UKALL14

A randomized trial for adults with newly diagnosed acute lymphoblastic leukaemia

TRAINING MANUAL

To accompany Protocol v11.0 11.09.2017

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Foreword

- This training manual is primarily intended to be used as a training tool for site staff working on the UKALL14 trial.
  - **New staff** are encouraged to read the manual in addition to the protocol and other essential documents for their role.
  - **Existing staff** can also use the manual to update themselves following amendments, or as an *aide-memoire.*

- Please do not use this manual as a substitute for the current approved protocol and drug supply guidelines.

- If you have any questions, please contact the UKALL14 study team at UCL CTC.

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GENERAL INFORMATION

UKALL14 Trial Team Contact Details

General enquiries:

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Address:

UKALL14 Trial
Haematology Trials Group
CR-UK & UCL Cancer Trials Centre
90 Tottenham Court Road
London W1T 4TJ

Refer to ISF section 2 or PSF section 1 for details of current team

UCL CTC Website

www.ctc.ucl.ac.uk

The UCL CTC website can be used by site staff to access current versions of Investigator Site File & Pharmacy File documents mentioned within this manual:

- Go to website http://www.ctc.ucl.ac.uk
- Click on ‘All trials’ tab > ‘UKALL14’
- Scroll down to ‘View trial documents’
- Click on the ‘Download’ icon for the relevant document
- Protocols are password-protected – contact UCL CTC for the password.

Central laboratory addresses

Lab name	Address	Samples to be sent
UCL Cancer Institute MRD lab, London *(See protocol appendix 8 for more information about this lab)*	Adult ALL MRD Laboratory UCL Cancer Institute Paul O'Gorman Building 72 Huntley Street London WC1E 6DD	• BM samples at: ○ Baseline ○ End of phase 1 ○ End of phase 2 ○ 3 monthly post RIC transplant ○ Relapse • Buccal swabs • Pre-and post-asparaginase samples
Leukaemia Research Cytogenetics Group, Newcastle *(See protocol appendix 7 for more information about this lab)*	Leukaemia Research Cytogenetics Group Northern Institute for Cancer Research Level 5, Sir James Spence Institute Royal Victoria Infirmary Queen Victoria Road Newcastle upon Tyne NE1 4LP	• Local cytogenetics report at: ○ Baseline

Sample postage information

See protocol section 8.2.1 and appendix 8

- MRD samples, pre-and post asparaginase samples should be sent by courier or 1st class post (at site's own cost)
- Samples taken on a Friday should be kept in the fridge over the weekend and sent first thing on Monday morning
- Kits are provided for taking and sending buccal swabs. Please contact UCL CTC if you need more kits.

- When posting sample(s), include a sample request form to identify the sample type(s) and timepoint(s)

- Plasma samples should be stored at -80°C wherever possible. Failing that, they should be stored at -20°C. Collection will be arranged at the end of the trial. Please ensure you keep a log of the samples you have stored.

Ensure all samples & paperwork are anonymised prior to sending to labs

Patients have only consented to share initials/DOB/trial number/NHS no.
Names must <u>not</u> be included

Charges for MRD analysis

Please refer to Protocol Appendix 8.

Charges apply to both randomised and 'registration only' sub-study patients.

- The MRD laboratory is required to charge for MRD analysis
- MRD samples must be sent for both randomised patients and 'registration only' patients to ensure standardised testing and to achieve best patient management
- The standard cost is £3,200 per patient
- A reduced fee of £200 will be charged if no marker can be identified on the baseline sample
- A list of charges is available on request
- Invoices will be sent directly to site – please pay promptly
- Queries can be sent to the MRD lab allmrdlab@ucl.ac.uk and UKALL14 team at UCL CTC ctc.ukall14@ucl.ac.uk

Transfer of care to another centre

Whenever a patient is referred to another hospital for part of their treatment or follow up, their care must be formally transferred:

- Complete and send the '**Centre Transfer'** form to UCL CTC (this is so we know where to direct our queries)
- Copies of the patient's CRFs up until the point of transfer must be provided to the new site
- The **original site** remains responsible for submitting and resolving queries on data for **all visits up to the date of transfer**
- The **new centre** will assume responsibility for submitting and resolving queries on data for **all visits after the date of transfer**
- If a patient's care is then transferred back, another Centre Transfer form must be completed and sent to UCL CTC.

Incident Reporting

Please refer to Protocol section 13.1

- Sites must notify UCL CTC of deviations from the protocol or GCP **immediately**
- Sites should contact UCL CTC if they are in any doubt as to whether a certain situation constitutes an incident
- UCL CTC may detect an incident at site and request completion of an Incident Report form
  - UCL CTC provide an incident report form, but a Trust incident report form may also be acceptable (if available)
  - Please respond promptly to any queries
- UCL CTC will assess whether the case constitutes a serious breach – if deemed to be a serious breach, UCL CTC will report to the REC and MHRA within the required 7 day timeline (refer to Protocol section 13.2)

Monitoring

Please refer to UKALL14 Monitoring Plan (held in ISF Section 1)

- There is no routine on-site monitoring for UKALL14
  - 'For cause' monitoring may be undertaken in the event of non-compliance or poor CRF returns
  - On site monitoring may also be carried out if requested by the site
- Central monitoring requests are emailed to sites annually on the anniversary of the site activation date. This includes collection of:
  - *ISF/PSF checklists*
  - *Site delegation logs*
  - *Screening logs*
  - *Drug accountability logs*
  - *PI's CV and evidence of GCP training*

- Please ensure we are kept up to date with site staff changes so that requests are directed to the correct people. An updated delegation log should be sent whenever there is a staff change. Up-to-date CVs & GCP training records must be held centrally at site.

Important note:
Randomised and registration only patients

Following completion of recruitment to the Rituximab randomisation in July 2017 and from implementation of protocol v11.0 onwards, a 'registration only' sub-study has been introduced for patients with precursor B-cell ALL.

Please note that there are different requirements for these patients, including:

- Different Patient Information/Informed Consent document
- Treatment of treating clinician's choice
- Different case report forms
- No AE/SAE/pregnancy reporting required

Please refer to pages 20 - 87 for procedures for randomised patients

Please refer to pages 88 - 100 for details of the 'registration only' sub-study.

UKALL14 TRIAL SCHEMA

***Phase 1 Induction (4 weeks)*: precursor B-cell & T-cell patients (Philadelphia –ve patients only) to receive Pegylated-Asparaginase plus standard phase 1 induction therapy**

Pre B-cell ALL

- B1: Standard Phase 1 Therapy Alone
- B2: Standard Phase 1 Therapy + CD20 (Rituximab)

T-cell ALL

- Standard Phase 1 Therapy

***Phase 2 Induction (4 weeks)*: precursor B-cell & T-cell patients to receive standard phase 2 induction therapy**

Pre B-cell ALL

- Standard Phase 2 Therapy

T-cell ALL

- T1: Standard Phase 2 Therapy
- T2: Standard Phase 2 Therapy + Nelarabine

PATIENTS IN COMPLETE REMISSION (CR) – Risk Assessment performed on all patients at this time point

SIBLING DONOR

Aged 41 years and over*
Intensification with HD-Methotrexate + pegylated asparaginase ***(Philadelphia –ve patients only to receive pegylated asparaginase)***

To receive allo SCT (sibling), non-myeloablative conditioning with fludarabine-melphalan and alemtuzumab
SCT (sibling)

Aged 40 years and under*
To receive allo SCT (sibling), myeloablative conditioning with Etopside-TBI or Cyclophosphamide-TBI

NO SIBLING DONOR

High Risk

Aged 41 years and over*
Intensification with HD-Methotrexate + pegylated asparaginase ***(Philadelphia –ve patients only to receive pegylated asparaginase)***

To receive allo SCT (MUD), non-myeloablative conditioning with fludarabine-melphalan and alemtuzumab

Aged 40 years and under*

To receive allo SCT (MUD), myeloablative conditioning with Etopside-TBI or Cyclophosphamide-TBI

Standard Risk

Continue methotrexate intensification, consolidation and maintenance

***Age at study entry**

Trial Aims

Please refer to Protocol section 2.11

- **Aim 1B:** To determine if the addition of rituximab to standard induction chemotherapy results in improved event free survival (EFS) in patients with precursor B-cell ALL
- **Aim 1T:** To determine if the addition of nelarabine improves outcome for patients with T-cell ALL

Aim 1B & 1T are addressed by the 'B' and 'T' randomisations at study entry:

- *B cell patients – standard induction +/- rituximab (B-cell randomisation closed as of July 2017)*
- *T-cell patients - standard induction +/- nelarabine*

- **Aim 2:** To determine the tolerability of pegylated asparaginase in induction treatment of all patients; to compare anti-asparaginase antibody levels between patients in the 2 randomisation groups from aim 1B

Aim 2 is addressed by capturing data for all Philadelphia negative patients registered to the trial

Trial Aims

- **Aim 3:** To determine whether risk-adapted introduction of unrelated donor SCT results in greater EFS for patients at highest risk of relapse

  Aim 3 will be investigated in patients with high risk disease who do not have a sibling donor

- **Aim 4:** To compare 2 schedules of administration (standard vs collapsed) of keratinocyte growth factor (palifermin) for efficacy in preventing the severe mucosal toxicity of etoposide/TBI HSCT conditioning regimen.

  Aim 4 was addressed by the 'P' randomisation in patients aged 40 and under having a sibling or unrelated donor myeloablative transplant (Palifermin randomisation closed as of April 2016)

Trial Drugs - IMPs

The following IMPs are supplied for the trial free of charge:

- **Rituximab** (Mabthera®) - licensed - supplied by Roche *(randomisation now closed)*
- **Nelarabine** (Atriance®) - licensed - supplied by Novartis AG
- **Palifermin** (Kepivance®) - licensed until April 2016 – previously supplied by Swedish Orphan Biovitrum *(randomisation now closed)*

The following IMP is supplied for the trial at site's own cost:

- **Pegylated Asparaginase** (Oncaspar®) - licensed - supplied by Baxalta, now part of Shire

Please liaise with pharmacy as early as possible when patients are consented to ensure there is sufficient stock of drugs.

IMP supplied for the UKALL14 trial must only be used to treat randomised UKALL14 patients.

Trial Drugs - NIMPs

Please refer to Protocol section 7.1.2 for full details

- Backbone chemotherapy, transplant conditioning and supportive care drugs specified in the protocol are standard treatment for this disease and are classified as NIMPs
- NIMPs for the trial must be sourced from hospital stock. Pharmacies are responsible for ensuring adequate supplies are maintained
- Dose banding is not allowed for IMPs, but local policy on dose banding may be followed for NIMPs
- Generic brands of NIMPs can be used as per local policy
- Every effort should be made to give NIMPs as per the protocol. See Protocol appendix 3 for details of dose modifications in case of toxicity. If further advice is required, please contact the TMG via ctc.ukall14@ucl.ac.uk

Please see Drug Supply Guidelines for further information

Supportive care

Please refer to Protocol section 7.2.1 for full details

Local policies may be followed for:

- Tumour lysis prophylaxis
- Anti HSV and VZV prophylaxis
- PCP prophylaxis
- Antifungal prophylaxis (avoid azoles during treatment with vincristine)
- GCSF support

See protocol section 7.2.1 for guidance on thromboprophylaxis and management of methotrexate encephalopathy.

Expert advice on haemostasis for individual patients can be obtained from:

- Professor Beverly Hunt (Beverley.hunt@gstt.nhs.uk)
- Dr Charlotte Bradbury (c.bradbury@bristol.ac.uk)
- Copy in ctc.ukall14@ucl.ac.uk to any correspondence

RANDOMISED PATIENTS

Study entry

Informed Consent 1

Please refer to Protocol section 4.0.

- Informed consent must be obtained from the patient by a delegated person prior to any trial-specific intervention

- There are 2 patient information sheets & 2 consent forms to give to patients:
  - **Main** PIS & consent
  - **Optional Additional Genetic Testing – Buccal Swab** PIS & consent
    - Consent can be obtained for buccal swab at any time. We ask that as many patients as possible give samples to further our understanding of leukaemia.

- Document details of the consent process in the patient's notes:
  - when the PIS was given
  - discussion(s) about the trial with the patient
  - when consent was taken
  - who took consent

Informed Consent 2

Please refer to Protocol section 4.0.

- 24 hours should be allowed for patients to consider participation in the trial
  - If not possible, patients may consent on the same day provided the member of staff taking consent is satisfied that the patient understands the trial and its implications, and follows up with the patient to confirm ongoing willingness to participate

- Remember to complete the patient number on the top of the consent form following trial registration.

- The original consent form plus one copy must be stored at site (one in the ISF & one in the patient's medical notes).

- The patient must also be given a copy – document in the notes that this has been done.

- Do not send consent forms to UCL CTC.

Results required before study entry

Patients cannot enter the trial until the results below confirming eligibility are known:

Results required before registration	Results not required in order to register
Percentage of bone marrow blasts to confirm diagnosis of ALL *(if not yet available, copy of diagnostic report)*	Biochemistry Liver function tests
Patient's disease lineage	
Full blood counts *(taken prior to starting steroid pre-phase treatment)*	
Hepatitis B & C serology	
Negative pregnancy test *(women of childbearing potential)*	

Please refer to Protocol section 5.1 for a full list of screening investigations.

Eligibility criteria

Please refer to Protocol section 5.2

Inclusion criteria	Exclusion criteria
a) Patients aged ≥25 and ≤65 old with acute lymphoblastic leukaemia (ALL) or aged ≥19 and ≤65 old with Philadelphia chromosome positive ALL	a) Mature B-cell leukaemia i.e. Burkitt's lymphoma t(8;14)(q24;q32) and variant c-myc translocations e.g. t(2;8)(p12;q24), t(8;22)(q24;q11)
b) Newly diagnosed, previously untreated ALL (a steroid pre-phase of 5-7 days is required and can start before registration)	b) Known HIV infection
c) Written informed consent	c) Hepatitis B infection (positive HBsAg and/or HBcAb). Positive HBsAb only may be acceptable
	d) Hepatitis C infection (antibodies against hepatitis C or a PCR evaluation positive for hepatitis C DNA)
	e) Pregnant or lactating women
	f) Blast transformation of CML

Study Registration

Please refer to Protocol section 5.3.1.

- Complete ‘Registration & Randomisation Request’ form in full (including contact details on front page) and fax/email to UCL CTC
  - If sending by email, patient identifiable information (day/month of birth, NHS no) must be redacted before sending and then provided to UCL CTC by telephone
  - Please contact UCL CTC if you require any guidance completing the registration form
- Send ‘Registration & Randomisation Request’ form as early as possible, allowing minimum 2 hours for registrations to be processed (4pm cut off time for processing)
- UCL CTC will fax/email confirmation of the patient’s randomisation, with trial number, back to the site
- Provide patient with a copy of their signed consent form and give them a contact card containing out-of-hours medical care details

Samples to be sent at study entry

Please refer to Protocol sections 5.1, 8.1.2, and appendix 8.

Samples taken prior to consent can be used, but cannot be sent until patient has given their consent.

Test	Sample required	Send to
MRD baseline testing	3-5ml bone marrow in EDTA *Or* 30-50ml blood in EDTA	UCL Cancer Institute MRD lab
Constitutional DNA (optional)	Buccal swab	UCL Cancer Institute MRD lab
Cytogenetics	Report from local cytogenetics tests	Leukaemia Research Cytogenetics Group, Newcastle

Ensure all samples & paperwork are anonymised prior to sending to labs

Patients have only consented to share initials/DOB/trial number/NHS no.
Names must <u>not</u> be included

RANDOMISED PATEINTS

Trial Treatment

Treatment Randomisation

Patients will undergo randomisation at study entry to determine their induction therapy:

- Pre-B cell patients randomised to:

B1 (standard induction) **or B2** (standard induction **+ Rituximab**) *– now closed*

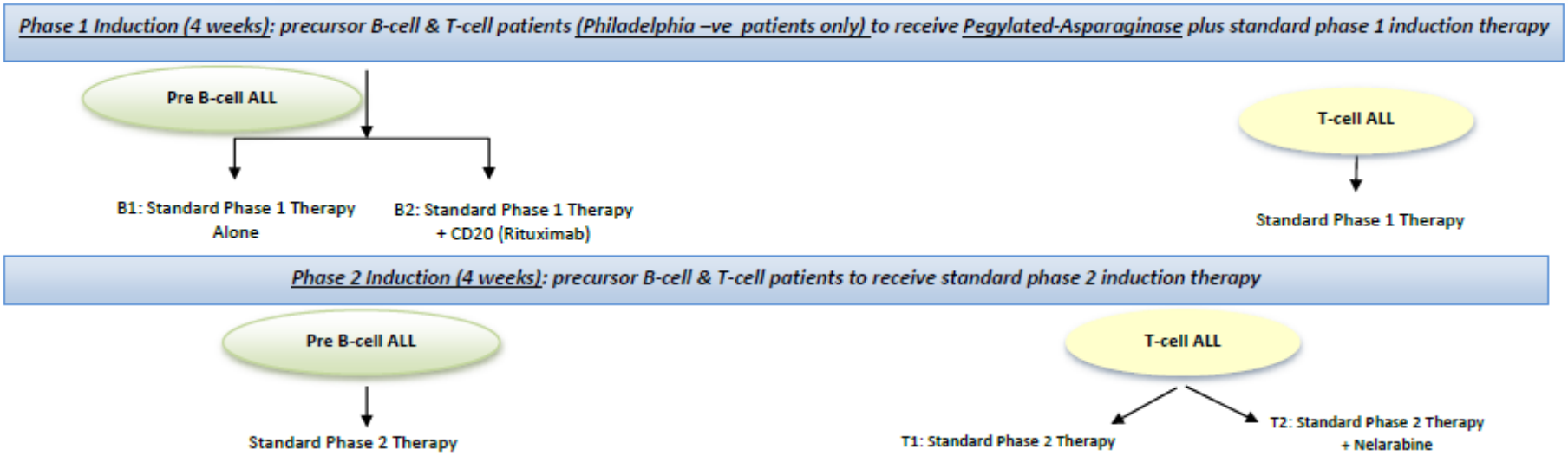
- T-cell patients randomised to:

T1 (standard induction) **or T2** (standard induction **+ Nelarabine**)

- Trial number format:

  B-cell randomised patients: 14-**1**-xxx

  T-cell randomised patients: 14-**2**-xxx



Steroid pre-phase

Please refer to Protocol section 7.2.1

- A steroid pre-phase is required prior to starting induction
- Dexamethasone 6mg/m^2 per day for 5-7 days
- May be started prior to trial registration

Phase 1 induction – important safety information

Please refer to Protocol section 7.2.3

- Pegylated asparaginase must not be given to Philadelphia positive patients at any point
- Day 4 pegylated asparaginase dose must be omitted in patients aged ≥41 years
- Liver function tests should be performed regularly whilst receiving pegylated asparaginase
- Blood counts must recover to the following levels before continuing to the next treatment phase:
  - Neutrophils >0.75 x 10^9/L
  - Platelets >75 x 10^9/L

Phase 1 induction - treatment

Please see Protocol section 7.2.3

UKALL14 Phase 1 induction																														
Drug	Dose	Route	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
Daunorubicin	30 mg/m^2	IV	X							X							X							X					
Vincristine	1.4mg/m^2 Max 2mg	IV	X							X							X							X					
Dexamethasone	10mg/m^2 Max 20mg	PO	X	X	X	X				X	X	X	X				X	X	X	X										
Pegylated Asparaginase**	1000IU/m^2	IV				X*														X										
Methotrexate	12.5mg	IT														X														
Imatinib (Philadelphia positive patients)	400mg – 600mg***	PO	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

* Omit day 4 dose in patients aged ≥41
** Pegylated asparaginase must not be given to patients with Philadelphia positive disease
*** Start imatimib at 400mg/day, escalate to 600mg/day within 2 weeks, if tolerated. Imatinib should be given continuously until transplant, if possible

Rituximab was given to B-cell patients randomised to standard treatment + rituximab during Phase 1 Induction.

Treatment deviations must be documented in patient notes, giving the reason why and associated clinical review/justification, and reported on relevant CRFs

Phase 1 induction - samples

Please see Protocol sections 7.2.3 & 7.2.4

Test	Sample required	When	Send to
Asparaginase activity & anti-asparaginase antibodies*	5ml peripheral blood in serum tube	*Patients aged ≤40:* D3/4 & D18 *Patients aged ≥41:* D18	UCL Cancer Institute MRD lab
Asparaginase coagulation activity	4.5ml peripheral blood in citrate tube – spin @2000G for 5 minutes and store serum in 5 eppendorfs	*Patients aged ≤40:* D3/4 & D18 *Patients aged ≥41:* D18	Store locally at -80°C – collection to be arranged at end of trial
End of phase 1 MRD	3-5ml bone marrow aspirate in EDTA	Count recovery at end of phase 1, or D35, whichever is sooner **	UCL Cancer Institute MRD lab

* Not required for Philadelphia positive patients

** Repeat on D42 if hypocellular and no evidence of residual disease on Dd35

Phase 1 induction - data collection

See protocol section 8.1.1 for details of investigations to be carried out during treatment.

CRF	When to send	How to send
Induction Treatment Phase 1 form	Within 1 month of completing treatment phase	Post
Induction Phase 1 AE form	Within 1 month of completing treatment phase	Post
SAE reports	Within 24 hours of becoming aware of SAE	Fax/email

- See page 66 for details on reporting withdrawals from treatment
- See page 76 for details on reporting SAEs
- See page 70 for details on reporting deaths

Phase 2 induction – important safety information

Please refer to Protocol section 7.2.5

- Nelarabine should be given as soon as possible after count recovery following phase 2 induction, and no earlier than day 29
- Nelarabine must not be given to patients who have unresolved grade ≥2 CNS toxicity at the end of phase 2. Monitor patients for signs of neurotoxicity & discontinue if grade ≥2 neurotoxicity toxicity
- Blood counts must recover to the following levels before continuing to the next treatment phase:
  - Neutrophils >0.75 x 10^9/L
  - Platelets >75 x 10^9/L

Phase 2 induction - treatment

Please see Protocol section 7.2.5

UKALL14 Phase 2 induction																														
Drug	Dose	Route	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
Cyclophosphamide	1000 mg/m^2	IV	X														X													
Cytarabine	75mg/ m^2	IV		X	X	X	X				X	X	X	X				X	X	X	X				X	X	X	X		
Mercaptopurine	60mg/ m^2	PO	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	x	X	X	X	X	X	X	X	X	X	X	X	X
Methotrexate	12.5mg	IT	X							X							X							X						
Imatinib (Philadelphia positive patients)	400mg - 600mg	PO	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Nelarabine (arm T2) to start after count recovery – no earlier than day 29.

UKALL14 Phase 2 induction – Nelarabine (arm T2 only)							
Drug	Dose	Route	Day 1	Day 2	Day 3	Day 4	Day 5
Nelarabine	1.5g/m^2	IV	X		X		X

Treatment deviations must be documented in patient notes, giving the reason why and associated clinical review/justification, and reported on relevant CRFs

Phase 2 induction - samples

Test	Sample required	When	Send to
End of phase 2 MRD	3-5ml bone marrow aspirate in EDTA	Count recovery at end of phase 2, and before Nelarabine if on arm T2	UCL Cancer Institute MRD lab

- Result of end of phase 2 MRD will be sent to site within 10 days of receipt
- Please note that the MRD result is used for risk stratification so it is important that this sample is sent in a timely fashion

Phase 2 induction - data collection

See protocol section 8.1.1 for details of investigations to be carried out during treatment.

CRF	When to send	How to send
Induction Treatment Phase 2 form	Within 1 month of completing treatment phase	Post
Induction Phase 2 AE form	Within 1 month of completing treatment phase	Post
SAE reports	Within 24 hours of becoming aware of SAE	Fax/email

- See page 66 for details on reporting withdrawals from treatment
- See page 76 for details on reporting SAEs
- See page 70 for details on reporting deaths

Post phase 2
- response assessment

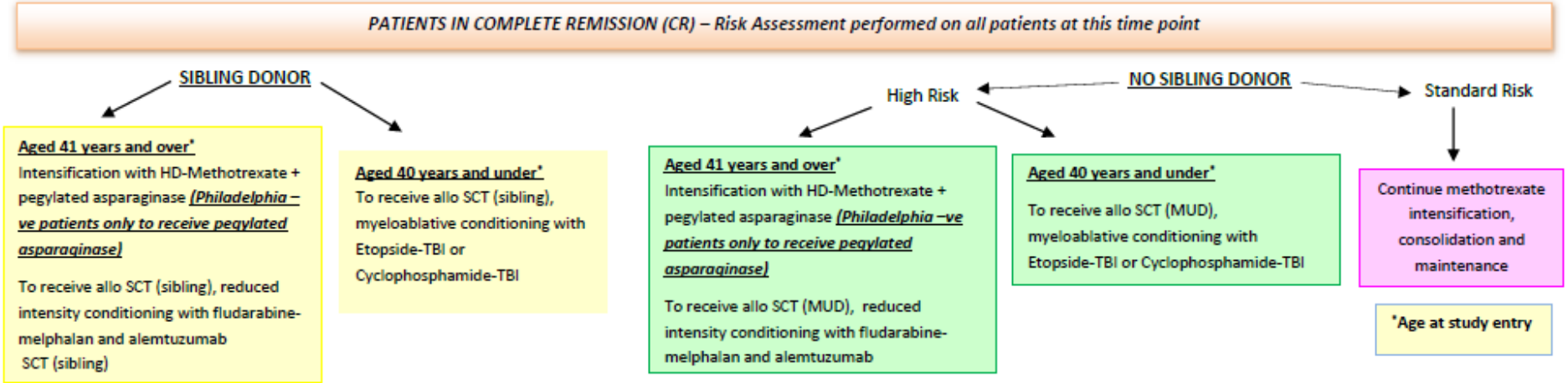
- Complete morphological remission should be confirmed locally on bone marrow examination upon count recovery (defined as ≤5% ALL blasts)

- **If patient is <u>not</u> in CR at the end of phase 2 treatment:**
    - Patient should stop protocol treatment
    - Further treatment will be at the local clinician's discretion
    - The patient should enter follow up for the trial
    - CRF required:

CRF	When to send	How to send
Treatment Summary form	ASAP after stopping trial treatment	Post

Post phase 2
- response assessment

- **If patient is in CR at end of phase 2 treatment:**
  - Risk assessment is performed
  - This determines whether the patient will continue with chemotherapy or have an allogeneic transplant



CRFs required after risk stratification

CRF	When to send	How to send
Post Induction Treatment Allocation (PITA) form	ASAP following completion of Induction Phase 2 treatment *(but after completion of any ongoing donor search)*	Fax/email
Post Induction Registration for Maintenance	ASAP following completion of Induction Phase 2 treatment *(but after completion of any ongoing donor search)*	Fax/email
or		
Post Induction Registration for Transplant form	ASAP following completion of successful donor search	Fax/email
Centre Transfer Form	Along with Post Induction Registration for Transplant form, if patient is to have transplant at another hospital	Fax/email

Eligibility for Transplant

Inclusion criteria for transplant

a) Completion of Phase 1 and Phase 2 treatment within the trial

b) The following subgroups of patients will proceed to transplant:

(i) Any patient with an HLA compatible sibling donor

(ii) High risk* patients with an 8/8 molecularly matched donor at HLA-A, B, C and DR

(iii) Patients with high risk* disease in whom no 8/8 match is available can proceed to transplant with a 7/8 matched unrelated donor OR umbilical cord unit(s) in the following circumstances:

- High risk cytogenetics
- Positive minimal residual disease (MRD) after phase 2 induction

* See page 41 for definition of high risk disease

Eligibility for Transplant

High risk disease
a) Age ≥41 years
b) Presenting WBC ≥30x10^9/l (precursor-B disease) or ≥100x10^9/l (T-lineage disease)
c) High risk cytogenetics: one or more of the following abnormalities: (i) t(4;11)(q21;q23)/MLL-AF4 (ii) Low hypodiploidy/near triploidy (30-39 chromosomes/60-78 chromosomes) (iii) Complex karyotype (five or more chromosomal abnormalities) (iv) Philadelphia chromosome t(9;22)(q34;q11)/BCR-ABL1 (detected by cytogenetic or molecular methods)
d) High risk minimal residual disease (MRD) following phase 2 of induction (N.B. where there is no MRD marker, or if there is no phase 2 MRD sample, the patient will be assumed to have standard risk MRD)

Eligibility for Transplant

- If a patient aged ≤40 with a sibling donor and standard risk disease elects not to proceed to transplant, they will be permitted to proceed to continue with chemotherapy and will remain on trial. The decision should be clearly documented in the patient notes and on the post-induction treatment allocation form.
- Patients aged ≥41 at study entry should be considered for non-myeloablative transplant, regardless of whether they have a sibling donor
- If, for any reason, the protocol defined transplant conditioning is not considered suitable for a patient, their treatment plan should be discussed and agreed with the transplant coordinator in advance (Prof David Marks; david.marks@UHBristol.nhs.uk, please copy correspondence to ctc.ukall14@ucl.ac.uk)
- Patients who have agreed non-protocol transplants will remain on study, including collection of transplant data, unless they explicitly withdraw consent.

Myeloablative transplant - treatment

Please refer to Protocol section 7.2.10.1

- The protocol allows for either TBI-etoposide (preferred) or TBI-cyclophosphamide conditioning, with IV methotrexate post transplant
- Local practice for scheduling conditioning regimens may be followed, but dosing must not change from that stipulated in the protocol.
- Immunosuppression should be given as per local policy – Cyclosporin is recommended.

Myeloablative transplant - treatment

TBI-Etoposide conditioning (preferred)										
Drug	Dose	Route	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0
Fractionated TBI	Total dose 1320cGy in 8 fractions		X	X	X	X				
Etoposide	60mg/kg	IV					X			
Haematopoietic stem cell infusion										X

TBI-Cyclophosphamide conditioning (alternative)										
Drug	Dose	Route	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0
Fractionated TBI	Total dose 1320cGy in 8 fractions		X	X	X	X				
Cyclophosphamide	60mg/kg	IV					X	X		
Haematopoietic stem cell infusion										X

- Immunosuppression as per local policy – suggest initially using Ciclosporin 3mg/kg/day IV starting on day -1
- IV methotrexate 15mg/m^2 day +1 and 10mg/m^2 days +3, +6 & +11

Myeloablative transplant – data collection

CRF	When to send	How to send
Myeloablative conditioning regimen form	Within 30 days following completion of conditioning	Post/fax/email
Transplant form	Within 30 days of transplant day 0	Post/fax/email
Day 100 form	Within 30 days after day 100 assessment	Post/fax/email
Post-transplant assessment form	Within 30 days of each 3-monthly assessment (months 6-24 post transplant)	Post/fax/email
Treatment summary form	Within 30 days after month 24 post transplant assessment	Post/fax/email
GVHD form	As soon as possible after confirmation of GVHD	Fax/email
Graft failure form	As soon as possible after confirmation of graft failure	Fax/email
SAE report	Within 24 hours of becoming aware of SAE	Fax/email

Myeloablative transplant – sample collection

The protocol does not require samples to be sent to the central lab following myeloablative transplant. However, please note that if the patient relapses within the first 2 years post transplant, the following sample will be required:

Test	Sample required	Send to
MRD testing at relapse	3-5ml bone marrow in EDTA *or* 30-50ml peripheral blood in EDTA (if WBC >30x10^9/l)	UCL Cancer Institute MRD lab

Non-myeloablative transplant - treatment

Please refer to Protocol section 7.2.10.2

Fludarabine – melphalan – alemtuzumab conditioning											
Drug	Dose	Route	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	3 monthly post transplant
Fludarabine	30mg/m^2	IV	X	X	X	X	X				
Melphalan	140mg/m^2	IV							X		
For recipients of unrelated donor allografts:											
Alemtuzumab	30mg	IV						X	X		
For recipients of sibling allografts:											
Alemtuzumab	30mg	IV							X		
Haematopoietic stem cell infusion		IV								X	
Methotrexate	12.5mg	IT									X

Immunosuppression as per local policy – suggest initially using Ciclosporin 3mg/kg/day IV starting on day -1

Non-myeloablative transplant – post transplant interventions

Please refer to Protocol section 7.2.10.2

	Months post transplant							
	3	6	9	12	15	18	21	24
Intrathecal methotrexate	X	X	X	X	X	X	X	X
BM Aspirate for MRD	X	X	X	X	X	X	X	X
Peripheral blood chimerism	X	X	X	X	X	X	X	X
Follow up visit/data collection	X	X	X	X	X	X	X	X

Non-myeloablative transplant – data collection

CRF	When to send	How to send
Non-myeloablative conditioning regimen form	Within 30 days following completion of conditioning	Post/fax/email
Transplant form	Within 30 days of transplant day 0	Post/fax/email
Day 100 form	Within 30 days after day 100 assessment	Post/fax/email
Post-transplant assessment form	Within 30 days of each 3-monthly assessment (months 6-24 post-transplant)	Post/fax/email
Treatment summary form	Within 30 days after month 24 post transplant assessment	Post/fax/email
GVHD form	As soon as possible after confirmation of GVHD	Fax/email
Graft failure form	As soon as possible after confirmation of graft failure	Fax/email
SAE report	Within 24 hours of becoming aware of SAE	Fax/email

Non-myeloablative transplant – samples

Test	Sample required	Send to
Mini-satellite regions* (pre-transplant)	Peripheral blood or buccal swab from **patient** and **donor** as per local policy	Local chimerism lab. Send anonymised results to UCL CTC
Post-transplant chimerism* (every 3 months until 24 months post transplant)	Peripheral blood from **patient** – quantity as per local policy	Local chimerism lab. Send anonymised results to UCL CTC
Post-transplant MRD (every 3 months until 24 months post transplant or relapse)	3-5ml bone marrow in EDTA	UCL Cancer Institute MRD lab
Cell banking at relapse	3-5ml bone marrow in EDTA *or* 30-50ml peripheral blood in EDTA (if WBC >$30x10^9$/l)	UCL Cancer Institute MRD lab

* Quantitative, lineage specific (myeloid & T-cell) chimerism should be performed by microsatellite PCR wherever possible.

Donor lymphocyte infusion

Please refer to Protocol section 7.2.10.7

- DLI to be given for:
  - Mixed chimerism
  - Continued or progressive minimal residual disease

- Up to 5 DLI infusions, with escalating doses, can be given at 3 month intervals until normalisation of chimerism or MRD (see protocol for details).

- Do not give DLI if the patient has graft versus host disease

- DLI should not be given earlier than 6 months post transplant unless agreed in writing by the Transplant Coordinator, Prof David Marks

- When arranging unrelated donor transplants, sites are encouraged to store aliquots of donor lymphocytes in case DLI is required.

Intensification – important notes

Please refer to Protocol section 7.2.7

The following patients will proceed on to intensification once counts have recovered after phase 2 induction:

- Patients with no sibling donor and standard risk disease
- Patients aged ≤40 with a sibling donor but no high risk features who have elected not to proceed to transplant will be permitted to proceed to intensification and remain on trial
- Patients who are proceeding to transplant but experiencing >3 week delay arranging their transplant/identifying a donor – intensification is given as holding therapy.

- Omit pegylated asparaginase in patients with Philadelphia positive disease
- Creatinine clearance must be >100mls/min before starting methotrexate. If creatinine clearance is <80mls/min, methotrexate must be reduced accordingly.

Intensification – treatment

Please refer to Protocol section 7.2.7

UKALL14 Intensification																															
Drug	Dose	Route	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	3 g/m^2	IV	X														X													
Pegylated asparaginase*	1000IU/ m^2	IV		X														X												
Imatinib (Philadelphia positive patients)	400-600mg	PO	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
* Pegylated asparaginase must not be given to patients with Philadelphia positive disease																														

Treatment deviations must be documented in patient notes, giving the reason why and associated clinical review/justification, and reported on relevant CRFs

Intensification - samples

Test	Sample required	When	Send to
Asparaginase activity & anti-asparaginase antibodies*	5ml peripheral blood in serum tube	Prior to peg-asparaginase dosing on D2 & D16	UCL Cancer Institute MRD lab
Asparaginase coagulation activity	4.5ml peripheral blood in citrate tube – spin @2000G for 5 minutes and store serum in 5 eppendorfs	Prior to peg-asparaginase dosing on D2	Store locally at -80°C – collection to be arranged at end of trial

* Not required for Philadelphia positive patients

Intensification - data collection

Please refer to Protocol section 8.1.1

CRF	When to send	How to send
Intensification form	Within 1 month of completing treatment phase	Post/fax/email
Intensification AE form	Within 1 month of completing treatment phase	Post/fax/email
SAE reports	Within 24 hours of becoming aware of SAE	Fax/email

Consolidation – important notes

Please refer to Protocol section 7.2.8

- Patients who have CNS involvement should have cranial irradiation before starting consolidation and be given maintenance mercaptopurine therapy during this time
- First cycle of consolidation to begin after counts recovered following intensification
- LFTs should be performed regularly whilst receiving pegylated asparaginase
- IT methotrexate can be moved +/-3 days to allow administration as per local & national guidance, for this phase
- Cytarabine treatment block schedule may be moved to take place during the week, as long as full dose is given for this phase
- Cycle 3 Days 1-42:
  - *D1-28: Treatment should be interrupted if patient experiences serious infection*
  - *Counts must have recovered sufficiently before starting D29. A pause can be taken after day 28 to allow counts to recover if necessary*

Consolidation
- treatment cycles 1 & 2

UKALL14 Consolidation 1

Drug	Dose	Route	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
Cytarabine	75mg/m^2	IV	X	X	X	X	X																							
Etoposide	100mg/m^2	IV	X	X	X	X	X																							
Pegylated asparaginase*	1000IU/m^2	IV					X																							
Methotrexate	12.5mg	IT	X																											
Imatinib (philadelphia positive patiens)	400-600mg	PO	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

* Pegylated asparaginase must not be given to patients with Philadelphia positive disease

UKALL14 Consolidation 2

Drug	Dose	Route	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Cytarabine	75mg/m^2	IV	X	X	X	X	X		
Etoposide	100mg/m^2	IV	X	X	X	X	X		
Methotrexate	12.5mg	IT	X						
Imatinib (philadelphia positive patiens)	400-600mg	PO	X	X	X	X	X	X	X

Treatment deviations must be documented in patient notes, giving the reason and associated clinical review/justification, and reported on relevant CRFs

Consolidation - treatment cycles 3 & 4

UKALL14 Consolidation 3

Drug	Dose	Route	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
Daunorubicin	25 mg/m^2	IV	X							X							X							X						
Vincristine	1.4mg/m^2 Max 2mg	IV	X							X							X							X						
Dexamethasone	10mg/m^2 Max 20mg	PO	X	X	X	X				X	X	X	X				X	X	X	X				X	X	X	X			
Pegylated Asparaginase*	1000IU/m^2	IV		X															X											
Methotrexate	12.5mg	IT		X																										
Imatinib (philadelphia positive patiens)	400-600mg	PO	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

* Pegylated asparaginase must not be given to patients with Philadelphia positive disease

UKALL14 Consolidation 3 (continued)

Drug	Dose	Route	Day 29	Day 30	Day 31	Day 32	Day 33	Day 34	Day 35	Day 36	Day 37	Day 38	Day 39	Day 40	Day 41	Day 42
Cyclophosphamide	1000mg/m^2	IV	X													
Cytarabine	75mg/m^2	IV		X	X	X	X				X	X	X	X		
Mercaptopurine	60mg/m^2	PO	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Imatinib (philadelphia positive patiens)	400-600mg	PO	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Treatment deviations must be documented in patient notes, giving the reason and associated clinical review/justification, and reported on relevant CRFs

Consolidation
- treatment cycle 4

UKALL14 Consolidation 4									
Drug	Dose	Route	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Cytarabine	75mg/m^2	IV	X	X	X	X	X		
Etoposide	100mg/m^2	IV	X	X	X	X	X		
Methotrexate	12.5mg	IT	X						
Imatinib (philadelphia positive patiens)	400-600mg	PO	X	X	X	X	X	X	X

Treatment deviations must be documented in patient notes, giving the reason and associated clinical review/justification, and reported on relevant CRFs

Consolidation – data collection

See protocol section 8.1.1 for details of investigations to be carried out during treatment.

CRF	When to send	How to send
Consolidation Treatment form	Within 1 month of completing consolidation treatment	Post/fax/email
Consolidation AE form	Within 1 month of completing treatment phase	Post/fax/email
SAE reports	Within 24 hours of becoming aware of SAE	Fax/email

- See page 66 for details on reporting withdrawals from treatment
- See page 76 for details on reporting SAEs
- See page 70 for details on reporting deaths

Consolidation – sample collection

The protocol does not require samples to be sent to the central lab during consolidation. However, please note that if the patient relapses during consolidation, the following sample will be required:

Test	Sample required	Send to
Cell banking at relapse	3-5ml bone marrow in EDTA *or* 30-50ml blood in EDTA (if WBC >$30x10^9$/l)	UCL Cancer Institute MRD lab

Maintenance – treatment

Please refer to Protocol section 7.2.9

- 2 years of maintenance treatment starts when count recovery is reached following Consolidation cycle 4
- No IMPs are given during maintenance treatment
- During maintenance, doses of mercaptopurine and methotrexate should be adjusted (+/- 25%) to maintain counts as follows:
  - Neutrophils 0.75-1.5 x 10^9/L
  - Platelets 75-150 x 10^9/L

Drug	Dose	Route	Frequency
Vincristine	1.4mg/m^2 (max 2mg)	IV	Every 3 months
Prednisolone	60mg/m^2	PO	5 days every 3 months
Mercaptopurine	75mg/m^2	PO	Daily
Methotrexate	20mg/m^2	PO or IV	Once per week (not on same day as co-trimoxazole)
Intrathecal therapy during maintenance (to be given once neutrophils reach 0.75x10^9/l and platelets reach 75x10^9/l)			
Methotrexate	12.5mg	IT	Every 3 months

Maintenance
- data collection

CRF	When to send	How to send
Maintenance Treatment forms	Within 30 days of completing each 3-month block of maintenance	Post/fax/email
Treatment Summary form	Within 30 days of completing/stopping maintenance treatment	Post/fax/email

Maintenance – sample collection

The protocol does not require samples to be sent to the central lab during maintenance. However, please note that if the patient relapses during consolidation, the following sample will be required:

Test	Sample required	Send to
Cell banking at relapse	3-5ml bone marrow in EDTA *or* 30-50ml peripheral blood in EDTA (if WBC >30x10^9/l)	UCL Cancer Institute MRD lab

Stopping Trial Treatment - forms

- **Send 'Treatment Summary' form within 30 days of last trial treatment**
  (*trial treatment includes 24m post transplant follow-up even if patient is not receiving active treatment)*
- A patient may stop trial treatment for any reason but will remain on trial and be followed up annually until death *unless*:
  - Patient specifically withdraws consent (in which case, please complete and send the 'Lost to follow-up form' as soon as possible)
  - Patient was proven to have been ineligible.
  - Relapsed?
    - Send 'Relapse' form as soon as possible following date of relapse
    - Send MRD sample (bone marrow, or peripheral blood if WBC >30x109L) from time of relapse
    - Relapse must be confirmed by morphological assessment and not molecular assessment
  - Second cancer?
    - Send 'Second Cancer' form as soon as possible following diagnosis of second cancer
  - Died?
    - Send 'Death' form within 7 calendar days of becoming aware of the death
    - Provide overall cause of death on death form and refer to the death certificate where possible
    - If the cause of death meets the criteria for an SAE (see protocol section 12.2.2), complete and send an SAE report alongside the death form.

Follow up – forms

- Follow-up begins from the anniversary of completing maintenance or end of 24 month post transplant follow-up or stopping trial treatment
- An annual follow-up form must be submitted every year (until the end of the study or death) for all surviving patients on the anniversary of their last trial treatment date (±30 days)
- There are 3 annual follow-up forms depending on the patient's status/progress:
  - Send **'Not in CR after Phase 2'** form if patient did not reach CR at any time during induction
  - Send **'Relapse/Secondary Malignancy'** form if patient has relapsed or been diagnosed with a second cancer
  - Send **'Annual Follow-up'** form if patient is in first CR and not diagnosed with a second cancer.
- Send **'Late Effects'** form within ±30 days of the 2 year follow-up appointment.
- Send **'Lost to Follow Up'** form as soon as possible for any patient who has been lost to follow up or who has withdrawn consent completely.

Relapses

If a patient relapses at any point during the trial, the following CRF and sample must be sent:

*Please note that this only relates to clinical/morphological relapse, **not** molecular relapse whereby the patient becomes MRD positive only.*

CRF	When to send	How to send
Relapse form	ASAP following confirmation of relapse	Fax/email

Test	Sample required	Send to
Cell banking at relapse	3-5ml bone marrow in EDTA *or* 30-50ml peripheral blood in EDTA (if WBC >$30x10^9$/l)	UCL Cancer Institute MRD lab

Reporting second malignancies

If a patient is diagnosed with a second primary malignancy at any point during the trial, the following CRF must be sent:

CRF	When to send	How to send
Second Cancer form	ASAP following confirmation of diagnosis	Fax/email

Reporting deaths

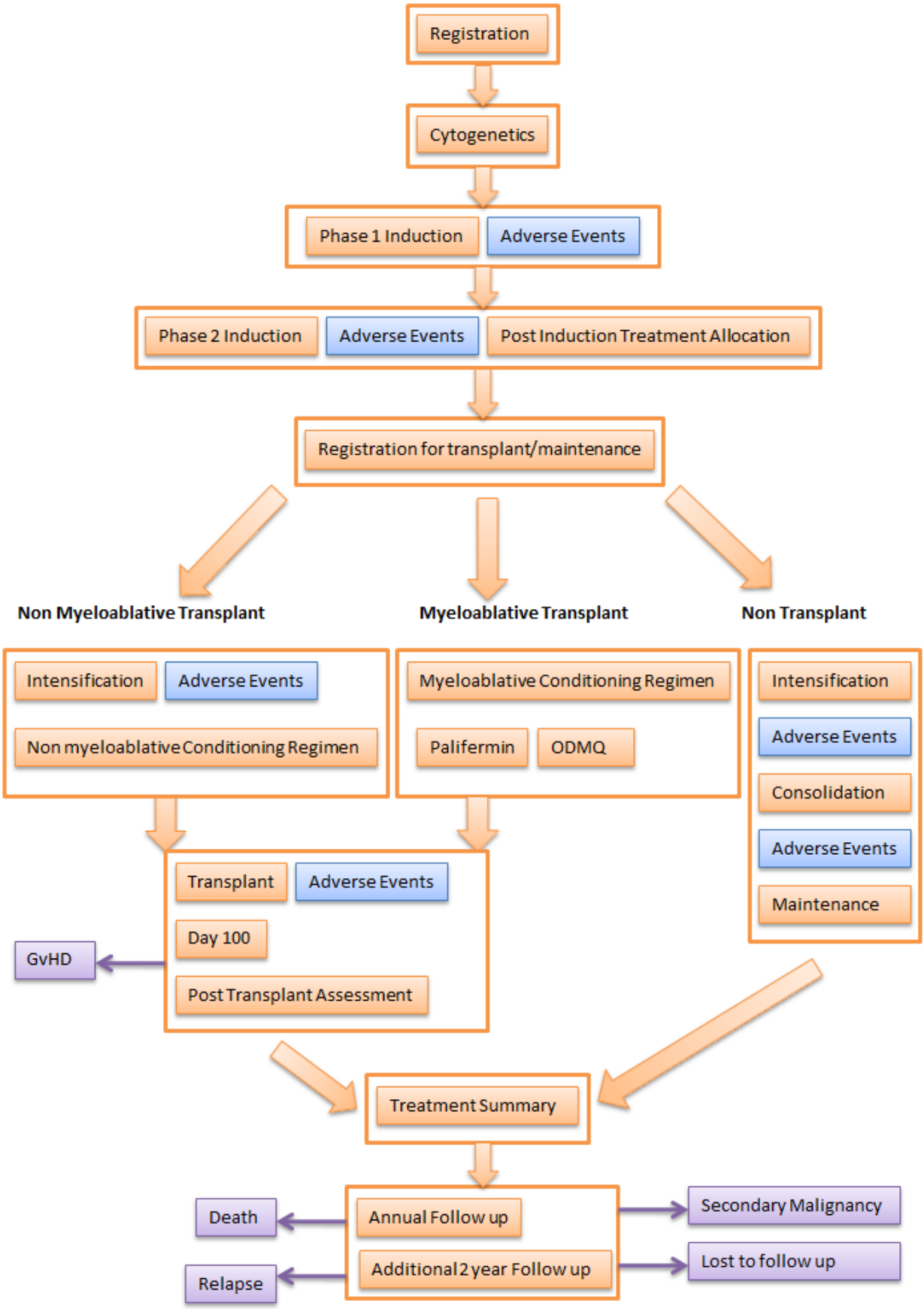
If a patient dies at any time during the trial, the following CRF must be sent:

CRF	When to send	How to send
Death form	Within 7 calendar days of becoming aware of death	Fax/email

RANDOMISED PATIENTS

Data Management & CRF Guidance

UKALL14 CRF Flowchart



Data Management

- See CRF Completion Guidelines.
- Ensure the current versions of the CRFs are used, as CRFs completed on outdated versions cannot be accepted
- Please return CRFs within the stated timeframes.
- Overdue CRF reports are sent out by UCL CTC to help sites keep track of what is outstanding
- UCL CTC will send each site batches of data clarification forms (DCFs) every 3 months
  - If you have started on the previously sent DCF but not yet finished/sent it to UCL CTC, please phone UCL CTC to discuss.
- Sites who persistently fail to return data within the required timelines may be subjected to a 'for cause' monitoring visit by UCL CTC

RANDOMISED PATIENTS

Safety Reporting

AE Reporting Procedures

Please refer to Protocol section 12.2.1

- The maximum severity grade must be recorded for all adverse events that occur between informed consent and 30 days post consolidation (for non-transplant patients) or 30 days post transplant (for transplant patients)
- There is an AE form for each treatment phase to be used for this purpose
- Event terms and grades should be assigned using CTCAE v4.0
- All grades of AEs must be reported in patient notes and AE forms, including Grade 1 & 2 events
- Pre-existing conditions do not qualify as AEs unless they worsen. Baseline AEs should be listed on the registration form
- Any AEs meeting the criteria for serious should be recorded on the AE form as well as an SAE report being submitted.

SAE Reporting Procedures

Please refer to Protocol section 12.2.2 and CRF completion guidelines

- The following events are exempt from SAE reporting, but must be documented on the relevant CRF:
  - Disease progression (use Relapse form)
  - Disease related deaths (use Death form)
  - Graft versus Host Disease (use GVHD form)
  - Graft Failure (use Graft Failure form)
  - Second primary malignancy (use second malignancy form)

Report SAEs using the following form:

CRF	When to send	How to send
SAE report form	Within 24 days of becoming aware of event	Fax/email

Please remember to include a contact name, phone number and email address in case of any queries

SAE Reporting Timeframes			
	Randomisation	**Timeframe (When IMP given)**	**Timeframe (When no IMP given)**
Phase 1 induction	B1	From informed consent until 30 days post last Pegylated Asparaginase administration	48 days from the date of randomisation for patients who do not receive Pegylated Asparaginase
	B2	From informed consent until 30 post last Rituximab administration	54 days from the date of randomisation for patients who do not receive Rituximab.
	T1, T2	From informed consent until 30 days post last Pegylated Asparaginase administration	48 days from the date of randomisation for patients who do not receive Pegylated Asparaginase
Phase 2 induction	B1, B2	Not required unless within phase 1 induction SAE reporting window or late effect of IMP	Not required unless within phase 1 induction SAE reporting window
	T2 after Nelarabine administration	From first dose of Nelarabine until 30 days post last Nelarabine administration	From count recovery at the end of Phase 2 Induction until 35 days after count recovery at the end of Phase 2 Induction for patients not who do not receive Nelarabine
Intensification	B1, B2, T1, T2	From first administration of Pegylated Asparaginase until 30 days post last Pegylated Asparaginase administration	Not required unless within phase 2 SAE reporting window

Table extracted from protocol section 12.2.2.1

SAE Reporting Timeframes				
		Randomisation	**Timeframe (When IMP given)**	**Timeframe (When no IMP given)**
Consolidation	1	B1, B2, T1, T2	From first administration of Pegylated Asparaginase until 30 days post last Pegylated Asparaginase administration	Not required
	2	B1, B2, T1, T2	Not required unless within consolidation 1 SAE reporting window or late effect of IMP	Not required
	3	B1, B2, T1, T2	From first administration of Pegylated Asparaginase until 30 days post last Pegylated Asparaginase administration	Not required
	4	B1, B2, T1, T2	Not required unless within consolidation 3 SAE reporting window or late effect of IMP	Not required
RIC transplant		B1, B2, T1, T2	From start of conditioning chemotherapy until 30 days post-transplant	From start of conditioning chemotherapy until 30 days post-transplant
MAC transplant		B1, B2, T1, T2	From start of conditioning until 30 days post-transplant	From start of conditioning until 30 days post-transplant
Maintenance		B1, B2, T1, T2	Not required unless late effect of IMP	Not required

Table extracted from protocol section 12.2.2.1

Reporting thromboembolic events

Venous thromboembolism (VTE) events are regarded as Adverse Events of Special Interest for this study

- Report as follows:

Onset of VTE	Report form to use	How/when to send
During SAE reporting window	SAE report	By fax/email within 24 hours of becoming aware
Outside SAE reporting window	Thromboembolic Event Urgent Event Form	By fax/email within 7 days of becoming aware

- See protocol section 12.3 for further information.

Pregnancy Reporting

Please refer to Protocol section 12.6

- Pregnancies occurring in randomised female patients or in partners of randomised male patients at any point between start of trial treatment until 12 months after completing trial treatment must be reported using the following form:

CRF	When to send	How to send
Pregnancy report form	Within 24 days of becoming aware of pregnancy	Fax/email

- SAEs occurring in randomised patients *during* pregnancy must be reported on an SAE report form according to SAE reporting procedures

Pregnancy Follow up

- The pregnant patient/partner should be approached to request her consent for pregnancy monitoring using:

Status of mother	Documents to use
Trial patient	Pregnancy monitoring information sheet & consent form (patients)
Partner of trial patient	Pregnancy monitoring information sheet & consent form (partners)

- If the mother consents to pregnancy monitoring:
  - The pregnancy must be followed-up until birth/termination.
  - A follow-up Pregnancy Report must be submitted to UCL CTC within 24 hours of becoming aware of the outcome
- If the mother declines to consent:
  - Please let UCL CTC know. No further data will be collected about the pregnancy.
- Completed consent forms must be filed in the ISF and patient notes.

INFORMATION FOR PHARMACIES

(see Drug Supply Guidelines for full details)

Trial Drugs - IMPs

Investigational Medicinal Products (IMPs)

The following IMPs are supplied for the trial free of charge:

- **Rituximab** (Mabthera®) - licensed - supplied by Roche
  (randomisation now closed; no further orders to be placed)
- **Nelarabine** (Atriance®) - licensed - supplied by Novartis AG
- **Palifermin** (Kepivance®) – licensed until April 2016 – supplied by Swedish Orphan Biovitrum December 2010-April 2016
  (randomisation now closed; no further orders to be placed)

The following IMP is supplied for the trial at site's own cost:

- **Pegylated Asparaginase** (Oncaspar®) - licensed - supplied by Baxalta, now part of Shire

- IMP supplied for the UKALL14 trial must only be used to treat randomised UKALL14 patients.

Ordering IMPs

Please refer to the Drug Supply Guidelines for full details

Site pharmacies are responsible for maintaining an adequate supply of IMP for each patient randomised

Nelarabine and Pegylated Asparaginase must be ordered using the trial specific drug order forms, and sent to the email address(es) specified on the form and ensure UCL CTC is copied in ctc.ukall14@ucl.ac.uk

Temperature Excursions

Please refer to the 'Pharmacy Procedure for Reporting Temperature Excursions'

- IMPs should be segregated and stored as per the SPCs
- All temperature readings outside the storage conditions specified in the SPC must be reported as excursions.
- If multiple temperature monitoring systems are used, report deviations which occur on ANY system.
- Actions to be taken upon identifying an excursion:
  - Quarantine all affected trial stock IMMEDIATELY
  - Complete the trial specific '**Notification of Temperature Excursion**' form
  - Email to ctc.excursions@ucl.ac.uk or fax to +44 (0)20 7679 9861
  - UCL CTC will check whether drug is safe to use and advise.

N.B. Treating a patient with drug affected by a temperature excursion before the case has been reviewed and confirmation received that the IMP is safe to use may constitute a serious breach.

IMP Accountability

- Accountability records must be kept up-to-date for all IMPs:
  - Records of ordering and receipt
  - Balance logs
  - Dispensing logs
  - Records of returns to pharmacy
  - Destruction records
- Trial specific logs are provided; pharmacies can use own logs if they collect equivalent information
- Copies of accountability logs must be sent to UCL CTC upon request as part of central monitoring, plus any ad-hoc requests
- Traceability must be maintained for NIMPs and drugs used to treat 'registration only' sub-study patients.

  Receipt of these drugs should be recorded centrally, so in the event of a batch recall pharmacy can identify which patients were given affected drug

IMP Destruction

- Ensure a copy of the local Drug Destruction Procedure has been filed in relevant section of PSF
- Expired trial drugs must be quarantined
- Email UKALL14 team to request approval
- Upon approval of destruction, the IMP can be destroyed at site according to local pharmacy policy
- Record destruction on the **Destruction Log** and in **Stock Balance accountability logs**:
  - Send a copy to UCL CTC
  - File in the relevant section of the site pharmacy file

‘REGISTRATION ONLY’ SUB-STUDY

‘Registration only’ sub-study - overview

From implementation of protocol v11.0 onwards, newly-diagnosed B-cell patients can now enter a UKALL14 ‘registration only’ sub-study.

- Main aim is to collect basic data and samples to address laboratory aims
- Standard ALL treatment as per local clinician’s choice
- No IMPs or NIMPs
- New CRFs to collect limited data
- No safety reporting

‘Registration only’ sub-study - aims

Please refer to Protocol Appendix 1, section 2

Data and samples collected on ‘registration only’ sub-study patients will be used to address the following laboratory aims:

- To characterise the genomic landscape of adult ALL
- To investigate the clonal origins of relapsed ALL
- To define a T-cell signature which predicts response to allo-HCT
- To develop global risk models in adult ALL that integrate demographic, genetic and response information

‘Registration only’ sub-study - informed consent

Please refer to Protocol Appendix 1, Section 3

- Informed consent must be obtained from the patient by a delegated person prior to any trial-specific intervention

- There are 2 patient information sheets/consent forms to give to patients:
  - **‘Registration only’ sub-study** PIS/consent
  - Optional **Additional Genetic Testing – Buccal Swab** PIS/consent
    - Consent can be obtained for buccal swab at any time. We ask that as many patients as possible give samples to further our understanding of leukaemia.

- Document details of the consent process in the patient’s notes:
  - when the PIS was given
  - discussion(s) about the trial with the patient
  - when consent was taken
  - who took consent

‘Registration only’ sub-study - informed consent

Please refer to Protocol Appendix 1, Section 3

- 24 hours should be allowed for patients to consider participation in the trial
  - If this is not possible, patients may consent on the same day provided the member of staff taking consent is satisfied that the patient understands the trial and its implications and follows up with the patient to confirm ongoing willingness to participate and documents this in patient notes
- Remember to complete the patient number on the top of the consent form following trial registration
- The original consent form plus one copy must be stored at site (one in the ISF & one in the patient’s medical notes).
- The patient must also be given a copy – document in the notes that this has been done.
- Do not send consent forms to UCL CTC.

Results required before sub-study entry

Patients cannot enter the sub-study until the results below confirming eligibility are known:

Results required before registration
Percentage of bone marrow blasts to confirm diagnosis of ALL (if not yet available, copy of diagnostic report)
Patient's disease lineage
Medical history (specifically history of hepatitis B & C and HIV)
Negative pregnancy test (women of childbearing potential)

Please refer to Protocol Appendix 1 for a full list of screening investigations and eligibility criteria.

'Registration only' sub-study - eligibility

Please refer to Protocol Appendix 1, section 5

Inclusion criteria	Exclusion criteria
a) Patients aged ≥25 and ≤65 old with B-cell ALL or aged ≥19 and ≤65 old with Philadelphia chromosome positive ALL	a) Mature B-cell leukaemia (eg. Burkitt's lymphoma)
b) Newly diagnosed, previously untreated ALL (a steroid pre-phase is permitted but not required)	b) Known HIV infection
c) Written informed consent	c) Known history of hepatitis B infection*
	d) Known history of hepatitis C infection*
	e) Pregnant or lactating women
	f) Blast transformation of CML

**As per national MHRA guidance, hepatitis testing must be done prior to administering rituximab*

‘Registration only’ sub-study - registration

Please refer to Protocol Appendix 1 Section 6

- Pre-registration evaluations should be carried out as per local policy.
- Complete ‘Registration only’ sub-study Registration form in full (including contact details on front page) and fax/email to UCL CTC
- If sending by email, patient identifiable information (NHS no, DOB) must be redacted before sending and then provided to CTC by telephone
- Please allow a minimum of 2 hours for registrations to be processed (cut off time for same day processing is 4pm)
- CTC will fax/email confirmation of the patient’s registration, with trial number, back to the site
- Provide patient with a copy of their signed consent form.

'Registration only' sub-study
- samples at study entry

Please refer to Protocol Appendix 1 Section 8.3

Samples taken prior to consent can be used, but cannot be sent until patient has given their consent.

Test	Sample required	Send to
MRD baseline testing	3-5ml bone marrow in EDTA or 30-50ml blood in EDTA	UCL Cancer Institute MRD lab
Constitutional DNA (optional)	Buccal swab	UCL Cancer Institute MRD lab
Cytogenetics	Report from local cytogenetics tests	Leukaemia Research Cytogenetics Group, Newcastle

‘Registration only’ sub-study - treatment

Please refer to Protocol Appendix 1 Section 7

- Treatment for ‘registration only’ patients is decided by the local clinician
- May follow the UKALL14 backbone regimen but it is not mandated
- Any drugs used to treat ‘registration only’ patients will not be regarded as IMPs
- Drugs must be sourced from hospital stock and will not be reimbursed
- Follow local practice with regards to recovery/continuation at each phase
- Accountability logs are not required - follow standard local practice regarding drug traceability.

'Registration only' sub-study
- samples during treatment/follow up

Test	Sample required	When	Send to
End of phase 1 MRD	3-5ml bone marrow aspirate in EDTA	Count recovery at end of phase 1	UCL Cancer Institute MRD lab *Report can be sent on special request*
End of phase 2 MRD	3-5ml bone marrow aspirate in EDTA	Count recovery at end of phase 2	UCL Cancer Institute MRD lab *Report will be sent within 10 days of receipt*
Post-transplant MRD	3-5ml bone marrow aspirate in EDTA	Every 3 months post non-myeloablative transplant	UCL Cancer Institute MRD lab *Report will be sent within 10 days of receipt*
Cell banking at relapse	3-5ml bone marrow aspirate in EDTA *or* 30-50ml peripheral blood in EDTA (if WBC >$30x10^9$/l)	When relapse suspected/ confirmed	UCL Cancer Institute MRD lab

'Registration only' sub-study - data management

NEW CRFs

- **'Registration only' Sub-study Entry form** – study entry, before starting induction treatment
- **'Registration only' Induction Treatment form** – after induction phase 1 and phase 2
- **'Registration only' Post Induction Chemotherapy form** – after each phase of treatment/every 3 months during maintenance
- **'Registration only' Annual Follow Up form** – from anniversary of completion of treatment/transplant

And if transplant is given:

- **'Registration only' Transplant Day 100 form**
- **'Registration only' GvHD form**

EXISTING CRFs

- **Relapse form** *(send ASAP)*
- **Death form** *(send ASAP)*
- **Lost to Follow Up form** *(send ASAP)*
- **Centre Transfer form** *(send ASAP)*

CRFs should be sent within 30 days of timepoint unless stated otherwise

'Registration only' sub-study - safety reporting

- **AEs, SAEs or pregnancies do not need to be reported to the CTC for 'registration only' sub-study patients**

- Clinicians should report adverse reactions and serious adverse reactions to the MHRA via the Yellow Card scheme, as per routine post-marketing surveillance.