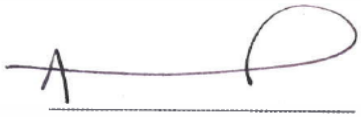
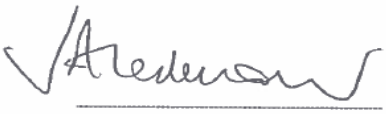
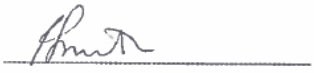
UKALL60+

(HOVON117 ALL)

A Phase 2 study for older adults with Acute Lymphoblastic Leukaemia

Trial Sponsor:	University College London
Trial Sponsor reference:	11/0532
Trial funder(s):	Cancer Research UK
Funder(s) reference:	CR UK/A13920
Clinicaltrials.gov no:	NCT01616238
REC no:	12/LO/1319
Protocol version no:	3.0
Protocol version date:	21.05.2015

Protocol version 3.0 21.05.2015 Authorisation signatures

Name & Role:	Signature:	Date authorised:
Chief Investigator: Dr Adele Fielding Senior Lecturer in Haematology, University College London		21/5/15
For the Sponsor: Professor Jonathan Ledermann Director, UCL CTC		21/5/15
Paul Smith Tumour Group Lead, Haematology & Brain Trials Group		21/5/15.

Please note: This study protocol must not be applied to patients treated outside the UKALL60+ study. UCL CTC can only ensure that approved study investigators are provided with amendments to the protocol.

Coordinating Centre:

For general queries, supply of study documentation and central data management please contact:

UKALL60+ Trial Coordinator
Cancer Research UK & UCL Cancer Trials Centre
90 Tottenham Court Road
London, W1T 4TJ
United Kingdom

Tel: +44 (0) 20 7679 9860
Fax: +44 (0) 20 7679 9861
09:00 to 17:00 (UK time) Monday to Friday, excluding Bank Holidays

Email: ctc.ukall60@ucl.ac.uk

Website: http://www.ctc.ucl.ac.uk/

Chief Investigator: Dr Adele K Fielding
Address: Reader in Haematology
UCL Cancer Institute

Paul O'Gorman Building
University College London
72 Huntley Street
London UK
WC1E 6DD
Phone number: 0207 679 6863
Fax number: 0207 679 6817
Email address: a.fielding@ucl.ac.uk

Trial Management Group (TMG):

Member	Job title	Site location
Bella Patel	Senior Clinical Lecturer	Barts Health NHS Trust
David Marks	Professor of Haematology	University Hospitals Bristol NHS Foundation Trust
Anthony Moorman	Professor of Genetic Epidemiology	Northern Institute for Cancer Research, Newcastle University
Clare Rowntree	Consultant Haematologist	University Hospital of Wales
John Snowden	Consultant Haematologist	Royal Hallamshire Hospital
Andrew McMillan	Consultant Haematologist	Nottingham City Hospital
Nick Morley	Consultant Haematologist	Royal Hallamshire Hospital
Anita Rijneveld	Consultant Haematologist	HOVON (Haemato-oncology Foundation for Adults in the Netherlands)
Anna Osadcow	Pharmacist	Royal Free Hospital, London
Amy Kirkwood	Statistician	UCL CTC
Paul Smith	Tumour Group Lead	UCL CTC
Pip Patrick	Senior Trial Coordinator	UCL CTC
Ellice Marwood	Trial Coordinator	UCL CTC
Ghada Zakout	Clinical Research Fellow	UCL School of Medicine

Table of Contents

1 PROTOCOL SUMMARY 7

1.1 SUMMARY OF STUDY DESIGN 7
1.2 STUDY SCHEMA 10

2 INTRODUCTION 11

2.1 BACKGROUND AND JUSTIFICATION 11
2.2 PROPOSED STUDY 14
2.3 STUDY ACTIVATION 15

3 SELECTION OF SITES/SITE INVESTIGATORS 16

3.1 SITE SELECTION 16
3.1.1 Selection of Principal Investigator and other investigators at sites 16
3.1.2 Training requirements for site staff 16
3.2 SITE INITIATION AND ACTIVATION 16
3.2.1 Site initiation 16
3.2.2 Required documentation 16
3.2.3 Site activation letter 17

4 INFORMED CONSENT 18

5 SELECTION OF PATIENTS 19

5.1 PRE-REGISTRATION EVALUATION 19
5.2 SCREENING LOG 20
5.3 PATIENT ELIGIBILITY 20
5.3.1 Patient Inclusion Criteria 20
5.3.2 Exclusion Criteria 20
5.3.3 Pregnancy and Birth Control for female patients 20
5.3.4 Contraceptive Advice for male patients and their female partners 20
5.3.5 Long term infertility 21

6 REGISTRATION PROCEDURES 22

6.1 REGISTRATION 22
6.2 STUDY DRUG SUPPLY 23

7 STUDY TREATMENT 24

7.1 TREATMENT SUMMARY 24
7.1.1 Study Pathways 24
7.1.2 Proceeding through study treatment 24
7.2 SUMMARY TREATMENT SCHEDULES 25
7.2.1 Philadelphia +ve patients (Pathway A) 26
7.2.2 Intensive pathway in Philadelphia –ve patients (Pathway B) 30
7.2.3 Intensive+ pathway in Philadelphia –ve patients (Pathway C) 35
7.2.4 Non-intensive pathway in Philadelphia –ve patients (Pathway D) 41
7.2.5 Registration only (Pathway E) 45
7.3 STUDY TREATMENT DETAILS 46
7.3.1 Pharmacy responsibilities 46
7.3.2 Dose modifications 46
7.4 SUPPORT MEDICATION 46
7.5 CLINICAL MANAGEMENT AFTER TREATMENT DISCONTINUATION 47

8 ASSESSMENTS 48

8.1 PRE-TREATMENT ASSESSMENTS 48
8.2 ASSESSMENTS DURING TREATMENT (PATHWAYS A, B, C & D) 48
8.2.1 At the end of Phase 1 & Phase 2 Induction 48

8.2.2 At the end of intensification (Patients in the Intensive treatment pathway (Pathway B) ONLY) 48
8.2.3 At the end of Consolidation 1 49
8.2.4 At the end of Consolidation 2 and 3 (if applicable) 49
8.3 ASSESSMENTS DURING MAINTENANCE 49
8.3.1 Before starting maintenance 49
8.3.2 6-12 Weeks after starting maintenance 49
8.3.3 Every 3 months during maintenance 50
8.3.4 End of maintenance 50
8.4 PATIENTS NOT IN COMPLETE REMISSION AND DISCONTINUING WITH STUDY TREATMENT 50
8.5 PATIENTS ASSIGNED TO REGISTRATION ONLY (PATHWAY E) 50
8.6 ASSESSMENTS DURING FOLLOW UP 51

9 DATA MANAGEMENT GUIDELINES 52

9.1 COMPLETING CASE REPORT FORMS 52
9.2 CORRECTIONS TO CRFS 52
9.3 MISSING DATA 52
9.4 TIMELINES FOR DATA RETURN 52
9.5 DATA QUERIES 52

10 SAFETY REPORTING 53

10.1 DEFINITIONS OF ADVERSE EVENTS 53
10.2 REPORTING PROCEDURES 53
10.2.1 All Adverse Events (AEs) 53
10.2.2 Serious Adverse Events (SAEs) 55
10.2.3 Urgent Events 57
10.3 RELATED AND UNEXPECTED SERIOUS ADVERSE EVENTS 57
10.4 SAFETY MONITORING 57
10.5 PREGNANCY 58

11 INCIDENT REPORTING AND SERIOUS BREACHES 59

11.1 INCIDENT REPORTING 59
11.2 SERIOUS BREACHES 59

12 STUDY MONITORING AND OVERSIGHT 60

12.1 CENTRAL MONITORING 60
12.2 'FOR CAUSE' ON-SITE MONITORING 60
12.3 OVERSIGHT COMMITTEES 61
12.3.1 Trial Management Group (TMG) 61
12.3.2 Trial Steering Committee (TSC) 61
12.3.3 Independent Data Monitoring Committee (IDMC) 61
12.3.4 Role of UCL CTC 61

13 WITHDRAWAL OF PATIENTS 62

14 STUDY CLOSURE 63

14.1 END OF STUDY 63
14.2 ARCHIVING OF STUDY DOCUMENTATION 63
14.3 EARLY DISCONTINUATION OF STUDY 63
14.4 WITHDRAWAL FROM STUDY PARTICIPATION BY A SITE 63

15 STATISTICS 64

15.1 SAMPLE SIZE CALCULATION 64
15.2 POPULATION FOR ANALYSIS 64
15.3 ANALYSIS OF THE PRIMARY ENDPOINT 64
15.4 ANALYSIS OF SECONDARY ENDPOINTS 64
15.4.1 Efficacy (secondary) 64
15.4.2 Safety 65
15.4.3 Health related Quality of Life 65
15.5 INTERIM ANALYSES 65

16 ETHICAL APPROVALS 66
16.1 ETHICAL APPROVAL 66
16.2 SITE APPROVALS 66
16.3 PROTOCOL AMENDMENTS 66
16.4 PATIENT CONFIDENTIALITY & DATA PROTECTION 67
17 SPONSORSHIP AND INDEMNITY 68
17.1 SPONSOR DETAILS 68
17.2 INDEMNITY 68
18 FUNDING 69
19 PUBLICATION POLICY 70
20 TRANSLATIONAL RESEARCH 71
20.1 MRD SAMPLES 71
20.2 CONSTITUTIONAL DNA SAMPLES 73
20.3 LEUKAEMIA RESEARCH CYTOGENETICS GROUP (LRCG) 74
21 REFERENCES 75
APPENDIX 1: ABBREVIATIONS 78
APPENDIX 2: CRITERIA FOR ASSESSING RESPONSE 79
APPENDIX 3: ECOG AND KARNOFSKY SCORING SYSTEMS 80
APPENDIX 4: CHARLSON INDEX 81
APPENDIX 5: CHEMOTHERAPY RISK ASSESSMENT SCALE FOR HIGH RISK PATIENTS (CRASH) 82
APPENDIX 6: FACIT- FATIGUE SCALE (VERSION 4) 84
APPENDIX 7: FACT-LEU (VERSION 4) 85
APPENDIX 8: EORTC QLQ C30 88
APPENDIX 10: EXPECTED ADVERSE EVENTS 92
APPENDIX 11: QUICK REFERENCE GUIDES TO PATIENT VISITS 94
APPENDIX 12: DOSE MODIFICATIONS 98
APPENDIX 13: PROTOCOL VERSION HISTORY 103
APPENDIX 14: COUNTRY-SPECIFIC APPENDIX: NETHERLANDS 108

1 Protocol Summary

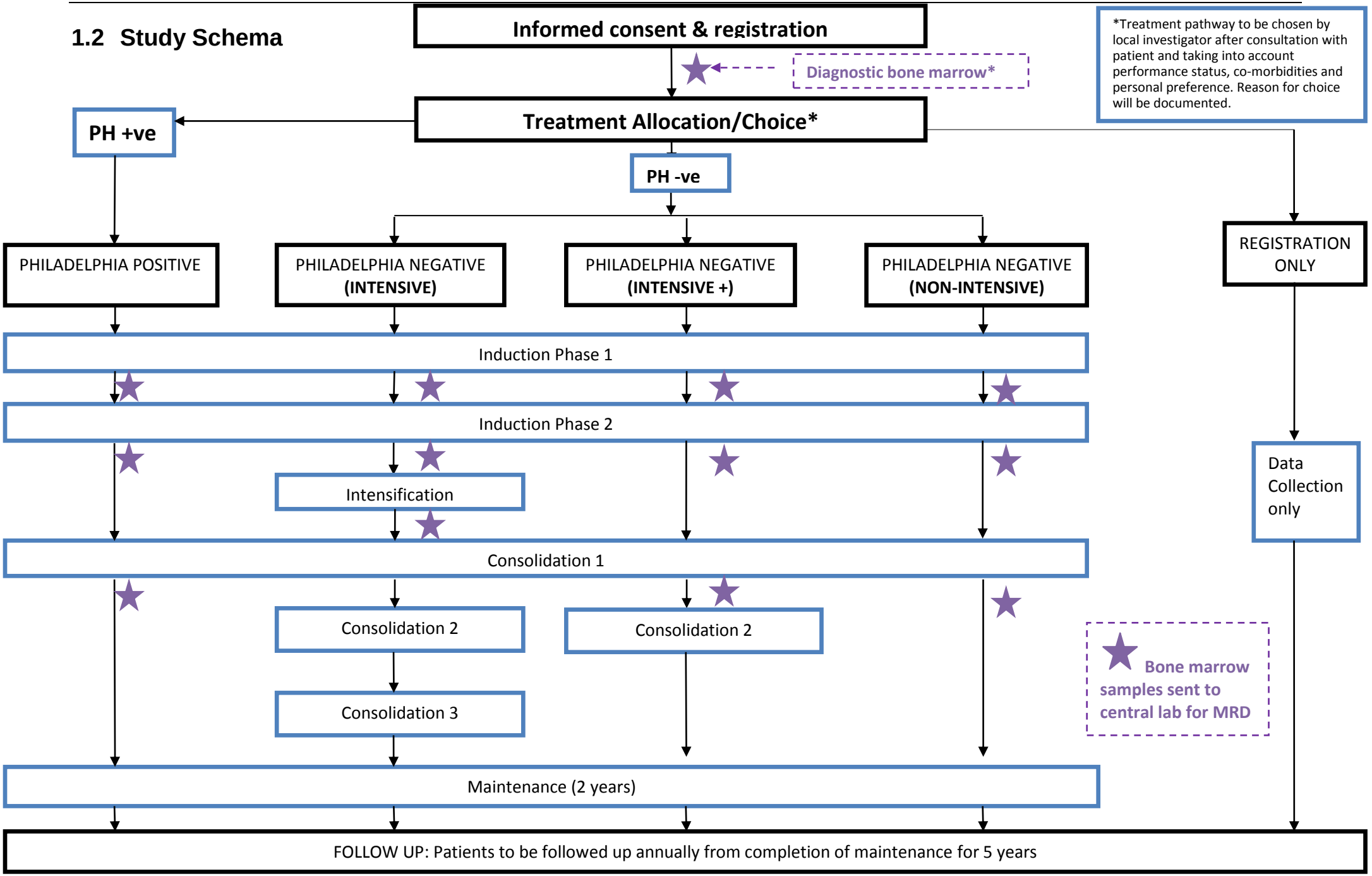
1.1 Summary of Study Design

Title:	A Phase 2 study for older adults with Acute Lymphoblastic Leukaemia
Short Title/acronym:	UKALL60+
REC no:	12/LO/1319
Sponsor name & reference:	University College London – 11/0532
Funder name & reference:	Cancer Research UK - CR UK/A13920
Clinicaltrials.gov no:	NCT01616238
Design:	Phase 2 multi-pathway non-randomised observational study
Overall aim:	To document the safety, tolerability and feasibility of therapeutic protocols currently in standard use for patients ≥ 60 years old with de novo Acute Lymphoblastic Leukaemia (ALL).
Primary endpoints:	• Complete remission rate after 2 phases of induction
Secondary endpoints:	• EFS at 1 year • Treatment related mortality • Complete remission rate after 1 phase of induction • Prognostic significance of molecularly determined minimal residual disease (MRD) at various time-points during therapy with respect to relapse occurrence. • Overall Survival at 1 year • Tolerability of treatment as determined by occurrence of key adverse effects • Duration of in-patient hospitalisation • Relationship between performance status/co-morbidity and treatment option chosen • Quality of life aspects assessed at diagnosis/baseline at various time points.
Target accrual:	148. (Not including the registration only pathway) It is anticipated that the UK will recruit approximately 100 patients and international collaborators approximately 48.
Inclusion & exclusion criteria:	**Inclusion Criteria:** • Age ≥ 60 with Acute Lymphoblastic Leukaemia (ALL) **OR** ≥ 55 with Acute Lymphoblastic Leukaemia (ALL) unsuitable for the UKALL14 or HOVON 100 trial • Newly diagnosed, previously untreated ALL (a steroid pre-phase of 5-7 days may be given before study registration) • Written informed consent **Exclusion Criteria** • Known HIV infection • Blast transformation of CML

	• Mature B-cell leukemia i.e. Burkitt's disease t(8,14)(q24;q32) and variant c-myc translocations e.g. t(2;8)(p12;q24),t(8;22)(q24;q11) • Women who are pregnant or lactating
Planned number of sites:	UK (50+) Netherlands/Belgium (10+) Denmark (6+)
Target countries:	UK, Netherlands, Belgium, Denmark & Ireland
Treatment summary:	**Philadelphia +ve patients** *(Pathway A)* • Phase 1 Induction • Phase 2 Induction • Consolidation 1 • Maintenance (24 months) **Philadelphia –ve patients** *Intensive pathway (Pathway B)* • Phase 1 Induction • Phase 2 Induction • Intensification • Consolidation 1-3 • Maintenance (24 months) *Intensive+ pathway (Pathway C)* • Phase 1 Induction • Phase 2 Induction • Consolidation 1-2 • Maintenance (24 months) *Non-intensive pathway (Pathway D)* • Phase 1 Induction • Phase 2 Induction • Consolidation 1 • Maintenance (24 months) **Registration only** *(Pathway E)* • Treatment as per local protocol • Data collection only
Anticipated duration of recruitment:	5 years
Duration of patient follow up:	Patients will be followed up annually for five years
Definition of end of study:	The end of study will be defined as 1 year after the date the last patient completes all study treatment (including 2 years of maintenance).
Translational component:	• Rate of MRD positivity at baseline and 3 time-points during treatment thus identifying the number and proportion of patients likely to be identified as high risk. • Flow cytometric determination of antigen expression at diagnosis. • Genomic profiling in order to discover and characterise novel prognostic markers and to identify known sub-microscopic copy number alterations (CNA) beyond the resolution of standard diagnostic testing (i.e. cytogenetics and

	FISH). • Analysis of DNA from non-leukaemic cells for genetic changes that may be associated and/or linked with ALL in adults.
Other related research:	Quality of Life will be assessed at various time points during the study using the following questionnaires: EORTC QLQ–C 30 EORTC CIPN FACT-Leu FACIT-FATIGUE

1.2 Study Schema



2 Introduction

2.1 Background and justification

Large clinical trials have undoubtedly advanced the overall management of adult lymphoblastic leukaemia (ALL) and US SEER registry data (Pulte *et al*, 2009) from 5 year periods 20 years apart, demonstrate considerable improvements in outcome for all age groups except in the over 60 year old group. Large studies have typically not included patients over the age of 65 and this may be one of the reasons for patients of this age being the only group in whom survival has not improved over time. This leads to a particular unmet need, since the median age of adults with ALL is above 60 years. The age specific annual incidence of ALL in the UK rises from 0.45/100 000 in adults aged 35-39 to 0.78/100 000 in patients aged 60–64 to 1.2/100 000 cases in the >85 year old group (Moorman *et al*, 2010). The predicted rise in the proportion of people aged over 65 in the UK from 16% of the population in 2009 to 23% by 2034 (Office of National Statistics), will result in a national increase in the number of older patients with ALL in the future.

There is no agreed standard regimen for the treatment of older patients with ALL worldwide, however a number of regimens have been developed and are in common use. This study will focus on four ALL treatments currently in common use in the UK and Netherlands. For patients up to the age of 65 years entry onto the national study UKALL12 was possible and entry to UKALL14 is still a potential option. However, the intensity of UKALL12, UKALL14 and similar such protocols leads to the selection of only “fitter” older individuals. Despite this, data from the previous trial UKALL12 shows that older patients fared extremely poorly with less than 15% 5 year OS (Rowe *et al*, 2005). For the older patient with ALL, deemed unsuitable for trial entry either because of eligibility criteria or “fitness”, treatment is scheduled only according to prevailing local practice. It is not known whether treatment is with “curative“ or “palliative” intent. It is not known whether long term disease-free survival equating to cure is a realistic goal. Moreover, there are no data investigating Quality of Life (QoL) in elderly patients with ALL and its relationship with the intensity of treatment regimens and response.

The NCRI Adult ALL sub-group propose to collaborate with the Dutch/Belgian group HOVON to carry out a prospective, non-randomised multi-pathway observational study (including a choice of pathway intensity) to investigate the safety, tolerability and feasibility of a standardised therapy protocol for patients ≥ 60 years old with de novo ALL. The overall aim is to document the characteristics of these treatments, in order to potentially inform trials of novel therapies will be based in future. The design of the study will enable collection of a comprehensive dataset regarding the clinical outcome, Complete Response Rate (CR) and Minimal Residual Disease (MRD) response rates in a previously completely uncharacterised population, thus providing the essential platform for designing future randomised advanced phase studies in which new therapeutic approaches and novel therapies can be prospectively investigated.

The study will:

(a) establish baseline expectations for Event Free Survival (EFS), Overall Survival (OS), MRD responses and quality of life measures for older patients of all ages and pre-morbid states;
(b) disclose how best to use knowledge of pre-morbid characteristics to apply the appropriate intensity of therapy in order to balance the best disease related outcomes against quality of life;
(c) establish national standards of care for this patient group;
(d) provide the essential platform for careful design of future randomised advanced phase studies of new therapeutic approaches and agents.

Patients with Philadelphia chromosome negative ALL will receive one of three treatment pathways:

(1) intensive,

(2) augmented intensive (defined at Intensive+) or
(3) non-intensive, assigned by performance status scoring at presentation.

For patients with Philadelphia chromosome positive disease, the tyrosine kinase inhibitor imatinib will be incorporated into the backbone combination chemotherapy (pathway A).

For patients perceived to have good performance status and who are willing to undergo intensive in patient therapy during induction, local PIs and patients will be able to elect between an intensive (pathway B) and augmented intensive treatment (pathway C; defined as Intensive+, and based on the HOVON71 regimen). In the case of poor performance status and/or patient choice for a less intensive approach, a non-intensive option (pathway D) may be selected.

Although we will require fastidious documentation of baseline status, we will not mandate how this information should be used to select the treatment pathway. Local PIs, together with their patient, will elect between pathways, recapitulating current practice, except that the pathways will be standardised and followed by comprehensive data collection. We aim to investigate the relationship between performance status and choice of treatment to help us decide in future RCTs how we should mandate these assignments.

A registration only option (pathway E) will be permitted for eligible patients not wishing to enrol on the main study, so that basic data regarding treatment and outcome can be collected.

Why is a study needed now?

There is a high level interest within the UK and elsewhere in Europe in defining a uniform approach to older patients with ALL.

Table 1 - English Cancer Registry data from 1996 to 2007 showing the number of patients aged 60+ with newly diagnosed ALL

Year	Patient incidence	Year	Patient incidence
1996	89	2002	106
1997	107	2003	95
1998	84	2004	108
1999	95	2005	108
2000	101	2006	94
2001	104	**TOTAL**	**1091**
Average per annum = 99 patients			

The optimal management of older patients with ALL, a subgroup underrepresented in clinical trials, remains undefined. Data that are available indicate a universally poor outcome for older patients when compared to younger adults or study groups as a whole (Rowe *et al*, 2005). In the SWOG study the median survival of 40 patients aged 50 years or older was one month vs 17.1 months for the whole cohort of 168 patients (Hussein *et al*, 1989). A CR rate of just 77% was reported on CALGB 9111 in 35 patients aged 60 years or older vs 85% in the whole group. Median survival in the over 60s was 12 months as compared to 23 months for the cohort as a whole (Larson *et al*, 1998). In a study of patients treated with HyperCVAD, only 79% of the 44 patients aged 60 years or older achieved a CR as compared to 91% in the 204 total patient cohort (Kantarjan *et al*, 2000). Five year survival in this study was only 17% in the over 60s vs 39%. Recent data from the UKALL12 ECOG 2993 study also confirm significantly inferior CR rates, EFS, OS in patients over the age of 55 (Sive *et al*, 2010). Two population based registry studies (both from the Northern region, UK) report even lower response and survival rates. Taylor *et al* (1992) and Moorman *et al* (2010) reported CRs in only 20% and 51% of adults aged over 60 years with five year survival of 5% and 12% respectively. The contrast between outcomes reported in studies and population based surveys suggest a significant bias towards including only younger and fitter older patients in therapy trials. It is likely that the overall outcome for older patients with ALL may be even poorer

than are reported from published studies. The Dutch/Belgian group HOVON have recently trialled an intensive regimen in patients up to 70 years. In the HOVON 71 study patients between 40 and 70 years were included. CR rate in the pilot study was 85%, OS at 3 years in patients over 60 was 54% (median follow up 30 months), but EFS was 41%, in part due to transplant-related toxicity (personal communication). However, the H-71 treatment also has considerable risks: many patients developed severe mucositis and the mortality rate for patients over 60 was 21% during induction, mainly due to infections. Thus patient selection as to which older patients would benefit from such a regimen is vital to understand. This can only be understood by a permissive approach to patient selection and entry.

For older patients with Ph+ ALL, there has been some recent progress in improving outcomes. The understanding that CR might be achieved with less toxicity when tyrosine kinase inhibitors are added to therapy has emerged from two studies which included older people. One of the early studies, by the German multi-centre ALL group (Wassmann *et al*, 2006), was performed in patients older than 55 years of age and randomised participants to receive imatinib or multi-agent chemotherapy for initial induction. In this randomised comparison of the two approaches, the overall CR in the imatinib arm was 96%, whereas in the chemotherapy arm it was 50%. The suggestion that imatinib may offer good initial responses with less toxicity is also borne out by the imatinib and steroid combination results reported in 30 elderly patients (median age, 69 years) by the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) (Vignetti *et al*, 2007), with all achieving hematologic CR with a median survival from diagnosis of 20 months, although continuing drops in the survival curves suggest that there are unlikely to be any long-term disease-free survivors. Remarkably, within this study, most patients did not require admission to hospital. No formal assessment of quality of life was carried out in either study. It is clear that the addition of imatinib to treatment would now be considered standard of care (Fielding, 2011) and the Ph+ pathway has been designed accordingly. Long term outcome of and QoL assessments of the treatment of Ph+ ALL in older persons remain to be investigated; it remains unclear what is the appropriate intensity of chemotherapy to administer in conjunction with imatinib.

Treatment efficacy is not the only influence on outcome in ALL. Age specific differences in disease biology are well characterised among adults with ALL. There is an increasing incidence of unfavourable risk factors such as adverse risk karyotype and elevated WBC with advancing age. However, disease biology alone does not explain the poor outcome of this patient subgroup. A major contributor is tolerability to treatment. Drug induced hepatotoxicity, steroids toxicity and CNS toxicity are some of the major problems. Recent data from the largest study of adult ALL; UKALL12/ECOG 2993 has highlighted this important issue. Sive *et al* (2010) reported significantly more infections during phase I induction in patients aged ≥55 years vs those <55 years (67% vs 45% respectively p<0.0001) and a need for more drug dose reductions during induction in the ≥55 year old patients (46% vs 28% P=0.0009) compared to those <55 year old. Crucially, infection during induction in addition to adverse karyotype and high WBC, predicted for worse EFS and this was especially significant in those who had infection in both phases of induction (6% vs 38%, p=0.007). Overall, published data indicate a 3–10 times higher high rate of induction deaths in older individuals following treatment for ALL (Annino *et al*, 2002; Sive *et al*, 2012).

Hence, balancing toxicity of treatment against potentially a more aggressive disease phenotype is an enormous challenge in the management of older patients with ALL. Emerging novel agents such as monoclonal antibodies have the tremendous potential of adding independent anti-leukaemia effect without the addition of substantial toxicity. However, the challenge is how best to integrate these novel agents into ALL protocols for older individuals where a standard of care is not defined. The absence of a well-defined treatment protocol for elderly patients with ALL has prevented proper understanding of the risks of ALL treatment in this group. Such data will be necessary for the design of therapy trials in which optimal management is being investigated.

Another important issue which remains undefined in older patients is whether biomarkers which have become standard of care in childhood, and more recently, adult, are predictive of outcome and can be used to risk-stratify in older people. To date, none of the large-scale studies investigating the prognostic significance of MRD in adult ALL (Brüggemann *et al* 2006, Patel *et al,*

2010) have included patients over 65 years of age. However, some European studies are beginning to define MRD as standard of care for patients of all ages in the absence of hard evidence to support this. We believe that it will be essential to define MRD dynamics in an elderly population before deciding whether and when this risk stratification tool can be used to assign therapy.

Recruiting ALL trials

Worldwide, there are three on-going trials in older patients with ALL. Two studies include patients with Ph- ALL; the Dana Faber Cancer Centre is carrying out a non-randomised phase II study of an aggressive multi-agent chemotherapy approach in patients of good performance status aged 51-75 (2009-2012). Since 2007 the Italian group GIMEMA has been investigating a "geriatric assessment" led treatment protocol for "fit, intermediate and frail" older patients in a manner analogous to our plan. However, they plan to evaluate autologous bone marrow transplant in the fitter patients, an approach that UKALL12 showed was inferior to chemotherapy.

The third study is recruiting patients with Ph+ ALL, and is a collaboration of several European countries to investigate dasatinib with combination chemotherapy. This study has almost completed accrual and it is too late for the UK to join. HOVON have recently piloted the approach (discussed earlier) in selected patients up to the age of 70. This seems a reasonable approach to offer to fitter patients within the UK should investigators and patients wish to try it. For this reason, we have chosen to work with HOVON to extend their work to the UK and to introduce this proposed study protocol to a wider, unselected population across 3 countries. Together, we will also work to define the role of MRD assessment in older individuals.

2.2 Proposed Study

Design:
This multicentre prospective observational study will test the safety, tolerability and efficacy of a standard "backbone" chemotherapeutic regime for older patients with ALL thereby providing essential baseline data to inform the design of advanced phase II/III studies in ALL in which the activity and tolerability of novel agents/therapeutic approaches in this patient group will be assessed.

There are 5 treatment pathways to choose from in this study:

- Pathway for Philadelphia +ve patients (pathway A)
- Intensive pathway in Philadelphia –ve patients (pathway B)
- Intensive+ pathway in Philadelphia –ve patients (pathway C)
- Non-intensive pathway in Philadelphia –ve patients (pathway D)
- Registration Only - Treatment as per local protocol, data collection only (pathway E)

Due to the design, allowing choice of treatment pathway, the study will inform us how physicians use information about co-morbidities and performance status at diagnosis to make treatment decisions in ALL so that a future study will have the most pragmatic and suitable design.

The option of a registration only pathway is intended to provide the important denominator for estimating the percentage of patients within the elderly ALL population that are willing to enter prospective therapy trials.

Primary objectives:

- Complete remission rate after 2 phases of induction

Secondary objectives:

- EFS at 1 year
- Treatment related mortality

- Complete remission rate after 1 phase of induction
- Prognostic significance of molecularly determined minimal residual disease (MRD) at various time-points during therapy with respect to relapse occurrence.
- Overall Survival at 1 year
- Tolerability of treatment as determined by occurrence of key adverse effects
- Duration of in-patient hospitalisation
- Relationship between performance status/co-morbidity and treatment option chosen
- Quality of life aspects assessed at various time points.

Translational research:
We will identify the rate of MRD positivity at discriminatory time-points thus identifying the number and proportion of patients likely to be identified as high risk. MRD measurements found to be discriminatory in this protocol will form the basis of a risk stratification in future studies. Such information will be necessary for the design of future studies in which randomisation of treatment is planned. Flow cytometric determination of antigen expression at diagnosis. Genomic profiling will be carried out in order to discover and characterise novel prognostic markers and to identify known sub-microscopic copy number alterations (CNA) beyond the resolution of standard diagnostic testing (i.e. cytogenetics and FISH). DNA from non-leukaemic samples will be analysed for genetic changes that may be associated and/or linked with ALL in adults.

2.3 Study activation

UCL CTC will ensure that all study documentation has been reviewed and approved by all relevant bodies and that the following have been obtained prior to activating the study:

- Research Ethics Committee approval
- 'Adoption' into NIHR portfolio
- NHS permission
- Adequate funding for central coordination
- Confirmation of sponsorship
- Adequate insurance provision

3 Selection of Sites/Site Investigators

3.1 Site selection

In this protocol, 'study site' refers to the hospital where study-related activities are conducted.

Sites must be able to comply with:

- Study treatment(s), investigations , clinical care, follow up schedules and all requirements of the study protocol
- Requirements of the Research Governance Framework
- Data collection requirements
- Non-UK sites: all local regulations relevant to the conduct of this study.

3.1.1 Selection of Principal Investigator and other investigators at sites

Sites must have an appropriate Principal Investigator (PI), i.e. a health care professional authorised by the site and ethics committee, to lead and coordinate the work of the study on behalf of the site. Other investigators at site wishing to participate in the study must be trained and approved by the PI. All investigators must be medical doctors and have experience of treating acute lymphoblastic leukaemia.

3.1.2 Training requirements for site staff

All site staff must be appropriately qualified by education, training and experience to perform the study related duties allocated to them, which must be recorded on the site delegation log.

CVs for all staff must be kept up-to-date, with signed and dated and copies held in the Investigator Site File (ISF). An up-to-date, signed copy of the CV for the PI must be forwarded to UCL CTC upon request.

GCP training is required for all staff responsible for study activities. The frequency of repeat training may be dictated by the requirements of their employing institution, or 2 yearly where the institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials.

3.2 Site initiation and activation

3.2.1 Site initiation

Before a site is activated, the UCL CTC study team will arrange a site initiation with the site which the PI, and site research team must attend. A representative of pharmacy is also encouraged to attend. The site will be trained in the day-to-day management of the study and essential documentation required for the study will be checked.

3.2.2 Site initiation will be performed for each site by teleconference. Required documentation

The following documentation must be submitted by the site to UCL CTC prior to a site being activated by UCL CTC study team:

- Study-specific Site Registration Form
- All relevant institutional approvals (e.g. local NHS permission)
- A completed site delegation log that is signed and dated by the PI (with all tasks and responsibilities delegated appropriately)

- A completed Site Contacts form (with contact information for all members of local staff)
- A copy of the PI's current CV that is signed and dated (with documented up to date GCP training, or copy of GCP training certificate)

The UCL CTC study team will ensure that, for UK sites:

- If the site was not included in the original CSP application, the Part C is updated and the R&D form is resubmitted to CSP (who will notify the lead CLRN of the new site)
- An SSI form is transferred to the site via IRAS

In addition, the following agreements must be in place:

- For UK sites: a signed Clinical Trial Site Agreement (CTSA) between the Sponsor and the relevant institution (usually an NHS Trust/Health Board)
- For non-UK sites: a signed International Clinical Trials Site Agreement (ICTSA).
- For countries with a Country Coordinating Centre (CCC)**:**
    - a signed International Country Coordinating Centre Agreement
    - a signed clinical trial agreement between the CCC and the relevant institutions
- For countries with a Country Lead Site (CLS):
    - a signed International Country Lead Site Agreement
    - a signed clinical trial agreement between the sponsor and the relevant intuitions.

3.2.3 Site activation letter

Once the UCL CTC study team has received all required documentation and the site has been initiated, a site activation letter will be issued to the PI, at which point the site may start to approach patients.

Following site activation, the PI is responsible for ensuring:

- adherence to the most recent version of the protocol;
- all relevant site staff are trained in the protocol requirements;
- appropriate recruitment and medical care of patients in the study;
- timely completion and return of CRFs (including assessment of all adverse events);
- prompt notification and assessment of all serious adverse events (see section 10.2.2) and pregnancies (see section 10.5);
- that the site has facilities to provide **24 hour medical advice** for study patients.

4 Informed consent

Sites are responsible for assessing a patient's capability to give informed consent.

Sites must ensure that all patients have been given the current approved version of the patient information sheet, are fully informed about the study and have confirmed their willingness to take part in the study by signing the current approved consent form.

The PI, or, where delegated by the PI, other appropriately trained site staff, are required to provide a full explanation of the study and all relevant treatment options to each patient prior to study entry. During these discussions, the current approved patient information sheet for the study should be discussed with the patient. A minimum of twenty four hours must be allowed for the patient to consider and discuss participation in the study. Written informed consent on the current approved version of the consent form for the study must be obtained before any study-specific procedures are conducted. The discussion and consent process must be documented in the patient notes.

Non-UK Sites will need to consent patients to the study according to local practice and ethical requirements.

Site staff are responsible for:

- checking that the correct (current approved) version of the patient information sheet and consent form are used;
- checking that information on the consent form is/are complete and legible;
- checking that the patient has completed/initialled all relevant sections and signed and dated the form;
- checking that an appropriate member of staff has countersigned and dated the consent form to confirm that they provided information to the patient;
- checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e. information given, consent signed etc.);
- giving the patient a copy of their signed consent form, patient information sheet and, patient contact card;
- documenting and providing details of the consent process to UCL CTC;
- following registration: adding the patient study number to all copies of the consent form, which should be filed in the patient's medical notes and investigator site file.

The right of the patient to refuse to participate in the study without giving reasons must be respected. All patients are free to withdraw at any time. Also refer to section 13.0 (Withdrawal of patients).

Patients will also be asked to consider taking part in Translational Research and will be asked if they wish to consent for sample collection. (See section 20 for more details).

5 Selection of Patients

5.1 Pre-registration Evaluation

Patients should undergo clinically relevant investigations for diagnosis and evaluation for treatment; however the following assessments or procedures are required to evaluate the suitability of patients for the study:

- Full medical history (including family history of cancer) and physical examination (including hepatomegaly/splenomegaly and lymphadenopathy – to be reported on sample request form at time of diagnosis sample being sent)
- Height, weight, BSA and blood pressure
- Full blood count (with differential) and biochemistry (i.e. U&Es & LFTs, specifically LDH, Creatinine, Bilirubin & ALT/AST
- Assessment of performance status
  - ECOG and Karnofsky score (See Appendix 3)
- Assessment of Co-morbidities using the CRASH score (including Mini Mental Status, Mini Nutritional Assessment & Instrumental Activities of Daily Living), (see Appendix 5)
- Assessment of Co-morbidities using the Charlson Index, (Appendix 4)
- Bone marrow aspirate and trephine biopsy[1]
- Confirmation of disease diagnosis from bone marrow aspirate (or peripheral blood where there is a high presenting WCC) using Immunophenotyping/Flow cytometry
- Cytogenetic, FISH and molecular genetic analysis on a pre-treatment bone marrow to confirm the presence or absence of the Philadelphia (Ph) chromosome
- Buccal swab (See section 20)
- Lumbar puncture[2]
- Quality of Life Assessment
  - Demographic data (age, partner status, ethnicity, employment, postcode for deprivation index)
  - EORTC QLQ–C 30, EORTC CIPN, FACT-Leu, FACIT-FATIGUE (See Appendices 6-9)

Providing the patient has consented, the following should be sent to the MRD laboratory at UCL Cancer Institute:

- **Buccal swab in the kit provided for genetic analysis**

- **2-5mls of bone marrow in EDTA for baseline MRD assessment should be sent to the MRD laboratory at UCL Cancer Institute for baseline MRD assessment (providing patient's consent). For the diagnostic sample only, 10-20mls of peripheral blood collected into an EDTA tube is also acceptable if a bone marrow sample is not available/feasible. (Please see section 20 for details of translational research).**

[1]Bone marrow aspirate AND trephine should be performed prior to registration wherever possible. However if a bone marrow trephine has not been performed then the patient may still be registered.

[2]Lumbar puncture is not required at diagnosis except in the case of suspected central nervous system involvement. Otherwise, it should be avoided (in case of traumatic puncture and CNS seeding) until the first dose of intrathecal methotrexate is due, at which time blasts should have been cleared from the peripheral blood. The first lumbar puncture should always be given by the most experienced operator available, to reduce the incidence of traumatic taps.

5.2 Screening Log

A screening log must be maintained by the site and kept in the Investigator Site File. This must record each patient screened for the study and the reasons why they were not registered in the study if this is the case. The log must be sent to UCL CTC when requested, with patient identifiers removed prior to sending.

5.3 Patient Eligibility

There will be no exception to the eligibility requirements at the time of registration. Queries in relation to the eligibility criteria must be addressed prior to calling/faxing for registration. Patients are eligible for the study if all the inclusion criteria are met and none of the exclusion criteria applies.

5.3.1 Patient Inclusion Criteria

- Age ≥ 60 with Acute Lymphoblastic Leukaemia (ALL) **OR** ≥ 55 with Acute Lymphoblastic Leukaemia (ALL) unsuitable for the UKALL14 or HOVON 100 trial
- Newly diagnosed, previously untreated ALL (a steroid pre-phase of 5-7 days may be given before study registration)
- Written informed consent

5.3.2 Exclusion Criteria

- Known HIV infection
- Blast transformation of CML
- Mature B-cell leukaemia i.e. Burkitts disease t(8,14)(q24;q32) and variant c-myc translocations e.g. t(2;8)(p12;q24), t(8;22)(q24;q11)
- Women who are pregnant or lactating

5.3.3 Pregnancy and Birth Control for female patients

All patients entering the UKALL60+ study will be aged over 55. While we anticipate that women are highly unlikely to be of child bearing potential, this must be confirmed at the point of registration.

A woman of childbearing potential is a sexually mature woman (i.e. any female who has experienced menstrual bleeding) who has not:

- undergone a hysterectomy or bilateral oophorectomy/salpingectomy
- been postmenopausal for 24 consecutive months (i.e. who has had menses at any time in the preceding 24 consecutive months without an alternative medical cause)

All women of childbearing potential who are at risk of becoming pregnant, including patients who have undergone IVF within 3 months prior to study entry, must undergo a pregnancy test at screening.

If a female patient, or the female partner of a male patient becomes pregnant during the study UCL CTC must be informed immediately (See section 10.0 Safety Reporting for details on the reporting procedure).

5.3.4 Contraceptive Advice for male patients and their female partners

Due to the effects of the study treatment during pregnancy and lactation, female patients should be counselled against becoming pregnant either naturally or via IVF from the time of consent until 6 months post last treatment administration, and both female patients of childbearing potential, and male patients with partners of childbearing potential must consent to use one of the following

acceptable methods of contraception from the time of consent until 6 months post last treatment administration.

Acceptable methods of effective contraception for this study are:

- Established use of oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository). The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted:
  - Failure rates indicate that, when used alone, the diaphragm or condom are **not** highly effective forms of contraception. Therefore the use of additional spermicides does confer additional theoretical contraceptive protection.
  - However, spermicides alone are inefficient at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and must not be used alone.
- Male sterilisation (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). Please note that sterilisation is not usually regarded as completely reliable enough on its own to ensure that pregnancy can never occur.
- Absolute and continuous abstinence: When this is in line with the preferred and usual lifestyle of the patient. Please note that periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

The method(s) of contraception used must be stated in the patient medical notes and CRFs.

If a partner of a male study patient becomes pregnant during the study UCL CTC must be informed immediately (See section 10.0 Safety Reporting for details on the reporting procedure).

5.3.5 Long term infertility

Due to the potential effects of study treatment on fertility it is recommended that male patients consider sperm banking before commencing treatment.

6 Registration Procedures

6.1 Registration

Patient registration will be undertaken centrally at UCL CTC and this must be performed prior to commencement of any study treatment/intervention. **Patients may be given a steroid pre-phase of 5-7 days prior to study registration. This should be sufficient time to obtain confirmation of Philadelphia status.**

Following pre-treatment evaluations (as detailed in section 5.1), confirmation of eligibility and consent of a patient at a site, the registration form must be fully completed and then faxed to UCL CTC. The faxed registration form will be used to confirm patient eligibility at UCL CTC.

A patient may be entered onto the registration only pathway of the study retrospectively at any point during their first phase of treatment. All efforts should still be made to send diagnostic samples to the MRD laboratory at UCL Cancer Institute for MRD analysis.

A study number and confirmation of treatment allocation will be assigned for the patient and details added to the form.

Patient study numbers

For UK sites, the patient's study number will take the format of 60-1-XXX

For HOVON sites, the patient's study number will take the format of 60-2-XXX

For Danish sites, the patient's study number will take the format of 60-3-XXX

For Irish sites, the patient's study number will take the format of 60-4-XXX

A letter will be added after the study number to indicate which pathway the patient has been assigned to.

A: Philadelphia Positive, **B**: Intensive, **C**: Intensive +, **D**: Non Intensive, **E**: Registration only

For patients entering the study through the pathways with defined treatment, UCL CTC will fax confirmation of the patient's inclusion in the study, their study number and treatment allocation to the main contact and pharmacy.

For patients entering the study under the registration pathway, the fax confirmation will be sent to the site's main contact only.

Registration telephone number:	+44 (0)20 7679 9860
Registration fax number:	+44 (0)20 7679 9861
UCL CTC Office hours:	09:00 to 17:00 (UK time) Monday to Friday, excluding Bank Holidays

Once a patient has been registered onto the study they must be provided with the following:

- A copy of their signed consent form and patient information sheet
- A patient contact card. Site on-call contact details for 24 hour medical care must be added to this card and patients advised to carry this with them at all times while participating in the study. Patients registered from international sites may not be given a copy of the contact card, if the contact details are provided on the signed consent form and patients are encouraged to keep this with them at all times during the study. CCC/CLS will provide international sites with country specific contact information.

6.2 Study drug supply

All drugs must be sourced from hospital commercial stock. Pharmacies must ensure they have adequate supplies for the study.

7 Study Treatment

7.1 Treatment summary

Patients may be treated with a steroid pre-phase of 5-7 days prior to study registration. The steroid pre-phase consists of Dexamethasone 6mg/m^2/d, PO for 5 to 7 days capped at 10mg/d.

7.1.1 Study Pathways

There are 5 treatment pathways in this study:

- A:Philadelphia +ve patients
- B:Intensive pathway in Philadelphia –ve patients
- C:Intensive+ pathway in Philadelphia –ve patients
- D:Non-intensive pathway in Philadelphia –ve patients
- E:Registration Only - Treatment as per local protocol, data collection only

7.1.2 Proceeding through study treatment

Patients must meet the following criteria at the end of each phase or cycle of treatment in order to proceed through to intensification/consolidation:

- Patients must be in complete remission or benefitting from treatment*
- Absence of severe renal and liver function abnormalities (specifically Creatinine ≤ 1.5 x upper limit of normal and Bilirubin & ALT/AST ≤ 3 x upper limit of normal)
- ECOG performance status of 0-2
- Absence of severe cardiac, pulmonary, neurologic or metabolic disease
- Absence of uncontrolled infections
- Haematological recovery i.e. neutrophils > 0.75 x 10^9/L and platelets > 75 x 10^9/L.

Treatment should be postponed until the eligibility criteria are met.

Patients should meet the following criteria in order to continue through maintenance:

- Persistent complete remission and having completed induction/consolidation/ intensification chemotherapy*
- Haematological recovery from previous treatment i.e. neutrophils > 0.75 x 10^9/L and platelets > 75 x 10^9/L.
- Absence of active uncontrolled infection
- Absence of severe hepatic, renal, cardiac, neurological or psychiatric complications.

***Patients who are not in complete remission at the end of each phase or cycle of treatment may continue with their chosen study treatment if, in the opinion of the treating clinician, they are deriving clinical benefit and are fit enough to continue on treatment. Assessments for these patients should continue as normal; please refer to section 8.2 for further details.**

If patients are not benefiting from treatment, or are not deemed fit enough to continue with the selected study treatment, they should discontinue study treatment. Further treatment will be at the discretion of the treating clinician, and follow up data will be collected on such patients every 3 months. Please refer to section 8.4 for further details.

7.2 Summary Treatment Schedules

Please see overleaf. CNS involvement at presentation should be treated in accordance with local policy. The treatment given should be appropriate for the patient's fitness and the intensity of the chosen treatment pathway.

7.2.1 Philadelphia +ve patients (Pathway A)

Table 1 – Phase 1 Induction (28 Days)

Drug	Dose	Route of administration	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Dexamethasone	**3mg/m^2**	PO	1	2	3																									
Idarubicin	**10mg/m^2**	PO	1																											
Vincristine	**1mg/m^2** (cap at 2mg)	IV	1																											
Methotrexate	**12.5mg**	Intrathecal								8							15							22						
Imatinib	**400mg/day** escalating to 600mg within 2 weeks, if tolerated	PO	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28

A bone marrow aspirate should be performed after day 28 as soon as minimum counts are reached. If counts have not recovered on or after Day 35 clinicians should consider doing the bone marrow aspirate anyway. **Providing the patient has consented, 2-5mls of bone marrow in EDTA should be sent to the central lab at this point (see section 20).**

Patients can only proceed to Phase 2 Induction when neutrophils > 0.75 x 10^9/L and platelets > 75 x 10^9/L and other criteria in section 7.1.2 are met.

Please note that timing of Intrathecal therapy can be moved +/- 3 days to allow administration as per local and national guidance.

Imatinib should continue daily throughout therapy while counts are recovering if possible, however treatment with imatinib may be temporarily stopped at the discretion of the treating clinician if this is felt necessary.

Table 2 – Phase 2 Induction (28 Days) - to begin after Phase 1 Induction, when neutrophils > 0.75 x 10^9/L and platelet > 75 x 10^9/L and other criteria in section 7.1.2 are met

Drug	Dose	Route of administration	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Dexamethasone	**3mg/m²**	PO	1	2	3																									
Idarubicin	**10mg/m²**	PO	1																											
Vincristine	**1mg/m²** (cap at 2mg)	IV	1																											
Methotrexate	**12.5mg**	Intrathecal									8					15								22						
Imatinib	**Continue with previously tolerated dose**	PO	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28

A bone marrow aspirate should be performed after day 28 as soon as minimum counts are reached. If counts have not recovered on or after Day 35 clinicians should consider doing the bone marrow aspirate anyway. **Providing the patient has consented 2-5mls of bone marrow in EDTA should be sent to the central lab at this point (see section 20) .**

Patients can only proceed to Consolidation when neutrophils > 0.75 x 10^9/L and platelets > 75 x 10^9/L and other criteria in section 7.1.2 are met.

Please note that timing of Intrathecal therapy can be moved +/- 3 days to allow administration as per local and national guidance.

Table 3 – Consolidation - to begin after Phase 2 Induction, when neutrophils > 0.75 x 10^9/L and platelet > 75 x 10^9/L and other criteria in section 7.1.2 are met

Drug	Dose	Route of administration	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Dexamethasone	**3mg/m^2**	PO	1	2	3																									
Idarubicin	**10mg/m^2**	PO	1																											
Vincristine	**1mg/m^2** (cap at 2mg)	IV	1																											
Methotrexate	**12.5mg**	Intrathecal		2																										
Imatinib	**Continue with previously tolerated dose**	PO	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28

A bone marrow aspirate should be performed after day 28 as soon as minimum counts are reached. If counts have not recovered on or after Day 35 clinicians should consider doing the bone marrow aspirate anyway. **Providing the patient has consented 2-5mls of bone marrow in EDTA should be sent to the central lab at this point (see section 20).**
Please note that timing of Intrathecal therapy can be moved +/- 3 days to allow administration as per local and national guidance.

Patients can only proceed to maintenance after consolidation when neutrophils > 0.75 x 10^9/L and platelets > 75 x 10^9/L and other criteria in section 7.1.2 are met.

Table 4 – Maintenance (24 months) - to begin after Consolidation, when neutrophils > 0.75 x 10^9/L and platelet > 75 x 10^9/L and other criteria in section 7.1.2 are met.

Drug	Dose	Route of administration	Frequency
6-mercaptopurine*	**25mg/m^2 - 75mg/m^2 starting dose. Titrate for counts as per protocol.**	PO	daily
Imatinib	**Continue with previously tolerated dose**	PO	daily
Prednisolone	**60mg/m^2**	PO	5 days every 3 months
Methotrexate	**12.5mg**	Intrathecal	Every 3 months
Vincristine	**1.4 mg/m^2 (max 2 mg/dose)**	IV	Every 3 months

*6-mercaptopurine should be started at 25mg/m^2/day and then should be increased upwards in 25% increments to tolerance.

Dosing of maintenance therapy should be adjusted to maintain the Neutrophil count between 0.75 and 1.5 x 10^9/l and platelet count between 75 and 150 x 10^9/l. Dose of 6-MP should be altered in 25% increments or decrements to achieve the above counts. e.g. if neutrophils > 1.5 x 10^9/l, increase 6-MP dose by 25%. There is no maximum dose of 6MP. If neutrophils fall below 0.75 x 10^9/l, reduce by 50%, if neutrophils fall below 0.5 x 10^9/l, stop maintenance and restart at 100% when neutrophils > 0.75 x 10^9/l. Similar adjustments need to be made for the platelet count to maintain above counts. Maintenance should not be interrupted unnecessarily but if doses are omitted for cytopaenias or infectious complications, they do not need to be made up with additional doses later.

7.2.2 Intensive pathway in Philadelphia –ve patients (Pathway B)

Table 1 – Induction Phase 1 (28 day cycle)

Drug	Dose	Route of administration	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Dexamethasone	**6mg/m^2**	PO	1	2	3				7	8	9																			
Idarubicin	**14mg/m^2**	IV	1																											
Vincristine	**1mg/m^2** (cap at 2mg)	IV	1														15							22						
Methotrexate	**12.5mg**	Intrathecal							7							14							21							

A bone marrow aspirate should be performed after day 28 as soon as minimum counts are reached. If counts have not recovered on or after Day 35 clinicians should consider doing the bone marrow aspirate anyway. **Providing the patient has consented 2-5mls of bone marrow in EDTA should be sent to the central lab at this point (see section 20).**

Please note that timing of Intrathecal therapy can be moved +/- 3 days to allow administration as per local and national guidance.

Patients can only proceed to Induction Phase 2 when neutrophils > 0.75 x 10^9/L and platelets > 75 x 10^9/L and other criteria in section 7.1.2 are met.

Table 2 – Induction Phase 2 (17 day cycle) – to begin after Phase 1 Induction, when neutrophils > 0.75 x 10^9/L and platelet > 75 x 10^9/L and other criteria in section 7.1.2 are met.

Drug	Dose	Route of administration	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17
Vincristine	**1mg/m^2** (cap at 2mg)	IV	1														15		
Cytarabine	**75mg/m^2**	IV	1	2	3												15	16	17
Cyclophosphamide	**300mg/m^2**	IV	1														15		
Methotrexate	**12.5mg**	Intrathecal							7							14			

A bone marrow aspirate should be performed as soon as possible after day 17 once minimum counts are reached. If counts have not recovered on or after Day 28 clinicians should consider doing the bone marrow aspirate anyway. **Providing the patient has consented 2-5mls of bone marrow in EDTA should be sent to the central lab at this point (see section 20).**

Please note that timing of Intrathecal therapy can be moved +/- 3 days to allow administration as per local and national guidance.

Patients can only proceed to Intensification when neutrophils > 0.75 x 10^9/L and platelets > 75 x 10^9/L and other criteria in section 7.1.2 are met.

Table 3 – Intensification - to begin after Phase 2 Induction, when neutrophils > 0.75 x 10^9/L and platelet > 75 x 10^9/L and other criteria in section 7.1.2 are met.

Drug	Dose	Route of administration	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
*Methotrexate	**1g/m^2**	IV (infusion duration as per local policy)	1														15													

* Local policies may be followed for folinic acid rescue after IV methotrexate administration during Induction 2. A recommended schedule is to give Leucovorin (Folinic Acid) (60mg in 4 doses) on days 5 and 12 of Induction 2 after IV Methotrexate administration. This should then continue until plasma Methotrexate levels are <15 µg/l.

A bone marrow aspirate should be performed after day 28 as soon as minimum counts are reached. If counts have not recovered on or after Day 35 clinicians should consider doing the bone marrow aspirate anyway.
Providing the patient has consented 2-5mls of bone marrow in EDTA should be sent to the central lab at this point (see section 20).

Patients can only proceed to Consolidation 1 after Intensification when neutrophils > 0.75 x 10^9/L and platelets > 75 x 10^9/L and other criteria in section 7.1.2 are met.

Table 4 - Consolidation Cycle 1, 2 & 3 (28 day cycle repeated 3 times) - to begin when neutrophils > 0.75 x 10^9/L and platelet > 75 x 10^9/L and other criteria in section 7.1.2 are met.

Drug	Dose	Route of administration	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Dexamethasone	**3mg/m^2**	PO	1	2	3																									
Idarubicin	**10mg/m^2**	PO	1																											
Vincristine	**1mg/m^2** (cap at 2mg)	IV	1																											
Methotrexate	**5mg/m^2**	PO	1							8							15							22						
6-mercaptopurine	**50mg/m^2**	PO	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28

Patients can only proceed to Maintenance after Consolidation 3 when neutrophils > 0.75 x 10^9/L and platelets > 75 x 10^9/L and other criteria in section 7.1.2 are met.

Table 5 - Maintenance (24 months) - to begin after Consolidation 3, when neutrophils > 0.75 x 10^9/L and platelet > 75 x 10^9/L and other criteria in section 7.1.2 are met

Drug	Dose	Route of administration	Frequency
6-mercaptopurine*	**25mg/m^2 - 75mg/m^2 starting dose. Titrate for counts as per protocol.**	PO	Daily
Methotrexate	**5mg/m^2**	PO	Weekly
Prednisolone	**60 mg/m^2**	PO	5 days every 3 months
Methotrexate	**12.5mg**	Intrathecal	Every 3 months
Vincristine	**1.4 mg/m^2 (max 2 mg/dose)**	IV	Every 3 months

*6-mercaptopurine should be started at 25mg/m^2/day and then should be increased upwards in 25% increments to tolerance.

Dosing of maintenance therapy should be adjusted to maintain the neutrophil count between 0.75 and 1.5 x 10^9/l and platelet count between 75 and 150 x 10^9/l. *Dose of 6-MP and MTX should be altered in 25% increments or decrements to achieve the above counts. E.g. if neutrophils > 1.5 x 10^9/l, increase 6-MP dose by 25%. If neutrophils remain > 1.5 x 10^9/l after 4 weeks, increase MTX by 25% etc. There are no maximum doses of 6-MP and MTX.
If neutrophils fall below 0.75 x 10^9/l, reduce both drugs by 50%, if neutrophils fall below 0.5 x 10^9/l, stop maintenance and restart at 100% when neutrophils > 0.75 x 10^9/l. Similar adjustments need to be made for the platelet count to maintain above counts.

Maintenance should not be interrupted unnecessarily but if doses are omitted for cytopaenias or infectious complications, they do not need to be made up with additional doses later.

7.2.3 Intensive+ pathway in Philadelphia –ve patients (Pathway C)

Table 1 – Induction Phase 1 (28 day cycle)

Drug	Dose	Route of administration	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Methotrexate + *Dexamethasone	**12.5mg* 4mg**	Intrathecal		2							9							16												
Vincristine	**1mg/m^2** (cap at 2mg)	IV	1							8							15													
Doxorubicin	**40mg/m^2**	IV	1							8							15													
**Prednisolone	**40mg/m^2, divided into 2 daily doses**	PO	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28

Taper dose of Prednisolone to 0 within 7 days from day 22

Please note that timing of Intrathecal therapy can be moved +/- 3 days to allow administration as per local and national guidance.

* IT Dexamethasone 4mg may be substituted with either: Hydrocortisone 100mg or Prednisolone 25mg suspended in 3-6ml saline. Methotrexate can be added into the same syringe.

** The dose of Prednisolone should be rounded to the nearest 5mg. The dose should be tapered to 0 within 7 days from day 22. It is suggested that the dose is lowered every day by 10-15 mg until 0 on day 28.

A bone marrow aspirate should be performed after day 28 as soon as minimum counts are reached. If counts have not recovered on or after Day 35 clinicians should consider doing the bone marrow aspirate anyway. **Providing the patient has consented *2-5mls of bone marrow in EDTA should be sent to the central lab at this point (see section 20).***

Patients can only proceed to Phase 2 Induction when neutrophils > 1.0 x 10^9/L and platelets > 100 x 10^9/L and other criteria in section 7.1.2 are met.

Table 2 –Induction Phase 2 (1 x 22 day cycle) - to begin after Phase 1 Induction, when neutrophils > 1.0 x 10^9/L and platelets > 100 x 10^9/L and other criteria in section 7.1.2 are met.

Drug	Dose	Route of administration	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22
Cytarabine	**200mg/m^2**	IV (over 1 hour)	1							8														
Etoposide	**120mg/m^2**	IV (over 1 hour)	1							8														
*Methotrexate	**500mg/m^2**	IV (over 2 hours)				4							11											
Methotrexate + **Dexamethasone	**12.5mg** **4mg**	Intrathecal	1																					

* Local policies may be followed for folinic acid rescue after IV methotrexate administration during Induction 2. A recommended schedule is to give Leucovorin (Folinic Acid) (60mg in 4 doses) on days 5 and 12 of Induction 2 after IV Methotrexate administration. This should then continue until plasma Methotrexate levels are <15 µg/l.

** IT Dexamethasone 4mg may be substituted with either: Hydrocortisone 100mg or Prednisolone 25mg suspended in 3-6ml saline. Methotrexate can be added into the same syringe.

Please note that timing of Intrathecal therapy can be moved +/- 3 days to allow administration as per local and national guidance.

A bone marrow aspirate should be performed after day 22 as soon as minimum counts are reached. If counts have not recovered on or after Day 35 clinicians should consider doing the bone marrow aspirate anyway. **Providing the patient has consented *2-5mls of bone marrow in EDTA should be sent to the central lab at this point (see section 20).***

Patients can only proceed to Consolidation when neutrophils > 1.0 x 10^9/L and platelets > 100 x 10^9/L and other criteria in section 7.1.2 are met.

Table 3 – Consolidation 1 (21 day cycle) – to start as soon as Neutrophils > 1.0 x 10^9/l and platelets >100 x 10^9/l and other criteria in section 7.1.2 are met.

Drug	Dose	Route of administration	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
Methotrexate + *Dexamethasone	**12.5mg 4mg**	Intrathecal														14							
Vincristine	**1mg/m^2** (cap at 2mg)	IV	1							8							15						
Doxorubicin	**40mg/m^2**	IV	1							8							15						
Prednisolone	**40mg/m^2, divided into 2 daily doses**	PO	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21

* IT Dexamethasone 4mg may be substituted with either: Hydrocortisone 100mg or Prednisolone 25mg suspended in 3-6ml saline. Methotrexate can be added into the same syringe.

Please note that timing of Intrathecal therapy can be moved +/- 3 days to allow administration as per local and national guidance.

A bone marrow aspirate should be taken after day 21 as soon as minimum counts are reached. If counts have not recovered on or after Day 35 clinicians should consider doing the bone marrow aspirate anyway. **Providing the patient has consented *2-5mls of bone marrow in EDTA should be sent to the central lab at this point (see section 20).***

Patients in complete remission should continue with Consolidation 2.

Patients can only proceed to Consolidation 2 when neutrophils > 1.0 x 10^9/l and platelets >100 x 10^9/l and other criteria in section 7.1.2 are met.

Table 4 – Consolidation 2 (1 x 22 day cycle) - to start no sooner than day 22 (day 1 being the start of Consolidation 1), as soon as Neutrophils > 1.0 x 10^9/l and platelets >100 x 10^9/l and other criteria in section 7.1.2 are met.

Drug	Dose	Route of administration	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22
Cytarabine	**1000mg/m^2**	IV (over 1 hour)	1	2																				
Pegylated-Asparaginase	**1000IU/m^2**	IV			3															18				
OR																								
E.coli Asparaginase	**6000IU/m^2**	IV			3	4	5	6	7	8	9	10	11	12										
Methotrexate + *Dexamethasone	**12.5mg** **4mg**	Intrathecal	1																					

*Dexamethasone 4mg may be substituted with either: Hydrocortisone 100mg or Prednisolone 25mg suspended in 3-6ml saline. Methotrexate can be added into the same syringe.

Please note that timing of Intrathecal therapy can be moved +/- 3 days to allow administration as per local and national guidance.

Patients can only proceed to Maintenance after Consolidation 2 when neutrophils > 1.0 x 10^9/L and platelets > 100 x 10^9/L and other criteria in section 7.1.2 are met.

Table 5 Maintenance Year 1 – (13 x 28 day cycles) - to begin after Consolidation 2, when neutrophils > 1.0 x 10^9/L and platelets > 100 x 10^9/L and other criteria in section 7.1.2 are met.

Drug	Dose	Route of administration	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Prednisolone	**1mg/kg/d**	PO	1	2	3	4	5	6	7																					
Vincristine	**1.4mg/m^2** (cap at 2mg)	IV	1																											
6-mercaptopurine	**75mg/m^2**	PO	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Methotrexate	**15mg/m^2**	PO								8							15							22						
Methotrexate + *Dexamethasone[1]	**12.5mg** **4mg**	Intrathecal		2																										

Day 29 = Day 1 of the next cycle.

[1]Please note that Methotrexate (12.5mg) + Dexamethasone (4mg) IT is to be given at day 2 ONLY during the first 4 cycles of Maintenance Treatment. The maximum number of IT injections for prophylaxis is 10 (maintenance inclusive).

*Dexamethasone 4mg may be substituted with either: Hydrocortisone 100mg or Prednisolone suspended in 3-6ml saline.
Methotrexate can be added into the same syringe.

Please note that timing of Intrathecal therapy can be moved +/- 3 days to allow administration as per local and national guidance.

Dosing of maintenance therapy should be adjusted to maintain the neutrophil count between 0.75 and 1.5 x 10^9/l and platelet count between 75 and 150 x 10^9/l. *Dose of 6-MP and MTX should be altered in 25% increments or decrements to achieve the above counts. E.g. if neutrophils > 1.5 x 10^9/l, increase 6-MP dose by 25%. If neutrophils remain > 1.5 x 10^9/l after 4 weeks, increase MTX by 25% etc. There are no maximum doses of 6-MP and MTX. If neutrophils fall below 0.75 x 10^9/l, reduce both drugs by 50%, if neutrophils fall below 0.5 x 10^9/l, stop maintenance and restart at 100% when neutrophils > 0.75 x 10^9/l. Similar adjustments need to be made for the platelet count to maintain above counts.

Patients can only proceed to Maintenance Year 2 after Year 1 when neutrophils > 0.75 x 10^9/L and platelets > 75 x 10^9/L and other criteria in section 7.1.2 are met.

Table 6 – Maintenance Year 2 (13 x 28 day cycles) - to begin after Maintenance year 1, when neutrophils > 0.75 x 10^9/L and platelets > 75 x 10^9/L and other criteria in section 7.1.2 are met.

Drug	Dose	Route of administration	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Methotrexate*	**15mg/m^2**	PO	1							8							15							22						
6 Mercaptopurine*	**75mg/m^2**	PO	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28

Day 29 = Day 1 of next cycle

Dosing of maintenance therapy should be adjusted to maintain the neutrophil count between 0.75 and 1.5 x 10^9/l and platelet count between 75 and 150 x 10^9/l. *Dose of 6-MP and MTX should be altered in 25% increments or decrements to achieve the above counts. E.g. if neutrophils > 1.5 x 10^9/l, increase 6-MP dose by 25%. If neutrophils remain > 1.5 x 10^9/l after 4 weeks, increase MTX by 25% etc. There are no maximum doses of 6-MP and MTX. If neutrophils fall below 0.75 x 10^9/l, reduce both drugs by 50%, if neutrophils fall below 0.5 x 10^9/l, stop maintenance and restart at 100% when neutrophils > 0.75 x 10^9/l. Similar adjustments need to be made for the platelet count to maintain above counts.

7.2.4 Non-intensive pathway in Philadelphia –ve patients (Pathway D)

Table 1 –Induction Phase 1

Drug	Dose	Route of administration	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Dexamethasone	**3mg/m^2**	PO	1	2	3																									
Idarubicin	**10mg/m^2**	PO	1																											
Vincristine	**1mg/m^2** (cap at 2mg)	IV	1																											
Methotrexate	**5mg/m^2**	PO	1							8							15							22						
6-mercaptopurine	**25mg/m^2**	PO	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Methotrexate	**12.5mg**	Intrathecal	To be given once during Induction Phase 1 – timing at the discretion of the treating clinician																											

A bone marrow aspirate should be performed after day 28 as soon as minimum counts are reached. If counts have not recovered on or after Day 35 clinicians should consider doing the bone marrow aspirate anyway. **Providing the patient has consented 2-5ml of bone marrow in EDTA should be sent to the central lab at this point (see section 20).**

Patients can only proceed to Phase 2 when neutrophils > 0.75 x 10^9/L and platelets > 75 x 10^9/L and other criteria in section 7.1.2 are met.

Table 2 –Induction Phase 2 - to begin after Phase 1 Induction, when neutrophils > 0.75 x 10^9/L and platelet > 75 x 10^9/L and other criteria in section 7.1.2 are met.

Drug	Dose	Route of administration	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Dexamethasone	**3mg/m^2**	PO	1	2	3																									
Idarubicin	**10mg/m^2**	PO	1																											
Vincristine	**1mg/m^2** (cap at 2mg)	IV	1																											
Methotrexate	**5mg/m^2**	PO	1							8							15							22						
6-mercaptopurine	**25mg/m^2**	PO	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Methotrexate	**12.5mg**	Intrathecal	To be given once during Induction Phase 2 – timing at the discretion of the treating clinician																											

A bone marrow aspirate should be performed after day 28 as soon as minimum counts are reached. If counts have not recovered on or after Day 35 clinicians should consider doing the bone marrow aspirate anyway. **Providing the patient has consented 2-5ml of bone marrow in EDTA should be sent to the central lab at this point (see section 20). Patients can only proceed to Consolidation when neutrophils > 0.75 x 10^9/L and platelets > 75 x 10^9/L and other criteria in section 7.1.2 are met.**

Table 3 – Consolidation 1 - to begin after Phase 2 Induction, when neutrophils > 0.75 x 10^9/L and platelet > 75 x 10^9/L and other criteria in section 7.1.2 are met.

Drug	Dose	Route of administration	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Dexamethasone	**3mg/m^2**	PO	1	2	3																									
Idarubicin	**10mg/m^2**	PO	1																											
Vincristine	**1mg/m^2** (cap at 2mg)	IV	1																											
Methotrexate	**5mg/m^2**	PO	1						7							14							21							
6-mercaptopurine	**25mg/m^2**	PO	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Methotrexate	**12.5mg**	Intrathecal	To be given once during Consolidation 1 - timing at the discretion of the treating clinician																											

A bone marrow aspirate should be taken after day 28 as soon as minimum counts are reached. If counts have not recovered on or after Day 35 clinicians should consider doing the bone marrow aspirate anyway. **Providing the patient has consented 2-5 ml of bone marrow in EDTA should be sent to the central lab at this point (see section 20).**

Patients can only proceed to Maintenance after Consolidation 1 when neutrophils > 0.75 x 10^9/L and platelets > 75 x 10^9/L and other criteria in section 7.1.2 are met.

Table 4 - Maintenance (24 months) - to begin after Consolidation 1, when neutrophils > 0.75 x 10^9/L and platelet > 75 x 10^9/L and other criteria in section 7.1.2 are met.

Drug	Dose	Route of administration	Frequency
6-mercaptopurine*	**25mg/m^2 - 75mg/m^2 starting dose. Titrate for counts as per protocol.**	PO	daily
Methotrexate*	**5mg/m^2**	PO	weekly
Prednisolone	**60 mg/m^2**	PO	5 days every 3 months
Methotrexate **(may be omitted at the discretion of the treating clinician)**	**12.5mg**	Intrathecal	Every 3 months
Vincristine	**1.4 mg/m^2 (max 2 mg/dose)**	IV	Every 3 months

*6-mercaptopurine should be started at 25mg/m^2/day and then should be increased upwards in 25% increments to tolerance.

Dosing of maintenance therapy should be adjusted to maintain the neutrophil count between 0.75 and 1.5 x 10^9/l and platelet count between 75 and 150 x 10^9/l. *Dose of 6-MP and MTX should be altered in 25% increments or decrements to achieve the above counts. E.g. if neutrophils > 1.5 x 10^9/l, increase 6-MP dose by 25%. If neutrophils remain > 1.5 x 10^9/l after 4 weeks, increase MTX by 25% etc. There are no maximum doses of 6-MP and MTX. If neutrophils fall below 0.75 x 10^9/l, reduce both drugs by 50%, if neutrophils fall below 0.5 x 10^9/l, stop maintenance and restart at 100% when neutrophils > 0.75 x 10^9/l. Similar adjustments need to be made for the platelet count to maintain above counts.
Maintenance should not be interrupted unnecessarily but if doses are omitted for cytopaenias or infectious complications, they do not need to be made up with additional doses later.

7.2.5 Registration only (Pathway E)

Patients entered into the registration only option will be treated at the discretion of the local centre. Data will be collected as described in section 8 (Assessments).

7.3 Study Treatment Details

All drugs used in the UKALL60+ study are to be supplied from hospital stock. Sites should administer the drugs according to the SPC and/or any local guidance in place.

We recommend that body surface area should be calculated according to the Dubois formula:
Body Surface Area (m^2) = 0.007184 x (patient height in cm)$^{0.725}$ x (patient weight in kg)$^{0.425}$

Body surface area should be recalculated after each cycle of chemotherapy and with any major weight change.

It is recommended that sites follow local guidelines for dose adjustments for obese patients and for the use of actual or ideal body weight.

Please consult the SPC for the brand used at site for detailed information regarding reconstitution, administration and storage conditions. http://www.medicines.org.uk/emc/
Please note that timing of Intrathecal therapy can be moved +/- 3 days to allow administration as per local and national guidance.

7.3.1 Pharmacy responsibilities

Although UKALL60+ is a non-CTIMP, it is nevertheless important that pharmacists at the site are aware of the study. A Pharmacy Lead will be identified on the site staff delegation log; they will be responsible for ensuring the correct drugs are dispensed for the selected treatment pathway. Drug accountability is not required for this study.

7.3.2 Dose modifications

Please refer to Appendix 12 for recommendations for dose modifications. Please note that these are recommendations only and local guidance may be followed if there is a strict policy in place.

7.4 Support medication

All patients should receive prophylaxis against infection with HSV, VZV, fungal organisms and PCP according to local guidelines. Azoles must be avoided when the patient is on vincristine. This should continue during maintenance therapy.

The use of granulocyte colony stimulating factor (G-CSF) is strongly recommended for all patients to hasten neutrophil recovery in association with phases 1 and 2 and is recommended for patients with severe neutropenic sepsis. This can be given as per local policy.

IV Methotrexate folinic acid rescue

Local policies may be followed for folinic acid rescue after IV methotrexate administration during Induction 2. A recommended schedule is to give Leucovorin (Folinic Acid) (60mg in 4 doses) on days 5 and 12 of Induction 2 after IV Methotrexate administration. This should then continue until plasma Methotrexate levels are <15 µg/l.

7.5 Clinical management after treatment discontinuation

If a patient stops treatment early, all further treatment should be at the discretion of the treating clinician.

Also refer to section 13 (Withdrawal of Patients) for further details regarding treatment discontinuation, patient withdrawal from study treatment and withdrawal of consent to data collection.

8 Assessments

Please refer to Appendix 11 for a table of schedule of assessments

The assessment section has been split into 6 distinct stages:

1. Pre Treatment assessments (Section 8.1)
2. Assessments during Treatment (Section 8.2)
3. Assessments during Maintenance (Section 8.3)
4. Patients not in complete remission and discontinuing with study treatment (Section 8.4)
5. Patients assigned to Registration only (Section 8.5)
6. Assessments during Follow Up (Section 8.6)

8.1 Pre-treatment assessments

Please refer to Section 5.1 (Pre-Registration Evaluations) for assessments performed pre-treatment.

8.2 Assessments during treatment (Pathways A, B, C & D)

The following assessments will be performed routinely throughout treatment at the investigator's discretion:

- **Clinical examination** - should be carried out as part of routine clinical care.
- **Full blood count with differential** - will be carried out as part of the routine management of acute leukaemia.
- **Biochemistry and other laboratory tests** - e.g. LFTs, U&Es will be carried out as part of the routine management of acute leukaemia.

The following assessments as listed below should be carried out as described at each time point.

8.2.1 At the end of Phase 1 & Phase 2 Induction

- Physical examination
- ECOG and Karnofsky performance status
- Full blood count (including differential) & blood Biochemistry (i.e. U&Es & LFTs specifically Creatinine, Bilirubin & ALT/AST)
- Remission status (% bone marrow blasts)
- Bone marrow aspirate and trephine biopsy (A bone marrow sample should be taken after day 28 as soon as minimum counts are reached. If counts have not recovered on or after day 35 clinicians should consider doing the bone marrow aspirate anyway)
- Quality of life questionnaires (EORTC QLQ-C30, EORTC CIPN20, FACT-Leu, FACIT-FATIGUE)
- Number of inpatient days
- Review of adverse events
- If patient has consented, 2-5 ml bone marrow to be sent to the central lab for MRD analysis

8.2.2 At the end of intensification (Patients in the Intensive treatment pathway (Pathway B) ONLY)

- Physical examination
- ECOG and Karnofsky performance status

- Full blood count (with differential) & blood biochemistry (i.e U&Es & LFTs specifically Creatinine, Bilirubin & ALT/AST)
- Remission status (% bone marrow blasts)
- Bone marrow aspirate and trephine biopsy (A Bone Marrow Sample should be taken after day 28 as soon as minimum counts are reached. If counts have not recovered on or after day 35 clinicians should consider doing the Bone Marrow Aspirate anyway)
- Quality of life questionnaires (EORTC QLQ-C30, EORTC CIPN20, FACT-Leu, FACIT-FATIGUE)
- Number of inpatient days
- Review of adverse events
- If patient has consented, 2-5ml bone marrow to be sent to the central lab for MRD analysis

8.2.3 At the end of Consolidation 1

- Physical examination
- ECOG and Karnofsky performance status
- Full blood count (with differential) & blood biochemistry (i.e U&Es & LFTs specifically Creatinine, Bilirubin & ALT/AST)
- Remission status (% bone marrow blasts Pathways A, C & D, as per local practice Pathway B)
- Bone marrow aspirate and trephine biopsy, Pathways A, C & D ONLY (A bone marrow sample should be taken as soon as haematopoietic recovery has occurred following completion of the therapy block or upon clinical suspicion of delayed recovery).)
- Quality of life questionnaires (EORTC QLQ-C30, EORTC CIPN20, FACT-Leu, FACIT-FATIGUE)
- Number of inpatient days
- Review of adverse events

If the patient has consented, 2-5ml bone marrow to be sent to the central lab for MRD analysis (Pathways A, C & D only)

8.2.4 At the end of Consolidation 2 and 3 (if applicable)

- Patient remission status to be assessed as per local practice
- Physical examination
- ECOG and Karnofsky performance status
- Full blood count (with differential) & blood biochemistry (i.e U&Es & LFTs specifically Creatinine, Bilirubin & ALT/AST
- Quality of life questionnaires (EORTC QLQ-C30, EORTC CIPN20, FACT-Leu, FACIT-FATIGUE)
- Number of inpatient days
- Review of adverse events

8.3 Assessments during maintenance

8.3.1 Before starting maintenance

- ECOG and Karnofsky performance status
- Comorbidity Assessment (CRASH score & Charlson Index)

8.3.2 6-12 Weeks after starting maintenance

- Quality of life questionnaires (EORTC QLQ-C30, EORTC CIPN20, FACT-Leu, FACIT-FATIGUE)

8.3.3 Every 3 months during maintenance

- Patient remission status to be assessed as per local practice
- Physical examination
- ECOG and Karnofsky performance status
- Full blood count (with differential) & blood biochemistry (i.e U&Es & LFTs) as per local practice
- Number of inpatient days
- Quality of life questionnaires (EORTC QLQ-C30, EORTC CIPN20, FACT-Leu, FACIT-FATIGUE)

8.3.4 End of maintenance

- Quality of life questionnaires (EORTC QLQ-C30, EORTC CIPN20, FACT-Leu, FACIT-FATIGUE)
- Remission status to be assessed as per local practice

8.4 Patients not in complete remission and discontinuing with study treatment

As per section 7.1.2, if patients are not in CR at the end of a phase or cycle of treatment and the clinician decided they are not benefiting from treatment or are not deemed fit enough to continue with the selected study treatment they should discontinue study treatment. These patients should be assessed every 3 months. The following information will be required:

- Patient status
- Assessment of disease status
- Details of any treatment received

All other assessment carried out at these time points should be as per local standards.

8.5 Patients assigned to Registration only (Pathway E)

Data will be collected about patients assigned to the Registration only pathway but this will be in a different format than patients receiving active treatment.

Patients should be assessed at the end of each block of treatment that patients receive and the following information will be required:

- Physical examination
- ECOG and Karnofsky performance status
- Full blood count (with differential) & blood biochemistry (i.e U&Es & LFTs) as per local practice
- Remission status (% bone marrow blasts)
- Bone marrow aspirate and trephine biopsy (A bone marrow sample should be taken after day 28 as soon as minimum counts are reached. If counts have not recovered on or after day 35 clinicians should consider doing the bone marrow aspirate anyway)
- Quality of life questionnaires (EORTC QLQ-C30, EORTC CIPN20, FACT-Leu, FACIT-FATIGUE)
- Number of inpatient days
- If the patient has consented, 2-5ml bone marrow to be sent to the central lab for MRD analysis at up to 3 clinically relevant timepoints.

Sites will be encouraged to collect as much as possible of the information above but if a specific test/assessment is not done at that time point, it will not be collected.

8.6 Assessments during follow up

Annual follow-up begins when study treatment is completed, i.e. after the last dose of maintenance therapy has been given (or last treatment given for patients in the Registration only pathway.

- Clinical examination as necessary (often there are no expected abnormal findings)
- Full blood count (including differential)
- Any other tests as dictated by the patient's clinical condition
- Assessment of disease status as per local practice
- Record of any occurrence of AVN or serious cardiac problems

Patients will be followed up annually for five years. All efforts should be made by the Site to contact the patient's GP to assess their condition, if a patient fails to attend a clinic or cannot be followed up at site. Patients recruited from UK centres will also be consented to follow up through the NHS Information Centre.

9 Data Management Guidelines

Data will be collected from sites on version controlled case report forms (CRFs) designed for the study and supplied by UCL CTC. Data must be accurately transcribed onto CRFs must reflect source data at site.

Where supporting documentation (e.g. autopsy reports, pathology reports, CT scan images etc) is being submitted to UCL CTC, the patient's study number must be clearly indicated on all material and any patient identifiers removed/blacked out prior to sending to maintain patient confidentiality.

9.1 Completing Case Report Forms

All CRFs must be completed and signed by staff who are listed on the site staff delegation log and authorised by the PI to perform this duty. The PI is responsible for the accuracy of all data reported in the CRF.

Once completed the original CRFs must be sent to UCL CTC and a copy kept at site. All entries must be clear, legible and written in ball point pen. The use of abbreviations and acronyms must be avoided.

9.2 Corrections to CRFs

Any corrections made to a CRF at site must be made by drawing a single line through the incorrect item ensuring that the previous entry is not obscured. Each correction must be dated and initialled. Correction fluid must not be used. The amended CRF must be sent to UCL CTC and a copy retained at site.

9.3 Missing Data

To avoid the need for unnecessary data queries CRFs must be checked at site to ensure there are no blank fields before sending to UCL CTC. When data are unavailable because a measure has not been taken or test not performed, enter "ND" for not done. If an item was not required at the particular time the form relates to, enter "NA" for not applicable. When data are unknown enter the value "NK" (only use if every effort has been made to obtain the data).

9.4 Timelines for Data Return

Sites must complete and return CRFs to UCL CTC as soon as possible after patient visit and within one month of the patient being seen.

Sites who persistently do not return data within the required timelines may be suspended from recruiting further patients into the study by UCL CTC and subjected to a 'for cause' monitoring visit. See section 12.3 ('For cause' on-site monitoring) for details.

9.5 Data Queries

Data arriving at UCL CTC will be checked for legibility, completeness, accuracy and consistency, including checks for missing or unusual values. Queries will be sent to the data contact at site. When responding to a query, site staff must print the query report, annotate their response on the report and ensure each page has been signed and dated by a member of staff delegated to data management duties on the Delegation Log and return the original copy to UCL CTC. There is no need to send updated CRFs unless specifically requested.

10 Safety Reporting

10.1 Definitions of Adverse Events

The following definitions have been adapted from Directive 2001/20/EC, ICH E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" and ICH GCP E6:

Adverse Event (AE)

Any untoward medical occurrence in a patient treated on a study protocol, which does not necessarily have a causal relationship with a study treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a study treatment, whether or not related to that study treatment.

Adverse Reaction (AR)

All untoward and unintended responses to a study treatment related to any dose administered. A causal relationship between a study treatment and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that at any dose:

- Results in death
- Is life threatening (the term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires in-patient hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is otherwise medically significant (e.g. important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above)

Related and Unexpected Serious Adverse Events

A serious adverse reaction, the nature or severity of which **is not consistent** with the applicable study treatment reference safety information (RSI).

10.2 Reporting Procedures

10.2.1 All Adverse Events (AEs)

All adverse events that occur between informed consent and 30 days post consolidation treatment (30 days post last study treatment if treatment is stopped early) must be recorded in the patient notes. Adverse events do not need to be reported for registration only patients (pathway E). Grade 3 and Grade 4 adverse events must be recorded on the study CRFs. Those meeting the definition of a Serious Adverse Event (SAE) must also be reported to UCL

CTC using the study specific SAE Report. Also refer to section 10.2.2 (Serious Adverse Events (SAEs)).

Pre-existing conditions do not qualify as adverse events unless they worsen.

Overdoses

All accidental or intentional overdoses, whether or not they result in adverse events, must be recorded in the patient notes and CRFs. Adverse events resulting from overdoses are classified as SAEs and must be reported to UCL CTC according to SAE reporting procedures. The fact that an overdose has occurred must be clearly stated on the SAE Report. Also refer to section 10.2.2 (Serious Adverse Events (SAEs)).

Sites must inform UCL CTC immediately when an overdose has been identified. Also refer to section 11 (Incident Reporting and Serious Breaches).

Adverse Event Term

An adverse event term must be provided for each adverse event, preferably using the term listed in the Common Terminology Criteria for Adverse Events (CTCAE) v4.0, available online at:

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Severity

Severity of each adverse event must be determined by using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 as a guideline, wherever possible. The criteria are available online at:

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

In those cases where the CTCAE criteria do not apply, severity should be coded according to the following criteria:

1 = Mild (awareness of sign or symptom, but easily tolerated)
2 = Moderate (discomfort enough to cause interference with normal daily activities)
3 = Severe (inability to perform normal daily activities)
4 = Life threatening (immediate risk of death from the reaction as it occurred)
5 = Fatal (the event resulted in death)

Causality

The PI, or other delegated site investigator, must perform an evaluation of causality for each adverse event.

Causal relationship to the treatment pathway must be determined as follows:

- **None**
  There is no evidence of any causal relationship.
- **Unlikely**
  There is little evidence to suggest a causal relationship (e.g. because the event did not occur within a reasonable time after administration of a study treatment). There is another reasonable explanation of the event (e.g. the patient's clinical condition, other concomitant treatments).

- **Possibly**

  There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of a study treatment). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).

- **Probably**

  There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

- **Definitely**

  There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

NOTE: Events will be classified as related to study treatment if evaluated as possibly, probably or definitely related by the investigator.

10.2.2 Serious Adverse Events (SAEs)

All SAEs that occur between the signing of informed consent and 30 days post consolidation treatment in patients on arms A-D (30 days post last study treatment if treatment is stopped early), or after this date if the site investigator feels the event is related to the study treatment) must be submitted to UCL CTC by fax within **24 hours** of observing or learning of the event, using the study specific SAE Report. All sections on the SAE Report must be completed. If the event is **not being reported within 24 hours** to UCL CTC, the circumstances that led to this must be detailed in the SAE Report to avoid unnecessary queries.

SAEs do not need to be reported for Registration only patients (pathway E).

Exemptions from SAE Report Submission

For this study, the following events are exempt from requiring submission on an SAE Report, but must be recorded in the relevant section(s) of the study CRFs:

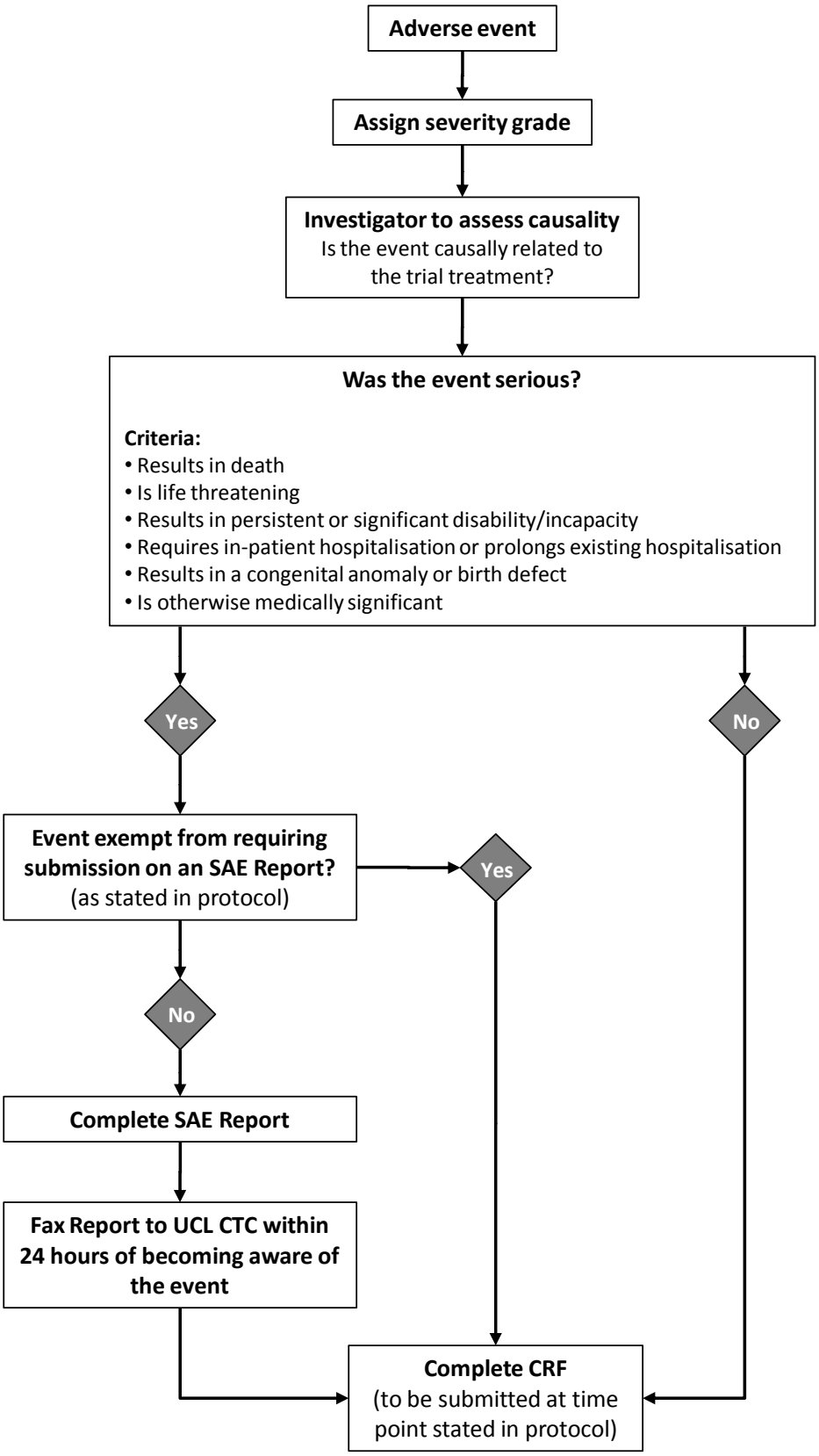
- deaths (refer to section 10.2.3 Urgent Events)
- disease progression
- secondary malignancy
- **any event that is listed in Appendix 10 as expected for ALL treatment**
- registration only (pathway E) patients
- SAEs during Maintenance unless specifically considered to be related to study treatment

Please note that hospitalisation for elective treatment or palliative care does not qualify as an SAE.

Completed SAE Reports must be faxed within 24 hours of becoming aware of the event to UCL CTC

Fax: +44 (0)20 7679 9861

Adverse Event Reporting Flowchart



SAE Follow-Up Reports

All SAEs must be followed-up until resolution and until there are no further queries. The PI, or other delegated site investigator, must provide follow-up SAE Reports if the SAE had not resolved at the time the initial report was submitted.

SAE Processing at UCL CTC

On receipt of the SAE Report, UCL CTC will check for legibility, completeness, accuracy and consistency. Expectedness will be evaluated, to determine whether or not the case qualifies for expedited reporting, using the list of expected adverse events in protocol appendix 10 for the study treatments.

The CI, or their delegate (e.g. a clinical member of the TMG), may be contacted to review the SAE and to perform an evaluation of causality on behalf of UCL CTC. If UCL CTC has considered expectedness difficult to determine, the CI, or their delegate, will be consulted for their opinion at this time.

10.2.3 Urgent Events

All deaths whether related to the disease or treatment pathway must be reported within 7 days using a Death form.

10.3 Related and Unexpected Serious Adverse Events

If the event is evaluated as a related and unexpected SAE, i.e. an unexpected serious adverse event that is evaluated as possibly, probably or definitely related to a study treatment UCL CTC will submit a report to the UK REC within 15 calendar days and to CCCs/CLSs for forwarding to their ethics committee(s) within the timeframe required in that country. UCL CTC will ensure that consideration is given where the reporting deadline occurs at a weekend to allow reporting within the required timeframe. Where there are conflicting evaluations of causal relationship by the site and UCL CTC/CI, both opinions will be reported.

Informing Sites of related and unexpected SAEs

UCL CTC will inform all UK PIs of any related and unexpected SAEs that occur on the study. PIs will receive a quarterly line listing which must be processed according to local requirements.

For participating countries outside the UK, UCL CTC will submit reports to CCC/CLSs for forwarding to the PIs in their country within one business day. Where there is no CCC/CLS, UCL CTC will submit related and unexpected SAEs reports directly to sites in that country.

10.4 Safety Monitoring

UCL CTC will provide safety information to the TMG and the IDMC on a periodic basis for review.

Study safety data will be monitored to identify:

- new adverse reactions to the study treatment combinations or individual components of the treatment pathways;
- study-related events that are not considered related to the study treatment pathway.

Should UCL CTC identify or suspect any issues concerning patient safety at any point throughout the study, the CI or TMG will be consulted for their opinion.

10.5 Pregnancy

If the a female patient on pathways A-D or the female partner of a male patient on pathways A-D becomes pregnant at any point during the study, a completed study-specific Pregnancy Report must be submitted to UCL CTC by fax within **24 hours** of learning of its occurrence. Consent to report information regarding the pregnancy must be obtained from the pregnant partner. The study-specific pregnancy monitoring information sheet and informed consent form for the partners of study patients must be used for this purpose.

All pregnancies must be reported by faxing a completed Pregnancy Report within 24 hours of becoming aware of the pregnancy to UCL CTC
Fax: +44 (0)20 7679 9861

Pregnancy Follow-Up Reports

For pregnant patients or partners who consent, their pregnancies must be followed-up until an outcome is determined. Follow-up Pregnancy Reports must be submitted to UCL CTC by fax within **24 hours** of learning of the outcome. Reports must include an evaluation of the possible relationship of each study treatment to the pregnancy outcome.

Pregnancy Report Processing at UCL CTC

UCL CTC will submit a report to the UK REC and CCCs/CLSs should the pregnancy outcome meet the definition of a related and unexpected SAE. Refer to section 10.3 (Related and Unexpected Serious Adverse Event) for details.

11 Incident Reporting and Serious Breaches

11.1 Incident Reporting

Organisations must notify UCL CTC of all deviations from the protocol or GCP immediately. UCL CTC may require a report on the incident(s) and a form will be provided if the organisation does not have an appropriate document (e.g. Trust Incident Form for UK sites).

If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the UCL CTC study team can be contacted immediately to discuss.

Where the incident has occurred in a site outside the UK, the CCC/CLS in that country must also notify the relevant ethics committee in accordance with local requirements. Where UCL CTC identifies an incident at a site outside the UK, the CCC/CLS in the country where the incident occurred will be informed.

UCL CTC will use an organisation's history of non-compliance to make decisions on future collaborations.

11.2 Serious Breaches

Systematic or persistent non-compliance by a site with GCP and/or the protocol, including failure to report SAEs occurring on study within the specified timeframe, may be deemed a serious breach.

In cases where a serious breach has been identified, UCL CTC will inform the REC within 7 calendar days of becoming aware of the breach.

The serious breach report may also be forwarded to CCCs/CLSs for submission to their ethics committees, as required.

UK sites must have written procedures for notifying sponsors of serious breaches, and are referred to the MHRA Guidance on the Notification of Serious Breaches.

12 Study Monitoring and Oversight

Participating sites and PIs must agree to allow study-related on-site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/documents as required. Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the consent form.

UCL CTC will determine the appropriate level and nature of monitoring required for the study. Risk will be assessed on an ongoing basis and adjustments made accordingly.

12.1 Central Monitoring

Sites will be requested to submit screening logs and staff delegation logs to UCL CTC at the frequency detailed in the study monitoring plan or on request and these will be checked for consistency and completeness. Also refer to sections 3.2.2 (Required Documentation) and 5.2 (Screening Logs).

Eligibility of all patients entered in the study is assessed by the PI, or, if delegated by the PI, other appropriately trained site staff. Checks of the criteria listed on the registration form will be undertaken by an appropriately trained UCL CTC staff member prior to registration. Also refer to section 6.1 (Registration).

Details relating to the informed consent process will be collected on the Registration form and are subject to review by CTC as part of patient eligibility.

Sites will be requested to conduct quality control checks of documentation held within the Investigator Site File at the frequency detailed in the study monitoring plan. Checklists detailing the current version/date of version controlled documents will be provided for this purpose.

Data received at UCL CTC will be subject to review in accordance with section 9.5 (Data Queries).

Where central monitoring of data and/or documentation submitted by sites indicates that a patient may have been placed at risk (e.g. an overdose) the matter will be raised urgently with site staff and escalated as appropriate (refer to section 11 (Incident Reporting and Serious Breaches) and 12.2 ('For cause' on-site monitoring) for further details).

12.2 'For Cause' On-Site Monitoring

On-site monitoring visits may be scheduled where there is evidence or suspicion of non-compliance at a site with important aspect(s) of the study protocol/GCP requirements. Sites will be sent a letter in advance outlining the reason(s) for the visit. The letter will include a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities, who will be performing the visit and when the visit is likely to occur.

Following a monitoring visit, the Trial Monitor/Trial Coordinator will provide a report to the site, which will summarise the documents reviewed and a statement of findings, deviations, deficiencies, conclusions, actions taken and actions required. The PI at each site will be responsible for ensuring that monitoring findings are addressed (this may be delegated to an appropriate member of staff).

UCL CTC will assess whether it is appropriate for the site to continue participation in the study. Refer to section 11 (Incident Reporting) for details.

12.3 Oversight Committees

12.3.1 Trial Management Group (TMG)

The TMG will include the Chief Investigator, clinicians and experts from relevant specialities and UKALL60+ study staff from UCL CTC (see page 3). The TMG will be responsible for overseeing the study. The group will meet regularly approximately twice a year and will send updates to PIs (via newsletters or at Investigator meetings) and to the NCRI Heamatology-Oncology Clinical Studies Group.

The TMG will review substantial amendments to the protocol prior to submission to the REC. All PIs will be kept informed of substantial amendments through their nominated responsible individuals. All members will sign a TMG charter.

12.3.2 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the study. The TSC will review the recommendations of the Independent Data Monitoring Committee and, on consideration of this information, recommend any appropriate amendments/actions for the study as necessary. The TSC acts on behalf of the funder and Sponsor. All members will sign a TSC charter.

12.3.3 Independent Data Monitoring Committee (IDMC)

The role of the IDMC is to provide independent advice on data and safety aspects of the study. Meetings of the Committee will be held annually to review interim analyses, or as necessary to address any issues. The IDMC is advisory to the TSC and can recommend premature closure of the study to the TSC. All members will sign an IDMC charter.

12.3.4 Role of UCL CTC

UCL CTC will be responsible for the day to day coordination and management of the study and will act as custodian of the data generated in the study (on behalf of UCL). UCL CTC is responsible for all duties relating to safety reporting which are conducted in accordance with section 10.0 (Safety Reporting).

13 Withdrawal of Patients

In consenting to the study, patients are consenting to study treatment, assessments, follow-up and data collection.

Discontinuation of Study Treatment for clinical reasons

A patient may be withdrawn from study treatment whenever continued participation is no longer in the patient's best interests, but the reasons for doing so must be recorded. Reasons for discontinuing treatment may include:

- Disease progression whilst on therapy
- Unacceptable toxicity
- Intercurrent illness which prevents further treatment
- Patients withdrawing consent to further study treatment
- Any alterations in the patient's condition which justifies the discontinuation of treatment in the site investigator's opinion

Patient withdrawal from study treatment

If a patient expresses their wish to withdraw from study treatment, sites should explain the importance of remaining on study follow-up, or failing this of allowing routine follow-up data to be used for study purposes and for allowing existing collected data to be used. If the patient gives a reason for their withdrawal, this should be recorded.

Withdrawal of Consent to Data Collection

If a patient explicitly states they do not wish to contribute further data to the study their decision must be respected and recorded on the relevant CRF. In this event details should be recorded in the patient's hospital records. Data up to and including the date of withdrawal must be sent to UCL CTC. Thereafter, no further CRFs must be completed and no further data sent to UCL CTC (or CCC/CLS for non-UK sites).

Losses to follow-up

If a patient moves from the area, every effort should be made for the patient to be followed up at another participating study site and for this new site to take over the responsibility for the patient, or for follow-up via GP. Details of participating study sites can be obtained from the UCL CTC study team who must be informed of the transfer of care and follow up arrangements. If the patient cannot be transferred to another participating site, the site that registered them into the study remains responsible for obtaining and submitting follow up data on the patient.

If a patient is lost to follow-up at a site, every effort should be made to contact the patient's GP to obtain information on the patient's status.

UK patients lost to follow up will be tracked by UCL CTC via the NHS Information Centre.

14 Study Closure

14.1 End of Study

The end of study will be defined as 1 year after the date the last patient completes all study treatment (including 2 years of maintenance),, at which point the 'declaration of end of study' form will be submitted to participating ethical committees, as required.

Following this, UCL CTC will advise sites on the procedure for closing the study at the site.

Once the end of study has been declared, no more prospective patient data can be collected.

14.2 Archiving of Study Documentation

At the end of the study, UCL CTC will archive securely all centrally held study related documentation for a minimum of 5 years. Arrangements for confidential destruction will then be made. It is the responsibility of PIs to ensure data and all essential documents relating to the study held at site are retained for a minimum of 5 years after the end of the study, in accordance with national legislation and for the maximum period of time permitted by the site.

Essential documents are those which enable both the conduct of the study and the quality of the data produced to be evaluated and show whether the site complied with the principles of GCP.

UCL CTC will notify sites when study documentation held at sites may be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

14.3 Early discontinuation of study

The study may be stopped before completion as an Urgent Safety Measure on the recommendation of the TSC or IDMC (see section 12.3.2 TSC and 12.3.3 IDMC). Sites will be informed in writing by UCL CTC of reasons for early closure and the actions to be taken with regards the treatment and follow up of patients.

14.4 Withdrawal from study participation by a site

Should a site choose to close to recruitment the PI must inform UCL CTC in writing. Follow up as per protocol must continue for all patients recruited into the study at that site and other responsibilities continue as per CTSA.

15 Statistics

15.1 Sample size calculation

We will aim to recruit 148 patients to pathways A-D over 5 years. This figure does not include patients who are entered into the registration only pathway (pathway E).

Any patient found to be ineligible due to a misdiagnosis will be excluded and replaced.

We hope to find a 75% complete response rate for each treatment pathway, however a complete response rate of 60% or more would be considered clinically worthwhile and merit investigating further. With these parameters and using an A'Hern single stage, Phase II design, with a 15% significance level and 80% power we require 37 patients for each treatment pathway, giving a total of 148 patients.

15.2 Population for analysis

All analyses will be on the ITT population however we may also look at subgroups of patients that completed 2 sessions of induction.

15.3 Analysis of the primary endpoint

Primary Endpoint
Complete remission rate after 2 phases of induction.

The primary endpoint is the complete response rate and pathway will be judged to be effective if the lower bound of the 70% confidence interval is greater than 60%.

15.4 Analysis of secondary endpoints

15.4.1 Efficacy (secondary)

- EFS at one year
- Overall survival
- Rates of complete remission after 1 phase of induction.
- The Prognostic significance of molecularly determined minimal residual disease (MRD) at various time-points during therapy with respect to relapse occurrence.

Kaplan Meier methods will be used to examine the event free and overall survival proportions at one year as well as the median time to event and death.

Event free survival will be measured as the time between registration and progression, relapse, death or the development of a second malignancy. Patients alive without progression/relapse/second malignancy will be censored at the date they were last seen.

Overall survival time will be measured as the time between registration and death.

The baseline characteristics of each group will also be investigated to see which patients are chosen for each pathway. Due to the relatively small numbers (patients in each group) mainly descriptive statistics will be used.

15.4.2 Safety

Rates of treatment related mortality, toxicity and duration of hospitalisation will be calculated for each pathway.

15.4.3 Health related Quality of Life

Quality of life will be measured at baseline, after each discrete block of therapy, before starting maintenance and 3 monthly during maintenance, and will be analysed using methods for repeated measures, such as mixed modelling.

The following questionnaires will be used:
EORTC QLQ-C30, EORTC CIPN20, FACT-Leu, FACIT-FATIGUE

15.5 Interim analyses

There are no formal interim analyses for efficacy planned however an independent data monitoring committee will review the study once a year.

Stopping rules for toxicity:
The treatment related mortality (TRM) rate will be examined after 10 patients have been recruited in a pathway and every 5 patients thereafter.
The maximum acceptable treatment related mortality rate is 15%. If the rates exceed these the pathway would be considered too harmful. The table below shows the numbers of observed events we would need to trigger a TMG safety review or consider stopping recruitment.

Number of Patients (N)	Number of TRMs needed for TMG safety review (more than 15% of N)	Number of TRMs needed to consider stopping
10	2	4
15	3	6
20	4	7
25	4	8
30	5	9
35	6	10

The number of events needed to consider stopping recruitment early is such that the exact lower 95% CI (one-sided) exceeds 15% i.e. the true rate is likely to exceed these limits.

16 Ethical Approvals

In conducting the study, the Sponsor, UCL CTC and sites shall comply with all laws and statutes, as amended from time to time, applicable to the performance of clinical trials including, but not limited to:

- the principles of ICH Harmonised Tripartite Guideline for Good Clinical Practice the Human Rights Act 1998
- the Data Protection Act 1998
- the Freedom of Information Act 2000
- the Human Tissue Act 2004
- the Research Governance Framework for Health and Social Care, issued by the UK Department of Health (Second Edition 2005) or the Scottish Health Department Research Governance Framework for Health and Community Care (Second Edition 2006)

All non-UK sites shall comply with all their local laws and statutes applicable to the performance of clinical trials.

16.1 Ethical Approval

The study will be conducted in accordance with the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (1996 version) and in accordance with the terms and conditions of the ethical approval given to the study.

The study has received a favourable opinion in the UK from the London – Bloomsbury Research Ethics Committee. Non-UK collaborators will obtain separate ethical approval for their country.

UCL CTC will submit Annual Progress Reports to the REC, which will commence one year from the date of ethical approval for the study.

16.2 Site Approvals

The Lead Comprehensive Local Research Network (CLRN) **(**North Thames) has given NHS permission following global governance checks. Local governance checks will be undertaken by local CLRNs associated with individual study sites.

Evidence of approval from the Trust R&D for a study site must be provided to UCL CTC. Sites will only be activated when all necessary local approvals for the study have been obtained.

All non-UK sites must provide confirmation of approval of their local institution(s).

16.3 Protocol Amendments

UCL CTC will be responsible for gaining ethical approval for amendments made to the protocol and other study-related documents. Once approved, UCL CTC will ensure that all amended documents are available on the UCL CTC website (http://www.ctc.ucl.ac.uk/) and distributed to sites as appropriate.

Site staff will be responsible for acknowledging receipt of documents and for implementing all amendments.

16.4 Patient Confidentiality & Data Protection

Patient identifiable data, including patient initials date of birth and NHS/CHI number (UK sites only) will be required for the registration process and will be provided to UCL CTC. UCL CTC will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a secure manner and UCL CTC trials are registered in accordance with the Data Protection Act 1998 with the Data Protection Officer at UCL.

17 Sponsorship and Indemnity

17.1 Sponsor Details

Sponsor Name:	University College London
Address:	Joint Research Office Gower Street London WC1E 6BT
Contact:	Director of Research Support
Tel:	020 3447 9995/2178 (unit admin)
Fax:	020 3447 9937

17.2 Indemnity

University College London holds insurance against claims from participants for injury caused by their participation in the study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or not.

Hospitals selected to participate in this study shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

18 Funding

Cancer Research UK has provided funding for the study with a feasibility project grant (ref no. C27995/A13920) via the Clinical Trials Award & Advisory Committee (CTAAC) for the support of the central coordination of the study through UCL CTC.

19 Publication Policy

The TMG will authorise publications and presentation relating to the study.
The TMG will form the writing committee.
Named authors on main study publication will be CI, Trial Coordinator, TMG members and Trial Statistician.
All participating sites will be acknowledged e.g. Sites, PI, Co-Is, research nurses etc. at end of publication.
Sites need prior written consent from TMG to publish any data related to the study and may not request this prior to first publication by TMG.
The clinicaltrials.gov number (or equivalent unique trial I.D.) will be quoted in all publications relating to study.
UCL own the data.

20 Translational Research

The arrangements outlined below relate to samples from UK sites. Non UK sites should refer to the appropriate country-specific appendix for details of sample shipping in their country.

20.1 MRD Samples

For patients on pathways A-D who have consented to provide samples for MRD analysis, bone marrow samples will be sent to the MRD Laboratory at the UCL Cancer Institute for Minimal Residual Disease analysis at 4 points during the study.

1. At Diagnosis (pre-study registration*)
2. After Phase 1 of Induction
3. After Phase 2 of Induction
4. a) After Intensification (for patients on the pathway B ONLY)
   OR
   b) After Consolidation 1 (pathways A. C & D)

For patients on pathway E who have consented to provide samples for MRD analysis, a diagnostic sample should be sent, and follow up bone marrow samples sent at up to 3 clinically relevant timepoints.

Relapse: Please note that an additional bone marrow sample should be sent to the MRD Laboratory if a patient relapses. This sample should be from the routine sample taken to diagnose relapse.

*Please do not send the diagnostic sample until the patient has consented

Consent
Information about the samples to be sent for translational research will be presented in the patient information sheet. Patients will be required to consent to this by signing Part 2 of the consent form. The first question on this form refers to the extra bone marrow sample taken after Intensification/ Consolidation 1 which is currently not part of standard response assessment. The second question is for sending peripheral blood and/or bone marrow samples for MRD analysis. Patients do not need to consent to sending the additional sample to take part in the translational research. If a patient does not consent to this extra sample, but consents to sending samples for MRD Analysis, please still send the first 3 samples.
Consent for sample collection will be recorded on the registration form.

Patients registered into the Registration only pathway (pathway E) for data collection only will be able to consent to the translational research if they wish. The timing of follow up samples will vary depending upon the nature of treatment, however the treating clinician may send samples at up to 3 clinically relevant timepoints of their choice.

Samples required
At each time point, 2-5mls of bone marrow should be placed into an EDTA collection tube.
For the diagnostic sample only, 10-20mls of peripheral blood collected into an EDTA tube is also acceptable if a bone marrow sample is not available/feasible.

Level of Consent	Time point	Pathway			
		A	B	C	D
Consented to sending samples for analysis (Part 2, Q. 2)	Diagnosis	X	X	X	X
	After Phase 1 Induction	X	X	X	X
	After Phase 2 Induction	X	X	X	X
Consented to sending samples for analysis AND An additional bone marrow sample (Part 2, Q. 2)	After Intensification		X		
	After Consolidation 1	X		X	X

Request forms

MRD sample request forms will be provided in the Investigator Site File from UCL CTC. A sample request form should be included with each sample sent to the laboratory. It is important that you complete the blast % in the bone marrow as we need this to interpret the result. It is also important to give as much immunophenotyping information as you have available, since it assists us to set up the correct MRD marker panel.

Transport

The diagnostic sample should be sent using local packaging and sent by first class post.
Once a patient has been registered into the study, the site will be sent 3 Royal Mail Safe boxes from UCL CTC for the following 3 samples.

Samples should be posted to the address below:

Adult ALL MRD laboratory
URGENT (FAO Ghada Zakout, Adele Fielding) UKALL60+ STUDY SAMPLE
UCL Cancer Institute
Paul O'Gorman Building
University College London
72 Huntley Street
London UK
WC1E 6DD

A laboratory agreement will be in place between the MRD laboratory and UCL CTC.

For samples taken on a Friday, or before a Bank Holiday weekend, please store in a fridge until the next working day and send via 1st class post.

Sample processing

On receipt of the bone marrow sample, the MRD laboratory will assign the patient and the sample a unique number according to the Standard Operating Procedure.

Analysis

The laboratory will quantify MRD by immunoglobulin/T cell receptor gene re-arrangements for Ph-ALL and BCR-ABl quantification for Ph+ ALL and carry out flow cytometric determination of antigen expression at diagnosis.

UK MRD network of laboratories

MRD monitoring for this study will be undertaken at the UCL Cancer Institute headed by Dr Adele Fielding. This laboratory has recently joined the UK network of MRD laboratories. This network was conceived for the purpose of MRD monitoring for the current UK childhood trial (UKALL 2003) as such it has demonstrated a robust framework for providing quality assured results.

The UK MRD network acts as a virtual single laboratory using a standard operating procedure and centrally distributed reagents to measure MRD by the Real time quantitative (RQ PCR) Allele Specific Oligonucleotide (ASO) PCR method. This technique is considered to be the most widely applicable and sensitive approach to MRD detection in ALL. The network is co-ordinated by clinical and scientific leads based at Bristol Children's Hospital and headed by a Steering committee chaired by Professor Nicholas Cross. It participates in national and European External Quality Assurance schemes under Professor J Van Dongen's direction.

Funding

Sites will not be charged for the MRD analysis within the UKALL60+ study. Sites will be required to fund the cost of packaging and sending the initial bone marrow sample.

20.2 Constitutional DNA Samples

DNA from non-leukaemic samples will be analysed at the UCL School of Medicine for genetic changes that may be associated and/or linked with ALL in adults. This DNA will be obtained in one of two ways depending on when the patient was registered and their MRD status.

For patients registered on the study prior to protocol v3.0, constitutional DNA can be obtained from bone marrow remission samples (provided a MRD negative status was achieved), which are currently collected for MRD studies and then stored. If these patients did not achieve a MRD negative status then a buccal swab will be taken to collect DNA. The UCL CTC will notify sites which is required for their patient(s).

For patients registered into the study from the implementation of protocol v3.0 onwards, a buccal swab will be taken around the time of registration.

Consent

Information about the samples required for translational research/constitutional analysis will be presented in one of two additional patient information sheets; one for consent to use bone marrow samples previously collected and one for the collection of a buccal swab. This aspect of the study is optional, and patients may decline to donate constitutional DNA samples but remain on study.

Samples required

Bone marrow – This sample will have already been collected and stored, no additional sample is required.
Buccal swab – Cheek cells to be swabbed at baseline (or later in patients who have never achieved CR) as follows:

1. Verify that the patient’s mouth is empty
2. Wash or sanitize hands then put on gloves and mask
3. Use the swab provided by UCL CTC
4. Carefully remove swab from package
5. Avoid touching swab tip with gloves or against any surface
6. Have the patient open his or her mouth and immediately bring swab tip to inside of cheek
7. Gently rub and rotate swab along the inside of the cheek for 5-10 seconds, ensuring that the entire swab-tip has made contact with the cheek
8. Immediately remove swab, being careful not to touch swab tip against teeth, lips, or other surface
9. Place swab directly into dry transport tube or collection envelope
10. Label the tube or envelope with the patient’s study number and initials
11. Complete the Buccal Swab Sample Request Form and include with the swab
12. Send to the following address by first class post (NB if sending a MRD sample, the swab may be included in the same package):

Minimal Residual Disease Laboratory
URGENT (FAO Ghada Zakout, Adele Fielding) UKALL60+ STUDY SAMPLE
Adult ALL MRD laboratory
UCL Cancer Institute
Paul O'Gorman Building
University College London
72 Huntley Street
London UK
WC1E 6DD

Sample processing & Analysis
The laboratory will extract DNA and appropriate genomic analysis will be applied.

20.3 Leukaemia Research Cytogenetics Group (LRCG)

The leukaemia Research Cytogenetics Group (LRCG) will be coordinating cytogenetic analysis by working with regional cytogenetics laboratories. To do this they will be collecting patient details including study number, initials, date of birth and NHS/CHI number.

21 References

Annino, L., Goekbuget, N., and Delannoy, A. (2002) Acute lymphoblastic leukemia in the elderly. *Hematol.J.*, 3(5), pp. 219-223.

Aaronson, NK., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, NJ., Filiberti, A., Flechtner, H., Fleishman, SB., de Haes, JC., Kaasa, S., Klee, M., Osoba, D., Razavi, D., Rofe PB, Schraub S, Sneeuw K, Sullivan M, Takeda F.. (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 85(5), pp. 365-76.

Bennett, MI., Smith, BH., Torrance, N., Potter, J. (2005) The S-LANSS score for identifying pain of predominantly neuropathic origin: validation for use in clinical and postal research. *J Pain*. 6(3), pp.149-58.

Brüggemann, M., Raff, T., Flohr, T., Gökbuget, N., Nakao, M., Droese, J., Lüschen, S., Pott, C., Ritgen, M., Scheuring, U., Horst, HA., Thiel, E., Hoelzer, D., Bartram, CR., Kneba, M. (2006) Clinical significance of minimal residual disease quantification in adult patients with standard-risk acute lymphoblastic leukemia. *Blood*, 107(3), pp. 1116-1123.

Charlson, ME., Pompei, P., Ales, KL., MacKenzie, CR. (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 40(5),pp. 373-83.

Chu E. 2004. *Physician's Cancer Chemotherapy Drug Manual 2004*. First Edition. Sudbury: Jones and Bartlett Publishers.

Extermann, M., Boler, I., Reich, RR., Lyman, GH, Brown, RH., DeFelice, J., Levine, RM., Lubiner, ET,, Reyes, P., Schreiber, FJ 3rd., Balducci, L. (2012) Predicting the Risk of Chemotherapy Toxicity in Older Patients: The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) Score. *Cancer*, 118(13), pp. 3377-3386.

Fielding, AK. (2011) Philadelphia-positive acute lymphoblastic leukemia--is bone marrow transplant still necessary? *Biol. Blood Marrow Transplant*, 17(1), S84-S88.

Huguet, F., Leguay, T., Raffoux, E., Thomas, X., Beldjord, K., Delabesse, E., Chevallier, P., Buzyn, A., Delannoy, A., Chalandon, Y., Vernant, JP., Lafage-Pochitaloff, M., Chassevent, A., Lhéritier, V., Macintyre, E., Béné, MC., Ifrah, N., Dombret, H. (2009) Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. *J Clin Oncol*. 27(6), pp. 911-918.

Huntington, SF., Talbott, MS., Greer, JP., Morgan, DS., Reddy, N. (2012) Toxicities and outcomes among septuagenarians and octogenarians with diffuse large B-cell lymphoma treated with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone therapy. *Leuk Lymphoma*, 53(8), pp. 1461 – 1468.

Hussein, KK., Dahlberg, S., Head, D., Waddell, CC., Dabich, L., Weick, JK., Morrison, F, Saiki, JH., Metz, E., Rivkin, SE., Grever, MR.(1989) Treatment of acute lymphoblastic leukemia in adults with intensive induction, consolidation, and maintenance chemotherapy. *Blood*, 73(1) pp. 57-63.

Kantarjian, HM., O'Brien, S., Smith, TL., Cortes, J., Giles, FJ., Beran, M., Pierce, S., Huh, Y., Andreeff, M., Koller, C., Ha, CS., Keating, MJ., Murphy, S., Freireich, EJ. (2000) Results of Treatment With Hyper-CVAD, a Dose-Intensive Regimen, in Adult Acute Lymphocytic Leukemia. *Journal of Clinical Oncology*. 18(3), pp. 547-561.

Larson, RA., Dodge, RK., Linker, CA., Stone, RM., Powell, BL., Lee, EJ., Schulman, P., Davey, FR., Frankel, SR., Bloomfield, CD., George, SL., and Schiffer, CA. (1998) A randomized controlled trial of filgrastim during remission induction and consolidation chemotherapy for adults with acute lymphoblastic leukemia: CALGB study 9111. *Blood*, 92(5), pp. 1556-1564.

Loblaw, DA., Bezjak, A., and Bunston, T. (1999) Development and testing of a visit-specific patient satisfaction questionnaire: The Princess Margaret Hospital satisfaction with doctor questionnaire. *Journal of Clinical Oncology*, 17(6), pp. 1931-1938.

Martell, MP., Atenafu, EG., Minden, MD., Schuh, AC., Yee, KW., Schimmer, AD., Gupta, V., Brandwein, JM. (2013) Treatment of elderly patients with acute lymphoblastic leukaemia using a paediatric-based protocol. *Br J Haematol,* 3(4), pp. 458-464.

Moorman, AV., Chilton, L., Wilkinson, J., Ensor, HM., Bown, N., & Proctor SJ. (2010) A population based cytogenetic study of adults with acute lymphoblastic leukemia. *Blood*, 115(2), pp. 206-214.

Patel, B., Rai, L., Buck, G., Richards, SM., Mortuza, Y., Mitchell, W., Gerrard, G., Moorman, AV., Duke, V.,Hoffbrand, AV., Fielding, AK., Goldstone, AH., Foroni, L. (2010) Minimal residual disease is a significant predictor of treatment failure in non T-lineage adult acute lymphoblastic leukaemia: final results of the international trial UKALL XII/ECOG2993. *Br J Haematol*, 148(1), pp. 80-89.

Pulte, D., Gondos, A., & Brenner, H. (2009) Improvement in survival in younger patients with acute lymphoblastic leukemia from the 1980s to the early 21st century. *Blood*, 113(7), pp. 1408-1411.

Rowe, JM., Buck, G., Burnett, AK., Chopra, R., Wiernik, PH., Richards, SM., Lazarus, HM., Franklin, IM., Litzow, MR., Ciobanu, N., Prentice, HG., Durrant, J., Tallman, MS., Goldstone, AH. (2005). Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. *Blood*, 106(12)**,** pp. 3760-3767.

Shi, Q., Wang, XS., Mendoza, TR., Pandya, KJ., Cleeland, CS. (2009) Assessing persistent cancer pain: a comparison of current pain ratings and pain recalled from the past week. *J Pain Symptom Manage*. 37(2) pp. 168-174.

Sive, JI., Buck, G., Fielding, AK., Lazarus, HM., Litzow MR., Luger, S., Marks, DI., McMillan, A., Richards, SM., Rowe, J., Tallman, M., and Goldstone, AH. (2010) Inability to Tolerate Standard Therapy Is a Major Reason for Poor Outcome In Older Adults with Acute Lymphoblastic Leukemia (ALL): Results From the International MRC/ECOG Trial . (Abstract).American Society of Haematology 2010 meeting.

Sive, JI., Buck, G,, Fielding, AK,, Lazarus, HM., Litzow, MR., Luger, S., Marks, DI., McMillan, A., Moorman, AV., Richards, SM., Rowe, JM., Tallman, MS., Goldstone, AH. (2012) Outcomes in older adults with acute lymphoblastic leukaemia (ALL): results from the international MRC UKALL XII/ECOG2993 trial. *Br J Haematol*, 157(4), pp. 463-471.

Taylor, PR., Reid, MM., Bown, N., Hamilton, PJ., and Proctor, SJ. (1992) Acute lymphoblastic leukemia in patients aged 60 years and over: a population-based study of incidence and outcome. *Blood*, 80(7), pp. 1813-1817.

van de Schans, SA., Wymenga, AN., van Spronsen, DJ., Schouten, HC., Coebergh, JW., Janssen-Heijnen, ML. (2012) Two sides of the medallion: poor treatment tolerance but better survival by standard chemotherapy in elderly patients with advanced-stage diffuse large B-cell lymphoma. *Ann Oncol*, 23(5), pp. 1280-1286.

Vignetti, M., Fazi, P., Cimino, G., Martinelli, G., Di, RF., Ferrara, F., Meloni, G., Ambrosetti, A., Quarta, G., Pagano, L., Rege-Cambrin, G., Elia, L., Bertieri, R., Annino, L., Foa, R., Baccarani, M., and Mandelli, F. (2007) Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome-positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL0201-B protocol. *Blood*, 109(9), pp. 3676-3678.

Ware, JE. (2000) SF-36 health survey update. *Spine*, 25(4), pp 3130-3139.

Wassmann, B., Pfeifer, H., Goekbuget, N., Beelen, DW., Beck, J., Stelljes, M., Bornhauser, M., Reichle, A., Perz, J., Haas, R., Ganser, A., Schmid, M., Kanz, L., Lenz, G., Kaufmann, M., Binckebanck, A., Bruck, P., Reutzel, R., Gschaidmeier, H., Schwartz, S., Hoelzer, D., and Ottmann, OG. (2006) Alternating versus concurrent schedules of imatinib and chemotherapy as front-line therapy for Philadelphia positive acute lymphoblastic leukemia (Ph+ ALL). *Blood*, 108(5), pp. 1469-1477.

Yellen, SB., Cella, DF., Webster, K., Blendowski, C., Kaplan, E,. (1997) Measuring fatigue and other anaemia related symptoms with the functional assessment of cancer therapy (FACT) measurement system. *J. Pain Sympto Management*; 13(2) pp 63-74.

Appendix 1: Abbreviations

6MP	6-mercaptopurine
AE	Adverse Event
ALL	Acute lymphoblastic leukaemia
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute Neutrophil Count
AR	Adverse Reaction
AST	Aspartate aminotransferase
CCC	Country Coordinating Centre
CI	Chief Investigator
CLRN	Comprehensive Local Research Network
CLS	Country Lead Site
CR	Complete response
CrCl	Creatinine clearance
CRi	Complete response with incomplete haematopoietic recovery
CRF	Case Report Form
CTAAC	Clinical Trials Advisory & Awards Committee
CTCAE	Common Terminology Criteria for Adverse Events
CTSA	Clinical Trial Site Agreement
DPA	Data Protection Act
EDTA	Ethylene Diamine Tetra Acetate
EEA	European Economic Area
FBC	Full Blood Count
GFR	Glomerular Filtration Rate
ICH GCP	International Conference of Harmonisation-Good Clinical Practice
IDMC	Independent Data Monitoring Committee
ISRCTN	International Standard Randomised Controlled Trial Number
IT	Intrathecal
IV	Intravenous
LDH	Lactate Dehydrogenase
LFT	Liver Function Tests
MTX	Methotrexate
NCRI	National Cancer Research Institute
NCRN	National Cancer Research Network
NRES	National Research Ethics Service
OS	Overall Survival
PI	Principal Investigator
PO	By mouth
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SPC	Summary of Product Characteristics
SSA	Site Specific Assessment
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UCL CTC	CR UK and UCL Cancer Trials Centre
U&E	Urea and Electrolytes
ULN	Upper Limit of Normal
WBC	White Blood Cells

Appendix 2: Criteria for assessing response

CR

Less than 5% lymphoblasts by conventional light microscopy with haematological recovery

CRi

CR but with incomplete haematopoietic recovery in the absence of any other extramedullary disease

Definition of haematopoietic recovery

Neutrophils > 0.75 x 10^9/L and platelets > 75 x 10^9/L.

Appendix 3: ECOG and Karnofsky scoring systems

ECOG scoring system

Score	Definition
0	Asymptomatic and fully active
1	Symptomatic; fully ambulatory; restricted physically strenuous activity
2	Symptomatic; ambulatory; capable of self-care; more than 50 percent of waking hours are spent out of bed
3	Symptomatic; capable of limited self care; spends more than 50 percent of time in bed but not bedridden.
4	Completely disabled; no self-care; bedridden

Karnofsky scoring system

Karnofsky Performance Status Scale Definitions Rating (%) Criteria

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Appendix 4: Charlson Index

The Charlson comorbidity index or Charlson Score predicts the ten-year mortality for a patient who may have a range of co-morbid conditions such as heart disease, AIDS, or cancer (a total of 22 conditions). Each condition is assigned with a score of 1,2,3 or 6 depending on the risk of dying associated with this condition.

	SCORE: 0=No, 6=Yes
AIDS(Not just HIV positive)	
Metastatic solid tumour	
	SCORE: 0=No, 3=Yes
Moderate-severe liver disease	
	SCORE: 0=No, 2= Yes
Cerebrovascular disease (hemiplegia)	
Moderate or severe renal disease	
Diabetes with end organ damage	
Tumour without metastasis (exclude if >5 years from diagnosis)	
Leukaemia (acute or Chronic)	
Lymphoma	
	SCORE: 0=No, 1=Yes
Myocardial infarction (history, not ECG changes only)	
Congestive Heart Failure	
Peripheral Vascular Disease (includes aortic aneurysm >6cm	
Cerebrovascular disease (with mild or no residual TIA)	
Dementia	
Chronic Pulmonary Disease	
Connective Tissue Disease	
Peptic ulcer disease	
Mild Liver disease	
Diabetes	
TOTAL (max 37)	

Appendix 5: Chemotherapy Risk Assessment Scale for High risk patients (CRASH)

The CRASH score (Extermann et al, 2012) for each patient should be calculated using the online calculator:

http://eforms.moffitt.org/crashscore.aspx

The information below gives an outline of how the score is assessed:

Chemotherapy Risk (Score 0-2)

0	1	2
Capecitabine 2g	Capecitabine 2.5g	5-FU/LV (Roswell-Park)
Cisplatin/pemetrexed	Carboplatin/gemcitabine AUC 4-6/1g d1,d8	5-FU/LV (Mayo)
Dacarbazine	Carboplatin/pemetrexed	5-FU/LV + bevacizumab
Docetaxel weekly	Carboplatin/paclitaxel q3w	CAF
FOLFIRI	Cisplatin/gemcitabine d1,8	Carboplatin/docetaxel q3w
Gemcitabine 1g 3/4 weeks	ECF	CHOP
Gemcitabine 1.25g 3/4 weeks	Fludarabine	Cisplatin/docetaxel 75/75
Paclitaxel weekly	FOLFOX 85mg	Cisplatin/etoposide
Pemetrexed	Gemcitabine 7/8 weeks then 3/4	Cisplatin/gemcitabine d1,8,15
	Gemcitabine/irinotecan	Cisplatin/paclitaxel 135-24h q3w
	PEG doxorubicin 50mg q4w	CMF classic
	Topotecan weekly	Doxorubicin q3w
	XELOX	FOLFOX 100-130 mg
		Gemcitabine/pemetrexed d8
		Irinotecan q3w
		Paclitaxel q3w
		Docetaxel q3w
		Topotecan monthly

Haematological Risk Factors

Diastolic blood pressure (0-1)
Instrumental Activities of Daily Living (0-1)
LDH (0-2)

Diastolic blood pressure	
>72	1
Otherwise	0
IADL	
<26	1
Otherwise	0
LDH (If ULN = 618, otherwise, >0.75 ULN)	
>459	2
Otherwise	0

Non-Haematological Risk Factors

ECOG (0-2)
Mini Mental Status (0-2)
Mini Nutritional Assessment (0-2)

ECOG PS	
0	0
1-2	1
3-4	2
Mini Mental Status	
<30	2
30	0
Mini Nutritional Assessment	
<28	2
Otherwise	0

The calculator will generate three scores:
Haem score
Non Haem score
Combined score

The **combined** score will detail the patient's overall risk of toxicity in this chemotherapy pathway.
We expect that the **non-haematological** toxicity score will be potentially most informative in predicting overall risk of toxicity in this patient group, but the **haematological** and **combined** scores will also be analysed.

Appendix 6: FACIT- Fatigue Scale (version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some -what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

English (Universal)
16 November 2007
Copyright 1987, 1997

Reproduced with permission from http://www.facit.org/FACITOrg/Questionnaires

Appendix 7: FACT-LEU (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness.....	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying.....	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home).....	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life.....	0	1	2	3	4
GF4	I have accepted my illness.....	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
BRM2	I am bothered by the chills	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
TH1	I bleed easily	0	1	2	3	4
TH2	I bruise easily	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU5	I feel uncertain about my future health	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4

English (Universal) 16 November 2007
Copyright 1987, 1997

Reproduced with permission from http://www.facit.org/FACITOrg/Questionnaires

Appendix 8: EORTC QLQ C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

© Copyright 1995 EORTC Quality of Life Group. All rights reserved. Version 3.0

Appendix 9: EORTC QLQ CIPN20

ENGLISH

EORTC QLQ – CIPN20

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31	Did you have tingling fingers or hands?	1	2	3	4
32	Did you have tingling toes or feet?	1	2	3	4
33	Did you have numbness in your fingers or hands?	1	2	3	4
34	Did you have numbness in your toes or feet?	1	2	3	4
35	Did you have shooting or burning pain in your fingers or hands?	1	2	3	4
36	Did you have shooting or burning pain in your toes or feet?	1	2	3	4
37	Did you have cramps in your hands?	1	2	3	4
38	Did you have cramps in your feet?	1	2	3	4
39	Did you have problems standing or walking because of difficulty feeling the ground under your feet?	1	2	3	4
40	Did you have difficulty distinguishing between hot and cold water?	1	2	3	4
41	Did you have a problem holding a pen, which made writing difficult?	1	2	3	4
42	Did you have difficulty manipulating small objects with your fingers (for example, fastening small buttons)?	1	2	3	4
43	Did you have difficulty opening a jar or bottle because of weakness in your hands?	1	2	3	4
44	Did you have difficulty walking because your feet dropped downwards?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week :	Not at All	A Little	Quite a Bit	Very Much
45 Did you have difficulty climbing stairs or getting up out of a chair because of weakness in your legs?	1	2	3	4
46 Were you dizzy when standing up from a sitting or lying position?	1	2	3	4
47 Did you have blurred vision?	1	2	3	4
48 Did you have difficulty hearing?	1	2	3	4
Please answer the following question only if you drive a car				
49 Did you have difficulty using the pedals?	1	2	3	4
Please answer the following question only if you are a man				
50 Did you have difficulty getting or maintaining an erection?	1	2	3	4

© QLQ-CIPN20 Copyright 2003 EORTC Quality of life Group. All rights reserved

Appendix 10: Expected Adverse Events

AEs Expected for ALL Treatment

It has been extensively documented in published literature that patients who are treated with chemotherapy for haematological malignancies, experience a number of common adverse events.

The individual drugs contained in the chemotherapy pathways may differ, however tend to be based around the same combination of three drug types:

Steroid (e.g. Dexamethasone or Prednisolone), Vinca-alkaloid (e.g. Vincristine or vinblastine) and Anthracycline (Doxorubicin or Idarubicin)

Therefore the following AEs will be considered expected for pathways A, B, C & D, even if fatal (see references below):

Blood and lymphatic system disorders Anemia Bone marrow hypocellular Febrile Neutropenia	Gastrointestinal Disorders Constipation Diarrhoea Gastritis Mucositis oral Nausea Vomiting
General Disorders and Administration Site Conditions Edema (any site listed in CTCAE v4.0) Fever Fatigue Malaise	Infections and Infestations (any site, any pathogen, to be classified as below:) Sepsis Infections and infestations- other- Pneumocystis Pneumonia Infections and infestations- other- bacterial Infections and infestations- other- viral Infections and infestations- other- fungal
Investigations Alanine aminotransferase Increased Alkaline phosphatase Increased Aspartate aminotransferase Increased Blood bilirubin increased Creatinine increased Neutrophil count decreased Platelet count decreased Serum amylase increased Weight loss White blood cell decreased	Metabolism and Nutrition Disorders Anorexia Dehydration Hypoalbuminemia Hyperglycemia Tumor lysis syndrome
Nervous System Disorders Paresthesia Peripheral motor neuropathy Peripheral Sensory Neuropathy	Vascular Disorders Thromboembolic event (e.g venous thrombosis, deep vein thrombosis, pulmonary embolism)
Hepatobiliary Disorders Hepatic failure	Skin and subcutaneous tissue disorders Rash maculo-papular
Musculoskeletal and connective tissue disorders Muscle weakness lower limb	

Reports of Serious Adverse Reactions not listed in this appendix will be considered unexpected and will be reported to the ethics committee.

Adverse events will not be collected for Registration only patients (pathway E).

References

Kantarjian *et al*, 2000, Chu, 2004, Huguet *et al*, 2009, van de Schans *et al*, 2011, Huntington *et al*, 2012, Sive *et al*, 2012, Martelle *et al*, 2013.

Appendix 11: Quick Reference Guides to Patient Visits

Philadelphia +ve patients (Pathway A)

Procedure/Time point	Prior to registration	At the end of Phase 1 & Phase 2 Induction	At the end of consolidation 1	Before starting maintenance	6-12 weeks after starting maintenance	Every 3 months during maintenance	At the end of maintenance	Follow up
Full medical history	X							
Physical examination	X	X	X			X		X
Height Weight, BSA & blood pressure	X							
Confirmation of disease diagnosis	X							
Bone marrow aspirate and trephine biopsy	X	X	X					
Cytogenetic, FISH & molecular genetic analysis to confirm Philadelphia –ve/+ve status	X							
Lumbar puncture	X[1]							
Full blood count & biochemistry i.e U&Es & LFTs, specifically Creatinine, Bilirubin & ALT/AST	X	X	X			X		X
ECOG & Karnofsky performance status	X	X	X	X		X		
Assessment of co-morbidities by CRASH & Charlson Index	X			X				
Remission status (% bone marrow blasts)		X	X					
Remission status (presence or absence of CR)						X[2]	X[2]	X[2]
Number of inpatient days		X	X			X		
Review of Adverse Events		X	X					
Demographic Data	X							
Quality of Life assessments (QLQ-C20, CIPM20, FACT-Leu, FACIT-Fatigue)	X	X	X		X	X	X	
Record of any occurrence of AVN or serious cardiac problems								X
2-5mls of bone marrow in EDTA sent to MRD lab at UCL Cancer Institute for MRD	X	X	X					

1 lumbar puncture not required at the time of diagnosis except in the case of suspected CNS involvement

[2] 2-5mls bone marrow in EDTA to be sent to the MRD lab at UCL Cancer Institute if patient relapses (providing the patient has consented).

Intensive pathway in Philadelphia -ve patients (Pathway B)

Procedure/Time point	Prior to registration	At the end of Phase 1 & Phase 2 Induction	At the end of intensification	At the end of consolidation 1	At the end of consolidation 2 & 3	Before starting maintenance	6-12 weeks after starting maintenance	Every 3 months during maintenance	At the end of maintenance	Follow up
Full medical history	X									
Physical examination	X	X	X	X	X			X		X
Height Weight, BSA & blood pressure	X									
Confirmation of disease diagnosis	X									
Bone marrow aspirate and trephine biopsy	X	X	X							
Cytogenetic, FISH & molecular genetic analysis to confirm Philadelphia –ve/+ve status	X									
Lumbar puncture	X[1]									
Full blood count & biochemistry i.e U&Es & LFTs, specifically Creatinine, Bilirubin & ALT/AST	X	X	X	X	X			X		X
ECOG & Karnofsky performance status	X	X	X	X	X	X		X		
Assessment of co-morbidities by CRASH & Charlson Index	X					X				
Remission status (% bone marrow blasts)		X	X							
Remission status (presence or absence of CR)				X[2]	X[2]			X[2]	X[2]	X[2]
Number of inpatient days		X	X	X	X			X		
Review of Adverse Events		X	X	X	X					
Demographic Data	X									
Quality of Life assessments (QLQ-C20, CIPM20, FACT-Leu, FACIT-Fatigue)	X	X	X	X	X		X	X	X	
Record of any occurrence of AVN or serious cardiac problems										X
2-5mls of bone marrow in EDTA sent to MRD lab at UCL Cancer Institute for MRD	X	X	X							

1 lumbar puncture not required at the time of diagnosis except in the case of suspected CNS involvement

[2] 2-5mls bone marrow in EDTA to be sent to the MRD lab at UCL Cancer Institute if patient relapses (providing the patient has consented).

Intensive + pathway in Philadelphia –ve patients (Pathway C)

Procedure/Time point	Prior to registration	At the end of Phase 1 & Phase 2 Induction	At the end of consolidation 1	At the end of consolidation 2	Before starting maintenance	6-12 weeks after starting maintenance	Every 3 months during maintenance	At the end of maintenance	Follow up
Full medical history	X								
Physical examination	X	X	X	X			X		X
Height Weight, BSA & blood pressure	X								
Confirmation of disease diagnosis	X								
Bone marrow aspirate and trephine biopsy	X	X	X						
Cytogenetic, FISH & molecular genetic analysis to confirm Philadelphia –ve/+ve status	X								
Lumbar puncture[1]	X[1]								
Full blood count & biochemistry i.e U&Es & LFTs, specifically Creatinine, Bilirubin & ALT/AST	X	X	X	X			X		X
ECOG & Karnofsky performance status	X	X	X	X	X		X		
Assessment of co-morbidities by CRASH & Charlson Index	X				X				
Remission status (% bone marrow blasts)		X	X						
Remission status (presence or absence of CR)				X[2]			X[2]	X[2]	X[2]
Number of inpatient days		X	X	X			X		
Review of Adverse Events		X	X	X					
Demographic Data	X								
Quality of Life assessments (QLQ-C20, CIPM20, FACT-Leu, FACIT-Fatigue)	X	X	X	X		X	X	X	
Record of any occurrence of AVN or serious cardiac problems									X
2-5mls of bone marrow in EDTA sent to MRD lab at UCL Cancer Institute for MRD	X	X	X						

1 lumbar puncture not required at the time of diagnosis except in the case of suspected CNS involvement

[2] 2-5mls bone marrow in EDTA to be sent to the MRD lab at UCL Cancer Institute if patient relapses (providing the patient has consented).

Non-intensive pathway in Phildelphia –ve patients (Pathway D)

Procedure/Time point	Prior to registration	At the end of Phase 1 & Phase 2 Induction	At the end of consolidation 1	Before starting maintenance	6-12 weeks after starting maintenance	Every 3 months during maintenance	At the end of maintenance	Follow up
Full medical history	X							
Physical examination	X	X	X			X		X
Height Weight, BSA & blood pressure	X							
Confirmation of disease diagnosis	X							
Bone marrow aspirate and trephine biopsy	X	X	X					
Cytogenetic, FISH & molecular genetic analysis to confirm Philadelphia –ve/+ve status	X							
Lumbar puncture	X[1]							
Full blood count & biochemistry i.e U&Es & LFTs, specifically Creatinine, Bilirubin & ALT/AST	X	X	X			X		X
ECOG & Karnofsky performance status	X	X	X	X		X		
Assessment of co-morbidities by CRASH & Charlson Index	X			X				
Remission status (% bone marrow blasts)		X	X					
Remission status (presence or absence of CR)						X[2]	X[2]	X[2]
Number of inpatient days		X	X			X		
Review of Adverse Events		X	X					
Demographic Data	X							
Quality of Life assessments (QLQ-C20, CIPM20, FACT-Leu, FACIT-Fatigue)	X	X	X		X	X	X	
Record of any occurrence of AVN or serious cardiac problems								X
2-5mls of bone marrow in EDTA sent to MRD lab at UCL Cancer Institute for MRD	X	X	X					

1 lumbar puncture not required at the time of diagnosis except in the case of suspected CNS involvement

[2] 2-5mls bone marrow in EDTA to be sent to the MRD lab at UCL Cancer Institute if patient relapses (providing the patient has consented).

Appendix 12: Dose Modifications

Drug dose alterations for toxicity

Prescribing multiple drugs for elderly patients, as in leukaemia treatment, brings particular challenges. Elderly patients are more likely to be on multiple drugs for co morbidities and clinicians and pharmacists need to pay particular attention to drug interactions for patients on this study.

The most important effect of age is reduction of renal clearance. Many elderly patients excrete drugs slowly and are highly susceptible to nephrotoxic drugs. Acute illness such as sepsis can lead to a rapid decline in renal clearance especially if accompanied by dehydration. The net result is that the tissue concentration of a drug is commonly increased by over 50% and debilitated patients may show even larger changes (British National Formulary).

Clinicians need to pay close attention to concomitant drugs prescribed in patients on this study, particularly in relation to diuretics, anti-hypertensives and other renal toxic drugs.
Renal clearance must be closely monitored, particularly following an episode of sepsis, and drug doses should be reduced accordingly. If a patient has borderline renal or hepatic function suggesting that a dose reduction may be appropriate then it is advisable to start with a drug dose reduction and increase if the drug is well tolerated rather than subsequently have to stop therapy for unacceptable toxicity.

Local policy should be followed for dose adjustments, however the following suggestions may be followed:

Pegylated- Asparaginase

Pegylated-Asparaginase is only given in the intensive + pathway (pathway C) as 2 doses in Consolidation 2.

Recommendations for dose adjustment in renal failure
No reductions required for renal failure

Recommendations for dose adjustment in hepatic failure
Withhold if bilirubin >50μmol/L
Do not alter dose for raised transaminases

Anaphylaxis or anaphylactoid reactions:
Peg-asparaginase should be discontinued if the patient develops a Grade 2 – 4 toxicity. Each dose can be replaced by Erwinia asparaginase at 15,000 IU/m^2 every three days for a total of 5 doses as per the SPC.

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 if there is a prior history of asparaginase induced pancreatitis.

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

Cyclophosphamide

Cyclophosphamide is given as a pro drug which is then converted by hepatic microsomal enzymes to alkylating metabolites (there is great interpatient variability in metabolism). Excretion is primarily renal. 30% is excreted as unchanged drug. t½ is 4-10 hours in adults

Recommendations for dose adjustment in renal failure:

GFR (ml/min)	Dose
>20	100%
10-20	75%
<10	50%

Recommendations for dose adjustment in hepatic failure -
SPC (Pharmacia 2007) - not recommended in patients with a bilirubin >17μmol/L or serum transaminases or ALP more than 2-3 x upper limit of normal. In all such cases doses should be reduced. However, exposure to active metabolites may not be increased suggesting that dose reductions may not be necessary. This should be a clinical decision.

Cytarabine

Recommendations for dose adjustment in renal failure
If dose < 1gm/m^2, no dose reduction necessary for renal impairment (intensive + pathway only)

High Dose 1-5g/m^2	
GFR (ml/min)	Dose
>60	100%
46-60	60%
31-45	50%
<30	Omit

Recommendations for dose adjustment in hepatic failure
If bilirubin >34μmol/L, give 50% dose. Escalate in subsequent cycles in the absence of toxicity.

Doxorubicin

Recommendations for dose adjustment in renal failure
No reduction is needed for renal impairment

Recommendations for dose adjustment in hepatic failure
Note that liver function can be very deranged at diagnosis due to disease infiltration of the liver. In this situation investigators may wish to make a clinical decision to give some anthracycline despite the raised bilirubin.

Bilirubin μmol/L	Dose
20-51	50%
51-85	25%
>85	omit

AST	Dose
2-3 x ULN	75%
>3 x ULN	50%

Etoposide

Recommendations for dose adjustment in renal failure

CrCl (min)	Dose
>50	100%
15-50	75%
<15	50%

Further dose changes should be considered depending on clinical response.

Recommendations for dose adjustment in hepatic failure
Bilirubin 26-51 or AST 60-180 – give 50% dose
Bilirubin >51 or AST >180 – clinical decision but consider 25% dose

Imatinib

Recommendations for dose adjustment in renal failure
No dose adjustments necessary for renal impairment

Recommendations for dose adjustment in hepatic failure
SPC (Novartis 2008) If bilirubin >3xULN or liver transaminases >5X ULN withhold imatinib until bilirubin < 1.5 x ULN or liver transaminases < 2.5 x ULN. Treatment can be continued at a reduced dose ie 400 mg od → 300 mg od; 600 mg od → 400 mg od.

Idarubicin

Recommendations for dose adjustment in renal failure

Creatinine (µmol/L)	Dose
<100	100%
100-175	75%
>175	Clinical decision

Recommendations for dose adjustment in hepatic failure

Bilirubin µmol/L	Dose
<40	100%
40-85	50%
>85	omit

High dose Methotrexate

Methotrexate is given by IV in intensification (In the Intensive pathway only) at a dose of 1g/m^2.

Recommendations for dose adjustment in renal failure

Pre day 1

CrCl(ml/min)	Dose
> 80 mls/min	100%
50-80 mls/min	50 %
<50 mls/min	0 %

Pre Day 14

CrCl(ml/min)	Dose
> 50 mls/min	100%
<50 mls/min	0 %

Recommendations for dose adjustment in hepatic failure

Bilirubin μmol/L		AST	Dose
<50	AND	<180	100%
51-85	OR	>180	75%
>85			omit

Maintenance: PO Methotrexate 5-15mg/m^2

Check LFT's only if patient jaundiced. If bilirubin is >50 μmol/L omit MTX until it is less than 20 μmol/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.

Recommendations for dose adjustment in renal failure

CrCl (ml/min)	Dose
>80	100%
60	65%
45	50%
<30	Omit

This should be a clinical decision. There may be no need for adjustment for patients needing low dose methotrexate ie 5mg/m^2

Vincristine

Recommendations for dose adjustment in renal failure
No reductions for renal impairment are required

Recommendations for dose adjustment in hepatic failure

Bilirubin μmol/L		AST/ALT/(IU)	Dose
26-51	OR	60-180	50%
>51	AND	≤ ULN	50%
>51	AND	>180	omit

Neuropathy
Elderly patients are particularly at risk of developing neuropathy with vincristine. Clinicians should stop vincristine for any neuropathy grade 2 or above and reintroduce at a reduced total dose of 1mg (normally capped at 2mg) when symptoms resolve.

Constipation
Elderly patients are particularly at risk of developing constipation with vincristine. Clinicians should stop vincristine for any constipation grade 2 or above and reintroduce at a reduced total

dose of 1mg (normally capped at 2mg) when symptoms resolve. Clinicians should also consider dose reducing to 1mg for grade 1 symptoms

6-MP

Recommendations for dose adjustment in renal failure

Clinical decision:
Consider increasing dosing interval to every 48 hours for those patients with creatinine clearance of < 50ml/min

Recommendations for dose adjustment in hepatic failure

Hyperbilirubinaemia: If bilirubin >50μmol/l omit mercaptopurine until it is less than 20μmol/l and then restart at half 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 aminotranseferases.

Steroid toxicity

As with other drugs, the side effects of corticosteroids are often much more severe in the elderly compared to the other adult patients and close supervision is required.
A PPI should be given alongside corticosteroids in all cases. Patients should be monitored for hyperglycaemia. Psychological toxicities are more common in the elderly and include osteoporosis and fracture, depression and psychosis. Patients are at risk of hypoadrenalism and high dose steroids must always be tapered slowly to lower risk.

Where possible, side effects should be managed with continuation of the steroids but severe toxicity such as psychosis should result in termination of all further steroid therapy.

Herpes-Zoster risk

All patients should be on acyclovir prophylaxis because of the increased herpes-zoster risk in elderly patients on steroids.
It is recommended that patient's immune status to varicella-zoster is checked at diagnosis. Non immune patients exposed to varicella-zoster who have had systemic steroids within the past 3 months should be given passive immunisation with varicella-zoster immunoglobulin (BNF).

Appendix 13: Protocol Version History

Protocol:		Amendments:		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version.**
1.0	20.07.12	N/A	N/A	N/A
2.0	22.08.2013	1.0	Trial Management Group 1.2 – Trial Schema 5.1 – Pre-Registration Evaluation 6.1 – Registration 20 – Translational Research Appendix 5: CRASH Score Appendix 11	Addition of Laura Clifton-Hadley. Removal of Jo Gambell Removal of until death. Addition of 'for 5 years'. Addition of (including hepatomegaly/splenomegaly and lymphadenopathy – to be reported on sample request form at time of diagnosis sample being sent) **A patient may be entered onto the registration only arm of the trial retrospectively at any point during their first phase of treatment. All efforts should still be made to send diagnostic samples to the Royal Free MRD Lab for MRD analysis.** Please note that an additional bone marrow sample should be sent to the MRD Laboratory if a patient relapses. This sample should be from the routine sample taken to diagnose relapse (see appendix 11). Change of web address to current correct address. Addition to key of'd' – a reminder for sites to send in relapse samples to the MRD Laboratory. Minor administrative changes

3.0		2.0	Throughout	Removal of word 'trial', replaced with 'study' as well as removal of the word 'arm', replaced with 'pathway'.
			Chief Investigator	Administrative changes and corrections of typographical errors. Amended to reflect move from Royal Free to UCL Cancer Institute.
			Trial Management Group	Changes in the composition of the TMG.
			1.1	Design: Addition of 'observational' Overall aim: amended to 'To document the safety, tolerability and feasibility of therapeutic protocols currently in standard use for patients ≥ 60 years old with de novo Acute Lymphoblastic Leukaemia (ALL).' Target accrual: 'HOVON group' amended to 'International collaborators' Planned number of sites: Addition of Denmark Translational component: Additional investigations added Additional information regarding translational research added.
			2.2	Addition of analyses listed in laboratory agreements but missed in protocol. Also updated to include the additional translational research relating to constitutional DNA
			3.0	Updated in line with current UCL CTC protocol template and updated UKALL60+ Monitoring Plan and to reflect international collaboration.
			4.0	Updated to reflect amended Monitoring Plan
			5.1	Addition of collection of family history of cancer, buccal swab, creatinine, bilirubin and ALT/AST. Removal of requirement of white cell count to be 30 x 10^9/L.
			5.3.3	Addition of definition of a woman of childbearing potential. Addition of inclusion of female partner of male patient in safety reporting criteria.
			5.3.4	Addition of instructions for female patients avoiding pregnancy.
			6.1	MRD lab name updated. Study number of Danish and Irish patients. Details of international patient contact cards amended.

		7.1.2	Addition: Patients who are not in complete remission at the end of each phase or cycle of treatment may continue with their chosen study treatment if, in the opinion of the treating clinician, they are deriving clinical benefit and are fit enough to continue on treatment**.** If patients are not benefiting from treatment, or are not deemed fit enough to continue with the selected study treatment, they should discontinue study treatment. Further treatment will be at the discretion of the treating clinician.
		7.2	Details regarding CNS involvement added. Dose capping of vincristine (2mg) added to all pathways. Addition of 'and other criteria on section 7.1.2 are met' to criteria to proceed to next phase/cycle of treatment. Criteria to proceed to next phase/cycle of treatment added to header of tables. Pathway letter added throughout. Reminder that bone marrow should only be sent to central lab if the patient has consented added.
		7.3.1	Pharmacy responsibility reworded.
		7.4	Amended guidance to cover UK sites that might not have a local policy for folinic acid rescues after IV methotrexate. Clarification of the route of methotrexate and phase of treatment this guidance is referring to.
		8.0	Specified need for creatinine, bilirubin and ALT/AST to be collected. Reminder added that patients must have consented to bone marrow being sent to central lab.
		8.2.3	Clarification that only pathways A, C and D require a bone marrow aspirate and trephine biopsy at this point.
		8.2.4; 8.3.3; 8.3.4; 8.6	Clarification that remission status is to be assessed as per local practice at these timepoints.
		8.3.3	Addition of QoLs to be completed every 3 months during maintenance.
		8.4	Addition of section regarding assessments for patients not in complete remission and discontinuing with study treatment.
		8.5	Clarification that a bone marrow sample for pathway E patients should be sent at up to 3 clinically relevant timepoints.

			9.0	Amended to reflect update to Data Management procedures.
			10.0	'Suspected Unexpected Serious Adverse Reaction (SUSAR)' amended to Related and Unexpected Serious Adverse Events throughout.
			10.2.1	Clarification of the AE reporting period if study treatment is stopped early. Clarification AEs do not need to be reported for pathway E patients. Addition of reference to serious breaches.
			10.2.2	Clarification of the SAE reporting period if study treatment stopped early. Clarification SAEs so not need to be reported for pathway E patients. Exemptions from SAE reporting added; pathway E patients, SAEs during maintenance unless specifically considered to be related to study treatment.
			10.5	Addition of female patients. Clarified only required for pathways A-D.
			11.0	Serious breaches added to reflect new REC SOP.
			12.1	Details of recording informed consent amended in line with updated monitoring plan.
			13.0	Clarification that data up to and including withdrawal must be sent to UCL CTC. Addition that sites registering patients remain responsible for obtaining and submitting follow up data.
			14.1	End of study amended to 1 year after the date the last patient completes all study treatment (including 2 years of maintenance).
			15.1	Amended duration of recruitment to 5 years. Addition that any patient found to be ineligible due to a misdiagnosis will be excluded and replaced.
			16.1	Addition of details for non-UK collaborators.

			20.1	MRD lab name and address updated. Clarification that for pathway E patients bone marrow samples should be sent for analysis at up to 3 clinically relevant timepoints. Addition of table to clarify when samples should be taken.
			20.2	Addition of information regarding constitutional DNA sample collection.
			20.3	Addition of information regarding LRCG's involvement in the trial
			Appendix 10	Additional expected AEs added.
			Appendix 12	Addition of instructions that in the first instance local policies should be followed.
			Appendix 11	Separate tables added for each pathway.
			Appendix 14	Addition of country specific appendix for The Netherlands.

Appendix 14: Country-specific Appendix: Netherlands

Study Monitoring and Oversight (section 12)

- Arrangements stated in sections 12.1 and 12.2 will be adapted in the Netherlands in accordance with HOVON's standard monitoring procedures.

Funding (section 18)

- Funding for the conduct of the study in the Netherlands has been secured by HOVON

Translational Research (section 20)

- Arrangements to be outlined in a separate lab manual.