into three risk groups based on the following criteria: (See also pages 76 - 77 for guidance on treatment of Down syndrome patients)

- (a) **Standard risk:** all children >1<10 years with a highest white cell count before starting treatment of $<50 \times 10^9/l$, and who do not have BCR-ABL, hypodiploidy (≤ 44 chromosomes), or an MLL gene rearrangement.
- (b) **Intermediate risk:** all children ≥ 10 years old, or with a diagnostic WBC $\geq 50 \times 10^9/l$ (or both) and who do not have BCR-ABL, hypodiploidy (≤ 44 chromosomes), or an MLL gene rearrangement.
- (c) **High Risk:** all children, irrespective of initial risk category, who have a slow early response (SER) as defined below – see section 6 - together with those who have BCR-ABL (induction only), hypodiploidy (< 44 chromosomes), an MLL gene rearrangement or amplification of RUNX1 (previously AML1, see page 27 for definition of abnormality and further treatment recommendations). These patients will not be eligible for the MRD randomisation **except those > 16 years with a SER (see young adult appendix).**

Patients will then start treatment according to their risk group as follows:

- (a) **Standard risk**, (around 60-65% of the total): regimen A - three-drug induction.
- (b) **Intermediate risk**, (around 20- 30% of the total): regimen B - four-drug induction.
- (c) **High risk** (around 10-12% of the total): **Except > 16 year age group with a SER (see young adult appendix), these patients will not be eligible for MRD randomisation** They will be allocated regimen C - four drug induction, augmented BFM consolidation, Capizzi interim maintenance, and two further BFM-style intensification periods of extended duration.

5. MINIMAL RESIDUAL DISEASE (MRD) RISK STRATIFICATION AND RANDOMISATION (Flow diagram page 5)**The following patients will be eligible for entry into the randomisations:**

1. Standard or Intermediate Risk as defined above.
2. Morphological Complete Remission (BM1 Marrow) at Day 29 of Induction.
3. Availability of MRD results at Day 29.
4. Informed consent obtained.
5. Induction given as protocol.

Patients not eligible for entry into the MRD randomisation:

1. Down syndrome patients (as of June 2008, see pages 76 -77).
2. High Risk as defined above. These patients will receive Regimen C.
3. Day 28 non-remitters. These patients will receive Regimen C if BM2 or go off-protocol if BM3 (see below for definitions of BM2 and BM3).
4. MRD Indeterminate Group (No result) will continue on previously assigned therapy.
5. Sub-optimal induction therapy. The clinical significance of day 28 MRD is uncertain in patients who have received sub-optimal induction therapy. Please discuss these patients with a co-ordinator.

Randomisations**Patients will be assigned to MRD risk groups based on day 29 and post consolidation MRD results and randomised as follows:**

- MRD Low Risk Group (MRD negative or positive $<5 \times 10^{-5}$ at day 29) will continue on previously assigned Regimens (A or B) and receive a single delayed intensification (1 vs 2 DI randomisation closed August 2009).
- MRD High Risk Group (MRD positive $> 1 \times 10^{-4}$ at day 29) randomised between previously assigned Regimen (A or B) and Regimen C.
- MRD Indeterminate Group (No MRD result or MRD between 5×10^{-5} and 1×10^{-4}) will continue on previously assigned Regimen (A or B) and receive two delayed intensifications

6. DEFINITIONS OF MARROW STATUS AND MRD RESPONSE:

Day 8/15 Response will be assessed by routine light microscopy of Romanowski stained marrow locally and categorised as:

BM1 marrow	<5% blasts regardless of the number of lymphocytes present.
Hypocellular BM1 marrow	<5% blasts in a hypocellular marrow.
BM2 marrow	5-25% blasts, regardless of the number of mature lymphocytes present.
BM3 marrow	>25% blasts.

Rapid early responder (RER):

day 8 (regimen B) or 15 (regimen A) marrow equal to or less than 25% blasts.

Slow early responder (SER):

day 8 (regimen B) or 15 (regimen A) marrow more than 25% blasts.

NOTE THAT SLOW EARLY RESPONSE IN PATIENTS WHO HAVE PASSED THEIR 16th BIRTHDAY AT THE TIME OF DIAGNOSIS DOES **NOT** RESULT IN INTENSIFIED TREATMENT ie DO NOT TRANSFER SUCH PATIENTS TO REGIMEN C.

Day 29 MRD will be assessed centrally and response categorised as follows:

(The time-point at which these marrows are taken should be delayed if neuts < 0.5 and/or platelets < 50).

MRD Low Risk Negative or positive < 5×10^{-5} at day 29.

MRD High Risk Positive > 1×10^{-4} at day 28.

MRD Indeterminate No result or MRD between 5×10^{-5} and 1×10^{-4} .

7. SPECIAL CATEGORIES:

1. CNS disease at presentation (CNS3):

1. CNS disease at presentation :

These include patients with 1) CNS3 - the presence of $>5/\text{cumm}$ unequivocal lymphoblasts in the CSF or 2) cranial nerve palsy, parenchymal brain infiltrate or ocular infiltrate even in the absence of CSF blasts. CNS3 patients should start treatment on an NCI-risk directed induction regimen but receive weekly intrathecal methotrexate until two consecutive clear CSFs have been obtained for a total of 4 intra-theicals during weeks 1 – 4. Subsequent treatment will depend on treatment response during induction:

1) If CSF is clear of blasts after 2 ITs AND rapid marrow response at day 8/15 AND MRD low risk or indeterminate at day 29 – continue NCI-risk directed therapy.

2) If CSF is clear of blasts after 2 ITs BUT slow marrow response at day 8/15 OR MRD high risk at day 29 – transfer to Regimen C.

3) Persistent blasts in CSF after 2 ITs regardless of marrow response – transfer to Regimen C + cranial radiotherapy as below.

This is a change from previous versions of the protocol in which cranial radiotherapy was recommended for patients with CNS disease. The change is based on recently reported results from St Jude's (Pui NEJM 2009; 360:2730) showing that these patients have a good overall survival if they receive response directed intensive systemic therapy without radiotherapy.

In addition to the extra intra-theicals during induction as above, patients with ocular disease should receive ocular radiotherapy and patients with parenchymal brain infiltrates should receive 24Gy cranial radiotherapy in 15 daily fractions during weeks 5-8 (see appendix K) with three concurrent intrathecal methotrexate injections. **Following radiotherapy they should receive intrathecal methotrexate as prescribed in the relevant regimen. The individual regimens provide specific timing and dosages.** These patients are still eligible for the trial randomisations.

2. Traumatic or CNS2 LP at diagnosis

There is evidence that a traumatic LP *with blasts* (TLP+) or CNS2 (atraumatic with < 5 blasts/microlitre) tap at diagnosis is associated with a higher risk of CNS relapse, possibly because of poor penetration of MTX into the meningeal space at subsequent treatments due to a small extra-dural haematoma at the LP site. Therefore, patients with > 10 red cells/microlitre *and blasts* in their CSF or CNS2 tap at diagnosis should receive weekly IT MTX for a total of 4 intra-theicals during weeks 1-4 of induction. *Traumatic tap without blasts in the CSF should receive standard IT therapy.*

3. Formulation of IT MTX and post-LP care

Some centres may be using a highly concentrated formulation of Methotrexate which results in insufficient volume to fill the dead space and reach ventricular spaces. Methotrexate for intra-theical use should be made up at a maximum concentration of 2.5mg/ml so as to provide an adequate volume of distribution across the CNS. We recommend laying the patient prone for at least 1 hr after the intra-theical procedure. Experiments in primate models indicate better ventricular distribution of intra-theical chemotherapy if the subject lies prone for this period after the procedure.

4. Testicular Disease at Diagnosis

Patients with clinically enlarged testis at presentation should be assumed to have testicular disease. Biopsy is not required to confirm the presence of infiltrate. Routine ultrasound of the testis should not be performed to detect sub-clinical enlargement. Patients with testicular disease should start induction according to age and WCC. Those patients with persistent enlargement at day 28 should be transferred to the next more intensive schedule i.e. Regimen A to B or Regimen B to C. Testicular radiotherapy should only be given to those children who still have a clinically enlarged testis at week 8. In these patients, 24 Gy should be given in 12 fractions between weeks 9 to 12 while continuing with other treatment. (Details in Appendix L)

5. Amplified RUNX1 (also called iAMP21)

Not all patients with multiple copies of RUNX1 on FISH fit into this category. Please discuss result with your cytogenetics laboratory and, if any doubt, contact Dr Harrison at the Cytogenetics Co-ordinating Laboratory. Analysis of ALL97 indicates that dup (21)(q?) with amplification of the AML1 gene detected by FISH is associated with a poor prognosis. Patients with this abnormality should start treatment on Regimen C. Those who then have a Slow Early Response at day 8 and/or who are High Risk on MRD at day 29 should receive a Stem Cell Transplant in first Complete Remission **if a matched sibling or $\geq 9/10$ allelic match unrelated donor (cord blood $\geq 5/6$ match, class I antigen/class II allelic, with adequate cell dose) is available.** If an appropriately matched donor is not available, they should continue chemotherapy on Regimen C with 2 DIs.

6. t(17;19) (E2A-HLF)

A variant of the t(1;19) (E2A-PBX), t(17;19) (E2A-HLF) is a rare cytogenetic abnormality associated with a very high risk of early refractory relapse. All 4 ALL97 patients relapsed between 5 and 18 months from diagnosis and subsequently died. Limited literature on the abnormality is in concordance with the ALL 97 experience. Hence, the ALL task force has decided to stratify these patients as very high risk and **recommends that they receive Regimen C followed by allogeneic transplant after recovery from consolidation using any available donor.** It can be detected by routine karyotyping and FISH, and cytogenetics laboratories have been notified by the LRF reference laboratory to report it as a high risk abnormality.

7. First remission allogeneic transplantation:

Allogeneic transplant in first CR is recommended for the following groups:

1. iAMP21 with SER or day 29 MRD High Risk.
2. MLL rearrangement positive or hypodiploid < 44 with M2 marrow ($>5\%$ blasts) at day 28.
3. M3 marrow at day 28.
4. BCR:ABL positive, follow guidance within Philadelphia ALL protocol.
5. t(17;19) (E2A-HLF) positive

The optimal timing of transplant, as recommended by the CCLG BMT Group, is on recovery from the consolidation phase of Regimen C at around weeks 14 – 16. Where there is a delay beyond this time point, it is recommended that patients should receive standard maintenance therapy, rather than Cappizzi maintenance, during the interim. In due course, we may be able to identify patients with persistent high level MRD at the end of consolidation for further cyto-reductive therapy prior to transplant.

8. ENTRY PROCEDURE FOR ALL PATIENTS:

**Registration and Randomisation Telephone No 01865 -765615 (9 AM to 5 PM only).
Please do not register or randomise patients outside routine hours.**

Obtaining consent

Feedback from the early part of the trial has revealed difficulties with obtaining consent for randomisation at diagnosis and without knowing the patient's day 29 MRD risk group status. Taking account of these difficulties, we have amended the randomisation process and mechanism for notifying the day 29 MRD result. Since the randomised treatment changes do not take effect until after day 36, we recommend a two step consent procedure. At diagnosis, obtain consent for registration, data collection, and QOL and asparaginase studies and provide parents and patients with the study information sheet. Consent for randomisation can be obtained at day 36 *after* clinicians have been provided with the patient's day 29 MRD risk group status.

At diagnosis

Day 1 bone marrow sample must be sent to the MRD laboratory from all children with suspected ALL. Sample collection, transport and destination laboratory details are provided on page 22 and Appendices K and L.

When diagnosis of ALL and immunophenotypic sub-type is confirmed, please notify CTSU by telephone (01865-765615) with the following information:

Physician in charge.

Centre entering

Patient information:

name

date of birth

sex

white cell count

presence or absence of CNS disease

immunophenotype (precursor -B or T)

Treatment start date.

Confirm that consent for registration and despatch of MRD samples has been obtained and fax a copy of the signed consent form to CTSU (Fax: 01865-743986)

CTSU will provide the following details:

Trial Ref No.

Date for Day 29 bone marrow.

(Please notify all patients with ALL, regardless of eligibility or intention to enter into MRD randomisation, and be especially vigilant to register patients who die early.):

At day 29 (this marrow can be delayed if neuts < 0.5 and/or platelets < 50)

Send bone marrow sample to MRD laboratory from all patients, regardless of eligibility for randomisation.

At day 36 (before start of consolidation)

Your MRD laboratory will notify you of the patient's day 29 MRD risk group status. Contact CTSU by telephone to enter MRD high risk patients into randomisation (*see eligibility and exclusion criteria on page 13*). **We strongly recommend that a clinician makes this call and it is not left to a data manager. In patients on Regimen B or C with slow count recovery after induction, the day 29 marrow should be delayed until neutrophils > 0.5 and platelets >50. Such patients can be randomised up to week 7 of the protocol.**

Be prepared to provide following information:

Patient identification (Name and DOB, or trial ref no)

High risk cytogenetics? (Answer must be No)

Rapid Early Response at day 8/15? (Answer must be yes, unless young adult)

Informed consent for randomisation obtained? (Answer must be yes)

Date of morphological complete remission (should be between day 28 and 35)

Was induction given as protocol (In the event of a major protocol violation, please discuss with a co-ordinator prior to ringing CTSU)

CTSU will provide:

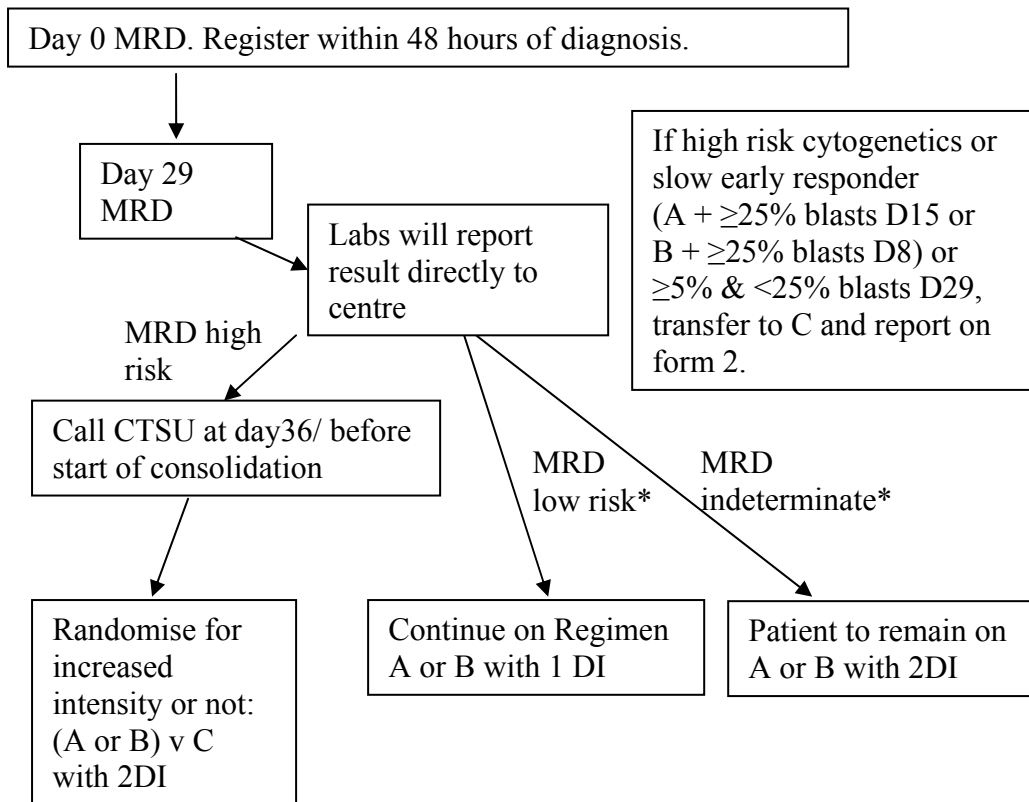
Randomised treatment allocation if MRD High Risk (A/B versus C) or recommendation to continue on existing treatment if MRD Low Risk or Indeterminate.

At week 11 (Regimens A and B) or week 15 (Regimen C)

Send Bone Marrow to MRD laboratory

From August 2009, the week 11 sample will not be analysed but archived for future research projects. Patients will be defined as low risk on the basis of day 29 result alone.

REGISTRATION AND RANDOMISATION PATHWAY



* Day 36 CTSU call not necessary

9. ESSENTIAL INVESTIGATIONS AT DIAGNOSIS:

Centres treating patients with leukaemia are expected to have appropriate investigation protocols for the pre-treatment assessment of new patients, for monitoring progress during treatment and once therapy has ended, and for dealing with any complications that may arise. For trial purposes, in addition to a blood count, mandatory investigations at the time of diagnosis include:

(a) *a bone marrow aspirate* with material being sent for:

- i) morphology (locally and by central review - see footnote)
- ii) immunophenotyping
- iii) Cytogenetic and molecular cytogenetic analysis: These will be performed locally and must include standard G-banded analysis, as well as FISH tests for the following rearrangements: *ETV6-RUNX1 (TEL-AML1)* / amplification of *RUNX1 (AML1)*, *BCR-ABL* and *MLL*. These tests must be carried out as soon as possible as positive findings may exclude the patient from the trial or alter therapy.
A copy of the reports of all diagnostic and relapse cytogenetic, FISH and genetic testing must be sent to the cytogenetic co-ordinating centre. From time to time the cytogenetic co-ordinating centre may request left-over fixed cell suspension, DNA, RNA or other material from the local genetics laboratory or the treating clinician to undertake further cytogenetic, molecular cytogenetic and genetic testing (including but not restricted to FISH, array CGH and RT-PCR) to refine the definition of known abnormalities and characterise novel subgroups. All these additional tests will be performed with the full knowledge of the trial co-ordinators
- iv) baseline bone marrow sample for MRD (see page 31 for instructions on sample collection and transport to MRD laboratory).
- v) Asparaginase study samples (see appendix Q, page 115)

NB. if any of these tests have been omitted on the first diagnostic sample, a second sample must be taken before treatment starts, unless prevented by clinical circumstances. A trephine biopsy is required if an adequate sample cannot be obtained by aspiration.

Routine central morphology review will cease from 1 October 2009 due to lack of funding. From that point on, slides for central review should be sent to Professor Vora from patients with CNS disease at presentation or those considered to be non-remitters at day 29 or where there is uncertainty over local assessment of day 8/15 marrow response..

If >25% blasts at DAY 8 (regimen B) or 15 (regimen A) slides must be reviewed by another haematologist and if confirmed switch patient to Regimen C. Day 8/15 marrows should not be done early but may be delayed up to day 10/18 if necessary.

- (b) *a lumbar puncture* for CSF cytology – please report CNS3, CNS2 and traumatic taps on Form 1.
- (c) *a pre-transfusion blood sample (3-5 ml lithium heparin)* for thiopurine methyltransferase assay . Referring paediatricians will need to be aware of the need for this sample in case they have to transfuse patients prior to transfer.

10. MRD SAMPLE COLLECTION AND TRANSPORT

At diagnosis

2 - 5mls of bone marrow from **all** children with suspected leukaemia should be placed into the ACD containers supplied by your local MRD network lab. Do NOT use EDTA or other transport media. In patients with peripheral white counts greater than 20×10^9 /litre, 5mls of blood collected into ACD is also acceptable at diagnosis. Please note that peripheral blood is of **no** value as an MRD sample at other time points.

At the end of induction and other times during therapy

5mls of bone marrow should be placed into ACD (and only as a last resort into EDTA). Peripheral blood is **NOT** an acceptable alternative. In addition to those that are required for treatment stratification (day 29 and week 11) , it is essential that marrow samples at post-remission time points (see table page 31) are sent to the MRD laboratories, even in patients who have been entered into the randomisations. We plan to perform retrospective analyses of archived batches to define further risk sub-groups on the basis of post-remission MRD kinetics.

Request forms

These will be supplied with the ACD bottles. They have been designed to provide sufficient information for each patient to be reliably identified whilst at the same time attempting to blind the network lab to clinical risk. Thus whilst the date of birth is required for identification and in due course the immunophenotype for directed PCR screening, we will not require information about WCC or treatment arm. We do wish to know if the patient has Philadelphia positive ALL so we can make RNA for MRD analysis.

Transport

Transport has been commissioned with DHL, an account has been set up so that each treatment centre can arrange DHL transport to their local network lab and the costs be paid by the co-ordinating lab in Bristol. Details of the codes for these accounts are available from your network lab or from the trial co-ordinators.

Sample processing

On receipt of bone marrow aspirates, the MRD laboratory will assign the patient and the sample a unique number according to the standard operating procedure. Cell counts will be recorded and DNA extracted within 24 hours of receipt of the sample. A minimum of 10micrograms of DNA is required at diagnosis and 5 micrograms at end of induction. In the event that an inadequate sample is obtained then a further sample will be requested.

11. SUMMARY TABLE OF ESSENTIAL INVESTIGATIONS.

	Regimen A	Regimen B	Regimen C
Diagnosis	Marrow, CSF, Thiopurine, Asparaginase study and MRD samples for all regimens		
Day 8	Marrow	Marrow Asparaginase study samples for all Regimens	-
Day 15	Marrow	Marrow	-
End of induction	Marrow for all regimens MRD for all regimens Asparaginase study samples for all Regimens		
Week 11	MRD	MRD	-
Week 11 -16	Thiopurine sample for all Regimens*		
Week 15	-	-	MRD
Capizzi I, day 32	Asparaginase		
Day 16 of DI1 and II	Asparaginase study samples for all Regimens		
Week 17 (DI1)	MRD		
Week 19 (DI1)	-	MRD	-
Week 23 (DI1)	-	-	MRD
Capizzi II, day 32	Asparaginase		
Week 41 (Maint)	MRD - (week 38 for 1 DI patients)	-	
Week 43 (Maint)	-	MRD (week 40 for 1 DI patients)	-
Week 49 (Maint)	-	-	MRD Thiopurine sample
Start of maintenance	Asparaginase study samples for all Regimens		
End of treatment	MRD	MRD	MRD

Marrow = Morphology Review**MRD = Send marrow for MRD status to network laboratory****Asparaginase Study samples – see Appendix Q, page 115***** See flowcharts for exact timing.**

12. GENERAL MANAGEMENT OF ALL REGIMENS:

The instructions set out in this document must be followed **strictly**.

The drugs must be given at full dosage at all times unless there is intolerance when the dosage must only be modified according to the instructions set out in this protocol. In exceptional circumstances, the responsible clinician may decide, in consultation with a trial co-ordinator that exact adherence is unjustifiably hazardous for the patient. Doses must be returned to that specified in this document thereafter and dosages must be regularly increased as the patient grows.

All drugs used in continuing therapy must be started at maximum dosage as specified in the protocol. In addition, in patients on daily thiopurine in whom no toxicity is evident, the thiopurine dose should be increased until toxicity occurs (see Appendix C).

If the 12 week maintenance therapy cycle includes gaps when treatment has been stopped because of toxicity or infection the omitted oral thiopurine and methotrexate, are counted as given and not made up; i.e. the clock does not stop when the drugs are stopped. In this way, cycles are maintained at 12 weeks; gaps in therapy and total dosage per cycle can be related to outcome.

All dosage modifications and interruptions must be recorded.

Because of drug preparation and dosage variations, it is essential that the protocol is discussed with pharmacies at participating hospitals.

NB:

- *Patients with obvious gross residual marrow disease (more than 25% unequivocal blasts) at day 8 (regimen B) or day 15 (regimen A), to be confirmed by another haematologist, will transfer to schedule C. This marrow must not be done before D8 or 15. It can be done up to D10 or 18.*
- *Note the following changes to the Regimens compared to ALL97/01:*
 1. Extra induction week after the day 28 marrow (week 5) to allow time for day 28 MRD result. This means that:
 - a. Regimen A - consolidation is shortened to 3 weeks but subsequent treatment remains the same as in ALL97/01.
 - b. Regimen B and C – Consolidation starts at week 6 and contains only 3 IT MTXs. Subsequent courses start a week later than in ALL97/01.
 2. Dexamethasone for all patients. Dexamethasone dose has been changed from 6.5 mg/m²/day to 6 mg/m²/day and is capped at 10 mg total daily dose during induction **only**. It is given at full dose for all other courses. Patients who experience serious dexamethasone toxicity should be switched to Prednisolone 40 mg/m²/day.
 3. Mercaptopurine throughout for all patients, **including during intensifications (as of February 2006)**.
 4. Co-trimoxazole starts at day 1 of induction.
 5. Extra Bone Marrow (and IT MTX in regimen A) at week 11 for MRD.

UKALL 2003 REGIMEN A.

Eligibility.

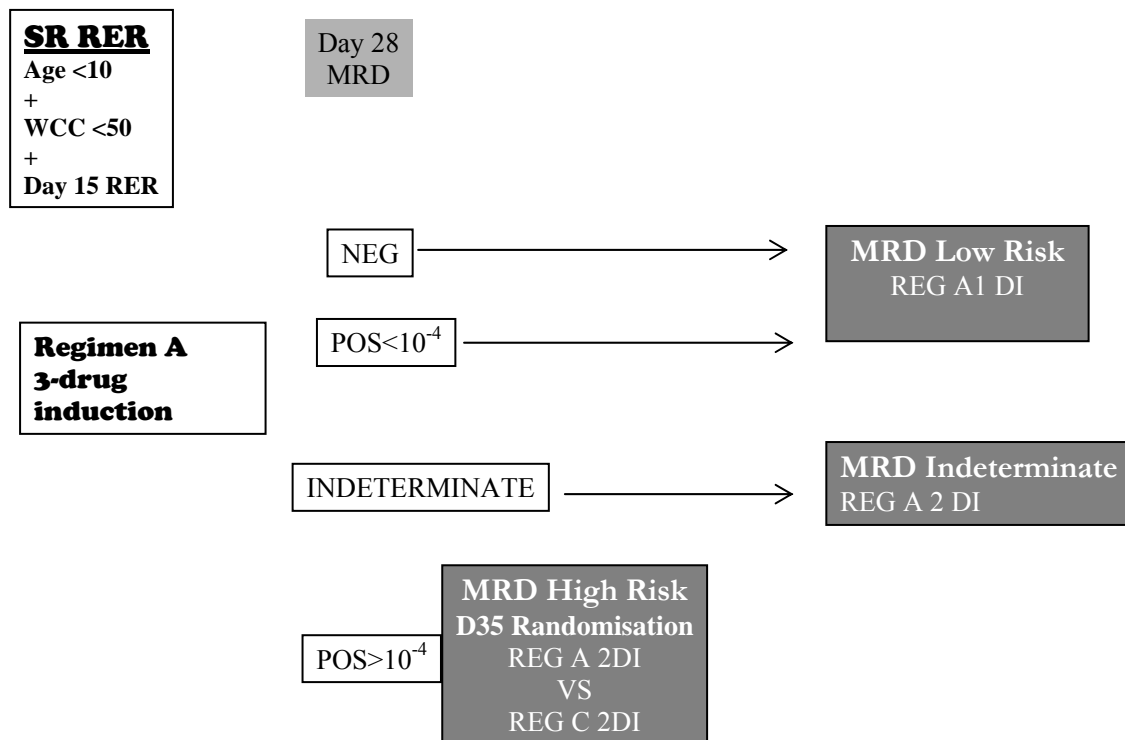
Patients treated on regimen A must be before their 10th birthday **and** have a highest white cell count before starting treatment less than $50 \times 10^9/L$.

MRD Randomisation

MRD High Risk patients will be randomised between Regimen A or C and should change to allocated treatment at day 35.

MRD Low Risk patients will receive one delayed intensification.

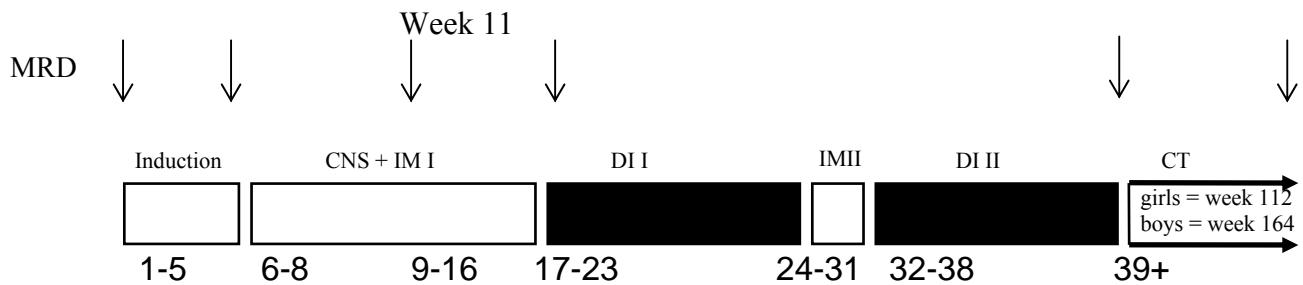
MRD Indeterminate patients will continue on Regimen A and receive 2 DIs



Summary of Regimen A.

Regimen A consists of the following phases:

1. Three drug induction (duration 5 weeks) with **dexamethasone** as steroid of choice.
2. Intensification/CNS-directed phase (duration 3 weeks) with **6-mercaptopurine**;
3. Interim maintenance I (duration 8 weeks) with **dexamethasone** and **6-mercaptopurine**;
4. Delayed intensification I (duration 7 weeks) with **6-mercaptopurine** in reconsolidation;
5. Interim maintenance II (**for MRD indeterminate patients and high risk patients allocated standard therapy**) (duration 8 weeks) with **dexamethasone** and **6-mercaptopurine**;
6. Delayed intensification II (**for MRD indeterminate patients and high risk patients allocated standard therapy**) (duration 7 weeks); with **6-mercaptopurine** in reconsolidation.
7. Maintenance chemotherapy with **dexamethasone and 6-mercaptopurine** to end of week 112 for girls and end of 164 for boys. Delays accrued during phases I-VI are taken off during the maintenance period.



UKALL 2003 REGIMEN A: DETAILS OF TREATMENT.**Schedule A - Remission induction – phase I (See flowchart 1.)**

This phase runs for 35 days from day 1 (beginning of week 1) to day 35 inclusive (end of week 5) (i.e. 5 weeks in total).

- a) **Fluids** All patients should be adequately hydrated (at least 2-2.5 l/m²/24hrs. given parenterally for the first 48 hours.
- b) **Allopurinol** 100 mg/m² oral three times daily should start 24 hours before chemotherapy and continue for 5 days.
- c) **Dexamethasone** 6 mg/m²/day (maximum dose 10 mg/day in induction only) for **28 days** and then tapered over the next 7 days. The steroid should be divided into two doses per day.
- d) **Vincristine** 1.5 mg/m² (maximum single dose 2 mg) IV weekly for five weeks starting on day 2 and continuing on days 9, 16, 23 and 30.
- e) **Pegylated L-asparaginase (Oncaspar)** 1000iu/m² **IM** , on day 4 and day 18
- f) **Intrathecal methotrexate** **On days 1, 8 and 28.** Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. NB Patients who have CNS disease at presentation should receive weekly doses until two clear CSF samples are obtained- see page 24. Do not schedule vincristine on the same day as the intrathecal methotrexate.
- g) **6-mercaptopurine** 75 mg/m²/day orally starting on day 29 (beginning week 5) (if neutrophils > 0.75 and platelets > 75) and continuing for 4 weeks in total (to end of consolidation, week 8) Doses should be taken at least one hour after the evening meal, without milk products. Dose adjustments are described in Appendix C.
- h) **Bone marrow Aspirates** Bone marrow should be checked at day 8, 15 and 28.

Patients with M3 marrow at day 15 (see definitions), are off regimen A and should continue therapy on regimen C. Day 28 MRD High Risk patients are randomised to stay on Regimen A or change to regimen C

i) Co-trimoxazole (trimethoprim and sulphamethoxazole)

This drug is given as PCP prophylaxis orally on 2 consecutive days throughout treatment *from the start of induction*. This dosage is lower than that recommended in previous studies, but has been found to be equally effective in CCG studies. The dose is tabulated below. Please ensure separation of the days on which oral Methotrexate and Cotrimoxazole doses are given during maintenance courses.

If a child remains cytopenic after being off chemotherapy for three weeks or more, then stop the co-trimoxazole. Reintroduce co-trimoxazole once both thiopurine and methotrexate are back at standard dose. If cytopenias recur once the co-trimoxazole is reintroduced, then it should be stopped for at least two months and an alternative form of prophylaxis used instead (see below). The alternative drug should then be continued

for the duration of the antileukaemic therapy

The maintenance of adequate doses of thiopurine and methotrexate should take precedence over continuing co-trimoxazole. If co-trimoxazole is stopped, however, it must be remembered that the child is at increased risk of PCP. Nebulised pentamidine or oral Dapsone are alternative drugs.

Surface area	Co-trimoxazole	Trimethoprim	Sulphamethoxazole
0.5-0.75 m ²	240 mg bd	40 mg bd	200 mg bd
0.76-1.0 m ²	360 mg bd	60 mg bd	300 mg bd
over 1.0 m ²	480 mg bd	80 mg bd	400 mg bd

See also appendix D for details of alternative PCP prophylaxis regimens.

Permitted dose modifications for toxicity – see Appendix E

Note: Patient may not be eligible for the MRD randomisation if induction therapy is modified. Please discuss with co-ordinators.

Regimen A: Consolidation/CNS phase, phase II (See flowchart 2.)

This phase runs for 21 days from day 1 (beginning of week 6) to day 21 inclusive (end of week 8) i.e. 3 weeks. Patients should have an ANC $>0.75 \times 10^9/L$ and platelets of $>75 \times 10^9/L$. Patients with refractory CNS disease at diagnosis will receive cranial irradiation during consolidation starting at day 36.

- a) **Intrathecal methotrexate** Days 1, 8 and 15 Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. Do not schedule vincristine on the same day as the methotrexate.
- b) **6-mercaptopurine** 75mg/m²/day orally continuing to day 21 (end of week 8) Doses should be taken at least one hour after the evening meal, without milk products. Dose adjustments are described in Appendix C.

Regimen A: Interim maintenance I – phase III (See flowchart 3.)

This phase runs from day 1 (beginning of week 9) to day 56 inclusive (end of week 16) (i.e. 8 weeks). Patients should have an ANC $>0.75 \times 10^9/L$ and platelets of $>75 \times 10^9/L$ to start.

- a) **Dexamethasone** 6 mg/m²/day orally, divided into twice-daily doses each day on days 1-5 (week 9) and days 29-33 (week 13).
- b) **Vincristine** 1.5 mg/m² (maximum single dose 2 mg) IV on day 1 (week 9) and day 29 (week 13).
- c) **6-mercaptopurine** 75 mg/m²/day orally, daily on days 1-49 (weeks 9-15) but **not days 50-56 (week 16)**. Doses should be taken at least one hour after the evening meal without milk products. Dose adjustments are described in Appendix C. The omission of 6-mercaptopurine for days 50-56 is in line with the relevant CCG protocol.
- d) **Oral methotrexate** 20 mg/m² orally weekly during weeks beginning on days 1, 8, 22, 29, 36, 43 and 50 (weeks 9-16). **Note none is given day 15 as an intrathecal dose is given during that week** Should be a single dose taken with 6-mercaptopurine. Dose adjustments are described in Appendix C.
- e) **Intrathecal methotrexate** on day 1 week 11. Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. Do not schedule vincristine on the same day as IT methotrexate.
- f) **Bone Marrow.** BM for MRD status on day 1 week 11.

Regimen A: Delayed intensification I – phase IV (See flowchart 4.)

This phase runs from day 1 (beginning of week 17) to day 49 inclusive (end week 23) i.e. 7 weeks. To start, ANC should be $>0.75 \times 10^9/L$ and platelets of $>75 \times 10^9/L$. Once begun, therapy during weeks 17 – 20 is not interrupted for myelosuppression alone. Therapy due day 1, week 21 should be delayed until ANC $>0.75 \times 10^9/L$ and platelets of $>75 \times 10^9/L$ and once begun should not be interrupted solely for myelosuppression. Any serious infection, such as Varicella, pneumocystis pneumonia, or neutropenia with fever, and presumed or proven infection, warrants chemotherapy interruption at any time during DI.

Remember to send Marrow for MRD status on day 1 of week 17.

Part 1; weeks 17 – 20:

- a) **Dexamethasone** 10mg/m²/day orally for 7 days on days 2- 8 (week 17) and 16-22 (week 19). No taper. Divide into two daily doses, adjusted upward to nearest 0.25 mg, as tablet size dictates. (Liquid preparation is acceptable).
- b) **Vincristine** 1.5 mg/m² (2.0 mg max) IV push on days 2 (week 17), 9 (week 18) and 16 (week 19).
- c) **Doxorubicin (Adriamycin)** 25 mg/m² IV on days 2 (week 17),9 (week 18) and 16 (week 19) given over a period of 1 hour.
- d) **Pegylated L-Asparaginase (Oncaspar)** 1000 iu/m² **IM** on day 4 (week 17)
- e) **Intrathecal methotrexate** on day 1 (week 17). Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. Do not schedule vincristine on the same day as IT methotrexate.

Part 2; weeks 21-23:

- f) **Cyclophosphamide** 1,000 mg/m² IV over 20-30 min day 29 (week 21). Give 125mls/m²/hr of Dextrose /Saline infusion for 30 minutes before the cyclophosphamide and for 3.5 hours afterwards, i.e. 4 hours in total. Do not add potassium. Mesna is not needed.
- g) **Mercaptopurine. All patients receive MP 60 mg/m²/day during delayed intensification 1.** The drug is given daily by mouth for 14 days from day 29 (beginning of week 21) to day 42 (end of week 22). No dose adjustments are made during this block. Doses should be taken at least one hour after the evening meal, without milk products.
- h) **Cytarabine (ara-C).** 75mg/m²/day by IV push or subcutaneously – 8 doses in two pulses of 4 days each; days 30-33 (week 21) and days 37-40 (week 22).
- i) **Intrathecal methotrexate.** Days 29 (week 21) and 36 (week 22). Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg.

Regimen A: Interim maintenance II – phase V (See flowchart 5.)

This phase is only for patients receiving two delayed intensifications. MRD low risk patients should proceed to Maintenance from day 1 of week 24.

This phase runs from day 1 (beginning of week 24) to day 56 inclusive (end week 31) (i.e. 8 weeks). Patients should have an ANC $>0.75 \times 10^9/L$ and platelets of $>75 \times 10^9/L$ to start.

- a) **Dexamethasone** 6 mg/m²/day orally, divided into twice daily doses each day on days 1-5 (week 24) and days 29-33 (week 28).
- b) **Vincristine** 1.5 mg/m² (maximum single dose 2 mg) IV on day 1 (week 24) and day 29 (week 28).
- c) **6-mercaptopurine** 75 mg/m²/day orally, daily on days 1-49 (weeks 24-30) but **not days 50-56 (week 31)**. Doses should be taken at least one hour after the evening meal without milk products. Dose adjustments are described in Appendix C. The omission of 6-mercaptopurine for days 50-56 is in line with the relevant CCG protocol.
- d) **Oral methotrexate** 20 mg/m² orally weekly during weeks beginning on days 1, 8, 15, 22, 29, 36, 43 and 50 (weeks 24-31). Should be a single dose taken with 6-mercaptopurine. Dose adjustments are described in Appendix C.

Note that there is no intrathecal therapy in this phase.

Regimen A: Delayed intensification II – phase VI (See flowchart 6.)**This phase is only for patients receiving two delayed intensifications.**

This phase begins day 1 (beginning of week 32) and continues to day 49 inclusive (end week 38) i.e. 7 weeks. To start, ANC should be $>0.75 \times 10^9/L$ and platelets of $>75 \times 10^9/L$. Once begun, therapy during weeks 32 – 35 is not interrupted for myelosuppression alone. Therapy due day 1 week 36 should be delayed until ANC $>0.75 \times 10^9/L$ and platelets of $>75 \times 10^9/L$ and once begun should not be interrupted solely for myelosuppression. Any serious infection, such as Varicella, pneumocystis pneumonia, or neutropenia with fever, and presumed or proven infection, warrants chemotherapy interruption at any time during DI.

Part 1; weeks 32 – 35:

- a) **Dexamethasone** 10mg/m²/day orally for 7 days on days 2- 8 (week 32) and 16-22 (week 34). No taper. Divide into two daily doses, adjusted upward to nearest 0.25 mg, as tablet size dictates. (Liquid preparation is acceptable).
- b) **Vincristine** 1.5 mg/m² (2.0 mg max) IV push on days 2 (week 32), 9 (week 33) and 16 (week 34).
- c) **Doxorubicin (Adriamycin)** 25 mg/m² IV on days 2 (week 32), 9 (week 33) and 16 (week 34) given over a period of 1 hour.
- d) **Pegylated L-Asparaginase (Oncaspar)** 1000 iu/m² **IM** on day 4 (week 32)
- e) **Intrathecal methotrexate** on day 1 (week 32). Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. Do not schedule vincristine on the same day as IT methotrexate.

Part 2; weeks 36 – 38:

- f) **Cyclophosphamide** 1,000 mg/m² IV over 20-30 min day 29 (week 36). Give 125mls/m²/hr of Dextrose /Saline infusion for 30 minutes before the cyclophosphamide and for 3.5 hours afterwards, i.e. 4 hours in total. Do not add potassium. Mesna is not needed.
- g) **Mercaptopurine. All patients receive MP 60 mg/m²/day during delayed intensification 2.** The drug is given daily by mouth for 14 days from day 29 (beginning of week 36) to day 42 (end of week 37). No dose adjustments are made during this block. Doses should be taken at least one hour after the evening meal, without milk products.
- h) **Cytarabine (ara-C).** 75mg/m²/day by IV push or subcutaneously – 8 doses in two pulses of 4 days each; days 30-33 (week 36) and days 37-40 (week 37).
- i) **Intrathecal methotrexate.** Days 29 (week 36) and 36 (week 37). Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg.

Regimen A: Maintenance – phase VII (See flowchart 7.)

Maintenance runs from day 1 cycle 1 (beginning of week 24 for patients allocated one delayed intensification and week 39 for those allocated two delayed intensifications) in 12-week cycles to end of week 112 for girls and end of week 164 for boys. The cycle in progress is stopped when the end of therapy is reached. This period equates to 2 years from the start of interim maintenance I for girls and 3 years for boys.

Maintenance should begin when the ANC is $>0.75 \times 10^9/l$ and the platelet count is $>75 \times 10^9/l$. Only 6-mercaptopurine and oral methotrexate will be interrupted for myelosuppression and not made up. Days off therapy for intercurrent infections are counted as days of maintenance and not made up. Omit the Vincristine and steroid pulse if it falls in the last week of therapy. *Anaemia* occurring in the course of maintenance therapy should be treated with transfusion and the dose of drug is maintained. If *persistent anaemia* occurs (i.e., haemoglobin below 8 g/dl) investigate for Parvovirus infection. Please contact trial co-ordinators for advice.

Remember to send Marrow for MRD on week 41 for patients randomised to two delayed intensifications, and week 38 for patients receiving one delayed intensification

- a) **Dexamethasone** 6 mg/m²/day orally, divided into twice-daily doses on days 1-5, 29-33 and 57-61 of each cycle.
- b) **Vincristine** 1.5mg/m² (maximum single dose 2 mg) IV on days 1, 29, and 57 of each cycle.
- c) **6-mercaptopurine** 75mg/m²/day orally daily throughout maintenance. Doses should be taken at least one hour after the evening meal without milk products. Dose adjustments are described in Appendix C.
- d) **Oral methotrexate** 20 mg/m² orally during weeks beginning days 1, 8, 22, 29, 36, 43, 50, 57, 64, 71 and 78 of each cycle. **Note none is given in the third week of each cycle as an intrathecal dose is given during that week.** Dose adjustments are described in Appendix C.
- e) **Intrathecal methotrexate** on day 15 of each cycle.
Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. Do not schedule vincristine for the same day as intrathecal methotrexate.
- f) **Bone marrow examination** should be carried out at the same time as the **week 41** (week 38 on patients randomised to one DI) and **End of Treatment** intrathecal methotrexates with samples being taken for MRD analysis. NB the end of treatment marrow should always be done BEFORE chemotherapy is stopped to prevent confusion due to “rebound” marrows.

END OF REGIMEN A

16. UKALL 2003 REGIMEN B.

Eligibility.

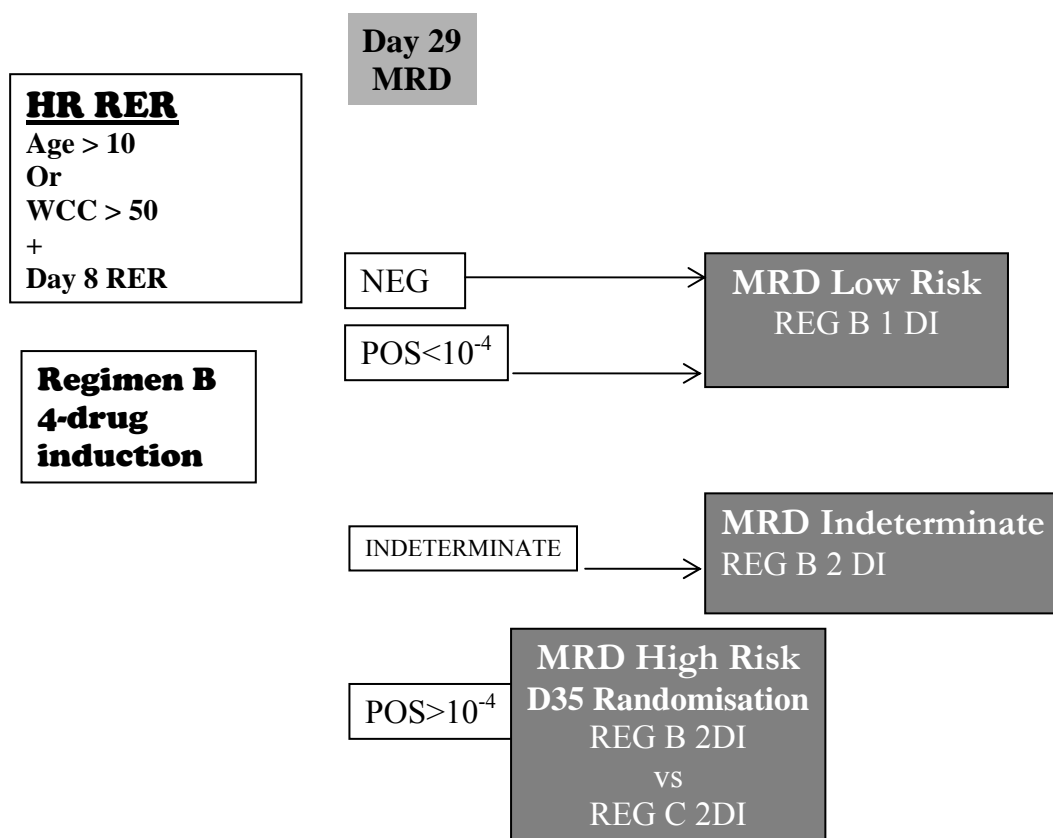
This regimen (B) is for patients defined as at high risk of relapse because of their age (≥ 10 years) or presenting white cell count ($\geq 50 \times 10^9/L$).

MRD Randomisation

MRD Low Risk patients will receive one delayed intensification.

MRD High Risk patients will be randomised between Regimen B or C and should change to allocated treatment at day 35.

MRD Indeterminate patients will continue on Regimen B + 2DI.



Summary of Regimen B.

Regimen B consists of the following phases:

1. Four drug induction (duration 5 weeks) with **dexamethasone** as steroid of choice.
2. Standard BFM consolidation (duration 5 weeks) with **6-mercaptopurine**;
3. Interim maintenance I (duration 8 weeks) - **dexamethasone and mercaptopurine**;
3. Delayed intensification I (duration 7 weeks); **6-mercaptopurine** in reconsolidation;
4. Interim maintenance II (**for patients allocated two delayed intensifications**) (duration 8 weeks) with **dexamethasone and 6-mercaptopurine**;
5. Delayed intensification II (**for MRD indeterminate and high risk patients allocated two delayed intensifications**) (duration 7 weeks); **6-mercaptopurine** in reconsolidation;
6. Maintenance chemotherapy with **dexamethasone and 6-mercaptopurine** to end of week 114 for girls and end of week 166 for boys. Delays accrued during phases I-VI are taken off the maintenance period.

**Prevention of Tumour Lysis**

Treatment centres should have a policy for the prevention and treatment of Tumour Lysis syndrome in patients with high white cell counts or bulky disease. Consideration should also be given to the use of Recombinant Urate Oxidase (Rasburicase) *instead of* Allopurinol in patients with very high white cell ($> 100 \times 10^9/l$) counts or bulky disease (Mediastinal mass or large abdominal lymph nodes).

UKALL 2003 REGIMEN B: DETAILS OF TREATMENT.

The convention for day/week numbering is that a new module of therapy begins on day 1 of whatever week of treatment has been reached. For example, induction begins on day 1 (week 1); consolidation on day 1 (week 6); delayed intensification II on day 1 (week 34); and so on. Each module runs for a number of days and induction therefore finishes on day 35 (end of week 5); interim maintenance I on day 56 (end of week 18); and delayed intensification II on day 49 (end of week 40).

Regimen B: Remission induction – phase I (See flowchart 8.)

This phase runs for 35 days from day 1 (beginning of week 1) to day 35 inclusive (end of week 5).

- a) **Fluids:** All patients should be adequately hydrated (at least 2-2.5 l/m²/24hrs given parenterally for the first 48 hours).
- b) **Allopurinol:** 100 mg/m² oral three times daily should start 24 hours before chemotherapy and continue for 5 days.
- c) **Dexamethasone:** 6 mg/m²/day (maximum dose 10 mg/day in induction only) for 28 days and then tapered over the next 7 days. The steroid should be divided into two doses per day.
- d) **Vincristine:** 1.5 mg/m² (maximum single dose 2 mg) IV bolus weekly for five weeks starting on day 2 and continuing on days 9, 16, 23 and 30.
- e) **Daunorubicin:** 25 mg/m² IV over 1 hour on days 2, 9, 16, and 23. Note that daunorubicin is included in induction in regimen B and that this dosage is different to that recommended in regimen C.
- f) **Pegylated L-asparaginase: (Oncaspar)** 1000 iu/m² IM, on day 4 and day 18.
- g) **Intrathecal methotrexate: On days 1, 8 and 28** Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. NB Patients who have CNS disease at presentation should receive weekly doses - see page 24. Do not schedule vincristine on the same day as the intrathecal methotrexate.
- h) **6-mercaptopurine:** 60 mg/m²/day orally starting on day 29 (beginning week 5) (if neutrophils > 0.75 and platelets > 75) and continuing for five weeks in total (to end of week 9). Adjust the dose of 6-MP to attain a weekly cumulative dose of as near 420mg/m² as possible. Doses should be taken at least one hour after the evening meal without milk products. Do not increase dosage for ANC>2.0.
- i) **Bone marrow:** Check marrow status on days 8, 15 and 28. Send Day 28 Marrow for MRD

Patients with M3 marrow at day 8 (see definitions), are off regimen B and should continue therapy on regimen C (except age ≥ 16 years). MRD High Risk patients are randomised to either continue on regimen B or switch to regimen C.

j) Co-trimoxazole (trimethoprim and sulphamethoxazole)

This drug is given as PCP prophylaxis orally on 2 consecutive days throughout treatment **from the start of induction**. The dose is tabulated below. Please ensure separation of the days on which oral Methotrexate and Cotrimoxazole doses are given during maintenance courses.

If a child remains cytopenic after being off chemotherapy for three weeks or more, then stop the co-trimoxazole. Reintroduce co-trimoxazole once both thiopurine and methotrexate are back at standard dose. If cytopenias recur once the co-trimoxazole is reintroduced, then it should be stopped for at least two months and an alternative form of prophylaxis used instead (see below). The alternative drug should then be continued for the duration of the antileukaemic therapy

The maintenance of adequate doses of thiopurine and methotrexate should take precedence over continuing co-trimoxazole. If co-trimoxazole is stopped, however, it must be remembered that the child is at increased risk of PCP. Nebulised pentamidine or oral Dapsone are alternative drugs.

Surface area	Co-trimoxazole	Trimethoprim	Sulphamethoxazole
0.5-0.75 m ²	240 mg bd	40 mg bd	200 mg bd
0.76-1.0 m ²	360 mg bd	60 mg bd	300 mg bd
over 1.0 m ²	480 mg bd	80 mg bd	400 mg bd

See also appendix D for details of alternative PCP prophylaxis regimens.

Permitted dose modifications for toxicity – see Appendix E:

Note: Patient may not be eligible for the MRD randomisation if induction therapy is modified. Please discuss with co-ordinators.

Regimen B: Standard BFM Consolidation – phase II (See flowchart 9.)

This phase runs for 35 days from day 1 (beginning of week 6) to day 35 inclusive (end of week 10) i.e. 5 weeks. To be eligible to enter standard BFM consolidation, patients must be in remission, and have an ANC $>0.75 \times 10^9/L$ and platelets of $>75 \times 10^9/L$. If the blood count has not recovered and marrow is hypocellular M1, delay the start of consolidation one week and repeat the bone marrow to confirm M1 status. Patients with refractory CNS disease at diagnosis will receive cranial irradiation during consolidation starting at day 36.

- a) **Cyclophosphamide:** 1,000 mg/m² IV over 20-30 minutes on days 1 and 15. Give 125mls/m²/hr of Dextrose/ Saline infusion for 30 minutes before cyclophosphamide and for 3.5 hours afterwards, i.e. 4 hours in total. Do not add potassium. Mesna is not needed.
- b) **Cytarabine (ara-C):** 75mg/m²/day by IV push or subcutaneously – 16 doses in four pulses of 4 days each; days 2-5, 9-12, 16-19 and 23-26.
- c) **6-Mercaptopurine:** Continue 6-mercaptopurine, 60mg/m²/day to Day 28 of standard BFM consolidation. (5 weeks in total from the start in week 5 of induction). Doses should be taken at least one hour after the evening meal without milk products. Adjust the dose of 6-MP to attain a weekly cumulative dose of as near 420mg/m² as possible. Do not increase dosage for ANC >2.0 .
- d) **Intrathecal methotrexate:** once a week for three doses on days 1, 8 and 15. Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. These doses are in line with CCG recommendations. There is no intravenous vincristine in this phase.

Regimen B: Interim maintenance I – phase III (See flowchart 10.)

This phase runs from day 1 (beginning of week 11) to day 56 inclusive (end of week 18) i.e. 8 weeks. Patients should have an ANC $>0.75 \times 10^9/L$ and platelets of $>75 \times 10^9/L$.

- a) **Dexamethasone:** 6 mg/m²/day orally, divided into twice daily doses each day on days 2-6 (week 11) and days 30-34 (week 15).
- b) **Vincristine:** 1.5 mg/m² (maximum single dose 2 mg) IV on day 2 (week 11) and day 30 (week 15).
- c) **6-mercaptopurine:** 75 mg/m²/day orally, daily on days 1-49 (weeks 11-17), but not days 50-56 (week 18). Doses should be taken at least one hour after the evening meal without milk products. Dose adjustments are described in Appendix C. The omission of 6-mercaptopurine for days 50-56 is in line with the relevant CCG protocol.
- d) **Oral methotrexate** 20 mg/m² oral weekly during weeks beginning on days 8, 15, 22, 36, 43 and 50 as single dose taken with 6-mercaptopurine. Dose adjustments are described in Appendix C.
- e) **Intrathecal methotrexate** on days 1 and 29. Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. Do not schedule vincristine on the same day as IT methotrexate.
- f) **Bone Marrow.** BM for MRD status at day 1 week 11.

Regimen B: Delayed intensification I – phase IV (See flowchart 11.)

This phase runs from day 1 (beginning of week 19) to day 49 inclusive (end week 25) i.e. 7 weeks. Patients should have an ANC $>0.75 \times 10^9/L$ and platelets of $>75 \times 10^9/L$. Once begun, therapy during weeks 19-22 is not interrupted for myelosuppression alone. Therapy due day 1 week 23 should be delayed until ANC $>0.75 \times 10^9/L$ and platelets of $>75 \times 10^9/L$. and once begun should not be interrupted solely for myelosuppression. Any **serious** infection, such as Varicella, pneumocystis pneumonia, or neutropenia with fever, and presumed or proven infection, warrants chemotherapy interruption at any time during DI.

Send Marrow for MRD on day 1 of week 19.

Part 1; weeks 19 – 22:

- a) **Dexamethasone** 10 mg/m²/day orally for 7 days on days 2-8 (week 19) and 16-22 (week 21). No taper. Divide into two daily doses, adjusted upward to nearest 0.25 mg, as tablet size dictates. (Liquid preparation is acceptable).
- b) **Vincristine** 1.5 mg/m² (2.0 mg max) IV push on days 2 (week 19), 9 (week 20) and 16 (week 21).
- c) **Doxorubicin (Adriamycin)** 25 mg/m² IV on days 2 (week 19), 9 (week 20) and 16 (week 21) given over a period of 1 hour.
- d) **Pegylated L-Asparaginase: (Oncaspar)** 1000 iu/m² **IM** on day 4 (week 19)
- e) **Intrathecal methotrexate** on day 1 (week 19). Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. Do not schedule vincristine on the same day as intrathecal methotrexate.

Part 2; weeks 23 – 25:

- f) **Cyclophosphamide** 1,000 mg/m² IV over 20-30 min day 29 (week 23). Give 125mls/m²/hr of Dextrose /Saline infusion for 30 minutes before the cyclophosphamide and for 3.5 hours afterwards, i.e. 4 hours in total. Do not add potassium. Mesna is not needed.
- g) **Mercaptopurine. All patients receive MP 60 mg/m²/day during delayed intensification 1.** The drug is given daily by mouth for 14 days from day 29 (beginning of week 23) to day 42 (end of week 24). No dose adjustments are made during this block. Doses should be taken at least one hour after the evening meal, without milk products.
- h) **Cytarabine (ara-C).** 75mg/m²/day by IV push or subcutaneously – 8 doses in two pulses of 4 days each; days 30-33 (week 23) and days 37-40 (week 24).
- i) **Intrathecal methotrexate.** Days 29 (week 23) and 36 (week 24). Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg.

Regimen B: Interim maintenance II – phase V (See flowchart 12.)

This phase is only for patients receiving two delayed intensifications. MRD low patients should proceed to the Maintenance phase from day 1 of week 26.

This phase runs from day 1 (beginning of week 26) to day 56 inclusive (end of week 33) (i.e. 8 weeks). Patients should have ANC $>0.75 \times 10^9/L$ and platelets of $>75 \times 10^9/L$ to start.

- a) **Dexamethasone:** 6 mg/m²/day orally, divided into twice daily doses each day on days 2-6 (week 26) and days 30-34 (week 30).
- b) **Vincristine:** 1.5 mg/m² (maximum single dose 2 mg) IV on day 2 (week 26) and day 30 (week 30).
- c) **6-mercaptopurine:** 75 mg/m²/day orally, daily on days 1-49 (weeks 26-32), **but not days 50-56 (week 33)**. Doses should be taken at least one hour after the evening meal without milk products. Dose adjustments are described in Appendix C. The omission of 6-mercaptopurine on days 50-56 is in line with the relevant CCG protocol.
- d) **Oral methotrexate:** 20 mg/m² orally weekly during weeks beginning on days 8, 15, 22, 36, 43 and 50 as a single dose taken with 6-mercaptopurine. Dose adjustments are described in Appendix C.
- e) **Intrathecal methotrexate:** on days 1 and 29 (weeks 26 and 30). Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. Do not schedule vincristine on the same day as intrathecal methotrexate.

Regimen B: Delayed intensification II – phase VI (See flowchart 13.)**This phase is only for patients receiving two delayed intensifications.**

This phase runs from day 1 (beginning of week 34) to day 49 inclusive (end of week 40) (i.e. 7 weeks). Patients should have ANC $>0.75 \times 10^9/L$ and platelets of $>75 \times 10^9/L$. Once begun, therapy during weeks 34-37 is not interrupted for myelosuppression alone. Therapy due on day 1 of week 38 should be delayed until ANC $>0.75 \times 10^9/L$ and platelets of $>75 \times 10^9/L$ and once begun should not be interrupted solely for myelosuppression. Any **serious** infection, such as Varicella, pneumocystis pneumonia, or neutropenia with fever, and presumed or proven infection, warrants chemotherapy interruption at any time during DI.

Part 1; weeks 34-37:

- a) **Dexamethasone** 10 mg/m²/day orally for 7 days on days 2-8 (week 34) and 16-22 (week 36). No taper. Divide into two daily doses, adjusted upward to nearest 0.25 mg, as tablet size dictates. (Liquid preparation is acceptable).
- b) **Vincristine** 1.5 mg/m² (2.0 mg max) IV push on days 2 (week 34), 9 (week 35) and 16 (week 36).
- c) **Doxorubicin** (Adriamycin) 25 mg/m² IV on days 2 (week 34), 9 (week 35) and 16 (week 36) given over a period of 1 hour.
- d) **Pegylated L-Asparaginase: (Oncaspar)** 1000 iu/m² **IM** on day 4 (week 34).
- e) **Intrathecal methotrexate** on day 1 (week 34). Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. Do not schedule vincristine on the same day as intrathecal methotrexate.

Part 2; weeks 38-40:

- f) **Cyclophosphamide** 1,000 mg/m² IV over 20-30 min day 29 (week 38). Give 125mls/m²/hr of Dextrose /Saline infusion for 30 minutes before the cyclophosphamide and for 3.5 hours afterwards, i.e. 4 hours in total. Do not add potassium. Mesna is not needed.
- g) **Mercaptopurine. All patients receive MP 60 mg/m²/day during delayed intensification 1.** The drug is given daily by mouth for 14 days from day 29 (beginning of week 38) to day 42 (end of week 39). No dose adjustments are made during this block. Doses should be taken at least one hour after the evening meal, without milk products.
- h) **Cytarabine (ara-C).** 75mg/m²/day by IV push or subcutaneously – 8 doses in two pulses of 4 days each; days 30-33 (week 38) and days 37-40 (week 39).
- i) **Intrathecal methotrexate.** Days 29 (week 38) and 36 (week 39). Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg.

Regimen B: Maintenance – Phase VII (See flowchart 14.)

Maintenance begins from day 1 cycle 1 (beginning of week 26 for patients receiving one delayed intensification and week 41 for those allocated two delayed intensifications) in 12-week cycles to end of week 114 for girls and to the end of week 166 for boys. The cycle in progress is stopped when the end of therapy is reached. Omit the Vincristine and steroid pulse if it falls in the last week of therapy. This period of continuing treatment equates to 2 years from the start of interim maintenance I for girls and 3 years for boys.

Maintenance should begin when the ANC is $>0.75 \times 10^9/l$ and the platelet count is $>75 \times 10^9/l$. Only 6-mercaptopurine and oral methotrexate will be interrupted for myelosuppression and not made up. Days off therapy for intercurrent infections are counted as days of maintenance and not made up. *Anaemia* occurring in the course of maintenance therapy should be treated with transfusion and the dose of drug is maintained. If *persistent anaemia* occurs (i.e., haemoglobin below 8 g/dl) investigate for parvovirus infection. Please contact trial co-ordinators for advice.

- a) **Dexamethasone:** 6 mg/m²/day orally, divided into twice-daily doses on days 1-5, 29-33 and 57-61 of each cycle.
- b) **Vincristine:** 1.5 mg/m² (maximum single dose 2 mg) IV on days 1, 29, and 57 of each cycle.
- c) **6-mercaptopurine:** 75 mg/m²/day orally, daily throughout maintenance. Doses should be taken at least one hour after the evening meal without milk products. Dose adjustments are described in Appendix C.
- d) **Oral methotrexate:** 20 mg/m² orally during weeks beginning on days 1, 8, 22, 29, 36, 43, 50, 57, 64, 71 and 78 of each cycle. **Note none is given in the third week of each cycle as an intrathecal dose is given during that week.** Dose adjustments are described in Appendix C.
- e) **Intrathecal methotrexate:** On day 15 of each cycle. Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg.
- f) **Bone marrow examination** should be carried out at the same time as the **week 43** (week 40 for patients randomised to one DI) and **end of treatment** intrathecal methotrexates with samples being taken for MRD analysis. NB the end of treatment marrow should always be done BEFORE chemotherapy is stopped to prevent confusion due to “rebound” marrows.

END OF REGIMEN B

17. UKALL 2003 REGIMEN C.**Eligibility.**

To be eligible for regimen C, patients must either

- a) Have had a slow early response in regimens A or B, which **must** be confirmed by rapid second review, or
- b) Have MRD positive D29 bone marrow and randomised to regimen C, or
- c) Have unfavourable cytogenetics.

NOTE THAT PATIENTS OLDER THAN 16 YEARS (IE AFTER THE 16th BIRTHDAY) SHOULD NOT SWITCH TO THIS REGIMEN SOLELY BECAUSE OF SLOW EARLY RESPONSE.

Patients switching from regimen A at day 15 must have an M3 marrow at day 15. These patients will then have daunorubicin added to their induction schedule **Note: increased dose**. **Patients switching from regimen A at day 35** must be MRD High Risk at day 28 and be randomised to regimen C.

Patients switching from regimen B at day 8 must have an M3 marrow at day 8. These patients continue with a four drug induction schedule and then move onto augmented BFM consolidation. **Patients switching from regimen B at day 35** must be MRD High Risk at day 28 and be randomised to regimen C.

High-risk cytogenetic features that mandate a switch to regimen C are hypodiploidy (≤ 44 chromosomes); BCR-ABL gene rearrangement; Amplified AML1 (iAMP21) or MLL gene rearrangement. No other cytogenetic features are eligible.

Patients with M2 marrows at day 28 (blasts 5-25%) should continue with regimen C (augmented BFM consolidation) and should only be taken off protocol if they are not in remission at the end of consolidation.

Summary of Regimen C.

Regimen C consists of the following phases:

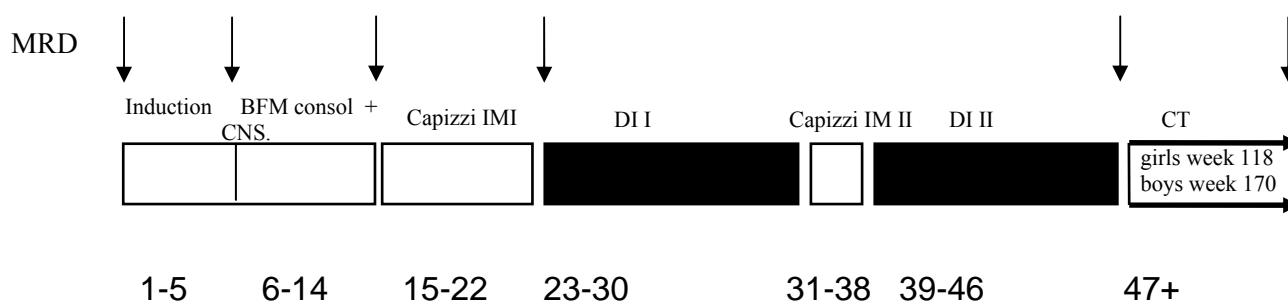
1. Completing a four drug induction with dexamethasone as steroid of choice;
2. Augmented BFM consolidation (duration 9 weeks); all patients receive 6 mercaptopurine;
3. Interim Capizzi maintenance I (duration 8 weeks) using PEG asparaginase and escalating doses of IV methotrexate;
4. Delayed intensification I (duration 8 weeks); **6-mercaptopurine** in reconsolidation; PEG asparaginase;
5. Interim Capizzi maintenance II (duration 8 weeks) using PEG asparaginase and escalating doses of IV methotrexate;
6. Delayed intensification II (duration 8 weeks); **6-mercaptopurine** in reconsolidation; PEG asparaginase;
7. Maintenance chemotherapy with dexamethasone and 6-mercaptopurine to the end of week 118 for girls and end of week 170 for boys. Delays accrued during phases I-VI are taken off the maintenance period.

Please read this protocol carefully before using it. Note that there are two induction schedules; one for patients switching from regimen A starting at day 15, and one for patients switching from regimen B starting at day 8.

Patients initially treated on regimen A who switch to regimen C because of the day 15 marrow status will start regimen C at day 15 regardless of the length of the interval since diagnosis. They then have augmented BFM consolidation and intrathecal methotrexate. Patients switching from regimen B continue a four-drug induction. Patients from either regimen A or B who are randomised to regimen C because of day 29 marrow status (MRD High Risk) will start augmented BFM consolidation on day 1 of week 6.

Not all drugs or courses of drugs due in given weeks start on the same day of that week. The prescribed scheduling must be maintained, particularly during the interim maintenance phases.

Patients having a bone marrow transplant in first remission should receive Regimen C up to the beginning of week 14, i.e. to the beginning of Escalating Capizzi I, but should then be given standard maintenance chemotherapy until the time of their transplant. It is not necessary for them to have either the delayed intensification blocks, or the Capizzi maintenance prior to transplant.



UKALL 2003 REGIMEN C: DETAILS OF TREATMENT.

The convention for day/week numbering is that a new module of therapy begins on day 1 of whatever week of treatment has been reached. Induction begins on day 1 (week 1) of schedule A or B prior to transfer, consolidation on day 1 (week 6), delayed intensification II on day 1 (week 39) and so on. Each module runs for a number of days and induction therefore finishes on day 35 (end of week 5), interim maintenance I on day 56 (end of week 22) and delayed intensification II on day 56 (end of week 46).

Regimen C Phase 1: Remission induction- see flowchart 15a.

Patients switching from regimen A should continue this induction modification for 21 days, regardless of the length of time that has elapsed since diagnosis. Patients starting on this protocol at day 15 will have more than 25% blasts in the bone marrow at day 15 or will have cytogenetically adverse features identified on the bone marrow sample taken at diagnosis.

This phase runs for 21 days from day 15 (beginning of week 3) to day 35 inclusive (end of week 5) (i.e. 3 weeks in all).

- a) **Dexamethasone:** 6mg/m²/day (maximum dose 10 mg/day in induction only) for a total of 28 days from commencing regimen A which is then tapered over the next 7 days, i.e. to stop on day 35. The steroid should be divided into two doses per day.
- b) **Vincristine:** 1.5 mg/m² (maximum single dose 2 mg) IV weekly on days 16, 23 and 30.
- c) **Daunorubicin:** 45mg/m² over 1 hour on days 16, and 23. Note that this dose is higher than that in regimen B and is for two doses only.
- d) **Pegylated L-asparaginase: (Oncaspar)** 1000 iu/m² IM, on day 18).
- e) **Intrathecal methotrexate :** **On day 28.** Dose by age: <2yrs: 8mg; 2 yrs: 10mg; 3yrs or more: 12mg. NB Patients who have CNS disease at presentation should receive weekly doses until two clear CSF samples are obtained – see page 24. Do not schedule vincristine on the same day as the intrathecal methotrexate.
- f) **6-mercaptopurine:** 60mg/m²/day starting on day 29 (beginning week 5) (if neutrophils > 0.75 and platelets > 75) and continuing for three weeks (end of week 2 of Augmented BFM consolidation). Adjust the dose of 6-MP to attain a weekly cumulative dose of as near 420mg/m² as possible. Doses should be taken at least one hour after the evening meal without milk products. Do not increase dosage for ANC>2.0
- g) **Bone Marrow:** Check marrow status at day 28 and send sample for MRD. Patients with persistent M3 marrow at day 29 are off protocol.
- h) Co-trimoxazole (trimethoprim and sulphamethoxazole). This drug is given as PCP prophylaxis orally on 2 consecutive days throughout treatment **from the start of induction.** See below for doses. Please ensure separation of the days on which oral Methotrexate and Cotrimoxazole doses are given during maintenance courses.

Regimen C – Induction phase for patients starting at day 8
see flowchart 15b

- a) **Dexamethasone:** 6 mg/m²/day (maximum dose 10 mg/day in induction only) for a total of 28 days from commencing Regimen B which is then tapered over the next 7 days i.e. to stop on day 35. The steroid should be divided into two doses per day.

- b) **Vincristine:** 1.5 mg/m² (maximum single dose 2 mg) IV on days 9, 16, 23 and 30.
- c) **Daunorubicin:** 25mg/m² over 1 hour on days 9, 16 and 23. This dosage is the same as that given in regimen B.
- d) **Pegylated L-asparaginase (Oncaspar)** 1000 iu/m² IM on day 18.
- e) **Intrathecal methotrexate : On day 28.** Dose by age: <2yrs: 8mg; 2 yrs: 10mg; 3yrs or more: 12mg. NB Patients who have CNS disease at presentation should receive weekly doses until two clear CSF samples are obtained – see page 19. Do not schedule vincristine on the same day as the intrathecal methotrexate.
- f) **6-mercaptopurine:** 60mg/m²/day starting on day 29 (beginning week 5) (if neutrophils > 0.75 and platelets > 75) and continuing for three weeks (end of week 2 of Augmented BFM consolidation). Adjust the dose of 6-MP to attain a weekly cumulative dose of as near 420mg/m² as possible. Doses should be taken at least one hour after the evening meal without milk products. Do not increase dosage for ANC > 2.0.
- g) **Bone Marrow:** Check marrow status at day 28. Patients with persistent M3 marrow at day 29 are off protocol. Co-trimoxazole (trimethoprim and sulphamethoxazole) This drug is given as PCP prophylaxis orally on 2 consecutive days throughout treatment from the start of induction. The dose is tabulated below. Please ensure separation of the days on which oral Methotrexate and Cotrimoxazole doses are given during maintenance courses.

If a child remains cytopenic after being off chemotherapy for three weeks or more, then stop the co-trimoxazole. Reintroduce co-trimoxazole once both thiopurine and methotrexate are back at standard dose. If cytopenias recur once the co-trimoxazole is reintroduced, then it should be stopped for at least two months and an alternative form of prophylaxis used instead (see below). The alternative drug should then be continued for the duration of the antileukaemic therapy

The maintenance of adequate doses of thiopurine and methotrexate should take precedence over continuing co-trimoxazole. If co-trimoxazole is stopped, however, it must be remembered that the child is at increased risk of PCP. Nebulised pentamidine or oral Dapsone are alternative drugs.

Surface area	Co-trimoxazole	Trimethoprim	Sulphamethoxazole
0.5-0.75 m ²	240 mg bd	40 mg bd	200 mg bd
0.76-1.0 m ²	360 mg bd	60 mg bd	300 mg bd
over 1.0 m ²	480 mg bd	80 mg bd	400 mg bd

See also appendix D for details of alternative PCP prophylaxis regimens.

Permitted dose modifications for toxicity – see Appendix E.

Regimen C: Consolidation - Augmented BFM - phase II

see flowchart 16

Patients on regimens A or B with MRD positive marrows at day 28 and have been randomised to regimen C should start Augmented BFM. Patients who have already switched to regimen C continue with augmented BFM consolidation.

Patients who are Slow Early Responders (SER) on regimen A (aged under 10 years or WBC under $50 \times 10^9/L$ at diagnosis) or regimen B (aged over 10 years or WBC over $50 \times 10^9/L$ at diagnosis) whose CSF was clear at diagnosis who switch to regimen C, will receive intrathecal methotrexate only for CNS directed treatment – see flowchart 16. Patients with refractory CNS disease at diagnosis will receive cranial irradiation during augmented BFM, starting at day 36

This phase runs from day 1 (beginning of week 6) to day 63 inclusive (end of week 14) i.e. 9 weeks. The block of treatment should be started at day 36 from diagnosis (week 6), or when the peripheral blood count recovers to an absolute neutrophil count (ANC) of $>0.75 \times 10^9/L$ and platelets of $>75 \times 10^9/L$. Once consolidation has begun it can be interrupted for myelosuppression (ANC $<0.75 \times 10^9/l$ or platelets $<75 \times 10^9/l$) at day 29, but once the cyclophosphamide has been given at day 1 or 29, therapy should continue, except in patients who are febrile **and proven to have infection** (i.e. do not stop because of neutropenia alone). Treatment should restart when signs of infection have abated.

- a) **Cyclophosphamide:** 1000 mg/m² IV over 20-30 minutes on days 1 and 29. Give 125mls/m²/hr of Dextrose /Saline infusion for 30 minutes before the cyclophosphamide and for 3.5 hours afterwards, i.e. 4 hours in total. Do not add potassium. Mesna is not needed.
- a) **Cytosine arabinoside:** 75mg/m² IV or SC - 16 doses in four pulses of 4 days each; days 2-5, 9-12, 30-33 and 37-40
- b) **6-Mercaptopurine:** All patients receive 6-mercaptopurine 60mg/m², PO, for 21 days, beginning week 5 of induction to end week 2 consolidation, and for 14 days on days 29-42 of consolidation. Mercaptopurine should be taken at least half an hour after evening meal, to obtain a weekly total dose of 420mg/m². Do not increase dose for neutrophils > 2.0 .
- c) **Vincristine:** 1.5 mg/m² IV (maximum of 2 mg) on day 16, 23, 44 and 51.
- d) **PEG-Asparaginase:** 1000 units/m² IM on days 16 and 44
- e) **Intrathecal methotrexate:** On days 1, 8 and 15. The dose is related to CSF volume as follows: 1-2 years: 8mg; 2-3 years: 10mg; over 3 years: 12 mg. Do not schedule vincristine on the same day as IT methotrexate.
- f) **Bone marrow aspirate** on day 1 of Capizzi Interim Maintenance. Patients with M2 marrows at the end of augmented BFM are off protocol. Send sample for MRD.

Regimen C: Escalating Capizzi Maintenance I Phase III

see flowchart 17.

This block of treatment should start at day 1 (beginning of week 15), or when blood count recovers to ANC $>0.75 \times 10^9/L$ and platelets of $>75 \times 10^9/L$, and lasts until day 56 inclusive (end of week 22) i.e. for 8 weeks. During phase III, therapy should be interrupted for serious infection such as Varicella or pneumocystis. Day 42 will be the last day of treatment in phase III, regardless of the number of methotrexate doses that have been omitted. The timings of administration of the drugs are important; do not reschedule any of the components. About 10-15% of patients are able to escalate the methotrexate dose to the maximum of $300 \text{mg}/\text{m}^2$. About 30-40% are able to make some escalation. The major toxicity is likely to be mucositis. The full toxicity grading is included in the section on toxicity assessment and reporting.

Start Capizzi I at a methotrexate dose of $100 \text{mg}/\text{m}^2$. Increase the dose for each subsequent course by $50 \text{mg}/\text{m}^2$, as tolerated, to a maximum dose, in Capizzi I, of $300 \text{mg}/\text{m}^2$. Prior to each course the patient will need to be assessed for oral, haematological, hepatic and renal toxicity, and the dosage modified as outlined below. Doses of vincristine and PEG-asparaginase should only be omitted for serious intercurrent illness.

Oral : For grade 2 mucositis of over 3 days duration, decrease IV MTX dose by 30%. For grade 3-4, mucositis, withhold IV MTX until resolved; resume at 50% of the previously attained dose and subsequently escalate to 75% to 100% dose at 10 day intervals provided grade 3-4 toxicity does not recur. Consider culturing lesions for herpes simplex if mucositis persists or recurs.

Haematological: omit methotrexate if ANC $<0.75 \times 10^9/L$ or platelets $<75 \times 10^9/L$; it should be reinstated on the first due date following the omitted dose when ANC $>0.75 \times 10^9/L$ and platelets $>75 \times 10^9/L$, and the dosage should be decreased by 20% from the previously administered dose. Missed doses will not be made up. If counts do not recover within 21 days, check bone marrow status.

Liver Dysfunction: If bilirubin is >50 micromoles/L omit IV MTX until it is less than 20 micromoles/L, and then restart at half of the previously attained dose. Escalate from 50% to 75% to 100% dose at 10-day intervals provided hyperbilirubinaemia does not recur. Do not modify dosage for elevated aminotransferases.

Kidney Dysfunction (Grade 3-4): Omit IV MTX until grade 0 toxicity (i.e. completely resolved). Resume at 100% of the previously attained dose and continue at 10-day intervals.

- (a) **Vincristine:** $1.5 \text{ mg}/\text{m}^2$ IV (maximum 2 mg) as a single dose on day 2, 12, 22, 32, and 42.
- (b) **Methotrexate:** $100 \text{mg}/\text{m}^2$ IV over 10-15 minutes as initial dose on day 2. Escalate subsequent doses by $50 \text{mg}/\text{m}^2$ to toxicity and modify dosage as necessary according to the above guidelines on days 12, 22, 32 and 42.
- (c) **PEG asparaginase:** $1000 \text{ units}/\text{m}^2$ IM on days 3 and 23.
- (d) **Intrathecal methotrexate:** on day 1 and 31. Dose by age: <2 yrs: 8mg; 2 yrs: 10mg; 3 yrs or more: 12 mg. Do not schedule vincristine on same day as IT methotrexate.

Regimen C: Delayed intensification I (Phase IV)

see flowchart 18.

This phase consists of reinduction and reconsolidation. For all patients in remission at the completion of phase III, phase IV begins on day 57 of phase III, day 1 (beginning of week 23) or when ANC $>0.75 \times 10^9/L$ and platelets of $>75 \times 10^9/L$, whichever occurs later, and lasts until day 56 inclusive (end of week 30) i.e. 8 weeks. Once started, reinduction and reconsolidation are not interrupted for myelosuppression alone. Reconsolidation is scheduled to begin on day 29, but should be delayed until ANC $>0.75 \times 10^9/L$ and platelets $>75 \times 10^9/L$. Treatment may be interrupted for **serious** infection such as Varicella, pneumocystis, or proven infection with neutropenia with fever. Bone marrows, which may be indicated because of persistent cytopenias, are often difficult to interpret in this phase. Pancytopenia is inevitable and M2 recovery marrows are common. **Note that delayed intensification in regimen C includes PEG asparaginase and additional doses of vincristine in the reconsolidation phase.**

Reinduction (weeks 23-26)

- (a) **Vincristine:** 1.5 mg/m² IV (maximum 2 mg) on days 2, 9 and 16.
- (b) **Doxorubicin:** 25mg/m² IV over 1 hour on days 2, 9 and 16.
- (c) **Dexamethasone** 10mg/m²/day divided into two doses on days 2-8 and 16-22.
- (d) **Intrathecal methotrexate** on day 1. Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. Do not schedule vincristine on the same day as IT methotrexate.
- (e) **PEG asparaginase:** 1000 units/m² IM on day 4.

Reconsolidation (weeks 27-30)

- a) **Cyclophosphamide** 1000 mg/m² IV over 20-30 minutes on day 29. Give 125mls/m²/hr of Dextrose /Saline infusion for 30 minutes before the cyclophosphamide and for 3.5 hours afterwards, i.e. 4 hours in total. Do not add potassium. Mesna is not needed.
- b) **Mercaptopurine. All patients receive MP 60 mg/m²/day during delayed intensification 1.** The drug is given daily by mouth for 14 days from day 29 (beginning of week 27) to day 42 (end of week 28). No dose adjustments are made during this block. Doses should be taken at least one hour after the evening meal, without milk products.
- c) **Cytarabine** 75mg/m² IV or SC on days 30-33 (four doses) and 37-40 (four doses).
- d) **Vincristine** 1.5mg/m² IV on days 43 and 50.
- e) **PEG asparaginase** 1000 units/m² IM on day 43.
- f) **Intrathecal methotrexate** on days 29 and 36. Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg.

Regimen C: Escalating Capizzi Maintenance II, Phase V

see figure 19.

For Interim Maintenance II (Phase V) methotrexate should be started at one level below (i.e. 50mg/m² less than) the maximum dose in Capizzi I and then escalate as tolerated.

This block of treatment should start at day 57 of phase IV, day 1 (beg. week 31), or when blood count recovers to ANC >0.75x10⁹/L and platelets of >75x10⁹/L and lasts until day 56 inclusive (end of week 38) i.e. 8 weeks. During phase V therapy should be interrupted only for serious infection such as Varicella or pneumocystis.

Start Capizzi II at a methotrexate dose of 50mg/m² below that attained in Capizzi I. Increase the dose for each subsequent course by 50mg/m², as tolerated, to the maximum tolerated dose. Prior to each course the patient will need to be assessed for oral, haematological, hepatic and renal toxicity, and the dosage modified as outlined below. Doses of vincristine and PEG-asparaginase should only be omitted for serious intercurrent illness

Oral: For grade 2 mucositis of over 3 days duration decrease dose of IV MTX by 30%. For grade 3-4, mucositis, withhold IV MTX until resolved; resume at 50% of the previously attained dose and subsequently escalate to 75% to 100% dose at 10 day intervals provided grade 3-4 toxicity does not recur. Consider culturing lesions for herpes simplex if mucositis persists or recurs.

Haematological: omit methotrexate if ANC<0.75x10⁹/L or platelets <75x10⁹/L; it should be reinstated on the first due date following the omitted dose when ANC>0.75x10⁹/L and platelets >75x10⁹/L, and the dosage should be decreased by 20% from the previously administered dose. Missed doses will not be made up. If counts do not recover within 21 days, check bone marrow status.

Liver Dysfunction: If bilirubin is >50 micromoles/L omit IV MTX until it is less than 20 micromoles/L, and then restart at half of the previously attained dose. Escalate from 50% to 75% to 100% dose at 10-day intervals provided hyperbilirubinaemia does not recur. Do not modify dosage for elevated aminotransferases.

Kidney Dysfunction (Grade 3-4): Omit IV MTX until grade 0 toxicity (i.e. completely resolved). Resume at 100% of the previously attained dose and continue at 10-day intervals.

- (a) **Vincristine:** 1.5 mg/m² IV (maximum 2 mg) as a single dose on day 2, 12, 22, 32, 42.
- (b) **Methotrexate:** Start at 50mg/m² below the dose attained in Capizzi I as initial dose IV over 10-15 minutes on day 2. Escalate subsequent doses by 50mg/m² to toxicity and modify dosage if necessary according to the above guidelines, on days 12, 22, 32 and 42.
- (c) **PEG asparaginase** dose 1000 units/m² IM on days 3 and 23.
- (d) **Intrathecal methotrexate** on day 1 and 31. Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. Do not schedule vincristine on the same day as IT methotrexate.

Regimen C: Delayed intensification II, (Phase VI)

see flowchart 20.

This phase again consists of reinduction and reconsolidation. For all patients in remission at the completion of phase V, phase VI begins on day 57 (day 1, beginning of week 39) or when ANC $>0.75 \times 10^9/L$ and platelets of $>75 \times 10^9/L$, whichever occurs later, and lasts until day 56, inclusive (end of week 46), i.e. 8 weeks. Once started, reinduction and reconsolidation are not interrupted for myelosuppression alone. Reconsolidation is scheduled to begin on day 29, but should be delayed until ANC $>0.75 \times 10^9/L$ and platelets $>75 \times 10^9/L$. Treatment may be interrupted for serious infection such as Varicella, pneumocystis, or proven infection with neutropenia with fever. Bone marrows are often difficult to interpret in this phase. Pancytopenia is inevitable and M2 recovery marrows are common.

Note that delayed intensification in regimen C includes PEG asparaginase and additional doses of vincristine in the reconsolidation phase.

Reinduction (weeks 39-42)

- (a) **Vincristine** 1.5 mg/m^2 IV (maximum 2 mg) as a single dose on days 2, 9, 16.
- (b) **Doxorubicin** 25 mg/m^2 IV over 1 hour on days 2, 9, 16.
- (c) **Dexamethasone** $10 \text{ mg/m}^2/\text{day}$ divided into two doses on days 2-8 and 16-22.
- (d) **Intrathecal methotrexate** on day 1. Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. Do not schedule vincristine on the same day as IT methotrexate.
- (e) **PEG asparaginase** dose 1000 units/m^2 **IM** on day 4.

Reconsolidation (weeks 43-46)

- a) **Cyclophosphamide** 1000 mg/m^2 IV over 20-30 minutes on day 29. Give $125 \text{ ml/m}^2/\text{hr}$ of Dextrose /Saline infusion for 30 minutes before the cyclophosphamide and for 3.5 hours afterwards, i.e. 4 hours in total. Do not add potassium. Mesna is not needed.
- b) **Mercaptopurine. All patients receive MP $60 \text{ mg/m}^2/\text{day}$ during delayed intensification 2.** The drug is given daily by mouth for 14 days from day 29 (beginning of week 43) to day 42 (end of week 44). No dose adjustments are made during this block. Doses should be taken at least one hour after the evening meal, without milk products.
- c) **Cytarabine** 75 mg/m^2 IV or SC on days 30-33 (four doses) and 37-40 (four doses).
- d) **Vincristine** 1.5 mg/m^2 IV on days 43 and 50.
- e) **PEG asparaginase** 1000 units/m^2 IM on day 43.
- f) **Intrathecal methotrexate** on days 29 and 36. Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg

Regimen C: Maintenance. (See flowchart 21.)

This phase runs from day 1 cycle 1 (week 47) in 12-week cycles to day 84, cycle 6 (end of week 118 for girls) and day 28, cycle 11 (end of week 170 for boys). The cycle in progress is stopped when the end of therapy is reached. This equates to 2 years from the start of interim maintenance I for girls and 3 years for boys.

Maintenance should begin when the ANC is $>0.75 \times 10^9/l$ and the platelet count is $>75 \times 10^9/l$. Only 6-mercaptopurine and oral methotrexate will be interrupted for myelosuppression and not made up. Days off therapy for intercurrent infections are counted as days of maintenance and not made up. **Anaemia** occurring in the course of maintenance therapy should be treated with transfusion and the dose of drug is maintained. If *persistent anaemia* occurs (i.e., haemoglobin below 8 g/dl) investigate for parvovirus infection. Please contact trial co-ordinators for advice.

- a) **Dexamethasone:** 6 mg/m²/day orally, divided into twice daily doses on days 1-5, 29-33 And 57-61 of each cycle.
- b) **Vincristine:** 1.5mg/m² (maximum single dose 2 mg)IV on days 1, 29, and 57 of each cycle.
- c) **6-mercaptopurine:** 75 mg/m²/day orally daily throughout maintenance. Dose adjustments are described in Appendix C.
- d) **Methotrexate** 20 mg/m² orally during weeks beginning days 1, 8, 22, 29, 36, 43, 50, 57, 64, 71 and 78 of each cycle. **Note none is given in the third week of each cycle as an intrathecal dose is given during that week.** Dose adjustments are described Appendix C.
- e) **Intrathecal methotrexate** given on day 15 of each cycle. On the final cycle, girls on cycle 6 can be given IT MTX either at day 15 or day 77 with the end of treatment BM, while boys will have their final dose on day 15 cycle 11. Dose is by age: 1-2 years: 8mg; 2-3 years: 10mg; over 3 years: 12 mg

Bone marrow examination should be carried out at same time as the **week 49 and end of treatment** intrathecal methotrexates with samples being taken for MRD analysis.

NB the end of treatment marrow should always be done BEFORE chemotherapy is stopped to prevent confusion due to “rebound” marrows. Treatment ends on the due date, whether or not a cycle is complete. Patients should have a final bone marrow aspirate and diagnostic lumbar puncture to confirm complete remission. All therapy, including prophylactic Septrin, should then stop.

END OF REGIMEN C

APPENDIX A

Determining weight for dosage calculations

All children should be weighed in underclothes and scales should be calibrated regularly. To ensure that children are treated effectively, without overdosing due to treatment related fat deposition, the Body mass index (BMI) should be checked at diagnosis, at the end of the 2nd delayed intensification and at 1 year and 2 years from diagnosis.

Calculate using the formula $BMI = \text{weight(kg)} / \text{Height}^2 \text{ (m x m)}$

The BMI can then be compared to the standard Child Growth foundation BMI charts* for the appropriate sex.

For children with a BMI that falls within the 2nd-98th percentiles, dose by **actual weight** using the UKCCSG weight/surface area (SA) charts to determine the surface area (SA) for dose calculation. These weights should be taken

- At diagnosis
- Immediately prior to each delayed intensification
- At the time of the intrathecal injection on each maintenance cycle

For children who have a BMI > 98th percentile read off the BMI at 98th percentile for their age. Calculate the **dosing weight** using the formula

Dosing weight (kg) = BMI x Ht² (m x m)

Use the UKCCSG Wt/SA charts to determine the SA for dose calculation.

For children < 2nd percentile, repeat as above reading the BMI at the 2nd percentile for calculation.

For children who have considerable weight loss due to illness during treatment it may be necessary to re- assess their BMI and dosing weight prior to recommencing treatment.

Rationale for frequency of weighing for determination of changes in drug dosage.

A normal child aged 2-10 years gains only 2-6kg/year¹. This equates to an average of 1kg every 3 months (maximum 1.5kg).

If children are weighed fully clothed rather than in underclothes, the extra weight will be greater than the quarterly change in weight. Scales, even regularly calibrated, also carry a measurement error. These errors, coupled with weight variation due to physical, endocrine, nutritional, and psychosocial effects make repeated measurements inaccurate².

Children having repeat doses of steroids will have greater than average weight gain, but this is primarily deposited as fat- particularly truncal fat³. Unless drug treatment is with very lipophilic drugs the weight gain should not affect the therapeutic doses required to treat ALL. Only Daunorubicin, doxorubicin and vincristine have longer T1/2 and larger volume of

distribution, indicating major transfer to body compartments other than the blood. Both anthracyclines are ionic compounds and they and their active metabolites are highly protein bound, which would suggest less deposit into fat than into lean mass. Vincristine is highly water soluble and readily distributed into tissues. As it is predominantly renally excreted it is again unlikely that it is highly deposited in fat⁴.

Do not adjust doses on the basis of weight change any more frequently than every 3 months. In practice the changes should equate to:

Prior to induction

Pre- 1st Delayed intensification

Pre-2nd Delayed intensification

Prior to starting each cycle of maintenance.

The UKCCSG Surface area charts have been validated for children with an understanding that they are less accurate at the extremes of obesity and underweight. There is no defined cut off. There is no defined BMI for obesity in children, but children with BMI > 98th percentile for age have been shown to have an increased risk of related morbidity in adult life⁵. The Child growth foundation BMI charts for boys and girls mark the 9th and 98th percentiles so it would logical to use these cut off points

Doses have traditionally been based on total weight rather than lean weight, so to change to lean body weight dosing could result in under-treatment. Dexamethasone is likely to cause greater weight gain than prednisolone¹. This may be compounded by the secular changes in UK society. It would therefore seem prudent to have a defined maximum BMI percentile, for dosing; weight percentiles taking no account of tall or small stature children.

References

1. Clinical Paediatric endocrinology. Brook and Hindmarsh.
2. Short term growth: rhythms, chaos or noise? Wales J et al Archives Dis Child 1994 71: 84-89
3. Bodyweight change as an adverse effect of drug treatment- Mechanisms and management Pijl H et al Drug Safety 1996 14(5); 329-42
4. Micromedex Drug database September 2004
5. Use of weight for height indices in children to predict adult overweight: the Bogalusa Heart Study Int J Obesity 1996 21:715-21

APPENDIX B

General drug information

The experimental aspect of the trial is not the treatment regimens or any particular drug within them, but a method for tailoring these “standard” treatments to risk groups defined in a novel fashion.

Therefore, the only drugs categorised as IMPs in the protocol are those that do not have a UK marketing authorisation. These are Oncospar, Mercaptopurine 10 mg tablets and special formulations of Mercaptopurine and Methotrexate solutions. **ALL OTHER DRUGS AND THE COMBINATIONS IN WHICH THEY ARE USED WITHIN THE TREATMENT REGIMENS ARE STANDARD THERAPY FOR ALL AND ARE THEREFORE NOT DEFINED AS IMPs.**

Risks of chemotherapy for females of child bearing potential

All chemotherapy agents can cause harm to the fetus and may be excreted in breast milk. Therefore, females of child bearing potential should be counselled about this risk and asked to adopt appropriate measures to prevent pregnancy whilst on treatment with this protocol.

1) PREDNISOLONE

To be used only for patients who experience serious dexamethasone toxicity.

Please specify clearly on the prescription charts that prednisolone and not prednisone is to be used and that tablets must **not** be enteric coated.

Formulation	1 mg, 5mg and 25 mg (scored ordinary and scored soluble) tablets available.
Dose	40 mg/m ² po daily in place of dexamethasone
Storage	At room temperature.
Administration	40 mg/m ² orally daily in two divided doses, with or after food.
Toxicity	Obesity, hirsutism, fluid and salt retention, hypertension, irritability, glycosuria, avascular necrosis of bone and hyperglycaemia.

2) DEXAMETHASONE

Formulation	0.5 mg, 2 mg tablets, oral solution 2mg/5ml (licensed formulation).
Storage	At room temperature.
Administration	6 mg/m ² (during induction, interim maintenance and maintenance phases, 10 mg/m ² during intensification) orally daily in two divided doses. Dose is capped at 10 mg/day during induction.
Toxicity	As for prednisolone, with or after food.

3) VINCRISTINE SULPHATE

Formulation	1mg/ml injection solution.
Storage	At 2-8°C in refrigerator.
Administration	1.5mg/m ² by bolus intravenous injection. Ensure that the needle is well into the vein and avoid extravasation. Children >10 years must have vincristine diluted to 0.1mg/ml unless the centre has signed a waiver with local PCT.

Toxicity Local necrosis if extravasation occurs. Jaw pain, paresis, constipation, systemic neurotoxicity and alopecia.

NB. Vincristine, given by the wrong route of administration, causes ascending myelitis, excruciating pain, paralysis and death, given into the CSF. The drug should not be drawn up or available in the same room to anyone performing a lumbar puncture.

4) DOXORUBICIN (ADRIAMYCIN)

Formulation 2mg/ml Red solutions in 10, 20 or 50 mg vials, or 10 or 50 mg vials of freeze dried powder.

Storage Refrigerated at 2-8°C. Protect from light.

Mixing Dissolve powder in sodium chloride for injection to give concentration of 2mg/ml.

Stability Depends on formulation/concentration

Administration 25 mg/m² diluted in 0.9% saline and given IV slowly over 1 hr, or in young adults as a slow bolus alongside a fast running fluid infusion. **NB** avoid extravasation. Protect from light

Toxicity Local necrosis if extravasation occurs. Myelosuppression, alopecia, cardiotoxicity. Small risk of secondary AML.

5) DAUNORUBICIN

Formulation Red lyophilised powder for intravenous administration following addition of sterile water for injections. Each vial contains 20mg of daunorubicin base.

Storage Protected from light at less than 25 degrees C. After reconstitution at 2-8 degrees C protected from light.

Mixing Dissolve powder in 4mls of water for injection to give concentration of 5mg/ml.

Stability Concentration dependent.

Administration 25-45mg/m² diluted in 0.9% saline or dextrose saline and given IV slowly over 1 hr, or in young adults as a slow bolus alongside a fast running fluid infusion. **NB** avoid extravasation

Toxicity Local necrosis if extravasation occurs. Myelosuppression, mucositis, alopecia, cardiotoxicity. Small risk of secondary AML.

6) ERWINASE- Only for use in patients with allergy to E-coli Asparaginase.

Formulation OPI: Crisantaspase (Asparaginase from *Erwinia chrysanthemi*; *Erwinia* L-asparaginase), 10,000 Units/vial. Freeze-dried powder for reconstitution.

Storage Store between +2°C and +8°C.

Mixing Reconstitute contents of each vial in 1 ml of Sodium Chloride for Injection BP and dissolved by gentle mixing.

Stability Administer within 15 minutes of reconstitution or within 8 hours in a latex free syringe, if aseptically prepared.

Administration 20000u/m² by intramuscular or subcutaneous injection. (see appendix F)

Toxicity Hypersensitivity including anaphylaxis. **Patients with systemic reactions should not be re-exposed to Erwinase.** Acute pancreatitis; hyperglycaemia; liver dysfunction and coagulopathy.

7) METHOTREXATE

a) MTX Injection (YELLOW LIQUID)

Formulation Ready mixed vials in the following strengths:
2.5 mg in 1 ml, 25mg/ml, 100mg/ml in various vial sizes.

NB Check label carefully before administration. These vials contain sodium chloride and sodium hydroxide adjusted to a pH of 8.5; there is no preservative present.

Stability After the vial has been used, discard remaining contents as there is no preservative, unless prepared in an aseptic facility.

Administration Variable, as per protocol. 100mg/ml strength is hypertonic- dilute before administration. Administer intrathecal doses at a concentration of not more than 2.5mg/ml.

Toxicity Neurotoxicity, mucositis, liver dysfunction, bone marrow depression.

b) MTX for oral use

Formulation 2.5 mg and 10 mg scored tablets, 10mg/5ml suspension.

Storage At room temperature in a dark place.

Stability Please note the expiry date.

Administration 20 mg/m² orally weekly all tablets taken together. Omit dose in the week of IT methotrexate.

Toxicity As for the injectable form.

NB Methotrexate suspension clinical trial supply will be available from Stockport Pharmaceuticals, Tel 0161 419 5657 Fax 0161 419 5664

8) MERCAPTOPYRINE

Formulation 10 and 50 mg scored tablets, 100mg/5ml clinical trial suspension

Storage At room temperature

Stability Please note expiry date

Administration 75 mg/m² (titratable) in regimen A and B IM 1 and 2, maintenance (all regimens) and 60 mg/m² (non-titratable) in regimen B and C consolidation. Doses to be taken once a day one hour after food in the evening.

Toxicity Bone marrow depression, liver dysfunction

NB Do not give allopurinol when the patient is on mercaptopurine as allopurinol blocks the major catabolic pathway of mercaptopurine. Clinical trial suspension will be available from Stockport Pharmaceuticals, Tel 0161 419 5657 Fax 0161 419 5664

9) CO-TRIMOXAZOLE

Formulation Paediatric suspension: 40 mg trimethoprim + 200 mg sulphamethoxazole BP in each 5 ml.

Tablets: 80 mg trimethoprim BP and 400 mg sulphamethoxazole.

Storage	At room temperature.
Stability	Please note expiry date.
Administration	.Twice daily on 2 consecutive days each week. See main protocol.
Toxicity	Marrow depression in some cases. Hypersensitivity to sulphonamide

10) CYTARABINE

Formulation	Vials containing freeze-dried powder of 100 mg cytarabine. Injection solution 100mg/5ml
Storage	At room temperature.
Reconstitution	With supplied diluent as recommended.
Stability	48 hours at room temperature.
Administration	By direct iv injection (slow bolus) 75 mg/m ² daily.
Toxicity	Bone marrow suppression, nausea, vomiting, oral ulceration, fever and arthralgia.

NB Intrathecal (if substituted for Methotrexate): Only preservative free cytarabine 20mg/ml (NOT Depocyte/liposomal cytarabine) should be given. The dose is 20mg <2yrs, 25mg 2-3 years and 30mg >3yrs. Rare side effects include aseptic meningitis and myelitis. *Solution reconstituted with preservative free saline should be discarded after 8 hours if not used.*

11) CYCLOPHOSPHAMIDE

Formulation	200 mg, 500 mg and 1 G vials for reconstitution.
Storage	At room temperature.
Administration	1000mg/m ² IV bolus or infusion with a minimum 4 hours of iv hydration.
Toxicity	Myelosuppression, alopecia, cystitis, vomiting.

12) PEG ASPARAGINASE (MEDAC - ONCOSPAR)

PEG asparaginase dose 1000 units/m² if SA>0.6 m² **IM, NOT SUBCUTANEOUSLY.**

Formulation	3,750 units per 5ml vial. DO NOT SHAKE
Storage	At 2-8°C in refrigerator.
Administration	By intramuscular injection. No more than 2 mls in any one site.
Side-Effects	Anaphylaxis, coagulopathy, pancreatitis, liver dysfunction
Precautions	The drug is given while there may be thrombocytopenia. Platelets may be necessary to cover the injection, but if it is given with extra local pressure they may not be needed.

Note. A DDX has been obtained for trial participants. The drug can be obtained from UDG, Derby, telephone 01 773 510123; fax 01 773 810646, specifying ONCOSPAR.

APPENDIX C.

Mercaptopurine and methotrexate dose alterations

Only MP and MTX will be interrupted for myelosuppression. The omitted doses will not be made up. The oral doses of MP and MTX should be adjusted to maintain ANC between 0.75 and $1.5 \times 10^9/l$ and platelets between 75 and $150 \times 10^9/l$.

TPMT Genotype and Thiopurine Dose Adjustment

Blood samples (5 ml lithium heparin) should be taken at diagnosis and at a convenient point from the end of week 10 to 15 (reg A), 14 to 17 (reg B) and at the end of week 11 and any time after week 49 for reg C. Forward to: Dr Lynne Lennard, Clinical Pharmacology, Floor M, Room M126, Royal Hallamshire Hospital, Sheffield, S10 2JF. The wild-type allele gives a high TPMT activity (H) and the variant allele a low activity (L). Results will be reported as Low/Low (L/L), High/Low (H/L) and High/High (H/H). Unless the analysis is suggestive of L/L genotype, the report will be issued after the analysis of the second sample.

Low/Low genotype patients should start mercaptopurine at 10% dose ($7.5 \text{ mg/m}^2/\text{day}$) in Consolidation/Interim Maintenance I and adjust by monthly 10% increments to maintain ANC $> 0.5 \times 10^9/l$ and platelets $> 50 \times 10^9/l$. Interim Maintenance II and continuing maintenance therapy starting dose should be the same as the dose tolerated at end of Interim Maintenance I. **These patients should also receive only 10% (6 mg/m^2) dose of mercaptopurine during Delayed Intensifications.**

For the purpose of thiopurine dose adjustment, patients with H/L and H/H genotypes will be categorised as non-variant genotype and treated the same:

Adjustment of mercaptopurine and methotrexate during consolidation in regimen A and interim maintenance I and II in regimens A and B. Note: MP dose during Regimen B and C consolidation is not count dependent and these rules do not apply.

Start at 100% MP ($75 \text{ mg/m}^2/\text{day}$) and MTX ($20 \text{ mg/m}^2/\text{week}$) and do not escalate. Follow dose reduction guidelines as described below.

Escalation of mercaptopurine and methotrexate during continuing maintenance therapy in all Regimens.

The aim is to adjust doses to maintain the ANC between 0.75 and $1.5 \times 10^9/l$ and the platelet count between 75 and $150 \times 10^9/l$. If the ANC was $> 1.5 \times 10^9/l$ and platelets $> 150 \times 10^9/l$ throughout IMI and II, the dose of mercaptopurine should be escalated by 25% (from $75 \text{ mg/m}^2/\text{day}$) at the start of continuing maintenance therapy.

If the subsequent monthly ANC is:

- 1) ANC $> 1.5 \times 10^9/l$ (and platelets $> 150 \times 10^9/l$), keep mercaptopurine at the 125% dose and increase methotrexate by 25% to $25 \text{ mg/m}^2/\text{dose}$.
- 2) Continue to increase the mercaptopurine and methotrexate dose in 25% steps alternately every eight weeks as outlined above if ANC $> 1.5 \times 10^9/l$ and platelets $> 150 \times 10^9/l$ persists. There are no maximum doses for mercaptopurine and methotrexate.

Reductions of mercaptopurine and methotrexate during regimen A consolidation, interim maintenance in regimens A and B and continuing maintenance in regimens A, B and C:

- i) If the neutrophil count falls to between 0.5 and $0.75 \times 10^9/l$ HALVE the dose of mercaptopurine and methotrexate: if $< 0.5 \times 10^9/l$, **STOP** mercaptopurine and methotrexate. **ONLY RESTART** when the count is over $0.75 \times 10^9/l$. Restart at 100% of protocol dose (not dose at which counts fell) when neut $> 0.75 \times 10^9/l$.
- ii) The same dose modifications apply to falling platelet counts. If the count is less than 75 but more than $50 \times 10^9/l$ HALVE dose as (i) above; if less than $50 \times 10^9/l$, STOP mercaptopurine and methotrexate. **REINTRODUCE** as above when the count is greater than $75 \times 10^9/l$.
- iii) If counts seesaw wildly when restarting @ 100% dose after cytopenias, starting at 50% and titrating upwards is permissible to avoid frequent interruptions to mercaptopurine exposure. (This manoeuvre is not often necessary).

NOTE: Tolerance of 150% or more of the target protocol mercaptopurine dose for prolonged periods may be indicative of partial or non-compliance, and is potentially dangerous if the patient suddenly starts to comply fully. Metabolite assays in such circumstances can be helpful to exclude non-compliance and can be arranged with Dr. Lennard (contact address on p.68). Rare individuals (1 in 300) taking thiopurine who are congenitally lacking intracellular TPMT will show profound myelosuppression at standard dose. These patients will be identified prospectively at the time of diagnosis, and advice on dosing will be given by the trial co-ordinators.

Thumb rules for maintenance

Dose Reduction

If ANC <0.5 or platelets <50



Stop both thiopurines and oral methotrexate



Weekly FBC

When ANC >0.75 and platelets >75, restart at 100% of protocol (NOT TOLERATED) dose

If ANC >0.5 <0.75 or platelets >50 <75

Reduce dose of both thiopurines and methotrexate to 50% of protocol (NOT TOLERATED) dose



Weekly FBC

ANC >0.75 and platelets >75



Increase dose to 100%

Dose Escalation

If ANC >1.5 and platelets >150 throughout previous eight weeks



Increase the mercaptopurine dose by 25%



If ANC >1.5 and platelets >150 throughout the 4 weeks following mercaptopurine dose escalation, increase MTX dose by 25%



Repeat above MP/MTX 25% dose escalation in alternating eight week cycles if ANC >1.5 and platelets >150

(see protocol guidance for those with persistent neutropenia or those with wildly see-sawing counts)

APPENDIX D

Pneumocystis Carinii Pneumonitis (PCP) Prophylaxis

Co-trimoxazole (trimethoprim and sulphamethoxazole)

This drug is given as PCP prophylaxis orally on 2 consecutive days throughout treatment from the start of induction. This dosage is lower than that recommended in previous studies, but has been found to be equally effective in CCG studies. The dose is tabulated below. Please ensure separation of the days on which oral Methotrexate and Cotrimoxazole doses are given during maintenance courses. If a child remains cytopenic after being off chemotherapy for three weeks or more, then stop the co-trimoxazole. Reintroduce co-trimoxazole once both thiopurine and methotrexate are back at standard dose. If cytopenias recur once the co-trimoxazole is reintroduced, then it should be stopped for at least two months and an alternative form of prophylaxis used instead (see below). The alternative drug should then be continued for the duration of the antileukaemic therapy. The maintenance of adequate doses of thiopurine and methotrexate should take precedence over continuing co-trimoxazole. If co-trimoxazole is stopped, however, it must be remembered that the child is at increased risk of PCP. Nebulised pentamidine or oral Dapsone are alternative drugs.

Surface area	Co-trimoxazole	Trimethoprim	Sulphamethoxazole
0.5-0.75 m ²	240 mg bd	40 mg bd	200 mg bd
0.76-1.0 m ²	360 mg bd	60 mg bd	300 mg bd
over 1.0 m ²	480 mg bd	80 mg bd	400 mg bd

Alternative PCP Prophylaxis

If a child must stop cotrimoxazole because of repeated cytopenias or other inability to tolerate it, PCP prophylaxis should continue with one of the alternative drugs. Data from HIV populations suggests that Dapsone is a more effective choice than nebulised Pentamidine or Atovaquone. Dapsone 2mg/kg (maximum dose 100mg) once daily or 4mg/kg weekly (maximum dose 200mg), orally is recommended as the alternative agent in patients who cannot tolerate cotrimoxazole. Side effects of dapsone include fever, rash, and haemolytic anaemia. **G6PD qualitative assay should be performed before starting dapsone therapy.** For patients who cannot tolerate dapsone, nebulised pentamidine or atovaquone is recommended. Nebulised Pentamidine 300 mg per month is given by nebuliser, using 6 ml sterile water delivered at 6 L/min until the reservoir is dry, usually over 45 minutes. Atovaquone is given at a dose of 30mg/kg for children orally once a day with food. Side effects include gastrointestinal intolerance, rash, headache, and fever. Pentamidine 4mg/kg IV every 2-4 weeks could be used if none of the other alternatives are suitable.

Table 1. Comparison of PCP Prophylaxis Regimens

Issue	CoTMox	Dapsone	NP	Atovaquone
Efficacy	high	moderate	moderate	moderate
Toxicity	moderate	low-moderate	high	low
Cost	low	low	high	very high
Bacterial infection protection	yes	?	no	no
Risk of extrapulmonary pneumocystosis	no	no	yes	no

APPENDIX E

DOSE MODIFICATIONS FOR TOXICITY

Steroids

Hypertension: Steroid should not be reduced. Sodium restriction and anti-hypertensives should be employed in an effort to control hypertension.

Malignant Hypertension: Reduce dose 33%. Sodium restriction and antihypertensive drugs may also be utilized.

Hyperglycemia: Steroids should not be reduced if the patient develops clinical signs of diabetes. Rather, insulin therapy should be employed to control the blood glucose level such that symptoms and signs are minimal.

Pancreatitis: Do not modify dose.

Psychosis: Administer half dosage of steroid.

Suspected steroid-induced myopathy: Measure CPK with isoenzymes, consider EMG studies

Avascular necrosis: Contact Trial Coordinators if AVN develops before Maintenance therapy has begun. Omit further steroids if AVN develops during maintenance.

Varicella Zoster: Steroids should be held during active infection except during Induction (Discuss with co-ordinators). They should not be held during incubation period following exposure to varicella.

Severe dexamethasone intolerance - change to Prednisolone 40 mg/m².

Vincristine (See also drug interactions – Appendix H)

Seizures: Hold 1 dose, then reinstitute.

Severe foot drop, paresis or ileus: Hold dose(s); institute aggressive regimen to treat constipation (except enemas if neutropenic), if present. When symptoms abate, resume at 1.0 mg/m²; escalate to full dose as tolerated.

Jaw pain: Treat with analgesics; do not modify vincristine dose.

Hyperbilirubinemia: **Check LFTs only if patient jaundiced.** Withhold if total bilirubin > 50. Administer 50% of dose if total bilirubin 25 - 50. **Do not alter dose for abnormal transaminases.**

Asparaginase

Anaphylaxis or anaphylactoid reactions: *PEG-asparaginase should be discontinued if the patient develops a Grade 2 –4 toxicity (see toxicity criteria Appendix F p69 - allergy).* Send blood samples to Centre for Integrated Genome Research (see Appendix Q) for asparaginase antibodies and change to Erwinase (see Appendix F).

Symptomatic pancreatitis: Discontinue L-asparaginase in the presence of symptomatic pancreatitis documented by an elevated serum amylase or lipase level or ultrasonographic abnormalities. **Do not give further doses if there is a prior history of asparaginase induced pancreatitis.**

Hyperglycemia: Do not modify dose. Administer Insulin as required.

Ketoacidosis: Hold L-Asparaginase until blood glucose can be regulated with insulin.

Coagulopathy When significant symptomatic coagulopathy occurs, withhold L-asparaginase until resolved. Routine clotting screens are not recommended. Coagulopathy without bleeding is not an indication to withhold L-asparaginase. Management of Asparaginase associated thrombosis is described in Appendix - .

Liver Dysfunction: **Check LFTs only if patient jaundiced.** Withhold if total bilirubin > 50. **Do not alter dose for abnormal transaminases.**

Anthracyclines (Doxorubicin and Daunorubicin)

Hyperbilirubinemia: If total bilirubin > 120 omit dose; if > 90 but ≤ 120 give 25% of dose. If > 50 but ≤ 90 give 50% of dose, and if ≤ 50 give full dose. **Check LFTs only if patient jaundiced. Do not alter dose for abnormal transaminases.**

Intrathecal Methotrexate

Any significant **neurotoxicity** not due to lumbar puncture syndrome (low opening pressure, slow CSF flow, orthostatic symptoms) should be reported.

Systemic toxicity: The dosage for IT methotrexate will not be reduced for systemic toxicity (myelosuppression, mucositis, etc.).

Viral, bacterial, or fungal meningitis: Omit until resolved.

Encephalopathy attributed to intrathecal methotrexate: See appendix .

Oral and Intravenous Methotrexate

Mucositis : For grade 2 mucositis of over 3 days duration, decrease MTX dose by 30%. For grade 3-4, mucositis, withhold MTX until resolved; resume at 50% of the previously attained dose and subsequently escalate to 75% to 100% dose at 10 day intervals provided grade 3-4 toxicity does not recur. Consider culturing lesions for herpes simplex if mucositis persists or recurs.

Liver: Check LFTs only if patient jaundiced. If bilirubin is >50 micromoles/L omit MTX until it is less than 20 micromoles/L, and then restart at half of the previously attained dose. Escalate from 50% to 75% to 100% dose at 10-day intervals provided hyperbilirubinaemia does not recur. Do not modify dosage for elevated aminotransferases.

Kidney (Grade 3-4): Omit MTX until grade 0 toxicity (i.e. completely resolved). Resume at 100% of the previously attained dose and continue at 10-day intervals.

Cyclophosphamide

Prior history of gross haematuria or microscopic haematuria: Hydrate at 125 ml/m²/hr for 24 hours after dose and use Mesna 360 mg/m² pre, and 4, 7, 11 hours post dose.

Acute fluid retention: Treat with frusemide and saline; do not modify dose.

Cytarabine

Hyperbilirubinaemia: If total bilirubin > 120 omit dose; if > 90 but ≤ 120 give 25% of dose. If > 50 but ≤ 90 give 50% of dose, and if ≤ 50 give full dose. **Check LFTs only if patient jaundiced. Do not alter dose for abnormal transaminases.**

Mercaptopurine

Hyperbilirubinaemia and Mucositis: As for oral MTX.

**Treatment Modifications for Downs Syndrome Patients
June 2008**

Background

In ALL 97, Downs Syndrome (DS) patients had a significantly worse EFS compared to non-DS patients (48% vs 78%) primarily because of a higher risk of CR death (28% vs <5%) due to sepsis. The majority of deaths occurred in consolidation and DIs. The increased risk has persisted in UKALL 2003 and has also become evident in the current COG standard risk protocol. EFS of DS patients is also worse in BFM (58%) and NOPHO (54%) studies but not due to increased incidence of septic deaths.

Since we issued supportive care recommendations in early 2007 there have been a further 3 deaths. Details of incidence, causes and timing of non-relapse deaths in DS patients are as below

DS mortality - January 2008

Total entered	46
Relapse	1
Non-relapse deaths	10 (20%)
Male	8/35
Female	2/9
Median age	5.5 y
NCI SR/HR	5/5
Induction	3 (7%) (2 Reg B, 1 Reg C) (1 – parainfluenza pneumonitis, 1 – NEC + sepsis, 1 –pseudomonas)
CR:	7 (15%)
Consolidation	1 (Reg B – aspergillus)
DI1	1 (Reg A – sepsis)
DI2	1 (Reg A – sepsis)
Maintenance	4 (56, 89, 112 and 140 weeks)

Treatment modifications

In view of the persisting high mortality, the co-ordinators feel compelled to recommend closure of the randomisations for DS patients and modifications to their treatment regimens as described below:

- Daunorubicin should be omitted from induction for NCI high risk patients. They should receive the same 3 drug induction as NCI SR patients with bone marrow assessment at day 15 instead of day 8.
- However, if the day 15 BM shows a slow early response, and in the absence of established serious morbidity, switch to regimen C induction as described on page 55 and flow chart 15a of the protocol. Consider giving a reduced dose of daunorubicin (25 mg/m² weekly x 2) or continue with 3 drug induction if it is judged that the patient may be unable to tolerate the 45 mg/m² dose of daunorubicin due to previous toxicity.
- Post-induction, DS patients will not be eligible for the randomisations. Instead:
 - MRD low risk and indeterminate patients who had a rapid early response at day 15 should receive Regimen A/B consolidation, depending on NCI risk, followed by a SINGLE DI.
 - MRD HR patients and SERs should receive Regimen C (in the absence of serious morbidity during induction) but with a SINGLE DI.
- Boys should stop maintenance therapy after two years same as girls.

Supportive care

The following supportive care recommendations issued in 2007 should remain in place:

During induction, Regimen B/C consolidation and both DIs:

- Administer prophylactic antibiotics. Ciprofloxacin 7.5 mg/kg po od is recommended but individual centres may wish to use alternatives based on local infection and resistance patterns in discussion with their microbiologists.
- Review 3 times a week if an out-patient.
- Treat all febrile neutropenia episodes as high risk if using risk stratified policy for admission/iv antibiotics.
- DS patients may not present with classic signs of sepsis such as pyrexia. Treat non-specifically unwell patients as septic until proven otherwise.
- Be alert to early signs of shock in septic patients and refer promptly for intensive care.

APPENDIX F

Guidance on Use of Erwinia Asparaginase (Erwinase®) in patients with systemic reactions to Oncospar.

1. A licensed preparation of Erwinia Asparaginase (Erwinase®) is now available, thus providing an effective alternative for patients with hypersensitivity to E.Coli Asparaginase.
2. Erwinase® will be marketed and distributed by OPi pharmaceuticals.
3. Erwinase® should be used in place of native or Pegylated E. Coli Asparaginase in the following circumstances:
 - Systemic hypersensitivity reactions to native (Medac asparaginase) or Pegylated E.Coli Asparaginase (Oncospar). This includes patients with generalised rash with or without anaphylactic symptoms, but not those with only local pain or redness at the site of injection.
 - Patients with previously documented systemic reactions to E.Coli Asparaginase should receive Erwinase® in any remaining Asparaginase containing courses.
4. Each dose of Pegylated Asparaginase (Oncospar) should be replaced with 6 doses of 20,000 Units/m² Erwinase® given on Mondays, Wednesdays and Fridays.
5. Each dose of native E.Coli Asparaginase (Medac E.Coli Asparaginase) should be replaced with a single dose of 20,000 Units/m² of Erwinase®.
6. Erwinase® should be administered by intra-muscular injection. For older patients requiring large volumes, the individual dose may be split between two injection sites.
7. Please notify the trials office of patients switching to Erwinase® on the notification form available on CTSU web site.

Table for converting from Peg-Asparaginase to Erwinase

Peg-asparaginase	Erwinase
Induction (all regimens) Peg Asparaginase 1000 units/m ² IM on day 4 and 18	Induction (all regimens) Day 4 N/A Day 18: Erwinase 20,000 units/m ² IM on day 18 and then Mon/Wed/ Friday for 6 doses in total
Consolidation Reg C Peg Asparaginase 1000 units/m ² IM on day 16 and 44	Consolidation Reg C Erwinase 20,000 units/m ² IM on day 16 and then Mon/Wed/ Friday for 6 doses in total Erwinase 20,000 units/m ² IM on day 44 and then Mon/Wed/ Friday for 6 doses in total
Capizzi maintenance I & II (Reg C only) Peg Asparaginase 1000 units/m ² IM on day 3 and 23	Capizzi maintenance I & II (Reg C only) Erwinase 20,000 units/m ² IM on day 3 and then Mon/Wed/ Friday for 6 doses in total Erwinase 20,000 units/m ² IM on day 23 and then Mon/Wed/ Friday for 6 doses in total
Delayed intensification 1 & II (all regimens) Peg Asparaginase 1000 units/m ² IM on day 4	Delayed intensification 1 & II (all regimens) Erwinase 20,000 units/m ² IM on day 4 and then Mon/Wed/ Friday for 6 doses in total
(Reg C only) Peg Asparaginase 1000 units/m ² IM on day 43	Erwinase 20,000 units/m ² IM on day 43 and then Mon/Wed/ Friday for 6 doses in total

APPENDIX G

Management of Encephalopathy related to intra-thecal Methotrexate

Background

Up to August 2005, 22 cases of Encephalopathy related to intra-thecal Methotrexate had been reported in patients entered on UKALL 2003. Typical presentation is with seizures, focal neurological deficit or loss of consciousness occurring within 1 – 21 days (average 3 days) of exposure to IT MTX. Full recovery within 48 hrs of the episode is the norm. Although episodes have occurred in all courses, just over half have been during the consolidation phase of Regimens B/C or part 2 of the Delayed Intensifications. This raises the possibility of an interaction with Ara-C in some patients. After discussion, the ALL task force and CLWP meetings approved the following recommendations for managing such patients:

Management

Encephalopathy during Regimen B/C consolidation or part 2 of Delayed Intensification.

No further IT MTX should be administered while patient is also receiving Ara-C (including in future courses containing Ara-C). Re-expose, and in the absence of recurrence, administer missed doses during interim maintenance or maintenance. In the event of recurrence, change to IT Ara-C + hydrocortisone in the doses given below.

Encephalopathy during other courses.

Re-expose as above and continue IT MTX if no recurrence. Change to IT Ara-C and hydrocortisone if problem recurs. Doses as below.

Doses:

Age	Ara- C	Hydrocortisone
1	20 mg	7.5 mg
2	25 mg	10 mg
3+	30 mg	12.5 mg

APPENDIX H**DRUG INTERACTIONS WITH CYTOTOXIC AGENTS**

These guidelines aim to address the more commonly reported and potentially serious drug interactions that may be encountered when using this protocol.

These guidelines are not intended to be a comprehensive list of all potential drug interactions and normal precautions should be taken when prescribing any combination therapy.

INTERACTIONS WITH POTENTIALLY SERIOUS CLINICAL CONSEQUENCES

DRUG	POTENTIAL INTERACTION	COMMENTS
Vincristine	Itraconazole +/- Nifedipine Fluconazole/voriconazole	<p>Causes inhibition of the cytochrome P450 3A4 enzyme system resulting in increased incidence of peripheral neuropathy^{1,2}. Hyponatraemia associated with SIADH has been reported with concomitant use of vincristine and azole anti-fungal agents² Nifedipine has been reported to enhance these effects.</p> <p>Fluconazole/voriconazole are not reported to have the same adverse effects although could be predicted to have similar adverse effects</p> <p>RECOMMENDATION: AVOID USE OF AZOLE ANTI-FUNGALS WITHIN ONE WEEK OF VINCRISTINE IF POSSIBLE. IF USED SUSPEND 48 HRS BEFORE AND AFTER VINCRISTINE DOSE.</p>
Anti-convulsants including phenytoin, carbamazepine, phenobarbitone	Possible reduced chemotherapy efficacy	<p>An association between increased risk of relapse in children with B-lineage ALL and concomitant treatment with anticonvulsant therapy has been reported (EFS hazards ratio 2.67 95% CI 1.5-4.76, p=0.0009)³ Many anti-convulsants induce hepatic enzyme activity. Significantly increased clearances of methotrexate and teniposide in patients receiving anti-convulsant therapy have been reported³.</p> <p>Also see Phenytoin/Dexamethasone interaction.</p>

Phenytoin	Dexamethasone	<p>Phenytoin and dexamethasone mutually lower the efficacy of the other drug: Phenytoin increases hepatic enzyme metabolism of dexamethasone and lowered levels of phenytoin are reported with concomitant dexamethasone therapy</p> <p>RECOMMENDATION: AVOID THE USE OF PHENYTOIN, CARBAMAZEPINE AND PHENOBARBITONE IF POSSIBLE.</p> <p>POSSIBLE ALTERNATIVE ANTI-CONVULSANTS INCLUDE GABAPENTIN WHICH IS RENALLY EXCRETED AND DOES NOT INDUCE HEPATIC ENZYMES. CLONAZAPAM, CLOBAZAM OR VALPROATE HAVE NO KNOWN CLINICALLY RELEVANT INTERACTIONS WITH CYTOTOXIC DRUGS NB VALPROATE HEPATOTOXICITY IS REPORTED</p>
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OTHER POTENTIAL INTERACTIONS WHICH REQUIRE CLOSE MONITORING

DRUG	POTENTIAL INTERACTION	COMMENTS
Anti-coagulants Warfarin	Concurrent chemotherapy, especially 6-MP and steroids, INCREASES INR Cotrimoxazole DECREASES INR	The use of low molecular weight heparin for prophylactic therapy post thrombus formation would be preferable ⁴
6-mercaptopurine	Allopurinol	Avoid concurrent use. Can cause a 5 fold increase in AUC of 6-MP
Methotrexate	Non Steroidal Anti-Inflammatory Drugs (NSAIDs) (including COX II inhibitors)	Increase in methotrexate levels due to competition for excretory pathways RECOMMENDATION: AVOID DURING CAPIZZI MAINTENANCE AND HIGH DOSE METHOTREXATE NB NSAIDs have adverse effects on platelet function

	Penicillins, Co-Amoxiclav	penicillins reduce methotrexate excretion. RECOMMENDATION: AVOID DURING CAPIZZI MAINTENANCE AND HIGH DOSE METHOTREXATE NB Clavulenic acid is hepatotoxic
	Tetracyclines	Increased methotrexate toxicity through displacement of methotrexate from plasma binding sites NB Tetracyclines should be avoided in children under 7 years due to discolouration of teeth
Cytarabine	Flucytosine	Uptake of flucytosine by fungi may be inhibited by cytarabine
Cyclophosphamide	Suxamethonium	Duration and effect of neuromuscular blockade may be increased ⁵

References

1. Sathiapalan R. K., El-Solh H. Enhanced vincristine neurotoxicity from drug interactions: case report and review of the literature. *Pediatric Hematology and Oncology* 2001,18: 543-6
2. Kamaluddin M., et al Potentiation of vincristine toxicity by intraconazole in children with lymphoid malignancy. *Acta Paediatrica* 2001 90: 1204-08
3. Relling M.V., et al Adverse effects of anticonvulsants on efficacy of chemotherapy for ALL *Lancet* 2000 356 285-90
4. Martin L.A., Mehta S.D., Diminishes anti-coagulant effects of warfarin with concomitant mercaptopurine therapy *Pharmacotherapy* 2003 23(2): 260-4
5. **KOSEGOGLU V. ET AL ACQUIRED PEUDOCHOLINESTERASE DEFICIENCY AFTER HIGH-DOSE CYCLOPHOSPHAMIDE BONE MARROW TRANSPLANTATION 1999 24(12): 1367-8**

APPENDIX I

ADVERSE EVENT REPORTING

Definitions

Serious adverse event (SAE)

Any adverse event that

- results in death,
- is life-threatening
- requires unexpected hospitalisation or unexpected prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity

Except the following which should NOT be reported as SAEs:

Hospitalisation due to febrile neutropenia.

Death following relapse.

Expected serious adverse drug reaction or event (SSAR)

All complications as a result of severe bone marrow failure, the adverse reactions or events described in Appendix B, Appendix E, Appendix G and Appendix H of the protocol and those described in the summary of product characteristics for each protocol drug are 'expected', even if they result in death. These will therefore be categorised as SSARs

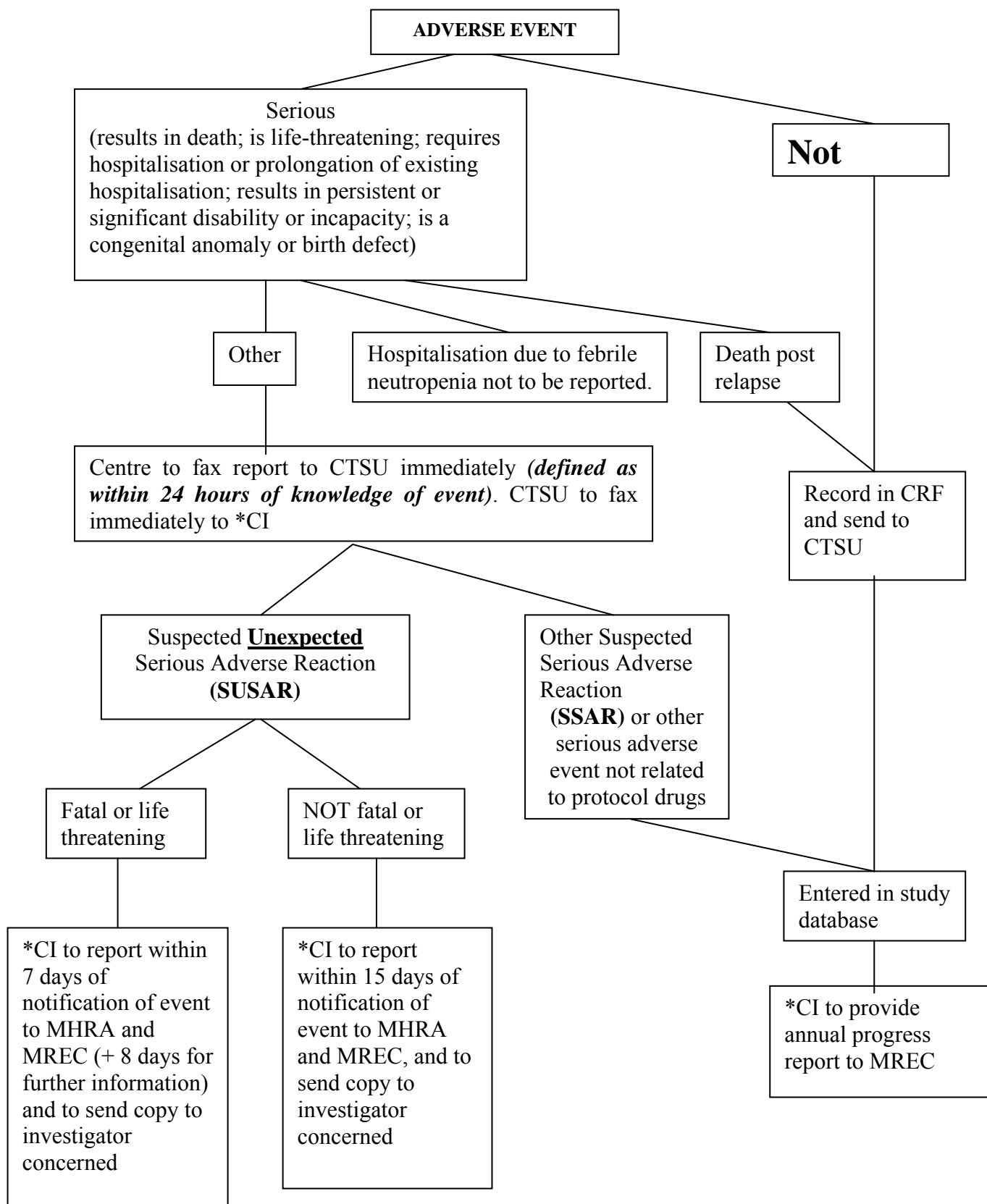
Suspected unexpected serious adverse reaction (SUSAR)

Any serious adverse event which is NOT a complication of bone marrow failure or an expected side effect of a drug as defined above, and which is judged as having a reasonable suspected causal relationship with a protocol drug will be considered a SUSAR. In addition, if a SSAR is encountered more frequently than seen in previous UK studies, or comparable studies elsewhere, it will be considered a SUSAR.

All such events should be reported to the CTSU within 24 hours.

Adverse Events (AE)

NCI Grade 3 or 4 toxicity should be reported on the toxicity form. There is no need to report Grade 1 and 2 toxicities.



*CI = Chief Investigator

MRC UKALL2003 SERIOUS ADVERSE EVENT REPORT

To be completed by local investigator and faxed to CTSU

Fax to: 01865-743986

A Serious Adverse Event is any adverse event that

- results in death,[#]
- is life-threatening
- requires unexpected hospitalisation or unexpected prolongation of existing hospitalisation[†]
- results in persistent or significant disability or incapacity

If death after relapse (i.e. off protocol treatment), report only on trial form 4.

† Hospitalisation due to febrile neutropenia alone should not be reported.

PATIENT NAME: _____ **AGE:** _____

TRIAL REFERENCE NUMBER: _____ **SEX:** M F

CONSULTANT: _____ **HOSPITAL:** _____

Date of Event ___/___/___ **Treatment:** A B C **Week of treatment:** _____

Brief description (Continue on separate page if necessary):

Was the event related to treatment?:

DEFINITELY PROBABLY POSSIBLY UNLIKELY NOT RELATED

If definitely, probably or possibly, name drug/course involved: _____

Did concomitant medication (non-protocol drug) contribute to event? If so, name drug involved:

Outcome:

Recovered Date recovered: ___/___/___
___/___/___

Died Date died: _____

Recovered with sequelae Date recovered: ___/___/___
___/___/___

Ongoing at _____

CTSU: Date original SAE form received: ___/___/___ Date faxed to chief investigator ___/___/___

To be completed by Chief Investigator (Trial Co-ordinator): Date original SAE form received ___/___/___

Signed: _____

Was the event related to treatment:

DEFINITELY PROBABLY POSSIBLY UNLIKELY NOT RELATED

If definitely, probably or possibly, name drug involved: _____

Classification: SUSAR SSAR Other serious adverse event

If SUSAR: Date informed MHRA ___/___/___ Date informed lead REC ___/___/___
(If fatal/life-threatening, to report within 7 days, (+8 for further info), otherwise within 15 days)

Copy of report sent to local investigator: ___/___/___

MEDICAL RESEARCH COUNCIL ALL2003 TRIAL**NON-SAE ADVERSE EVENT REPORTING FORM**

Please report (only) **Grade 3 and 4 toxicity** by circling or highlighting the appropriate site(s) and grade(s) of toxicity for each course.

Return to: FREEPOST RLUI-UUUU-UUAC, Patient's name.....
 CTSU, Richard Doll Building, Consultant.....
 Old Road, Headington, Oxford OX3 7LF
 Patient reference no Centre.....

Course: Induction Consolidation IMI DI 1
 IMII DI 2 Maintenance
 Cycle Week

TOXICITY CRITERIA AND GRADING (ADAPTED FROM NCI CTC)

SITE	MEASURE	GRADE				
		O/WNL	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Unacceptable)
LIVER	1. ALT	WNL	≤2.5 x N	2.6-5.0 x N	5.1-20.0 x N	>20.0 x N
	2. AST	WNL	≤2.5 x N	2.6-5.0 x N	5.1-20.0 x N	>20.0 x N
	3. ALK. PHOS- PHATASE	WNL	≤2.5 x N	2.6-5.0 x N	5.1-20.0 x N	>20.0 x N
	4. TOTAL BILI	WNL	<1.5 x N	1.5-3.0 x N	>3.0 x N	>10.0 x N
	5. LIVER-CLIN	WNL	---	---	precoma	hepatic coma
PANCREAS	1. Anylase	WNL	<1.5 x N	1.5-2.0 x N	2.1-5.0 x N	>5.0 x N
	2. Glucose mmol/l	WNL	6 -10	11 -15	16 - 25	> 25/ ketoacid
RENAL	1. Urea	WNL	<1.5 x N	1.5-3.0 x N	3.1-6.0 x N	>6.0 x N
	2. Creatinine	WNL	<1.5 x N	1.5-3.0 x N	3.1-6.0 x N	>6.0 x N
	3. Blood Pressure - systolic	baseline	±10%	±20%	±30%	±40%
	4. Blood Pressure - diastolic	baseline	±5%	±10%	±15%	±20%
	5. Hematuria	neg	micro only	gross, no clots	gross + clots	trans req'd
BONE		-	-	-	symptomatic severe osteopenia	Fracture/ avascular necrosis

MEDICAL RESEARCH COUNCIL ALL2003 TRIAL**TOXICITY REPORTING FORM (continued)** Patient reference no

		O/WNL	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Unacceptable)
GASTRO- INTESTINAL	1. Stomatitis	none	erythema, or mild soreness	painful/odema can eat	cannot eat or drink	requires parenteral or enteral support
	2. Abdominal pain: severity treatment	none ---	mild not required	moderate required – helps	moderate-severe required-no help	severe hospitalisation, heavy sedation
	3. Constipation	no chg	mild ileus	mod ileus	severe ileus	ileus >96 hrs
	4. Diarrhoea	none	↑2-3 stools/day	↑4-6 stools/day or mod. cramps	↑7-9 stools/day or severe cramps	↑≥10 stools/day bloody, parenteral support required
	5. Nausea 6. Vomiting	none none	reasonable intake 1 x/day	decreased intake 2-5 x/day	no sig. intake 6-10 x/day	--- >10 x/d or IV req'd
PULMONARY	1 O ₂ satn.	>90	80-89	65-79	50-64	<49
	2. Functional	normal	tachypnea	dyspnea	O ₂ required	assist vent
CARDIAC	1. Echo FS%	>30	24-30	20-24	<20	---
	2. Card. Function	WNL	asymptomatic/ ↓ej. Fr. <20%	asymptomatic/ej. fr. <80% baseline	mild CHF/ responds to Rx	severe or refractory CHF
	3. Hypertension	no chg	asympt./transient increase by >20mmHg, no RX req	recur./persist increase by 20mmHg, no Rx req	requires therapy	hypertensive crisis
NERVOUS SYSTEM	1. Peripheral: Sensory	no chg	mild paresthasias, loss tendon reflex	mod sensory loss, mod paresthasias	interferes with function	---
	Motor	no chg	subj weakness/no obj findings	mild obj weakness / no sig impair	obj weakness/ function impair	paralysis
	2. Central: Cerebellar	no chg	slight incoordination/dysdiadochinesis	intention tremor/dysmetria/slurred speech/nystagmus	locomotor ataxia	cerebellar necrosis
	CNS – general	no chg	drowsy/nervous	confused	seizures/psychosis	comatose
	Cortical	no chg	mild somnolence/agitation	mod somnolence/agitation	severe somnol/agit confusion/hallucin	coma/seizures/ toxic psychosis
ALLERGY		none	transient rash	mild bronchospasm	mod bronchospasm serum sickness	hypotension, anaphylaxis
COAGULATION	1. Haemorrhage (Clin)	none	mild/no transf	gross – 1-2 trans/episode	gross – 3-4 trans/episode	massive - >4 trans/episode
	2. Thrombosis	WNL	local	superficial	deep vein thrombosis	CNS thrombosis arterial thrombosis
INFECTION		none	mild	moderate	severe	life threatening
MOOD		no chg	mild anxiety or depression	moderate anxiety or depression	severe anxiety or depression	suicidal ideation
WEIGHT CHANGE		<5.0%	5.0-9.9%	10-19.9%	≥20%	---

Name of person completing this form Date/...../.....

APPENDIX J

GUIDELINES FOR THE INVESTIGATION AND MANAGEMENT OF THROMBO-EMBOLIC EVENTS

Background

Thrombosis is a recognised complication of the treatment and management of ALL. The true prevalence in this patient population is unknown and varies with the method of assessment. The PARKAA study (Cancer 2003, Vol.97, 2) reported a prevalence of symptomatic events of 5% and asymptomatic events of 36.5% in children undergoing induction chemotherapy for ALL with a central venous catheter insitu. Asymptomatic events were diagnosed by screening with bilateral venography or MRI, echocardiography and a MRI of the head on completion of induction chemotherapy. Whilst the authors recommend carefully designed clinical trials of primary prophylaxis for the prevention of TE's in this patient population, there is at present insufficient data from children treated on UK protocols to support this. However, the need to collect such information to judge the appropriateness of prophylaxis is recognised. In general, primary prophylaxis for children with CVL cannot be recommended at this time, because there is no evidence for the efficiency or safety of this approach.

Asparaginase therapy and the presence of a central venous catheter are accepted as the main predisposing factors. The literature on the role of inherited thrombophilia in predisposing to thrombotic events in these children is conflicting, with the BFM reporting a significant association, and the Canadians and other major groups, no association. It is, therefore, considered premature to recommend universal screening or primary prophylaxis, although it may be prudent to try to identify less common high-risk abnormalities eg AT deficiency, PC deficiency.

Screening

- 1 Universal thrombophilia screening is not recommended.
- 2 A careful family history of thrombosis should be taken. Children with a first or second degree relative with Protein C or A.T. deficiency should be screened for the relevant deficiency, as prophylaxis may be indicated. The literature is inconclusive for risk conferred by other inherited thrombophilias.
- 3 Teenage girls on the combined oral contraceptive pill should stop the pill and change to a low dose progesterone only preparation, or norethisterone.

Catheter (CVL) Related Thrombosis

1 Loss of CVL patency

Inability to withdraw blood +/- inability or impaired ability to infuse

- If there is no evidence to suggest displacement of the catheter tip and there are no signs to suggest the presence of occlusive thrombosis, proceed with urokinase (UK) lock

- Procedure: UK 2,500 iu each lumen for 2-4 hours.

2 **Failure to restore patency or recurrent loss of patency**

- CXR to check position of catheter tip
- Linogram to assess CVL patency
- If the linogram demonstrates the presence of a fibrin sheath with no evidence of significant clot formation around the tip, proceed to UK infusion.
- Procedure: UK 150 iu/kg/hr via each lumen for 12-24 hours.
Monitor coagulation prior to and every 8 hours during infusion
- Low dose t-PA(0.1mg/kg/hr for 4 – 6 hrs) may be considered as an alternative thrombolytic agent
- Repeat linogram following infusion to confirm resolution.
- If the linogram demonstrates (or is suspicious of) the presence of significant clot formation around the catheter tip, or of vessel thrombosis, proceed with further imaging studies.
- Imaging: consider doppler or MR venography.
- Comments on imaging –
 - Linograms have been shown to be relatively insensitive for the detection of large vessel CVL related thrombosis. In the presence of persistent line dysfunction despite a normal linogram, further imaging is indicated.
 - Doppler is a sensitive technique for imaging jugular veins, but has poor sensitivity for central intrathoracic veins.
 - MRV is less well evaluated but is likely to provide good sensitivity. Some children are likely to require a GA for this technique.

3 **Doppler or Venography confirms the presence of large vessel thrombosis.**

- Complete thrombosis toxicity form
- If the CVL is no longer required or is non-functioning it should be removed. If CVL access is required and the CVL is still functioning then the CVL can remain insitu.
- Unless otherwise contraindicated, anticoagulant therapy should be commenced.
- Comments on treatment –

- Low molecular weight heparin (LMWH) is probably the anticoagulant of choice for initial therapy in most cases.
- LMWH dosing: Enoxaparin (Clexane) 1mg/kg/bd by s/c injection. Monitor using anti-Xa levels taken at 4 hours post dose, therapeutic range 0.5-1.0 iu/ml. (LMWH pharmacokinetics for children have only been established [published] for enoxaparin and reviparin [not available in the UK] but the use of other LMWH may be acceptable with monitoring)
- Prior to a lumbar puncture, or any other invasive procedure, the preceding two doses of LMWH should be omitted.
- If there is occlusive thrombus in a major vessel e.g. IVC, consider local thrombolytic therapy prior to anticoagulation and/or catheter removal. Low-dose t-PA (0.1mg/kg/hr) may be administered locally via the CVL but higher doses (0.5mg/kg/hr) are required for systemic therapy. t-PA should be administered for 4 – 6 hours, followed by re-imaging.
- Following the initial 3 months of therapy for children with a first CVL-related DVT, prophylactic doses of oral anticoagulants (INR 1.5 to 1.8) or LMWH – (anti-factor Xa levels of 0.1-0.3) is an option until the CVL is removed. Children with recurrent CVL related DVT should have prophylactic anticoagulation until the removal of the CVL.
- Some children will be scheduled to receive Asparaginase as per protocol having had an earlier catheter-related thrombotic event. Consideration should be given to removal of the CVL but those children receiving Asparaginase with a CVL in-situ should receive prophylactic anticoagulation for the duration of their Asparaginase therapy.
- Thrombophilia screening should be performed following completion of anticoagulant therapy and should include Protein C, Protein S, AT, FV Leiden, lupus screen, anticardiolipin antibodies and prothrombin gene 20210A.

4 Clinical symptoms/signs of CVL related thrombosis

- Arrange imaging to confirm the presence and extent of thrombosis.
- Imaging: consider doppler, venography or MR venography.
- Complete thrombosis toxicity form
- If the CVL is no longer required or is non-functioning it should be removed. If CVL access is required and the CVL is still functioning then the CVL can remain insitu.
- If Doppler or Venography confirms the presence of large vessel thrombosis anticoagulant therapy should be commenced.

- Comments on treatment –
 - Low molecular weight heparin (LMWH) is probably the anticoagulant of choice for initial therapy in most cases.
 - LMWH dosing: Enoxaparin (Clexane) 1mg/kg/bd by s/c injection. Monitor using anti-Xa levels taken at 4 hours post dose, therapeutic range 0.5-1.0 iu/ml. (LMWH pharmacokinetics for children have only been established [published] for enoxaparin and reviparin [not available in the UK] but the use of other LMWH may be acceptable with monitoring)
 - The platelet count should be maintained around $50 \times 10^9/l$ for the period of anticoagulation.
 - Prior to a lumbar puncture, or any other invasive procedure, the preceding two doses of LMWH should be omitted.
 - If there is occlusive thrombus in a major vessel e.g. IVC, consider local thrombolytic therapy prior to anticoagulation and/or catheter removal – t-PA 0.1 mg/kg/hr for 4-6 hours and re-image.
 - Following the initial 3 months of therapy for children with a first CVL-related DVT, prophylactic doses of oral anticoagulants (INR 1.5 to 1.8) or LMWH – (anti-factor Xa levels of 0.1-0.3) is an option until the CVL is removed. Children with recurrent CVL related DVT should have prophylactic anticoagulation until the removal of the CVL.
 - Some children will be scheduled to receive Asparaginase as per protocol having had an earlier catheter-related thrombotic event. Consideration should be given to removal of the CVL but those children receiving Asparaginase with a CVL in-situ should receive prophylactic anticoagulation for the duration of their Asparaginase therapy.
 - Thrombophilia screening should be performed following completion of anticoagulant therapy and should include Protein C, Protein S, AT, FV Leiden, lupus screen, anticardiolipin antibodies and prothrombin gene 20210A.

CNS Thrombosis

Use of anticoagulants for treatment of the acute phase is contentious. Asparaginase should be suspended from that particular course but can be given in subsequent courses under prophylactic anticoagulant cover as described above.

APPENDIX K

Cranial radiotherapy guidelines

These guidelines only apply to patients with resistant or parenchymal CNS disease at presentation. Children under 2 years of age do not receive cranial irradiation.

- a) Megavoltage Apparatus should be used, preferably a linear accelerator.
- b) All fields should be treated on each treatment day.
- c) Midplane dose 24 Gy in 15 fractions of 1.6 Gy each, in 15-21 days. (Treatment may start on any day except Friday).
- d) Lateral opposed fields are used to include all cranial meninges including those surrounding the optic nerve in the retro-orbit, and extending down the spinal cord to level of C2.

The dose of 24 Gy has been chosen rather than 18 Gy, as this therapy is for patients with overt CNS disease and hence is an essential part of treatment, rather than being "prophylactic" in nature. The preferred technique is one which ensures adequate coverage of the whole of the cranial meninges while ensuring that the lens dose is kept as low as possible. The patient should be treated immobilized in a supine shell. A technique that centres on the orbit and uses customized lead blocks to minimise beam divergence is therefore preferred.

A treatment centre is selected clinically which is symmetrical and lies 15 mm behind the cornea on each side. Using a simulator these 2 points are opposed and a simulator film taken for the production of customised lead blocks. These should be designed so as to treat the cervical cord down to the level of C2 and to ensure adequate treatment to the origin of the facial nerve.

The use of this technique necessitates either the use of asymmetric jaws to block the lower part of the neck or else the use of a very large amount of lead. It may therefore not be possible at all centres and in such cases a similar blocking arrangement using field centred in the midcranium are acceptable. A third alternative is to use a rectangular field with one edge running parallel to Ried's baseline.

- (d) Treatment to additional fields, eg nasal electrons to the cribriform plate may be used at the discretion of the clinician. If such modifications are used they should be specified on the enquiry sheet and the reason they were considered necessary given.
- (e) Dose to the lens. Although there is uncertainty as to whether thermoluminescent dosimetry can adequately estimate the dose to the lens, it is nonetheless recommended that such dosimetry be performed and the results recorded, as it is intended to use the data collected to study cataractogenesis in long term survivors. TLDs should be placed on the patient underneath the shell, both on the eyelid in front of the position of the lens, and at the outer canthus of the eye. If possible the dose to the lens should be less than 10% of the mid-plane dose, although it is recognised that this may not always be achievable with adequate treatment of the cribriform plate. Where estimated doses are high, they should be discussed with the radiotherapy co-ordinator.
- (f) Quality control. An initial simulator film should be taken for planning purposes. Shielding block positions should where possible be checked at a second simulator session. Beam films should be taken on the treatment set to verify block positions. Simulator and beam films will be requested for review following the completion of treatment.

i) Interruptions to radiotherapy

Interruptions to radiotherapy should be kept to minimum. Treatment need not be interrupted for cytopenia unless the patient is unwell. In such cases treatment should be re-commenced as soon as possible. Interruptions longer than 48 hours should be discussed with the radiotherapy co-ordinator.

The patient will be on continuation thiopurine during cranial irradiation. Priority should be given to the continuation of the radiation rather than the thiopurine if cytopenias arise.

j) Recording of data

A separate sheet will be circulated for completion.

APPENDIX L

Testicular radiotherapy guidelines

(Patients with testicular disease at diagnosis)

- a) Megavoltage or Orthovoltage apparatus may be used.
- b) As in previous MRC studies, the volume should include the testes and the spermatic cord to the level of the deep inguinal ring with lead shielding to surrounding tissues including the penis.
- c) The dose will be 24 Gy in 12 daily fractions of 2 Gy. This should be given during weeks 5-8 (consolidation). Patients also receiving cranial RT should be given their testicular irradiation concomitantly with the cranial irradiation.

APPENDIX M

Relapse

Patients who relapse in any way and at any stage while on UKALL 2003 should be taken off study and entered into UKALL R3 or an equivalent adult protocol.

APPENDIX N

Measurement of MRD in ALL 2003

Therapy according to ALL 2003 is stratified according to MRD as defined by real time quantitative PCR (RQ-PCR) analysis of Ig and TCR gene rearrangements at day 28 and week 11. In addition MRD is measured at other time points as part of on-going research within ALL 2003.

MRD is measured by the laboratories of the UK MRD network acting as a virtual single laboratory.

The RQ PCR method is based on European best practice and in the developmental (pre NHS funding) phase has been subject to rigorous internal and external quality assurance.

Quality is overseen by the steering committee of the UK MRD network and the leukaemia task force of the CCLG.

The coordinators of ALL 2003 will only accept MRD results generated by laboratories of the UK MRD network for stratification of therapy in ALL 2003.

Patients with MRD results produced by a non network lab will be excluded from ALL 2003.

Laboratories which are not currently members of the UK MRD network can apply to join. Applications should be made in writing to Dr Nick Goulden.

Acceptance will be at the discretion of the UK MRD network steering committee and Inclusion will require fulfilment of **ALL** of the following criteria

1. Practical work to be carried out in a CPA accredited laboratory
2. Prior to adoption by the UK MRD network adequate performance in 3 sequential European Study Group on MRD QA rounds.
3. Strict compliance with the UK MRD network SOP
4. Adequate performance defined according to UK MRD network s during a 3 month “dry run” of production of results in real time for at least 30 patients. During this period the applicant lab will be required to self fund staff and consumables.

MRD Laboratories and their Catchment UKCCSG Centres

Adult centres wishing to enter patients into the trial should liaise with the local UKCCSG centre and laboratories listed below to send samples for MRD.

Laboratory	Region	Treatment Centres
Birmingham	West Midlands	Birmingham Children's Hospital
Bristol	South West	Royal Hospital For Sick Children, Bristol
	Southampton	Southampton University Hospital Trust
	Cardiff	University Hospital of Wales Children's Hospital
	Oxford	Oxford Radcliffe Hospitals
	Yorkshire	St James's University Hospital, Leeds
Glasgow	Scotland - West - East	Royal Hospital for Sick Children, Glasgow Royal Aberdeen Children's Hospital Royal Hospital for Sick Children, Edinburgh
	N Ireland	Royal Belfast Hospital Belfast City Hospital
	Republic of Ireland	Our Lady's Hospital, Dublin
	Newcastle	Newcastle General Hospital Royal Victoria Infirmary
	Mersey	Alder Hey Children's Hospital, Liverpool
	Great Ormond St	NE Thames
Sheffield		Trent
Bart's	North West	Royal Manchester Children's Hospital
	SW Thames	Royal Marsden Hospital
	East Anglia	Addenbrooke's NHS Trust, Cambridge

Contact Details For MRD laboratories.

Laboratory	Personnel	Contact Details
Birmingham	Susanna Akiki Christopher Bowles Rachel Doak Mike Griffiths	West Midlands Regional Genetics Laboratory Birmingham Women's Hospital Edgbaston Birmingham B15 2TG Tel: 0121 627 2710 Fax: 0121 627 2711 susanna.akiki@bwhct.nhs.uk christopher.bowles@bwhct.nhs.uk rachel.doak@bwhct.nhs.uk mike.griffiths@bwhct.nhs.uk
Bristol	Dr Jeremy Hancock Paul Archer Richard Hathway Kayleigh McDonagh Helen Tinline-Purvis	Bristol Genetics Laboratory Pathology Sciences Southmead Hospital Westbury-on-trym Bristol BS10 5NB Tel: 0117 323 6262 Fax: 0117 323 5572 Jeremy.Hancock@nbt.nhs.uk paul.archer@nbt.nhs.uk richard.hathway@nbt.nhs.uk Kayleigh.McDonagh@nbt.nhs.uk Helen.tinline-purvis@nbt.nhs.uk
Glasgow	Mary Gardiner Sandra Chudleigh Frances Fee Linda Smith Claire Walsh	Haematology Department Yorkhill NHS Trust Dalnair Street Glasgow G3 8SJ Tel: 0141 201 9281 Fax: 0141 201 0857 Mary.Gardiner@ggc.scot.nhs.uk Sandra.Chudleigh@ggc.scot.nhs.uk frances.fee@ggc.scot.nhs.uk linda.smith2@ggc.scot.nhs.uk claire.walsh3@ggc.scot.nhs.uk
Great Ormond St	Gary Wright	Great Ormond Street MRD Lab Haematology Department Bone Marrow Laboratory Level 2, Camelia Botnar laboratories Great Ormond Street Hospital for Children London WC1N 3JH

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APPENDIX O
Information sheets and Consent forms
are available as separate word documents on the CTSU
web site.

APPENDIX P

Health Economics

As a result of the trial randomisations, more patients will receive the higher intensity Regimen C in UKALL 2003 compared to the previous trial UKALL97/99/01. Since Regimen C is associated with higher drug costs than Regimens A and B, the trial related excess service cost will be proportionate to the number of extra patients on Regimen C. Nationally (UK and Northern Ireland), around 50 extra patients/annum will receive Regimen C, 30 of whom would have been treated on Regimen A and 20 on Regimen B in the previous trial. Regimen C costs roughly £9000 more than Regimen A and £8000 more than Regimen B. Based on these figures, *nationally* the *annual* excess service cost of this trial will be $30 \times 9000 + 20 \times 8000 = £430000$.

NHS trusts and PCTs may find it more helpful to think of the excess cost in terms of the extra cost of treatment per patient entered into the trial. Since we expect 350 patients/ annum to be entered into the trial, for each patient entered into the trial, the excess service cost to the NHS will be £430000 divided by 350 = £1228. There will be a small saving from the reduced intensification arm of the trial which will bring down the cost to around £1100/patient.

Compared to its predecessor, this treatment protocol will entail significantly fewer hospital visits because of a change from use of native to Pegylated Asparaginase for all patients. The reduced hospital visits will partially offset the excess drug cost of Pegylated asparaginase, which is more expensive than the native product.

It costs on average £50,000 to treat one child with relapse ALL (more if the patient receives a stem cell transplant). If even the conservative estimate of a 5% reduction in relapse risk for the high risk group is realised, there will be 15 fewer relapses/annum in the UK at an annual cost saving of £600,000. There will be further savings from the reduced acute and late toxicity in the treatment reduction arm.

APPENDIX Q

Asparaginase Study

Aims

- (i) Development of a rapid high throughput assay to accurately detect AEP expression at diagnosis in blast cells, bone marrow and peripheral blood plasma.
- (ii) Correlation of AEP levels with asparaginase levels and the formation of anti-asparaginase antibodies.
- (iii) Identify antigenic epitopes responsible for formation of antibodies to asparaginase.

Samples

Please send 5 mls of marrow and/or peripheral blood in EDTA. All samples are collected at routine sampling times required by the protocol. No additional invasive tests are required.

For Regimens A, B and C

At diagnosis

1. 5 mls of bone marrow aspirate collected from a separate aspirate site to the MRD sample.
2. 5 mls of peripheral blood.

All subsequent samples (peripheral blood only) are for asparaginase activity and antibody detection. For this we need to know the date the last dose of asparaginase was given and the date the sample was taken. Please ensure that the peripheral blood sample is taken at least 7 days and not more than 14 days after the last dose of asparaginase. Please fill the attached form with each sample and notify if there is hypersensitivity to L-Asparaginase.

During induction

5mls of peripheral blood on day 8 (along with 2nd Vincristine and 5 days after the first asparaginase)

5 mls of peripheral blood on day 30 (along with the 4th Vincristine)

During Delayed intensification I and II

5 mls of peripheral blood on day 16 (along with the 3rd Vincristine)

During Maintenance therapy

10 mls of blood along with the first intrathecal methotrexate. Please note, this sample will also be used for epitope analyses and therefore requires an adequate number of white cells. Please ensure that $WC > 1.5 \times 10^9/L$. If not, this sample may be sent at a later date.

Additional samples for Regimen C

Capizzi I and II

5 mls of blood on day 32 along with the 4th Vincristine

Contact Details

All samples need to be sent by courier. The courier is CitySprint and they can be contacted on 020 7880 1121. The reference for the study is "AEP". Please send the samples to Centre for Integrated Genome Research, Stopford Building, Oxford Road, University of Manchester M13 9PT, Tel: 0161 275 5698. If there are any queries, please contact Catriona Parker on 0161 446 3093.

Please keep the form on the next page in the patient's notes. Once a sample is collected, fill the details, photocopy the form and send it along with the sample.

Asparaginase and AEP Study Form ALL2003

Please keep the master copy with the patient's notes. With each sample, please send a photocopy of the updated sample sheet and notify if there is an allergic reaction to L-Asparaginase.

Initials:
Centre:

Trial No:
Date of Diagnosis:

Sample Check list – Please tick sample sent

Diagnosis

5 mls bone marrow aspirate Date collected:
5 mls peripheral blood

All subsequent samples are for asparaginase activity and antibody detection. For this we need to know the date the last dose of asparaginase was given and the date the sample was taken. Please ensure that the peripheral blood sample is taken at least 7 days and not more than 14 days after the last dose of asparaginase. Please collect 5 mls of peripheral blood on:

Induction

Day 8 Date collected:
Date of last Asparaginase:
Day 30 Date collected:
Date of last Asparaginase:

Delayed Intensification I

Day 16 Date collected:
Date of last Asparaginase:

Delayed Intensification II

Day 16 Not eligible (Only Regimen A)
 Date collected:
Date of last Asparaginase

Continuation Therapy

With intrathecal MTX Date collected:

(Note for this sample alone, peripheral white cell count needs to be $>1.5 \times 10^9/l$)

Regimen C (additional samples)**Capizzi I**

Day 32 Date collected:
Date of last Asparaginase:

Capizzi II

Day 32 Date collected:
Date of last Asparaginase:

Patient is allergic to E Coli Asparaginase Yes No Date of hypersensitivity:
Patient is receiving Erwinase Yes
Patient is allergic to Erwinase Yes Date of hypersensitivity:

Background

No new drugs have entered into routine clinical practice for childhood ALL for almost 4 decades. The impressive improvement in survival during this period has been achieved by optimising therapy with the drugs we have at our disposal. During the induction and intensification period we have perhaps achieved maximum efficiency in the use of the drugs vincristine, steroids and anthracyclines. Further optimisation with L-Asparaginase remains possible as is illustrated by the introduction of PEG-Asparaginase in ALL 2003.

We have identified a protease (AEP) produced by lymphoblasts that degrades both native and pegylated E Coli Asparaginase. Patients whose blast cells produce excess amounts of this protease may either fail to achieve sufficient asparagine depletion and/or develop anti-asparaginase antibodies. The study aims to correlate the levels of protease present at diagnosis with subsequent asparaginase activity and formation of antibody. If successful, we will be able to identify patients who will develop antibodies/hypersensitivity to asparaginase at diagnosis and prior to their receiving asparaginase. Such patients may benefit from Erwinase, or alternative asparaginases that are being developed.

Methodology

We have developed a real-time quantitative PCR (RQ-RTPCR) assay for AEP. Asparaginase hypersensitivity has been observed only in children with high AEP levels. These are single centre observations and need to be validated on a larger cohort of patients.

The majority of patients with high AEP levels (as analysed by blast RNA levels) however do not appear to develop hypersensitivity to asparaginase. There are two possible explanations, which may be linked to each other. The enzymatic degradation of asparaginase is more likely to occur in an extracellular environment, as there is no evidence to suggest that asparaginase is able to enter the cell. We have evidence that AEP protein and RNA is present in the plasma. While the latter is the result of lysis of blasts, the former could also be a result of lysosomal discharge of contents in to the plasma. Thus AEP protein levels, either in blast cells or peripheral blood/bone marrow plasma, may be more predictive of asparaginase inactivation. A second explanation is that as the amount of asparaginase is lower in the pegylated version (compared to the native), silent antibodies rather than hypersensitivity may pose a larger problem in UK based ALL protocols. Thus we will need to look not only at asparaginase activity but also antibody formation. We will also use the opportunity to see if we can identify the antigenic epitopes in E Coli Asparaginase that contribute to its immunogenicity. The information obtained from these investigations may allow us to design a less immunogenic recombinant enzyme with a longer half-life.

AEP expression will be assayed using RQ-RTPCR and ELISA in diagnostic blast cells, bone marrow and peripheral blood plasma. Asparaginase activity and antibody assay will also be performed on the baseline peripheral blood sample.

At subsequent time points during induction, delayed intensification and Capizzi blocks, assays for asparaginase activity and antibody formation will be performed. From the sample obtained during maintenance, epitope recognition studies and antibody assays will be carried out.

Sample Size: We aim to recruit 400 patients a year, or over the study period we will have recruited at least 1000 patients. We aim to use the first half of the data to obtain the best cut off point, and the second half to estimate the sensitivity and specificity at that cut off point for the assay(s). The predictive sample size is dependent on the sensitivity of the assay(s) and we have calculated the width of the confidence interval for four different plausible values of prevalence of antibody for our population, assuming that 500 patients are used to estimate the sensitivity and specificity once the optimal cut point has been selected (see Table below).

95% Confidence Intervals for sensitivity, for varying prevalence and sensitivity point estimates

Prevalence		Sensitivity point estimate			
		75%	80%	85%	90%
10%	10%	(62%, 87%)	(66%, 90%)	(73%, 94%)	(78%, 97%)
	15%	(63%, 84%)	(69%, 88%)	(75%, 92%)	(82%, 96%)
	20%	(65%, 83%)	(71%, 87%)	(76%, 91%)	(82%, 95%)
	25%	(67%, 82%)	(72%, 87%)	(77%, 91%)	(84%, 95%)

Laboratory Assays

RQ-RTPCR: We have standardised the use of the TaqMan 384 well microfluidic card for the RQ-RTPCR estimation of AEP expression. High and low expressing cell lines have been used to generate a standard curve and we will use 2 house keeping genes to generate $\delta\delta\text{CT}$ values.

ELISA: We have obtained both polyclonal (commercial) and monoclonal antibodies specific for AEP as well as purified recombinant AEP protein. There appears to be a good correlation between levels of AEP RNA and protein (as detected by western analyses). We have developed a sandwich ELISA, using a combination of mouse and rabbit antibodies. At the moment we are comparing the sensitivity of a HRP conjugated with the use of a biotinylated secondary antibody.

Asparaginase Activity: The diagnostic sample will serve as baseline, and subsequent samples are to be taken 7-14 days after the last L-Asparaginase dose. The quantification of enzymatic activity of all forms of L-Asparaginase is based on the measurement of substrate turnover at a maximum rate. One unit of activity is defined as the amount of enzyme which releases 1mmol of ammonia and aspartate from 1mmol asparagine per minute at 37°C. The liberated ammonia can be measured spectrophotometrically either after nesslerization or by an enzyme-coupled reaction. Thus, a number of assays have been developed. In brief, asparaginase hydrolyses AHA to aspartate and hydroxylamine. Asparaginase activity in serum samples is quantified by incubating the samples with an excess amount of L-aspartic acid β -hydroxamate (AHA) at 37°C. Asparaginase hydrolyses AHA to aspartic acid and hydroxylamine, which is detected at 710 nm after condensation with 8-hydroxyquinoline and oxidation to indoxine. This method allows the quantification of 2.5 U/L Asparaginase in 20 μl serum with coefficients of variations for intra- and interday reproducibility between 1.98 - 8.77 % and 1.73 - 11.0 %, respectively, and an overall recovery of 101 +/- 9.92 %. Peripheral blood samples will be collected 5-7 days after PEG-Asparaginase and assayed for activity

Asparaginase Antibody Assay: Briefly, microtitre plates are coated with purified (and recombinant) E coli asparaginase. The positive anti-asparaginase antibody controls,

calibrators with defined anti-asparaginase reactivities, normal human serum as negative control, and patient serum samples at certain dilutions are added and incubated for 1 h. After washing, a polyclonal goat anti-human IgG and IgM horseradish peroxidase conjugate is added and incubated for 1 h. After washing, 3,3',5,5'-tetramethylbenzidine is added and incubated for 30 min. Anti-asparaginase antibody levels are measured at 450 nm for the enzymatic product (subtracting the absorbance at about 630 nm for nonspecific absorbance) using a microplate reader. The OD values of the calibrators are plotted against their corresponding concentration, given as arbitrary units per ml, to construct a calibration curve over the whole measuring range of the assay. Positive reactivity in serum is calculated using this calibration curve.

Antigen presentation: Peripheral blood mononuclear cells (PBMC's) will be obtained from the sample taken prior to starting maintenance therapy as well as from controls not exposed to Asparaginase. These will be examined to identify T-cell clones specific for Asparaginase processing, to identify whether the AEP cleaved fragments are recognised and if AEP processing accelerates antigen presentation. The antigens used will be AEP digested L-Asparaginase fragments and synthesised peptides. Briefly, proliferation will be measured by ³H-thymidine incorporation after 2-5 days of culture. T cells from responding PBMC will be expanded with IL-2 and individual peptide specific responses will be assayed using a set of peptides covering the L-asparaginase sequence (15mers, overlapping by 10 residues). Autologous PBMC or EBV-transformed B cells will be used as antigen presenting cells. Additionally, T cells recognising specific asparaginase peptides will be cloned from these cultures by standard methods.

APPENDIX R

QUALITY OF LIFE STUDY

Aims

1. To assess the quality of life of the children treated in the ALL 2003 trial for acute lymphoblastic leukaemia.
2. To compare the impact of the different treatment regimens in ALL 2003 on QoL
3. To describe changes in QoL throughout treatment and up to 18 months after completion.

BACKGROUND

Integral to ALL 2003 is the randomisation based on MRD at day 28. MRD Low Risk Group (negative at d28) will be randomised between current standard UK ALL chemotherapy with two delayed intensifications (regimen A or B of ALL9701) and one delayed intensification only.

In contrast, MRD High Risk Group ($>1:10,000$ at d28) will be randomised between standard therapy and regimen C of ALL 97/01. In addition to standard indicators of trial efficacy including event free survival and survival, we propose to include measures of quality of life (QoL). QoL will be measured both in respect to the child and separately in terms of the 'total burden of therapy' for the whole family. Such an evaluation is important in considering the overall 'cost' of survival for any disease.

QUALITY OF LIFE

The question of measurement of QoL is complex especially in relation to children.

Gill and Feinstein (1994) have distinguished three ways in which QoL may be assessed in a health context. These include:

- 1 objective measures, such as clinical indices that patients would not themselves use or necessarily be aware (eg fever, neutropenia)**
- 2 functional performance (the ability to perform daily activities about which patients are aware, such as climbing stairs)**
- 3 patient's own evaluation of the subjective experience of being able to complete a given activity.**

Objective measures will be studied as described in the main proposal. In this paper, we clarify how we plan to measure both functional performance and subjective experience.

There is no evidence of any simple one-to-one correspondence between physical parameters and how a patient feels. While a child who is febrile and unwell is likely to be miserable, the child's perception of illness at relapse is rarely proportionate to the catastrophic objective significance of this diagnosis. The frequent lack of correspondence between objective indices and patient's experience of illness necessitates alternative approaches to assessing QoL.

This emphasis on subjectivity, or self-appraisal, is important. The original World Health Organisation's definition of health (1947), on which many QoL measures are based, emphasised that illness affects a very broad spectrum of behaviour including physical, social and emotional functioning. In work with children the need for additional domains to assess

family relationships, cognitive functioning, independence, body image and opportunities for the future have been emphasised.

Attempts to determine QoL have ranged from the very simple “how are you?”, use of proxy measures such as school absence, or the use of related measures already available for children. These include, for example, measures of self-esteem or depression. Reliance on any of these individual measures is limited, as no single measure will provide a comprehensive or sensitive indicator of QoL during treatment for childhood cancer. The use of multiple measures, or ‘batteries’, is cumbersome given the likely overlap in terms of specific items. There are in addition, considerable disadvantages to these ‘batteries’ of measures. They tend to be very lengthy, repetitive and may lack sensitivity to detect the specific impact of cancer on the child’s QoL. For this reason, a number of specifically developed measures of QoL for children with cancer have been reported.

The range of measures developed in recent years poses a problem for researchers and clinicians wanting to measure the child's QoL. Decisions need to be made about the most suitable *respondent* (parents, child, or both); and the *appropriateness* of the measure for work with children. Other considerations relate to the *psychometric properties* of the measure, and method of development. In particular, however good the psychometric properties, the critical question refers to whether or not the measure taps those aspects of caring for a child with cancer that are affected by involvement in a clinical trial.

As part of a larger review that included both generic and disease-specific measures for work with children (Eiser & Morse, 2001), we identified nine measures that are either cancer specific or developed from work involving children with cancer. Our decision to use both the generic and disease specific versions of QoL measures reported by Varni et al. 1998, 2002) is based on the following criteria:

- i) Availability of parallel versions, enabling comparisons to be made between parent and child views about QoL;
- ii) Adequate psychometric properties. In a series of papers Varni and colleagues have reported good reliability and validity for both measures (Varni et al 1998, 2002). (Children who had completed treatment had a better QoL than those who were still on treatment).
- iii) Brevity. The PedsQL remains one of the briefest and comprehensive measures of QoL.
- iv) Availability of population norms. Population norms are available for the US population and it is anticipated that British norms will be available in the near future (Williams et al, in progress). Comparisons with norms will be made to enable us to distinguish those changes in QoL that are the result of treatment compared with any that might be attributable to normal age-related changes.

Measurement of QoL is a relatively new science and therefore there are a number of limitations associated with this decision:

- i) age of self-report. Although self report versions are available for children of 5 years and above, we have experienced considerable practical problems in administering measures to children of this age. We feel these difficulties will be enhanced for children who are ill. In addition we would be dependent on research nurses in different centres to help the children complete questionnaires. (Use of mothers as helpers in our view results in such high levels of agreement that the

- child information is superfluous). Given the practical constraints likely to operate in oncology clinics, we therefore propose to collect self report data for children aged 10 years and above only.
- ii) The school and emotional domains of the generic version have been reported to lack internal reliability especially for the youngest children. This is especially a problem for this study given the mean age of diagnosis of ALL is approximately 4 years of age.
 - iii) There is some overlap between the generic and cancer specific scales. The generic version is preferred if the crucial comparison is between the child with cancer and healthy children, and clearly this is increasingly important as the time from diagnosis increases. Population data is also available for this measure. However the cancer specific measure is more appropriate for use during the period of active therapy, when comparing the impact of therapy of different treatment schedules, as it addresses important issues such as venepuncture, nausea and mouth ulcers. Varni et al (2002) provides mean data for a relatively large number of children but does not claim that this can be used as normative data. While both measures have merits, the disadvantages for our purposes are the duplication and consequent increase of burden to families. We have included both measures however, as removal of individual overlapping items might jeopardise the reliability and validity of the resulting measures.
 - iv) We see limitations of these measures to include specific aspects of wording that focus on the 'problems' experienced by children, rather than the extent to which they are able to continue with aspects of their normal lives. Indeed we would argue that this focus (on what the child can rather than can't do) more appropriately addresses quality of life avoiding the emphasis on psychiatric morbidity, common to many previous outcome measures.
 - v) Neither of these measures would be sensitive to ways in which the different treatment protocols affect the impact of therapy on the QoL of the family. In fact, this has not been the focus of QoL development in paediatric oncology at all. For this reason, we have adapted a measure previously used to assess family QoL in children with asthma (Juniper et al 1996).

Ideally, QoL should be elicited from the patient, since it is well-established that there are differences between patient and proxy report (Eiser & Morse, 2001). It is recommended that information is elicited directly from children where possible, though it is not always possible to elicit responses from sick children. For these reasons, we propose to rely on the principal care-giver for information about the child's QoL though we will provide child versions for completion by children 10 years of age and above.

Family burden of care

In the evaluation of clinical trials, it is also important to assess family burden of care. In one of the few studies to look at parents' difficulties with tasks involved in home based care of children with cancer, Manne et al. (1994) identified difficulties with i) administration of oral medications; ii) administration of mouth care; iii) administration of central access line care, iv) getting the child to drink fluids and v) getting the child ready for clinic visits. These practical issues are not included in contemporary QoL measures, but are likely to have considerable impact on the health and well-being of the family generally.

Thus, comprehensive evaluation of QoL needs to take into account parents' ability or willingness to carry out home-based treatments, however difficult or complex. In the absence of any

standardised measure, we have put together a questionnaire, originally described by Juniper (Juniper et al. 1996) to consider family QoL where a child has asthma, and further modified to take into account our clinical and research experience. In the original paper, Juniper et al. (1996) reported adequate reliability and validity and that the measure was sensitive to change (measured over a 4 week period). Inclusion of this measure, although not standardised for this population, very much takes into account issues raised by mothers looking after children treated on the UKALL 97 trial.

The generic and cancer specific QoL questionnaires to be used have been Anglicised according to guidelines described by Varni (Eiser et al., in preparation).

Timing of assessments

Parents will be asked to complete questionnaires during routine hospital visits. Five assessments are planned.

- i) During week 1. This will be used as a baseline assessment of the child's QoL before treatment. Parents will be asked to complete the QoL measure as they would have done before the child showed signs of illness. They will not complete the burden of care questionnaire at this stage. At all other time points both questionnaires will be completed.
- ii) At week 4. At this time patients will be coming to the end of induction. The assessment at this stage will reflect the impact of initial treatment on patients and parents QoL and burden of care before randomisation.
- iii) At the start of maintenance therapy (i.e. on full recovery from intensification so that answers are not unduly dominated by the most recent episode of illness). This comparison would enable us to distinguish between the effects of i) 1 versus 2 intensifications and between ii) Regimen C versus standard therapy.
- iv) 18 months. At this point girls will be coming to the end of treatment while boys will be only half way. We feel this is an important point enabling us to assess the burden of length of treatment.
- v) A final assessment at the end of treatment. Again this enables an evaluation of the length of treatment on QoL and family burden of care.

Procedure

Families will be recruited to the study as described in the main section of the proposal. Questionnaires will be given to mothers by the research nurse or nurse specialist within the unit. It is anticipated that most adults will be able to complete these with minimum explanation. Research nurses will be asked to explain the questionnaires to children and will offer help if required. We do not encourage parents to help their child as this leads to bias. The coordinators of the QoL study will liaise with each centre to identify the nurse (or other clinical personnel) responsible for the data collection and for whom they can provide support. Nurses will be given specific instructions about administration of questionnaires and ongoing support throughout the running of the study by the QoL leads.

Assessment of QOL in 18-25 year olds

QOL questionnaires that are age-appropriate with established reliability and validity will be used. Generic QOL will be assessed using the SF-12 (Ware et al. 1996) and cancer specific QOL using the QLQ-C30 (Aaronson et al. 1993). (There is no disease specific

leukaemia module currently available). In addition separate questions to determine participation in daily activities will parallel those used in the child study.

Patients in this age group will be recruited to the study as described in the main section of the proposal (i.e. at the time of recruitment to the main trial: full information will be given and separate consent for the QOL study is given on the consent form). Questionnaires will be given to eligible patients by the research nurse or nurse specialist within the unit. Most will be able to complete these with minimum explanation (time for completion approximately 10 minutes). Nurses will be given specific instructions about administration of questionnaires and ongoing support throughout the running of the study by the QOL leads. Questionnaires are returned to the Department of Psychology, University of Sheffield for analysis.

Please contact Professor Eiser for copies of the questionnaire:

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UKALL 2003

YOUNG ADULT APPENDIX

This appendix is written to aid clinicians in treating young adults aged 16-24 years on the UKALL 2003 protocol. It does not replace any part of the full UKALL2003 trial protocol and must be read in conjunction with that complete document. The purpose of this appendix is to simplify some of the issues relating to young adults.

The treatment regimens described herein have not been extensively used in this age group and are likely to be more toxic than current adult treatment regimens. Therefore, adult centres wishing to enter patients into this trial should liaise with their local UKCCSG centres (see page 91, Appendix N for list) and work closely with them in the day to day management of patients.

Please contact the following co-investigators for any queries about the treatment contained in this appendix or for any matters relating to young adults:

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RATIONALE FOR USING A PAEDIATRIC TREATMENT APPROACH FOR TREATING YOUNG ADULTS WITH ALL

Background

Substantial improvements in the outcome of therapy for acute lymphoblastic leukaemia (ALL) in children have been achieved by the use of more intensive chemotherapy, risk-based treatment allocation and improved supportive care. However, the outcome in adolescents with ALL has remained inferior to that achieved in younger children (1). Whether this is a reflection of biological differences in disease susceptibility to therapy, clinical differences in protocol tolerability or limitations in delivery of effective therapy because of compliance, is currently unknown (1). To date, adolescents have represented a unique patient group, in that they have received ALL therapy according to either paediatric or adult clinical trials, determined only by local referral patterns to paediatric or adult physicians.

Outcome of adolescents treated on UK national paediatric or adult trials

The UK paediatric and adult ALL working groups have recently performed a retrospective comparative analysis of adolescents, aged 15-17 years, treated on the Medical Research Council (MRC) clinical trials between 1997 and 2002 (2). 61 adolescents entered into the MRC paediatric ALL97/revised 99 trial were compared to 67 patients treated according to the MRC/ECOG adult UKALL XII/E2993 protocol. UKALL XII/E2993 patients were slightly older (mean 16.3 compared to 15.3 years, $p < 0.0001$), but there were no other significant differences in prognostic factors between the two groups, with equivalent presenting white blood count, gender ratio, immunophenotype and proportion of Philadelphia chromosome positivity.

Adolescents treated on the ALL 97/revised 99 trial had significantly higher overall (71 versus 56%; $p = 0.04$) and event-free (65 versus 49%; $p = 0.01$) survivals at 5 years compared to those receiving therapy according to UKALL XII/E2993 protocol. There were significantly fewer deaths in remission and a trend to fewer relapses in the ALL97/revised 99 group. In keeping with the trial protocols, more patients treated on the adult trial were transplanted. However, exclusion of these patients from the analysis did not impact on the superior event-free survival (EFS) observed in those adolescents treated on the paediatric protocol.

Despite the inherent methodological limitations of the design of this study, the results are entirely in keeping with those reported by other international groups.

International experience of paediatric and adult ALL strategies in adolescent ALL

The current international data regarding the outcome of paediatric and adult ALL treatment strategies specifically in adolescents are summarised in Table 1. All are retrospective comparative studies. However, these data show a consistent and large EFS or OS advantage in patients treated according to paediatric protocols. The reasons for this are unclear, but do not reflect patient or disease characteristics since the two cohorts compared in all studies were well matched for factors of prognostic significance, with the exception of a slightly younger age (15 years compared to 16 or 17 years) in patients receiving paediatric-type therapy.

Table 1

Protocol	N	Median age /years	% CR	% Relapse rate	% Mortality	% Survival	Study group (Ref)
ALL 97/99 (P) UKALL XII/E2993 (A)	61 67	15 16	98 94	23 28	28 43	EFS at 5 years (p=0.01) 65 49	MRC/ECOG (2)
AIEOP ALL 95 + 2000 (P) GIMEMA ALL 0496 + 2000 (A)	150 95	15 16	94 89	17 45	- -	OS at 2 years 80 71	Italy (3)
DCOG ALL 6-9 (P) HOVON ALL 5 + 18 (A)	47 44	15.4 16.9	- -	26 55	At 5 years 4 24	EFS at 5 years (p=0.0001) 69 34	Netherlands (4)
FRALLE 93 (P) LALA 94 (A)	77 100	15.9 17.9	94 83	15 46	- -	EFS at 5 years (p<0.0001) 67 41	France (5)
CCG (P) CALBG (A)	196 103	- -	96 93	- -	- -	EFS at 6 years 64 38	US (6)

N – number of patients

CR – complete remission

P – paediatric protocol, A – adult protocol

OS – overall survival, EFS – event free survival

While there are differences in the components and schedule of chemotherapy used by different groups, the paediatric protocols are broadly based on the German Berlin-Frankfurt-Munster (BFM) protocol, which incorporates induction and delayed dose-intensive use of non-myelosuppressive drugs, with continuous anti-metabolite-based maintenance. Adult protocols, however, tend to use blocks of intensive myelosuppressive chemotherapy, without delayed intensification phases, a shorter duration of therapy overall and more frequent use of first remission bone marrow transplantation.

Given the relatively small number of adolescents treated in clinical trials and the heterogeneity of different national approaches, it is impossible to determine which elements of the paediatric strategy improve outcome. Possibilities include physician experience and compliance, patient compliance, supportive care, use of bone marrow transplantation and specific aspects of protocol design, in particular, early dose intensification of chemotherapy, higher cumulative doses of steroids, vincristine and L-asparaginase and less frequent use of alkylating agents, anthracyclines and high dose cytarabine in paediatric protocols.

Treatment of young adults within UKALL2003

There is now both national and international expert consensus that the specific needs of this previously neglected group of patients should be addressed in the context of prospective clinical studies. The current study will provide a treatment framework for young adults with ALL in the UK based on the current MRC paediatric protocol, UKALL2003, with the following principles;

1. ‘Young adults’ will be defined as aged between the 16th and 25th birthdays.
2. Patients with high risk karyotypes will be entered onto regimen C and be ineligible for MRD randomisations.
3. All other patients will start treatment on regimen B.
4. US CCG 1882 showed no benefit of Regimen C for day 8 Slow Early Responders in patients > 16 years. **Therefore, patients in this age group will continue on Regimen B regardless of their day 8 marrow response.**
5. Treatment randomisation will be based on day 28 and post consolidation MRD results. Low risk patients will continue on regimen B but be randomised between one or two delayed intensifications. MRD high risk patients will be randomised between regimen B and C.

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ELIGIBILITY AND INITIAL RISK STRATIFICATION:

The protocol is open to all young adults between their 16th and 25th birthdays with ALL except the following:

1. Patients with B-ALL (Burkitt-like, t(8;14), L3 morphology, SMIg positive). Patients with this disease will be eligible for the current UKCCSG B cell NHL/ALL trial or corresponding adult trials.
2. Philadelphia-positive ALL (t(9;22) or BCR/ABL positive) will start induction therapy on the UKALL2003 protocol but will transfer to the adult UKALL XII protocol post induction if they have achieved a remission. They will join UKALL XII at phase II (subject to an amendment) where they will be entitled to Imatinib with chemotherapy. Adolescents with Philadelphia positive ALL not achieving a CR post induction will go off protocol. Centres also have the option of entering patients between 16th and 18th birthdays into the European paediatric Ph+ ALL trial, EsPHALL.

Initially, eligible patients will be stratified into two risk groups based on the following criteria:

- (a) **Intermediate risk:** All young adults who do not have BCR-ABL, hypodiploidy (<44 chromosomes), amplified RUNX1 or an MLL gene rearrangement will be classified as intermediate risk irrespective of presenting WCC.
- (b) **High Risk:** All young adults who have BCR-ABL (induction only), hypodiploidy (≤ 44 chromosomes), amplified RUNX1 (previously AML1, see page 27 of main protocol for definition of abnormality and further treatment recommendations) or an MLL gene rearrangement will be classified as high risk. These patients will not be eligible for the MRD randomisation. CCG 1882 showed no benefit for augmented BFM in Slow Early Responders in patients over 16 years of age. **Hence, Slow Early Response at day 8 is not a criterion for transfer to Regimen C in this age group they should continue on Regimen B regardless of day 8 response.** However, the day 8 marrow with MRD analysis remains a requirement for this age group to allow retrospective correlation with day 28 MRD and outcome.

Patients will then start treatment according to their risk group as follows:

- (d) **Intermediate risk:** Regimen B – four-drug induction.
- (e) **High risk: These patients will not be eligible for MRD randomisation.** They will be allocated Regimen C – four drug induction, augmented BFM consolidation, Capizzi interim maintenance, and two further BFM-style intensification periods of extended duration.

See page 26 of main protocol for treatment of patients in special categories, such as those with CNS or testicular disease, or traumatic LPs at presentation.

**MINIMAL RESIDUAL DISEASE (MRD) RISK STRATIFICATION
AND RANDOMISATION****Patients fulfilling the following criteria will be eligible for entry into the MRD randomisations:**

1. Intermediate Risk as defined above.
2. Morphological Complete Remission (BM1 Marrow) at Day 28 of Induction.
3. Availability of MRD results at Day 28.
4. Informed consent obtained.
5. Induction given as protocol.

Patients not eligible for entry into the MRD randomisation:

1. High Risk as defined above. These patients will receive Regimen C.
2. Day 28 non-remitters. These patients will receive Regimen C if BM2 (marrow blasts 5-25%) or go off-protocol if BM3 (marrow blasts > 25%).
3. MRD Indeterminate Group (no result) will continue on previously assigned therapy.
4. Sub-optimal induction therapy. The clinical significance of day 28 MRD is uncertain in patients who have received sub-optimal induction therapy. Please discuss these patients with a co-ordinator.

Randomisations**Patients will be assigned to MRD risk groups based on day 28 and post consolidation MRD results and randomised as follows:**

- MRD Low Risk Group (MRD negative or positive $< 5 \times 10^{-5}$ at day 29) will continue on previously assigned Regimen B and receive one delayed intensification.
- MRD High Risk Group (MRD positive $> 1 \times 10^{-4}$ at day 28) will be randomised between previously assigned Regimen B and Regimen C.
- MRD Indeterminate Group (No MRD result or MRD Positive between 5×10^{-5} and 1×10^{-4} at day 29) will continue on previously assigned Regimen B and receive two delayed intensifications

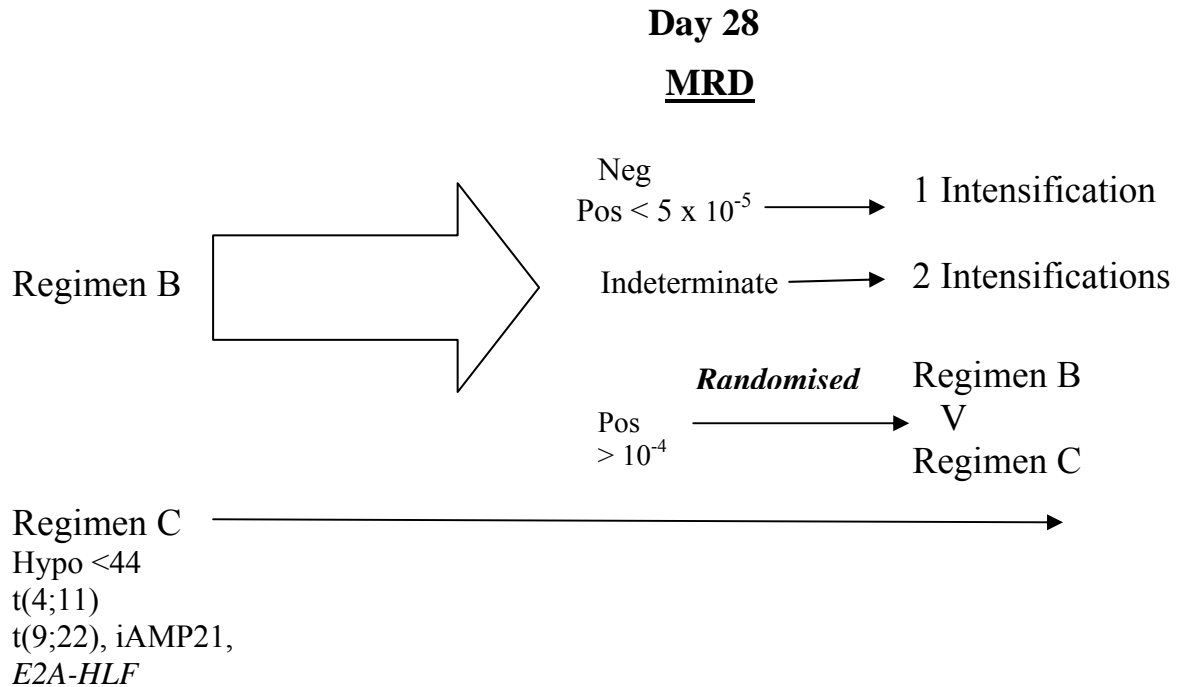
ENTRY FLOWCHART AND INITIAL TREATMENT ALLOCATION FOR YOUNG ADULTS**At diagnosis:**

BCR-ABL?	→	Yes	REGIMEN C Induction only then UKALL XII
↓ no			
MLL rearrangement ?	→	yes	REGIMEN C
↓ no			
Hypodiploid (≤ 44 chromosomes)?	→	Yes	REGIMEN C
↓ no			
RUNX1 amplification?	→	Yes	Regimen C (see page 27 of main protocol)
↓ no			
REGIMEN B			

Marrow morphology at day 28 on Regimen B

>5% but <25% blasts (M2)	→	yes	transfer to Regimen C
> 25% blasts (M3)	→	yes	OFF PROTOCOL
<5% blasts (M1)	→	yes	MRD high risk randomisation

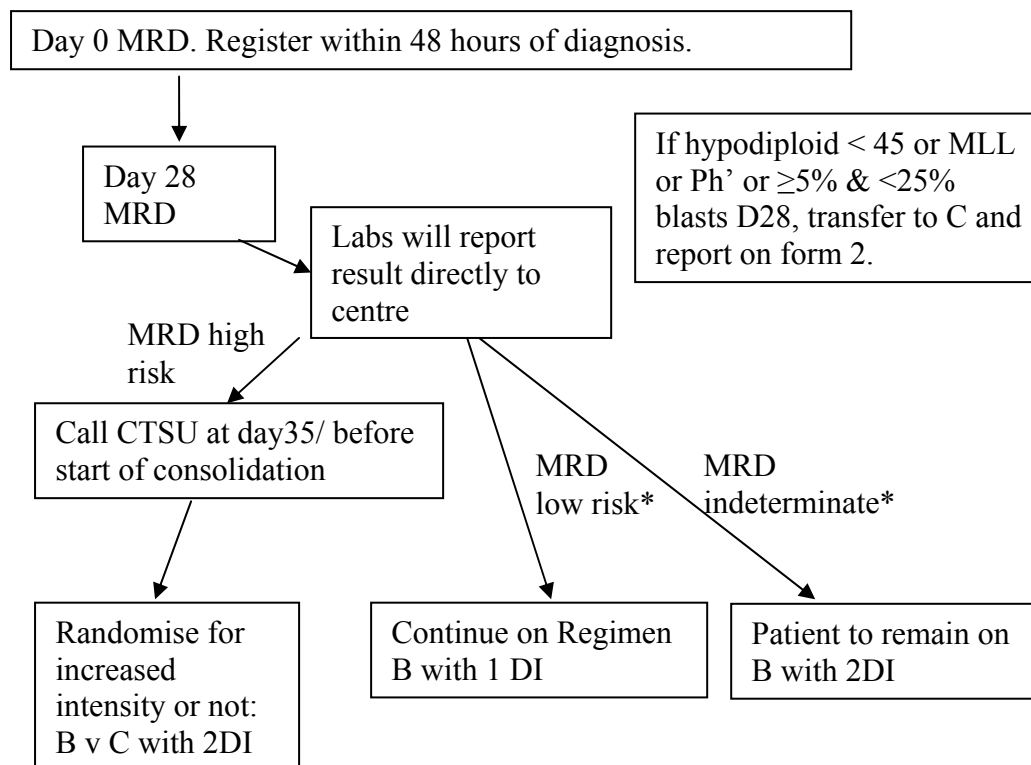
TREATMENT AND RANDOMISATION ALGORITHM FOR YOUNG ADULTS



DEFINITIONS OF MARROW STATUS AND MRD RESPONSE:

Day 28 and week 11 MRD will be assessed centrally and response categorised as follows:

- MRD Low Risk Negative or positive < 5×10^{-5} at day 29.
- MRD High Risk Positive > 1×10^{-4} at day 28.
- MRD Indeterminate No result or MRD between 5×10^{-5} and < 1×10^{-4} at day 29

REGISTRATION AND RANDOMISATION PATHWAY

* Day 35 CTSU call not necessary

See page 30 of main protocol for further details of essential investigations at diagnosis
SUMMARY TABLE OF ESSENTIAL INVESTIGATIONS.

	Regimen A	Regimen B	Regimen C
Diagnosis	Marrow, CSF, Thiopurine, Asparaginase study and MRD samples for all regimens		
Day 8	Marrow	Marrow Asparaginase study samples for all Regimens	-
Day 15	Marrow		-
End of induction	Review of bone marrow if not M1 for all regimens		
	MRD	MRD	MRD
	Asparaginase study samples for all Regimens		
Week 11	MRD	MRD	-
Week 11 -16	Thiopurine sample for all Regimens*		
Week 15	-	-	MRD
Capizzi I, day 32			Asparaginase
Week 17 (DI1)	MRD		
Week 19 (DI1)	-	MRD	-
Week 23 (DI1)	-	-	MRD
Day 16 of DI1 and II	Asparaginase study samples for all Regimens		
Capizzi II, day 32			Asparaginase
Week 41 (Maint)	MRD - (week 38 for 1 DI patients)	-	
Week 43 (Maint)	-	MRD (week 40 for 1 DI patients)	-
Week 49 (Maint)	-	-	MRD Thiopurine sample
Start of maintenance	Asparaginase study samples for all Regimens		
End of treatment	MRD	MRD	MRD

Marrow = Morphology Review

MRD = Send marrow for MRD status to network laboratory

Asparaginase Study samples – see Appendix Q, page 115

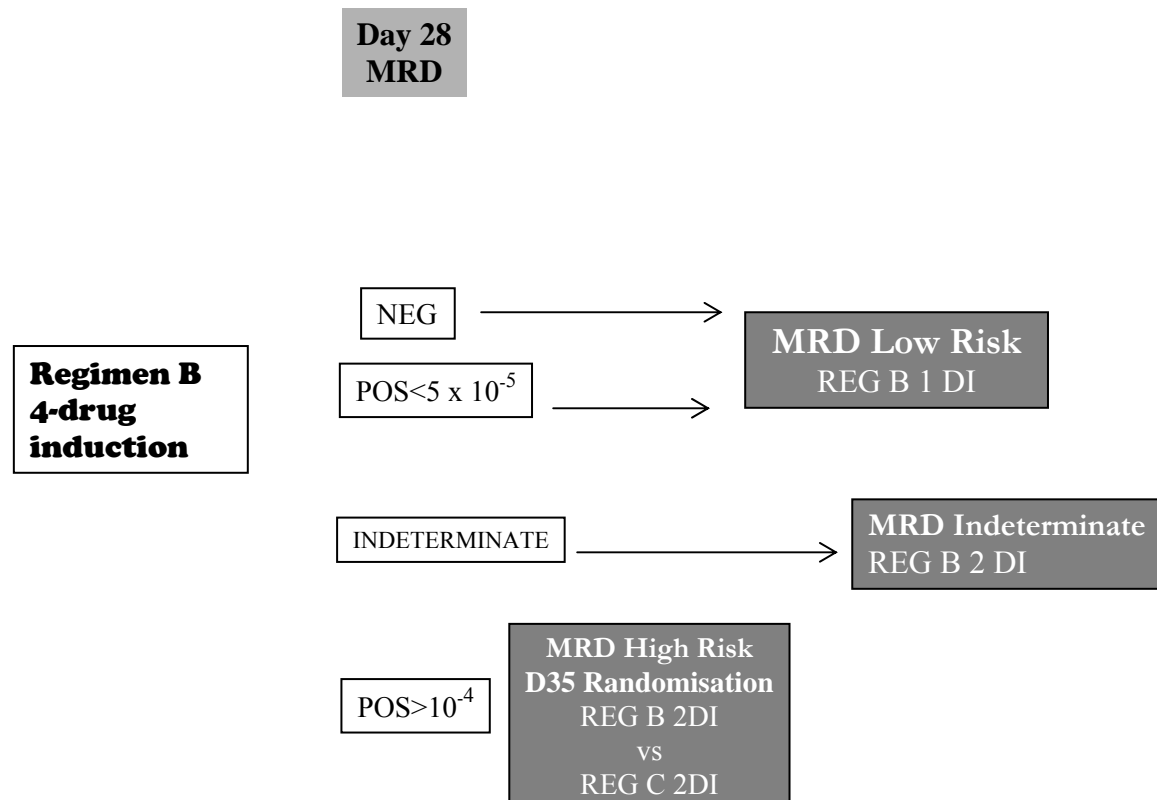
*** See flowcharts for exact timing.**

UKALL 2003 REGIMEN B for YOUNG ADULTS**MRD Randomisation**

MRD Low Risk patients will be randomised between one or two delayed intensifications.

MRD High Risk patients will be randomised between Regimen B or C and should change to allocated treatment at day 35.

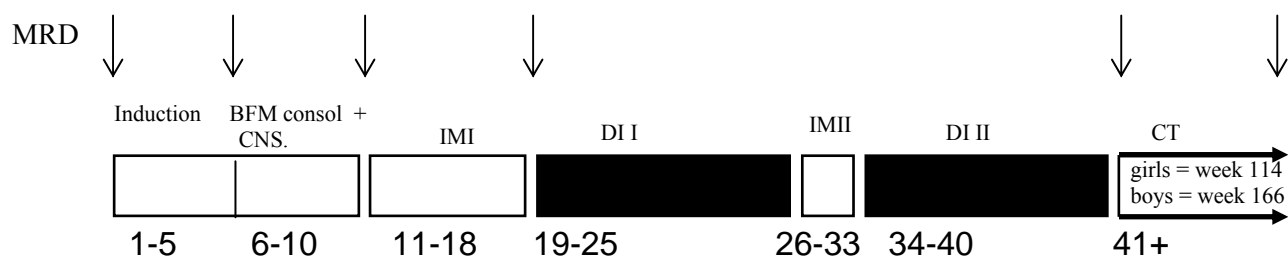
MRD Indeterminate patients will continue on Regimen B + 2DI.



Summary of Regimen B - YOUNG ADULTS.

Regimen B consists of the following phases:

1. Four drug induction (duration 5 weeks) with **dexamethasone** as steroid of choice.
2. Standard BFM consolidation (duration 5 weeks) with **6-mercaptopurine**;
3. Interim maintenance I (duration 8 weeks) with **dexamethasone and 6-**
4. **mercaptopurine**;
5. Delayed intensification I (duration 7 weeks); **6-mercaptopurine** in reconsolidation;
6. Interim maintenance II (**for patients allocated two delayed intensifications**) (duration 8 weeks) with **dexamethasone and 6-mercaptopurine**;
7. Delayed intensification II (**for patients allocated two delayed intensifications**) (duration 7 weeks); **6-mercaptopurine** in reconsolidation;
8. Maintenance chemotherapy with **dexamethasone and 6-mercaptopurine** to end of
9. week 114 for girls and end of week 166 for boys. Delays accrued during phases I-VI are taken off the maintenance period.

**Prevention of Tumour Lysis**

Treatment centres should have a policy for the prevention and treatment of Tumour Lysis syndrome in patients with high white cell counts or bulky disease. Consideration should also be given to the use of Recombinant Urate Oxidase (Rasburicase) *instead of* Allopurinol in patients with very high white cell ($> 100 \times 10^9/l$) counts or very bulky disease (Mediastinal mass or large abdominal lymph nodes).

UKALL 2003 REGIMEN B: DETAILS OF TREATMENT.

The convention for day/week numbering is that a new module of therapy begins on day 1 of whatever week of treatment has been reached. For example, induction begins on day 1 (week 1); consolidation on day 1 (week 6); delayed intensification II on day 1 (week 34); and so on. Each module runs for a number of days and induction therefore finishes on day 35 (end of week 5); interim maintenance I on day 56 (end of week 18); and delayed intensification II on day 49 (end of week 40).

Regimen B: Remission induction – phase I (See flowchart 8.)

This phase runs for 35 days from day 1 (beginning of week 1) to day 35 inclusive (end of week 5).

- a) **Fluids:** All patients should be adequately hydrated (at least 2-2.5 l/m²/24hrs given parenterally for the first 48 hours).
- b) **Allopurinol:** 100 mg/m² oral three times daily should start 24 hours before chemotherapy and continue for 5 days.
- c) **Dexamethasone:** 6 mg/m²/day (maximum dose 10 mg/day in induction only) for 28 days and then tapered over the next 7 days. The steroid should be divided into two doses per day.
- d) **Vincristine:** 1.5 mg/m² (maximum single dose 2 mg) IV bolus weekly for five weeks starting on day 2 and continuing on days 9, 16, 23 and 30.
- e) **Daunorubicin:** 25 mg/m² IV over 1 hour on days 2, 9, 16, and 23. Note that daunorubicin is included in induction in regimen B and that this dosage is different to that recommended in regimen C.
- f) **Pegylated L-asparaginase: (Oncaspar)** 1000 iu/m² **IM**, on day 4 and day 18.
- g) **Intrathecal methotrexate: On days 1, 8 and 28.** Dose 12 mg for all adolescents. NB Patients who have CNS disease at presentation should receive weekly doses - see page 24. Do not schedule vincristine on the same day as the intrathecal methotrexate. There is evidence that a traumatic tap *with blasts* or CNS2 (atraumatic with < 5 blasts/microlitre) tap at diagnosis is associated with a higher risk of CNS relapse, possibly because of poor penetration of MTX into the meningeal space at subsequent treatments due to a small extra-dural haematoma at the LP site. Therefore, patients with > 10 red cells/microlitre *and blasts* in their CSF or CNS2 tap at diagnosis should receive weekly IT MTX for a total of 4 intra-theicals during weeks 1-4 of induction. *Traumatic tap without blasts in the CSF should receive standard IT therapy.*
- h) **6-mercaptopurine:** 60 mg/m²/day orally starting on day 29 (beginning week 5) (if neutrophils > 0.75 and platelets > 75) and continuing for five weeks in total (to end of Standard BFM consolidation, week 10). Adjust the dose of 6-MP to attain a weekly cumulative dose of as near 420mg/m² as possible. Doses should be taken at least one hour after the evening meal without milk products. Do not increase dosage for ANC > 2.0.

- i) **Bone marrow:** Check marrow status on days 8, and 28. Send Day 28 Marrow for MRD

Patients with M3 marrow at day 8 (see definitions), will continue on Regimen B and will not transfer to regimen C. MRD High Risk patients (based on day 28 marrow) are randomised to either continue on regimen B or switch to regimen C (starting day 35). No MRD risk stratification will be made on the day 8 marrow in the adolescent patient group.

- j) **Co-trimoxazole (trimethoprim and sulphamethoxazole)**

This drug is given as PCP prophylaxis orally on 2 consecutive days throughout treatment **from the start of induction**. The dose is tabulated below. Please ensure separation of the days on which oral Methotrexate and Cotrimoxazole doses are given during maintenance courses.

If an adolescent remains cytopenic after being off chemotherapy for three weeks or more, then stop the co-trimoxazole. Reintroduce co-trimoxazole once both thiopurine and methotrexate are back at standard dose. If cytopenias recur once the co-trimoxazole is reintroduced, then it should be stopped for at least two months and an alternative form of prophylaxis used instead (see below). The alternative drug should then be continued for the duration of the antileukaemic therapy

The maintenance of adequate doses of thiopurine and methotrexate should take precedence over continuing co-trimoxazole. If co-trimoxazole is stopped, however, it must be remembered that the individual is at increased risk of PCP. Nebulised pentamidine or oral Dapsone are alternative drugs.

Surface area	Co-trimoxazole	Trimethoprim	Sulphamethoxazole
0.5-0.75 m ²	240 mg bd	40 mg bd	200 mg bd
0.76-1.0 m ²	360 mg bd	60 mg bd	300 mg bd
over 1.0 m ²	480 mg bd	80 mg bd	400 mg bd

See also appendix D for details of alternative PCP prophylaxis regimens.

Permitted dose modifications for toxicity – see Appendix E:

Note: Patient may not be eligible for the MRD randomisation if induction therapy is modified. Please discuss with co-ordinators.

Following induction and MRD risk stratification, all young adults will follow either schedule B or schedule C as described in the UKALL2003 main protocol. To be eligible to enter standard BFM consolidation, patients must be in remission, and have an ANC $>0.75 \times 10^9/L$ and platelets of $>75 \times 10^9/L$. If the blood count has not recovered and marrow is hypocellular M1, delay the start of consolidation one week and repeat the bone marrow to confirm M1 status. Patients with CNS disease at diagnosis will receive cranial irradiation during consolidation starting at day 36.

17. UKALL 2003 REGIMEN C – YOUNG ADULTS**Eligibility.**

To be eligible for regimen C, patients must either

- a) Have MRD positive D28 bone marrow and be randomised to regimen C, or
- b) Have unfavourable cytogenetics, or
- c) Have M2 morphology on the day 28 marrow
- d) Have persistent testicular enlargement at day 28

Patients switching from regimen B because of high risk cytogenetics continue with a four drug induction schedule and then move onto augmented BFM consolidation. **Patients switching from regimen B at day 35** must be MRD High Risk at day 28 and be randomised to regimen C or have M2 morphology at day 28 or have persistent testicular enlargement at day 28.

High-risk cytogenetic features that mandate a switch to regimen C are hypodiploidy (≤ 44 chromosomes); BCR-ABL gene rearrangement; AML1 amplification or MLL gene rearrangement. No other cytogenetic features are eligible.

Patients with M2 marrows at day 28 (blasts 5-25%) should continue with regimen C (augmented BFM consolidation) and should only be taken off protocol if they are not in remission at the end of consolidation.

Patients with testicular disease at presentation treated on Regimen B with persistent enlargement at day 28 should be transferred to regimen C. Testicular radiotherapy should only be given to those adolescents who still have a clinically enlarged testis at week 8. In these patients, 24 Gy should be given in 12 fractions between weeks 9 to 12 while continuing with other treatment. (See Appendix L)

Regimen C should be followed from the main UKALL2003 protocol

To be printed on local centre's headed note paper

**Study MRC UKALL 2003
Patient information sheet for older children and young adults**

Dear Patient

You are being invited to take part in a clinical trial called UKALL 2003 (UK Acute Lymphoblastic Leukaemia Research Trial 2003) conducted by the Medical Research Council.

Before you decide, 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 others if you wish. Ask us if there is anything that is not clear or if you would like more information.

What is a clinical trial and why do we need them?

You have been diagnosed with Acute Lymphoblastic Leukaemia - the commonest form of cancer in children and young people. It is a rapidly progressing cancer of the blood which affects those white blood cells known as lymphocytes.

The treatment for leukaemia in children and young people has improved steadily over the last 20 years, so that now the disease can be controlled and indeed the majority of our patients are now cured. This has enabled hospital teams to now focus on the side effects of the treatments with the aim of preventing them.

Also, recent research suggests that young adults up to the age of 25 years have a better chance of cure if they receive the treatment that is used for children rather than that used for older adults. Hence, we modified the entry criteria in 2007 to allow young adults up to the age of 25 years to enter into this trial.

Different treatments have been developed over many years and their success compared to find out which combinations and sequences of drugs are the most effective with the least harmful side-effects. The methods by which these treatments are compared are called clinical trials and they are important in making it possible to improve the treatment of children and young people with leukaemia.

To make the results achieved from such trials completely fair and reliable, the groups of patients receiving the different treatments must be as alike as possible. This goal is achieved by the treatment for each patient being chosen at random by a computer, from a choice of two or more treatments. The process is called a "randomised clinical trial" and means that a patient has a 50/50 chance of being chosen at random for a treatment, like drawing a name from a hat. Neither you nor the study doctor will be able to choose which programme of treatment you receive. Further details of the randomised and non-randomised parts of the trial are provided below starting with a description of the standard treatment of ALL.

You will be asked for your consent to taking part in the non-randomised parts of this trial within a few days after the diagnosis of ALL has been confirmed. After around 5 weeks of treatment, when you have had the opportunity to read this information sheet and discuss its contents with your doctor, you will be asked if you agree to taking part in the randomised parts of the trial.

What is the standard treatment for ALL at the moment?

The current standard therapy for children with Acute Lymphoblastic Leukaemia consists of drugs called chemotherapy given according to a treatment programme or 'protocol'. These drugs are given by mouth, as a jab (intra-muscular), directly into the blood stream (intravenous) or into the spinal fluid (intra-thecal) by a spinal tap (lumbar puncture). They are mostly given as out-patient therapy but there will be periods when you need to stay overnight in hospital, especially when poorly.

This chemotherapy 'protocol' is made up of four parts:

1. The aim of the first few weeks of treatment is to return the blood and bone marrow to normal function – we call this achieving a remission. This first part of the programme is called 'remission induction.'
2. The following weeks of treatment are given to maintaining the remission and also to prevent the spread of leukaemia cells into the brain and spinal cord. This second part of the programme is called 'consolidation and central nervous system treatment.'
3. A few months after diagnosis we must try to reduce the amount of leukaemia to a minimum. This third part of the programme uses powerful drugs which will affect your bone marrow and its' ability to produce blood cells. This leads to a fall in your blood count and associated problems such as infection and bleeding. The more intensive the treatment, the more likely it is that you will experience these serious side effects. The standard treatment protocol involves two such courses given at roughly 5 and 9 months from diagnosis for patients in the MRD high risk group and one course for those in the MRD low risk group (see below). This phase is called 'Delayed Intensification therapy.'
4. The final part of the treatment programme involves continuing or "maintenance" outpatient treatment for another 18 months or so for girls and 26 months for boys. This makes a total of two to three years for the whole programme.

This core of treatment has evolved over the course of many randomised clinical trials in the past. Possible future modifications to the plan can only be investigated by means of further trials. In Britain the trials for children and young people with Acute Lymphoblastic Leukaemia (ALL) are carried out by a team of specialist doctors from across the country, under the co-ordination of the Medical Research Council.

What are the side-effects of chemotherapy?

Chemotherapy has a lot of side effects. Some are more serious than others; these can include serious infection and bleeding. You may also find that your hair falls out, but it will grow back once your treatment is finished and you may feel and be sick when you are having your chemotherapy. The chemotherapy can also cause problems that last longer and these can include damage to your heart, problems with your growth and in rare cases you could get another type of cancer. Your doctor will give more information about these side effects to you and your family. The *stronger* the treatment, the more side effects you may have, that is why we want to try and give less of the strong treatment if possible. Chemotherapy can cause damage to the developing fetus and, therefore, girls who have achieved puberty should avoid getting pregnant by taking appropriate precautions.

What questions is UKALL 2003 asking?

UKALL 2003, the present trial, will examine whether we can more accurately predict the chance of cure in each patient with ALL and tailor make their treatment using a new monitoring technique called Minimal Residual Disease (MRD) assessment.

At the moment, we monitor how well a patient is responding to treatment by counting the number of leukaemic cells in their bone marrow using an ordinary microscope, and remission (a good response) is defined as less than 5% of leukaemia in the bone marrow.

Recent studies using more sensitive genetic technology have shown that the amount of residual leukaemia in patients whose leukaemia appears to be in remission varies considerably and the exact amount can accurately predict the chance of cure. There are a variety of such techniques to detect and count very little amounts of leukaemia, and they are called Minimal Residual Disease (MRD) assessment.

We wish to use very sensitive genetic technology for monitoring MRD. This simply means that we will use a different piece of machinery to measure the levels of residual leukaemia in your bone marrow.

At the outset, of the trial the following questions were being asked in UKALL 2003:

1. Can patients with very little leukaemia after eleven weeks of treatment (MRD- Low Risk group) have their treatment reduced without increasing the risk of leukaemia recurrence? This would mean they will have a reduced risk of damaging side effects. These patients have a more than 95% chance of cure with the current protocol containing two intensification courses. We have recruited sufficient patients to this part of the trial and it is now closed to further recruitment. Results from other trials indicate that a single course of intensification gives as good a chance of cure for MRD low risk patients as two courses. Therefore, we now give only one course of intensification to MRD low risk patients
2. Can patients with a relatively high level of leukaemia after one month of treatment (MRD-High Risk group) improve their chance of cure by having the intensity of their treatment increased? These patients have a less than 70% chance of cure with current treatment. We have still to recruit sufficient patients to this part of the trial and, if your child is in the MRD high risk group, we will seek your permission for him/her to be entered into the high risk randomisation (see below).
3. What is the effect of treatment on children's quality of life?
4. What is the best way of using an important drug in the treatment protocol called Asparaginase? This will involve taking some extra blood samples from you after you have had Asparaginase.

Why have I been chosen?

Over the next 6 years, parents of all new cases of childhood Acute Lymphoblastic Leukaemia in the UK will be offered the opportunity to enter into this study. We have already recruited 800 patients to the study and hope to recruit a further 1500 patients nationally over the next 4 years.

How will treatment be decided for me if I agree to take part?

The first month of your treatment will be based on standard criteria of age, white cell count and response to the first two weeks of treatment. Following this, we will check the one month bone marrow for residual leukaemia cells and the treatment will be chosen according to the results.

If you have very little leukaemia after one month of treatment (MRD low risk) the treatment will be with one course of intensification.

If however, you have a relatively high level of leukaemia after one month of treatment (MRD high risk), the treatment choice will be made between intermediate and high levels of drug intensity.

The exact details of the treatment will be provided to you once we know your response to the first month of treatment.

What are the additional procedures?

At the moment we have to collect some of your bone marrow for testing at diagnosis and again after one month of treatment. We normally collect around 5 mls (one teaspoon) of bone marrow for routine tests. During this trial we will collect an extra 10 mls (2 teaspoons) of your bone marrow at diagnosis, after one month of treatment and again after eleven weeks to do the MRD tests. Very occasionally, we may need to do a repeat bone marrow at diagnosis if enough samples could not be obtained for the MRD tests to be performed.

Collecting the additional amount will not harm you. Any sample left-over after the MRD tests will be stored for use in future ethically approved scientific studies or for double-checking the MRD test result in case of future doubt about its accuracy.

In order to determine any effects of treatment on the patient's quality of life, you will be asked to complete questionnaires on five occasions (during weeks 1, 4, at the start of maintenance therapy, at 18 months and at the end of treatment). The questions will take about 20 minutes to complete on each occasion. It will ask about different aspects of life (e.g. activities, feelings, different symptoms) and how you feel the treatment affects your lives as a whole.

Around one table spoon of blood will be collected after you have received Asparaginase during induction and intensification courses. This will be analysed in a specialist laboratory in Manchester to find out if the amount and frequency with which we use this drug currently is optimal.

What are the possible advantages and disadvantages of taking part in this study?

The **possible** benefit of improved cure for MRD-positive patients selected to receive the most intensive treatment programme, is balanced by the **likely** increased toxicity of this regimen.

On balance, the risks and benefits of the non-standard treatment options appear equal. However, we do not know this for certain or there would be no need to do a study.

What are the possible benefits of taking part?

There may be no direct benefit to you from entering the study. As stated above, the non-standard treatment options may have a benefit, but we will not know this until the results of this study are available. The information we get from this study may improve treatment of future children with ALL.

You may be withdrawn from this trial if results on your bone marrow suggest that another treatment regimen may be more appropriate for you. If you are withdrawn from the study, you will be given the choice of whether the data collected should also be withdrawn or kept for future study.

What if new information becomes available?

Sometimes during the course of a clinical trial new information becomes available about the treatment that is being studied. If this happens, we will tell you about it and discuss whether you should be withdrawn from the study or continue in it. If we were to decide that you should remain in the study, you may be asked to sign an updated consent form

What happens when the research study stops?

When we have an answer to the questions in this trial, all existing and new patients will be transferred on to the most effective and least toxic treatment in the trial.

What will happen to the results of the research study?

The results of this study will be published in reputable medical scientific journal. You will not be identified in the publications. A copy of the published results can be obtained from the doctor named at the end of this information sheet.

Who will have access to information about me?

All patient information will be stored in a database at Oxford. Only the doctors and technicians involved in the running of this trial will have access to it. Your GP will be informed with your consent about your participation in the study. The Office for National Statistics will also be informed about your participation in the study

Will any additional information be collected?

We are interested in learning about the long term success of your treatment and any ill effects from it. As you may be aware, the Office for National Statistics collects data on all births and deaths in the UK and this is one important source from which we gather information about the long term health of our patients. This is done through a process called “flagging” in which the Office for National Statistics will help us keep in touch with your progress by letting us know the Health Authority where you are registered with a GP.

What happens if I don't want to be in this trial?

If you do not want to be entered into the clinical trial, we will continue to treat you to the best of our ability, using the best standard treatment. It is entirely your choice whether or not you wish to take part in this study. If you decide to take part you are still free to withdraw at any time and without giving a reason.

What if I suffer injury due to this study?

If you are harmed by your participation in this study, there are no *special* compensation arrangements. If harmed due to someone's negligence, then you may have grounds for legal action. Regardless of this, if you have *any* cause to complain about the treatment whilst taking part in the trial, the normal complaints mechanisms available to anyone receiving care in the National Health Service are available to you and are not compromised in any way because you have taken part in a clinical research study.

Who is organising and funding the research?

The Leukaemia Research Fund, Medical Research Council and Cancer Research UK are all supporting and funding this trial. The hospital in which you are being treated is being paid a small sum to provide support for collecting the data for this study.

Who has reviewed the study?

National and international experts in the treatment of childhood leukaemia have scientifically reviewed the study. The Multi-Centre Research Ethics Committee for Scotland and the Ethics Committee in your local area has also reviewed the study from an ethics standpoint

Contacts for further information?

If you require any further information regarding the study at any stage, or in the event of an emergency please contact the following doctor or Nurse, who are the local investigators for this study:

Dr:..... Tel:.....

or

Nurse:..... Tel:.....

What if I have any other concerns or wish to seek independent advice about the study?

If you have any complaints about the way the investigator has carried the study, or wish independent advice about the study you should contact[Local patient representative].....

Thank you for taking the time to read this information sheet.

Dr:..... Tel:.....

or

Nurse:..... Tel:.....

You will be given a copy of this information sheet and a signed consent form to keep.

To be printed on local centre's headed note paper

Name:
Date of Birth:
Hospital Number:
Centre:
Trial Number:

PATIENT CONSENT FORM (For older children and those > 16 years)
For MRC UKALL 2003

Name of Researcher:
The patient should complete this sheet him/herself. (Please circle one)

At diagnosis

- 1. I confirm that I have read and understood the information contained in the information sheet version 7 dated August 2009 Yes/No
- 2. I have had the opportunity to ask questions and had satisfactory answers to them Yes/No
- 3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. Yes/No

Information from your medical notes will be passed to the UKCCSG (United Kingdom Childhood Cancer Study Group), the CCRG (Childhood Cancer Registry Group), the local Registry, the Regional Cancer Registry, the LRF/UKCCG Cytogenetics database and appropriate central trials offices, but all personal details will be treated with the strictest security and confidentiality.

- 4. Do you give permission for your information to be collected, stored, passed on for national registration and used for research in this centre? Yes/No
- 5. Do you give permission for your left-over samples to be stored and used for future ethically approved studies Yes/No
- 6. Do you give permission for us to inform your GP about this trial? Yes/No
- 7. Do you agree to taking part in UKALL 2003? Yes/No
- 8. Do you agree to take part in the Asparaginase study? Yes/No
- 9. Do you agree to complete the Quality of Life questionnaires? Yes/No
- 10. Information about you will be gathered from the Office for National Statistics through the flagging system. Do you agree to the Office for National Statistics providing us with information about you for long term follow-up purposes through the flagging system? Yes/No

PATIENT

Name (block letters)

SignedDate

DOCTOR/RESEARCH NURSE TAKING CONSENT (please delete)

Name (block letters)

Signed Date

At day 35 – Consent for Randomisation

- 11. Do you agree to take part in the trial randomisations as explained in the information sheet? Yes/No

PATIENT

Name (block letters)

SignedDate

DOCTOR/RESEARCH NURSE TAKING CONSENT (please delete)

Name (block letters)

Signed Date