Relapsed Acute Lymphoblastic Leukemia Protocol 2014 (RALL 14)

(Modified UKALL R3 trial protocol)

Outline of Management

Pediatric Leukemia Program,
Section of Pediatric Leukemia/Lymphoma

Department of Pediatric Hematology/Oncology

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ABBREVIATIONS
Allo –SCT Allogeneic Stem Cell Transplant
ALL Acute Lymphoblastic Leukaemia
BFM Berlin-Frankfurt-Münster
BMT Bone Marrow Transplant
CCR Complete Clinical Remission
CNS Central Nervous System
CR Complete Remission
CSF Cerebrospinal Fluid
DFS Disease Free Survival
DLI Donor Lymphocyte Infusions
DMC Data Monitoring Committee
DNA Deoxyribonucleic Acid
DNR Daunorubicin
DNX DaunoXome
ECG Electrocardiogram
EFS Event Free Survival
FLAD Fludarabine, High dose Cytosine and Liposomal Daunorubicin
FLAG Fludarabine, Cytosine with GCSF
G-CSF Granulocyte-Colony Stimulating Factor
GvHD Graft versus Host Disease
GvL Graft versus Leukaemia
kg kilograms
KM Kaplan Meier
MC Mixed Chimerism
mg milligrams
MHRA Medicines and Healthcare Products Regulatory Authority
MRC Medical Research Council
MRD Minimal Residual Disease
MREC Multi-centre Research Ethics Committee
MTD Maximum Tolerated Dose
PCR Polymerase Chain Reaction
PEG Polyethylene glycol
PFS Progression Free Survival
RNA Ribonucleic Acid
SAE Serious Adverse Event
SCT Stem Cell Transplant
SUSAR Suspected Unexpected Serious Adverse Reaction
TRM Treatment Related Mortality
UKCCSG
NOW CALLED CCLG
United Kingdom Childhood Cancer Study Group
CHILDRENS CANCER AND LEUKAEMIA GROUP
UKCLWP United Kingdom Childhood Leukaemia Working Party
Introduction:
This protocol standardizes the treatment of children with relapsed ALL who fail induction or relapse once a morphological remission has been obtained. It is evident from past experience that these children do not form one single clinical or biological entity. This therapy builds upon the results achieved in the MRC R1 protocol and also utilizes risk group stratification adopted by the BFM group.

Our current understanding of acute lymphoblastic leukemia (ALL) suggests that initial induction and intensification results in a dramatic decrease in the tumor load. The more speedily this is achieved, the better the therapeutic outcome. However, at least a two-year period of maintenance therapy may be required to maintain remission. It is likely therefore, for maintenance to work that the level of disease must be decreased to an optimum level, currently below the level of standard diagnostic tools. The key drugs and the dosages used in maintenance therapy are not specifically cytocidal for lymphoblasts but do appear to achieve a state of immunosuppression. It is possible that they stimulate immune-mediated pathways or alter the stroma upon which malignant cells thrive in order to eradicate or control the malignant clone. To be able to do so effectively requires a minimum lymphoblast: effector cell ratio. From the past experience with relapsed ALL, such an effect is probably strongest in the marrow and less so in Extramedullary sites.

Given this background, those who relapse early are likely to have more drug-resistant disease as primary treatment failed to decrease the initial tumor load adequately. These children may benefit from more intense induction, intensification and possibly from bone marrow transplantation. Those who relapse later may do so because they are unable to mount a proper immune response. Such children may benefit from a more direct lymphotoxic maintenance schedule.

The place of bone marrow transplant remains uncertain in ALL. However results from the MRC and BFM suggest the groups that benefit most are those with early bone marrow relapse and those with T cell disease.
ELIGIBILITY CRITERIA:

Inclusion Criteria
A subject will be eligible for inclusion in this protocol only if all of the following criteria apply:

1. All patients aged 1-14 years who have been previously diagnosed to have acute lymphoblastic leukemia and have relapsed after treatment.
2. For relapsed patients, only those patients in whom this is the first relapse are eligible.
3. Primary refractory disease.

Exclusion Criteria:
A subject will not be eligible for inclusion in this protocol if any of the following criteria apply:

1. Those who have first relapse but have already received chemotherapy or radiotherapy for the relapse.
2. Patients who have had a prior bone marrow transplant.
3. Those with mature B-cell ALL.

Risk Stratification:

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Very Early: Within 18 months of diagnosis; Early: After 18 months of diagnosis but within 6 months of stopping treatment; Late: More than 6 months after stopping treatment. EM= Extramedullary. Combined= Marrow and Extramedullary involvement, Isol = isolated

Standard Risk:

This category of patients will be treated with chemotherapy and localized radiotherapy.

Intermediate Risk:

Some patients in this group were treated with chemotherapy alone and others received an allogeneic stem cell transplant (allo-SCT). The considerable heterogeneity within the group precludes a single therapeutic option. In agreement with the I-BFM group, those who clear disease quickly, as measured by minimal residual disease (MRD) techniques, are most likely to sustain remission without an allogeneic stem cell transplant (allo-SCT).
Those children who have a disease level of $<10^{-3}$ (<0.1%) by Flowcytometry at the end of induction (day 35) will continue on chemotherapy with targeted radiotherapy if there is involvement of an extramedullary site. For those who have disease levels of $\geq 10^{-3}$ (≥0.1%), if there is a matched donor, then the intention is for an allo-SCT.

**High Risk:**
The recommendation for this group is to proceed to transplant after chemotherapy. A number of studies have shown that those with high levels of disease prior to allo-SCT usually relapse. Thus in common with the I-BFM, patients will have a MRD assessment at week 13. Those with disease levels of $\geq 10^{-3}$ (≥0.1%), will be offered an additional intensive phase, namely FLAD, prior to allo-SCT.

The treatment plan for those with isolated extramedullary disease has been debated in the IBFM-SG Resistant disease committee. Unpublished observations from previous UK trials suggest that a matched donor allo-SCT may be the best therapeutic option, as clearly chemotherapy results are poor. Thus for these children, where there is a matched donor available, the recommended treatment is an allo-SCT.
**Therapeutic Strategies for different risk groups:**

**Standard:**
Induction, Consolidation, Intensification, Interim Maintenance & Maintenance

**Intermediate:**
Induction, Consolidation and Intensification followed by:
- **MRD <10^3 (<0.1%) (post induction week 5)** continue chemotherapy with Phase V (Interim Maintenance) and then Phase VI (Maintenance).
- **MRD ≥10^3 (≥0.1%), (post induction week 5),** proceed to allo-SCT work-up if matched donor available (Matched Related Donor or MUD) and reassess **MRD at Week 13/14 (after consolidation).**

**High:**
All high risk patients will be offered an allo-SCT irrespective of MRD status at week 5. If **MRD ≥10^3 (≥0.1%),** at Week 13, they should proceed to FLAD prior to allo-SCT.
Induction, Consolidation and Intensification followed by:
- **Timepoint 2 (post Consolidation Week 13/15).**
- **MRD <10^3 (<0.1%) (proceed to allo-SCT post Intensification (Phase III).**
- **MRD ≥10^3 (≥0.1%),** proceed to FLAD (Phase IV) followed by allo-SCT.
Donor options will include **matched Sibling, Unrelated, Haploidentical donors, or UCBT**

In those children where MRD status is unknown, only high risk children should be considered for haploidentical donors.

**FLAD, prior to allo-SCT:**
Fludarabine, High-dose Cytosine and Daunorubicin (**FLAD**)

**Rare cases:**
In children who have previously received cranial irradiation, high dose methotrexate is considered inadequate therapy. However, two courses of cranial irradiation is toxic. In a previous survey, 20% of such relapses could be salvaged but 60-70% subsequently required special schooling (**these cases should be discussed in the Leukemia Section Meeting**)

**ALLOGENEIC STEM CELL TRANSPLANT ELIGIBILITY:**

1. All those in the High-Risk Group
2. Those in the Intermediate-Risk Group who have a MRD level of **≥10^3 (≥0.1%)** at day 35 and have a matched donor
3. Those in the Intermediate-Risk Group, in whom the day 35 MRD results are indeterminate or where this MRD cannot be performed are eligible for an allo-SCT if relapse occurred while still on treatment with the frontline protocol **AND** if there is a matched donor available (Matched Related Donor or MUD)
CNS Disease at relapse and proceeding to chemotherapy alone:

Patients with CNS disease at diagnosis (the presence of >5/cumm unequivocal lymphoblasts in the CSF) should receive weekly intrathecal methotrexate until two consecutive clear CSF’s have been obtained. Patients not being transplanted should receive cranial irradiation 24 Gy in 15 fractions of 1.6 Gy each of cranial radiotherapy starting week 14. **Following radiotherapy they should not receive any further intrathecal methotrexate** (see Appendix 7).

The individual regimens provide specific timing and dosages. These patients are still eligible for the trial randomisation. There is evidence to suggest that the use of thiopurines during cranial irradiation may predispose to the occurrence of brain tumours. Therefore during cranial radiotherapy, only the use of vincristine and dexamethasone is recommended.

**NB: Children under 2 years of age with CNS disease at diagnosis are not eligible for cranial radiotherapy.** We anticipate that this will be a rare occurrence. If you do have this problem, please discuss it with the leukemia team.

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

Testicular disease at relapse and proceeding to chemotherapy alone:

Boys with testicular infiltration at presentation should follow the protocol. Those not being transplanted should have 24Gy in 12 daily fractions of irradiation to both testes starting week 14. Other treatment should continue uninterrupted (see Appendix 7), during the period of Radiotherapy.

CHEMOTHERAPY SCHEDULES:

*Antifungal Prophylaxis:*
All children should receive antifungal prophylaxis during the phases I - III.
(See Appendix 1: Antifungal Prophylaxis)

SR/IR - INDUCTION

Standard/Intermediate Remission Induction: Phase I: Weeks 1-4
This phase runs for 28 days from day 1 (week 1) to day 28 (week 4) (i.e. 4 weeks).

Standard and Intermediate Risk Only
Phase I - Induction (wks 1 - 4)

Accumulative anthracyclin should be equal or less than 400 mg/ m2

Intrathecal Methotrexate on d1, wk1 and d1, wk2. <2yrs 8mg; 2-3yrs 10 mg; ≥3 yrs 12 mg
Mitoxantrone on d 1 and 2, wk1. 10mg/m2 iv infusion over 1 hour (Accumulative anthracyclin should be equal or less than 400 mg/ m2)
Dexamethasone on d 1-5, wk1 and d 1-5, wk3. 20 mg/m2 orally in 2 divided doses per day (max 40mg/day)
Vincristine on d3. Wk 1, d3 of wk2, d3 of wk 3, d3 of wk4. 1.5mg/m2 iv bolus MAX 2mg as a single dose
PEG Asparaginase on d 3, wk 1 and d3, wk3. 1000 u/m2 IV
OR if allergic to E.Coli asparaginase
Erwinase 20,000 units/m2 IM on day 3 of week 1 and then alternate days for 12 doses in total
Bactrim twice daily on two consecutive days from d 1 of weeks 1-4

Standard/Intermediate - Induction
All patients should be adequately hydrated (at least 2-2.5 l/m2/24hrs given parenterally for the first 48 hours)
a) Allopurinol 100 mg/m2 oral three times daily, should start 24 hours before chemotherapy and continue for 5 days.
b) Dexamethasone at 20mg/m2/day orally for 5 days, on days 1 - 5, week 1 and then again on days 1 - 5, week 3. The steroid should be divided into two doses per day with a maximum daily dose of 40mg.
c) **Vincristine** 1.5 mg/m² *(maximum single dose 2 mg)* IV bolus weekly on d3 of week 1, d3 of week 2, d3 of week 3, and d3 of week 4.

d) **PEG-Asparaginase** 1000 u/m² IV on d3 of week 1 and d3 of week 3. OR (if allergic to E Coli Asparaginase) **Erwinase** Erwinase 20,000 units/ m² IM on d3 of week 1 and then alternate days for 12 doses in total. (That is replacing each dose of PEG with 6 doses of Erwinase)

e) Intrathecal Methotrexate d1 of week 1 and d1 of week 2.

*Dose by age:*
- <2yrs: 8 mg
- 2-3 yrs: 10 mg
- ≥3yrs: 12 mg

Patients who have CNS disease at presentation should receive weekly doses until two clear CSF samples are obtained.

g) **Mitoxantrone** 10 mg/m², intravenously over 1 hour on d1 and 2 of week 1 *(Accumulative anthracyclin should be equal or less than 400 mg/m²)*

h) **Bactrim** given twice daily on two consecutive days each week from weeks 1-4, maintaining the longest possible interval from intrathecal methotrexate in order to avoid drug interactions.

**There is a high morbidity when inducing children with relapsed disease. It is advisable to keep these children in hospital during the induction period and when severely neutropenic. They will require proactive nutritional support. Antifungal prophylaxis is recommended throughout the protocol.**

**Notes:**
The high dose of dexamethasone during this 4 week period may cause hyperglycemia. It is easier to control this if hydration fluids are free of dextrose.
PROTOCOL FOR STANDARD AND INTERMEDIATE RISK PATIENTS – RALL-14:

SR/IR – CONSOLIDATION:
Standard/Intermediate Consolidation: Phase II: Weeks 5-8
This phase runs for 28 days from day 1 (week 5) to day 28 (week 8) (i.e. 4 weeks).

Standard and Intermediate Risk Only

Dexamethasone, d1-5, Wk 5. 6 mg/m² orally in 2 divided doses
Vincristine on d3, Wk 5. 1.5mg/m² iv bolus MAX 2mg as a single dose
Proceed to week 6 only when count is recovering and ANC ≥ 0.5 x 10⁹/l and platelets ≥ 50 x 10⁹/l,
Perform Bone marrow examination at the beginning of week 6 (d35)
Intrathecal Methotrexate on d1, wk6. <2yrs 8mg; 2 yrs 10 mg; ≥3 yrs 12 mg
Methotrexate, d1, Wk6 1000 mg/m² iv infusion over 36 hours
PEG Asparaginase, d 2 Wk 6, 4 hours after the end of the methotrexate infusion. 1000 u/m² IV
OR if allergic to E. Coli Asparaginase Erwinase 20,000 units/m² IM on day 2 of week 6, 4 hrs after end of MTX infusion
and then alternate days for 6 doses in total
Leucovorin 48 hrs after the beginning of methotrexate infusion. 15 mg/m² iv bolus at 48 and 54 hours
Proceed to week 7 only when count is recovering and ANC ≥ 0.5 x 10⁹/l and platelets ≥ 50 x 10⁹/l,
Cyclophosphamide, d1-5, Wk 7. 440 mg/m² iv infusion over 30 minutes
Etoposide, d1-5 Wk 7. 100 mg/m² iv infusion over 4 hours
Bactrim twice daily on two consecutive days Wk 7, 8
No Bactrim, the week prior to and the week of iv methotrexate

Standard/Intermediate - Consolidation
This phase of intensification starts as soon as the child is able to tolerate it. The day Methotrexate is given will be counted as the beginning of week 6.

Week 5
a) Vincristine 1.5 mg/m² (maximum single dose 2 mg) IV on day 3 of week 5
b) Dexamethasone 6 mg/m² orally for 5 days, d1-5 of week 5, in two divided doses.
Please prescribe Dexamethasone and Vincristine regardless of count recovery as long as the child is well.
Do not use Bactrim during this week.
Proceed to week 6, only when marrow is recovering and ANC >0.5 x 10⁹/l and platelets >50 x 10⁹/l
Week 6:  
**Bone marrow aspirate for MRD**  
If a patient has M3 marrow at day 35 they may be removed from the protocol and considered to be refractory.

a) **Intrathecal Methotrexate** On day 1, week 6  
*Dose by age:*  
< 2yrs: 8mg  
2-3 yrs: 10mg  
≥ 3yrs: 12 mg  
This is ideally given prior to starting the IV Methotrexate infusion or immediately after. If it needs to be given during the infusion, on no account should the infusion be stopped.

b) **Methotrexate** day 1, week 6, 1000 mg/m² IV.  
10% of this is given intravenously as a bolus and the remaining 90% as a continuous infusion on d1 for 36 hours with concomitant hydration (see Appendix 2).

c) **Leucovorin** 15 mg/m² per dose intravenously. Starts 48 hours after the beginning of the methotrexate infusion, and given at 48 and 54 hours (see Appendix 3).

d) **PEG-Asparaginase** 1000 u/m² IV on d 2, week 6 [4 hours after the end of the Methotrexate infusion]  
OR (if allergic to E Coli Asparaginase)  
**Erwinase** Erwinase 20,000 u/m² IM on d 2 of week 6 [4 hrs after end of MTX infusion] and then alternate days for 6 doses in total [this will overlap into Week 7]  
*Do not use Bactrim during this week.*

Weeks 7– 8  
**Commence this phase as long as the child is well and ANC >0.5 x 10⁹/l and platelets >50 x 10⁹/l and counts are recovering**  
Chemotherapy should be continued in a well child with fever of unknown origin but no neutropenia. Any serious infection, such as varicella, Pneumocystis pneumonia, or neutropenia with fever, and presumed or proven infection, warrants chemotherapy interruption at any time.

a) **Bactrim** given twice daily on two consecutive days in **week 7 and week 8**

b) **Etoposide** 100 mg / m² IV infused over 4 hours on d1, 2, 3, 4 and 5 of week 7

c) **Cyclophosphamide** 440 mg / m² IV infused over 30 minutes on d1, 2, 3, 4 and 5 of week 7. Maintain fluids at 2-x maintenance for at least 4 hours after the dose. Use furosemide 0.25 - 0.5 mg/kg IV for urine output <3ml/kg/hr after cyclophosphamide. Mesna is not required unless there is microscopic haematuria or past history of gross haematuria.
PROTOCOL FOR STANDARD AND INTERMEDIATE RISK PATIENTS – RALL-14

SR/IR – INTENSIFICATION:

Standard and Intermediate Risk Only

Start Phase III when marrow is recovering and ANC ≥0.5 and platelets ≥50
(It is acceptable to give Vincristine and steroids if there is a delay)
Dexamethasone, d1-5, Wk 9. 6 mg/m² orally in 2 divided doses
Vincristine on d3, Wk 9. 1.5mg/m² iv bolus MAX 2mg as a single dose
Intrathecal Methotrexate on d1, wk 9. <2yrs 8mg; 2yrs 10 mg; ≥3 yrs 12 mg
Cytarabine 3000 mg/m² as iv infusion over 3 hours, every 12 hours, d1 and 2 Wk9 and d1, 2 Wk10
Erwinia Aparaginase 20,000 units/m² IM on d 2 and d 4 of Wk 9 and on d 2 and d 4 of Wk 10
Bactrim twice daily on two consecutive days Wks 9-10 , 13
Dexamethasone eye drops every 2 hours from d1, wk9 and stopped 5 days after the
last cytarabine infusion

Start **Week 12** when marrow is recovering and ANC ≥0.5 and platelets ≥50

**No Bactrim, the week prior to and the week of iv methotrexate**
Intrathecal Methotrexate on d1 wk12. <2yrs 8mg; 2yrs 10 mg; ≥3 yrs 12 mg
Methotrexate, d1 Wk12. 1000 mg/m² iv infusion over 36 hours
Leucovorin 48 hrs after the beginning of methotrexate infusion. 15 mg/m² iv bolus at 48 and 54 hours
Erwinase 20,000 units/m² IM on d 2 of Wk 12, 4hrs after the end of the methotrexate infusion

This phase starts as soon as the child is able to tolerate it. The ANC should be
> 0.5 x 109/l and the platelets > 50 x 109/l, with evidence of count recovery.

**Vincristine and Dexamethasone may be given regardless of count recovery as long as the child is well.**
The day cytarabine is first given will be counted as the beginning of week

**Weeks 9-10:**
a) **Vincristine** 1.5 mg/m² *(maximum single dose 2 mg)* IV on day 3 of week 9

b) **Dexamethasone** 6 mg/m² orally for 5 days, d1-5 of week 9 in two divided doses.

c) **Intrathecal Methotrexate** On day 1 of week 9
   
   *Dose by age:*
   
   < 2yrs: 8mg
   
   2-3 yrs: 10mg
   
   ≥ 3yrs: 12 mg

d) **Cytarabine** 3000 mg/m² to be infused every 12 hrs via 3 hour IV infusions. Given on d1 and d2 week 9 d1 and d2 week 10(total of 8 doses)
   
   Patients should be prescribed **dexamethasone eye drops** 2 hourly from day 1, Week 9 until 5 days after the last dose of cytarabine.

e) Erwinia Aparaginase 20,000 units/m² IM on day 2 and day 4 week 9 and on day 2 and day 4 week 10 [given 4 hrs after last cytarabine infusion]

f) **Bactrim** given twice daily on two consecutive days per week, week 9 week 10/12 and week 15.

**Week 11**

**Stop Bactrim**

**Week 12**

This phase of intensification starts as soon as the child is able to tolerate it. The ANC should be > 0.5 x 10⁹/l and the platelets > 50 x 10⁹/l, with evidence of count recovery and the child should be clinically well.

a) **Intrathecal Methotrexate** On day 1 of week 12
   
   *Dose by age:*
   
   < 2yrs: 8mg
   
   2-3 yrs: 10mg
   
   ≥ 3yrs: 12 mg

   This is ideally given prior to starting the IV Methotrexate infusion or immediately after. If it needs to be given during the infusion, on no account should the infusion be stopped

b) **Methotrexate** On day 1, week 12 1000 mg/m² IV. 10% of this is given as an IV bolus and the remaining 90% as a continuous infusion from d 1 for 36 hours, with concomitant hydration (see Appendix 3).

c) **Leucovorin** 15 mg/m² per dose intravenously. Starts 48 hours after the beginning of the infusion, and given at 48 and 54 hours (see Appendix 3).

d) Erwinia Aparaginase 20,000 units/m2 IM on day 2 week 12 [4] hours post Methotrexate]

**Week 13:**

**Bone marrow aspirate for MRD**
### INTERIM MAINTENANCE:

#### Phase V - Interim Maintenance - Cycle 1

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- Dexamethasone, d1-5, wk14. 6 mg/m2 orally in 2 divided doses
- ORAL Methotrexate once weekly, wk 15, 16 and 18, 19. 20 mg/m2 orally
- Intrathecal Methotrexate on d1, wks 14, 20. <2yrs 8mg; 2 yrs 10 mg; ≥3 yrs 12 mg
- Tioguanine d1-7, wk 20, 40mg/m2/day orally
- Vincristine on d3, wk14. 1.5mg/m2 iv bolus **MAX 2.0 mg as a single dose**
- Etoposide, d1 wk20 and d1 wk21. 150 mg/m2 iv infusion over 4 hours
- HD ORAL Methotrexate d1, wk 17. 25 mg/m2 every 6 hours for 4 doses orally
- Cyclophosphamide, d1, wk20 and d1, wk21. 300 mg/m2 iv infusion over 30 mts
- Leucovorin, d3, wk17. 10 mg/m2 every 6 hours for 2 doses orally
- Cytarabine d2-5 wk20, d2-5, wk 21. 50 mg/m2 iv/sc per dose for 8 doses
- Mercaptopurine daily, wk 14-19. 75 mg/m2/day orally
- Bactrim twice daily on two consecutive days Wks 14-15, 17-21 (give the Bactrim on wk17 after the Leucovorin)

**Note**, children who have received cranial radiotherapy in RALL-14 do not receive intrathecal methotrexate during this phase (see alternative flowsheet)
Phase V - Interim Maintenance - Cycle 2

Dexamethasone, d1-5, wk 22 6 mg/m² orally in 2 divided doses ORAL Methotrexate once weekly, wk 23, 24 and 26, 27. 20 mg/m² orally
Intrathecal Methotrexate on d1, wks 22, 28. <2yrs 8mg; 2 yrs 10 mg; ≥3 yrs 12 mg Tioguanine d1-7, wk 28. 40mg/m²/day orally
Vincristine on d3, wk22. 1.5mg/m² iv bolus MAX 2.0 mg as a single dose Etoposide, d1 wk28 and d1 wk29. 150 mg/m² iv infusion over 4 hours
HD ORAL Methotrexate d1, wk 25. 25 mg/m² every 6 hours for 4 doses orally Cyclophosphamide, d1, wk28 and d1, wk29. 300 mg/m² iv infusion over 30 mts
Leucovorin, d3, wk25. 10 mg/m² every 6 hours for 2 doses orally Cytarabine d2-5 wk28, d2-5, wk 29. 50 mg/m² iv/sc per dose for 8 doses
Mercaptopurine daily, wk 22-27. 75 mg/m²/day orally Bactrim twice daily on two consecutive days Wks 22-23, 25-26 (give the Bactrim on wk25 after the Leucovorin)
Note, children who have received cranial radiotherapy in RALL-14 do not receive intrathecal methotrexate during this phase (see alternative flowsheet)
Phase V - Interim Maintenance - Cycle 1 for those receiving Cranial XRT

Dexamethasone, d1-5, wk14. 6 mg/m2 orally in 2 divided doses Tioguanine d1-7, wk 20. 1.5mg/m2 iv bolus MAX 2.0 mg as a single dose Etoposide, d1 wk20 and d1 wk21. 150 mg/m2 iv infusion over 4 hours

Vincristine on d3, wk14. 1.5mg/m2 iv bolus HD ORAL Methotrexate d1, wk17. 25 mg/m2 every 6 hours for 4 doses orally Cyclophosphamide, d1, wk20 and d1, wk21. 300 mg/m2 iv infusion over 30 mts

Leucovorin, d3, wk17. 10 mg/m2 every 6 hours for 2 doses orally Cytarabine d2-5 wk20, d2-5, wk 21. 50 mg/m2 iv/sc per dose for 8 doses

Mercaptopurine daily, wk 14-19. 75 mg/m2/day orally Bactrim twice daily on two consecutive days Wks 14-15, 17-21(give the ORAL Methotrexate once weekly, wk 14, 15, 16 and 18, 19. 20 mg/m2 orally Bactrim on wk17 after the Leucovorin)

Children who have received cranial radiotherapy in RALL-14 do not receive intrathecal methotrexate during this phase
Phase V - Interim Maintenance - Cycle 2 for those receiving Cranial XRT

Dexamethasone, d1-5, wk 22. 6 mg/m2 orally in 2 divided doses Tioguanine d1-7, wk 28. 40mg/m2/day orally

Vincristine on d3, wk22. 1.5mg/m2 iv bolus **MAX 2.0 mg as a single dose** Etoposide, d1 wk28 and d1 wk29. 150 mg/m2 iv infusion over 4 hours

HD ORAL Methotrexate d1, wk 25. 25 mg/m2 every 6 hours for 4 doses orally Cyclophosphamide, d1, wk28 and d1, wk29. 300 mg/m2 iv infusion over 30 mts

Leucovorin, d3, wk25. 10 mg/m2 every 6 hours for 2 doses orally Cytarabine d2-5 wk28, d2-5, wk 29. 50 mg/m2 iv/sc per dose for 8 doses

Mercaptopurine daily, wk 22-27. 75 mg/m2/day orally Bactrim twice daily on two consecutive days Wks 22-23, 25-26 (give the ORAL Methotrexate once weekly, wk 22, 23, 24 and 26, 27. 20 mg/m2 orally Bactrim on wk25 after the Leucovorin)

**Children who have received cranial radiotherapy in RALL-14 do not receive intrathecal methotrexate during this phase**
**Interim Maintenance: Phase V : Weeks 14-29**

Phase V is primarily for those who will not be transplanted. If there is a delay in those receiving a bone marrow transplant but not receiving FLAD, it is recommended that they proceed to Phase VI (maintenance) to avoid toxicity.

Children not being transplanted will receive a total of 104 weeks of continuous therapy from the start of phase V (week 14).

**Those receiving cranial irradiation should receive this prior to starting this phase of treatment. Those receiving testicular irradiation will receive interim maintenance concurrently.**

Phase V consists of 2 blocks of treatment which lasts for 56 days each.

a) **Vincristine** 1.5 mg/m2 (maximum single dose 2 mg) IV on day 3 of week 14 and day 3 of week 22

b) **Dexamethasone** 6 mg/m2 for 5 days, d1-5 of week 14 and d1-5 week 22, in two divided doses

c) **Intrathecal Methotrexate** On d1, of week 14, week 20, week 22 and week 28.

   *Dose by age:*
   - <2yrs: 8mg
   - 2-3 yrs: 10mg
   - > 3yrs: 12 mg

d) **ORAL Methotrexate** 20 mg/m2 orally once weekly on weeks 15,16,18,19, 23,24,26,27. Should be taken as a single dose. Dose adjustments are described in Appendix 5.

e) **HD ORAL Methotrexate** (High dose) 100 mg/m2 orally given as 25mg/m2 every 6 hours for four doses on day 1 of week 17 and day 1 week 25. To obtain maximum absorption of high dose oral Methotrexate the dose must be split, as per protocol. To avoid waking patients intervals can be stretched to 8 hours overnight.

f) **Leucovorin** 10 mg/m2 orally for 2 doses 6 hours apart, first dose on d3 of week 17 and d3 week 25. [48 hours] after first dose of methotrexate at 25mg/m2

g) **Mercaptopurine** 75 mg/m2 orally, daily from weeks 14 to 19, and weeks 22-27. Doses should be taken at least one hour after the evening meal without milk products.

Dose adjustments are described in **Appendix 3.**

h) **Tioguanine** 40 mg/m2 orally each day from d1-7, week 20 and d1-7 week 28. Doses should be taken at least one hour after the evening meal without milk products.

i) **Etoposide** 150 mg/m2 IV infused over 4 hours on d1, weeks 20 and 21 and day 1 weeks 28 and 29.

j) **Cyclophosphamide** 300 mg/m2 IV infused over 30 minutes on d1 of weeks 20 and 21 and d1 of weeks 28 and 29. Maintain fluids at 2-x maintenance for at least 4 hours after the dose. Use frusemide 0.25 - 0.5 mg/kg IV for urine output <3ml/kg/hr after cyclophosphamide. Mesna is not required unless there is microscopic haematuria or past history of gross haematuria.

g) **Cytarabine** 50mg/m2/day by IV push or subcutaneously – 8 doses in two pulses of 4 days each; d2-5 of weeks 20,21 and d2-5 of weeks 28, 29

h) **Bactrim** given twice daily on two consecutive days per week, weeks 14, 15, 17 – 21, 22, 23 and weeks 25-29.
Omit Bactrim on week 16 and 24 and give the Bactrim on weeks 17 and 25 after Leucovorin.

Please note, the cycle of therapy requires that the clock must stop at the end of weeks 19 and 27 if the ANC is $< 0.5 \times 10^9/l$ or the platelet count is $< 50 \times 10^9/l$. The remaining therapy is given once the count is fully recovered. If at the beginning of weeks 17 and 25, ANC is less than $0.5 \times 10^9/l$ or platelets less than $50 \times 10^9/l$, it is permissible to delay the high dose oral methotrexate by a week. However if counts are not requisite after a week, omit this for this cycle. Any **serious** infection, such as varicella, Pneumocystis pneumonia, or neutropenia with fever, and presumed or proven infection, warrants chemotherapy interruption at any time.

**Please note standard dose oral methotrexate is to be avoided on the weeks that high dose oral or intrathecal methotrexate is used.**

Children who have received cranial irradiation do not receive any further intrathecal methotrexate. For these patients, Intrathecal Methotrexate On d1 of week 14 and week 22 will be replaced by oral methotrexate, 20 mg/m2 taken once weekly.
MAINTENANCE

Phase VI

Intrathecal Methotrexate on d1, week 1. <2yrs 8mg; 2yrs 10 mg; ≥3 yrs 12 mg

Note, children who have received cranial radiotherapy in RALL-14 do not receive intrathecal methotrexate during this phase (see alternative flow sheet)

Dexamethasone, d1-5 Wk 1, 5, 9. 6 mg/m2 orally in 2 divided doses

Vincristine on d1, Wk 1, 5, 9. 1.5mg/m2 iv bolus MAX 2mg as a single dose

Mercaptopurine every day. 75 mg/m2/day orally

Oral Methotrexate once weekly. 20 mg/m2 (except on week of intrathecal methotrexate)

Bactrim twice daily on two consecutive days every week

Note duration of treatment is exactly for 104 weeks from the start of phase V

Each maintenance cycle of 12 weeks is repeated until 104 weeks are complete

This will mean that there are 7 cycles of 12 weeks and 4 weeks of cycle 8

The last dose of intrathecal methotrexate is in cycle 7 and the last dose of Vincristine on Cycle 8 week 1

Note: children who have received cranial radiotherapy in R3 do not receive intrathecal methotrexate during this phase (see alternative flow sheet)

Dexamethasone, d1-5 Wk 1, 5, 9. 6 mg/m2 orally in 2 divided doses

Vincristine on d1, Wk 1, 5, 9. 1.5mg/m2 iv bolus MAX 2mg as a single dose

Mercaptopurine every day. 75 mg/m2/day orally

Oral Methotrexate once weekly. 20 mg/m2

Bactrim twice daily on two consecutive days every week

Note duration of treatment is exactly for 104 weeks from the start of phase V

Each maintenance cycle of 12 weeks is repeated until 104 weeks are complete
This will mean that there are 7 cycles of 12 weeks and 4 weeks of cycle 8
The last dose of intrathecal methotrexate is in cycle 7 and the last dose of Vincristine on Cycle 8 week 1

Phase VI : Maintenance

After the completion of Phase V, Maintenance should begin when the ANC is ≥ 0.75 x 10^9/l and the platelet count is ≥ 75 x 10^9/l. Only the mercaptopurine and oral methotrexate will be interrupted for myelosuppression and not made up. Days off therapy for intercurrent infections are counted as days off maintenance and not made up.

Continuing therapy
Each cycle lasts 12 weeks and there are 7 complete cycles. The 8th cycle is of 4 weeks duration. Please stop once 104 weeks are reached.

a) Vincristine 1.5 mg/m2 (maximum single dose 2 mg) IV on d1 of week 1, d1 of week 5 and d1 of week 9.

b) Dexamethasone 6 mg/m2 for 5 days, d1-5 of week 1, d1-5 of week 5 and d1-5 of week 9, in two divided doses.

c) Intrathecal Methotrexate On d1 of week 1.
   Dose by age:
   <2yrs: 8mg;
   2-3 yrs: 10mg
   >3yrs: 12mg.
The last intrathecal methotrexate is on d1, week 3 of cycle 7. (NOT for children who have received cranial irradiation)

d) Mercaptopurine 75 mg/m2 orally every day. Doses should be taken at least one hour after the evening meal without milk products. Dose adjustments are described in Appendix 5.

e) Oral methotrexate 20 mg/m2 orally once weekly, as a single dose. Omit if intrathecal Methotrexate is given. Dose adjustments are described in Appendix 5.

f) Bactrim given twice daily on two consecutive days per week

The last intrathecal methotrexate is given on cycle 7. The 8th cycle is of 4 weeks duration only and there is no intrathecal methotrexate during this cycle, instead oral methotrexate will be given on week 1 of this cycle.
Children who have received cranial irradiation do not receive any further intrathecal methotrexate. For these patients, Intrathecal Methotrexate On d1 of week 1, of each cycle will be replaced by oral methotrexate, 20 mg/m2 taken once weekly.
PROTOCOL FOR HIGH RISK PATIENTS – RALL-14

HR- INDUCTION

8.1. High Risk Remission Induction: Phase I : Weeks 1-4
This phase runs for 28 days from day 1 (week 1) to day 28 (week 4) (i.e. 4 week

High Risk Only
Phase I - Induction (wks 1 - 4)

![Diagram of treatment schedule]

Intrathecal Methotrexate on d1, wk1. <2yrs 8mg; 2 yrs 10 mg; ≥3 yrs 12 mg
Dexamethasone, d1-7, Wk 1 and 3. 10 mg/m2 orally in 2 divided doses for 7 days
Clofarabine 40mg/m2 iv infused over 2 hours od, days 1-5
Cyclophosphamide 440 mg/m2 iv infusion over 30 - 60 minutes od, d1-5
Etoposide 100 mg/m2 iv infusion over 4 hours od, d1-5
PEG Asparaginase 1000 u/m2 IV on day 15 if serum amylase is normal

OR if allergic to E. Coli Asparaginase
Erwinase 20,000 units/m2 IM on day 15 and alternate days for 6 doses if serum amylase
Bactrim twice daily on two consecutive days Wk 1-4

HR-Induction
Fluids: All patients should be adequately hydrated (at least 2-2.5 L/m2/24hrs given parenterally for the first 48 hours). Subsequent parenteral fluids during the days of clofarabine infusion must be at least 1 L/m2/24hrs.

a) Allopurinol 100 mg/m2 oral three times daily, should start 24 hours before chemotherapy and continue for 5 days.
b) **Intrathecal Methotrexate** on day 1.

*Dose by age:*

- < 2yrs: 8mg
- 2 yrs: 10mg
- ≥ 3yrs: 12 mg

Patients who have CNS disease at presentation should receive weekly doses until two clear CSF samples are obtained.

c) **Dexamethasone** at 10mg/m2/day orally for 7 consecutive days, days 1 through 7 and days 15-21. The steroid should be divided into two doses per day with a maximum daily dose of 20mg.

**NB:** The dose of dexamethasone for high risk patients is lower than for standard & intermediate risk patients.

d) **Clofarabine** administered as a 2-hour IV infusion daily for 5 consecutive days (days 1 through 5) at a dose of 40 mg/m2/day THEN

e) **Cyclophosphamide** at a dose of 440mg/m2/day, daily for 5 days (days 1 through 5), as a 30-60 minute IV infusion.

f) **Etoposide** at a dose of 100 mg/m2/day, daily for 5 days, (days 1 through 5) as a 4-hour IV infusion

*Serum Amylase MUST be within normal limits prior to administration of asparaginase*

g) **PEG-Asparaginase** 1000 u/m2 IV on day 15 OR if known allergy to E Coli Asparaginase only **Erwinase** 20,000 units/m2 IM on day 15 and then alternate days for 6 doses in total.

**Bactrim** given twice daily on two consecutive days each week from weeks 1-4, maintaining the longest possible interval from intrathecal methotrexate in order to avoid drug interactions.
PROTOCOL FOR HIGH RISK PATIENTS

HR- CONSOLIDATION

8.2. High Risk Consolidation: Phase II: Weeks 5-10
This phase runs for 42 days from day 1 (week 5) to day 42 (week 10)

**Phases II-Consolidation (wks 5-10)**

Dexamethasone 6 mg/m² orally in 2 divided doses on d 1-5, wks 5, 7 and 9
Vincristine on d3 of wk5, d3 of wk 7, d3 of wk8, d3 of wk 9. 1.5 mg/m² IV bolus **MAX 2mg as a single dose**
Intrathecal Methotrexate on d1, wk6, <2yrs 8mg; 2 yrs 10 mg; ≥3 yrs 12 mg
Methotrexate on d1, wk6. 1000 mg/m² IV.
Mitoxantrone on d1 and 2, wk7. 10 mg/m² IV infusion over 1 hour
PEG Asparaginase on d3, wk6, d3, wk7 and d3 wk9. 1000 u/m² IV
**OR if allergic to E. Coli Asparaginase**
*Erwinase 20,000 units/m² IM on **day 3 of week 6** and then alternate days for 12 doses in total*
Bactrim twice daily on two consecutive days from d1 of weeks 7 to 10.

**HR- Consolidation**

**Week 5**

a) **Vincristine** 1.5 mg/m² (maximum single dose 2 mg) IV on day 3 of week 5

b) **Dexamethasone** 6 mg/m² orally for 5 days, d1-5 of week 5, in two divided doses. Please prescribe Dexamethasone and Vincristine if the count has not yet recovered but the child is well.

**Do not use Bactrim during week 5.**
Proceed to week 6, only when marrow is recovering and ANC >0.5 x 10⁹/l and platelets >50 x 10⁹/l

**Week 6**

**Bone marrow aspiration and Day 35 marrow sample to be sent to the MRD laboratory.**
a) **Intrathecal Methotrexate** on day 1, week 6

   *Dose by age:*
   - <2yrs: 8mg
   - 2-3 yrs: 10mg
   - ≥3yrs: 12 mg

This is ideally given prior to starting the IV Methotrexate infusion or immediately after. If it needs to be given during the infusion, on no account should the infusion be stopped. The day Methotrexate is given is counted as the beginning of week 6.

b) **Methotrexate** day 1, week 6, 1000 mg/m2 IV. 10% of this is given intravenously as a bolus and the remaining 90% as a continuous infusion on d1 for 36 hours with concomitant hydration (see Appendix 3).

c) **Leucovorin** 15 mg/m2 per dose intravenously. Starts 48 hours after the beginning of the methotrexate infusion, and given at 48 and 54 hours (see Appendix 2).

d) **PEG-Asparaginase** 1000 u/m2 IV on d3, week 6

   OR (if allergic to E Coli Asparaginase)

   **Erwinase** 20,000 u/m2 IM on d3 of week 6 and then on alternate days for 12 doses in total.

   **Do not use Bactrim during week 6**

*Weeks 7 – 10*

Commence this phase as long as the child is well and ANC >0.5 x 109/l and platelets>50 x 109/l and counts are recovering AND patient has achieved at least M2 BM status. Chemotherapy should be continued in a well child with fever of unknown origin but no neutropenia. Any serious infection, such as varicella, pneumocystis, or neutropenia with fever, and presumed or proven infection, warrants chemotherapy interruption at any time.

a) **Dexamethasone** 6 mg/m2 orally for 5 days, d1-5 of week 7 and d1-5 of week 9, in two divided doses

b) **Vincristine** 1.5 mg/m2 (maximum single dose 2 mg) IV bolus weekly on d3 of week 7, d3 of week 8 and d3 of week 9.

c) **PEG-Asparaginase** 1000 u/m2 IV on d3 of week 7 and d3 of week 9.

   (Omit if allergic to E Coli Asparaginase)

d) **Mitoxantrone** 10 mg/m2, intravenously over 1 hour on d1 and 2 of week 7

e) **Bactrim** given twice daily on two consecutive days each week from week 7 to week 10, maintaining the longest possible interval from intrathecal methotrexate in order to avoid drug interactions.
PROTOCOL FOR HIGH RISK PATIENTS:

HR INTENSIFICATION:

High Risk Intensification
This phase runs from weeks 11 -15.

Phase III - Intensification (wks 11 - 15)

Start Phase III when marrow is recovering and ANC ≥0.5 and platelets ≥50
(It is acceptable to give Vincristine and steroids if there is a delay)
Dexamethasone, d1-5, Wk 11. 6 mg/m2 orally in 2 divided doses
Vincristine on d3, Wk 11. 1.5mg/m2 iv bolus MAX 2mg as a single dose
Intrathecal Methotrexate on d1, wk 11. <2yrs 8mg; 2yrs 10 mg; ≥3 yrs 12 mg
Cytarabine 3000 mg/m2 as iv infusion over 3 hours, every 12 hours, d1 and 2 Wk11 and d1, 2 Wk12
Erwinase 20,000 units/m2 IM on d 2 and d 4 of Wk 11 and on d 2 and d 4 of Wk 12
Bactrim twice daily on two consecutive days Wks 11-12 , 15
Dexamethasone eye drops every 2 hours from d1, wk11 and stopped 5 days after the
last cytarabine infusion
Start Week 14 when marrow is recovering and ANC ≥0.5 and platelets ≥50

No Bactrim, the week prior to and the week of iv methotrexate
Intrathecal Methotrexate on d1 wk14. <2yrs 8mg; 2yrs 10 mg; ≥3 yrs 12 mg
Methotrexate, d1 Wk14. 1000 mg/m2 iv infusion over 36 hours
Leucovorin 48 hrs after the beginning of methotrexate infusion. 15 mg/m2 iv bolus at 48 and 54 hours
Erwinase 20,000 units/m2 IM on d 2 of Wk 14, 4hrs after the end of the methotrexate infusion
starts as soon as the child is able to tolerate it. The ANC should be
> 0.5 x 109/l and the platelets > 50 x 109/l, with evidence of count recovery.
Vincristine and Dexamethasone may be given if the counts have not recovered.
The day cytarabine is first given will be counted as the beginning of week 11.

Weeks 11-12

a) Vincristine 1.5 mg/m2 (maximum single dose 2 mg) IV on day 3 of week 11

b) Dexamethasone 6 mg/m2 orally for 5 days, d1-5 of week 11, in two divided doses.

c) Intrathecal Methotrexate On day 1 of week 11.

Dose by age:
<2yrs: 8mg
2-3 yrs: 10mg
≥3yrs: 12mg
d) **Cytarabine** 3000 mg/m2 to be infused every 12 hrs via 3 hour IV infusions. Given on d1 and d2 week 11, d1 and d2 week12 (total of 8 doses)
Patients should be prescribed **dexamethasone eye-drops** 2 hourly from day 1, Week 11 until 5 days after the last dose of cytarabine.
e) **Erwinase** Erwinase 20,000 units/m2 IM on day 2 and day 4 week 11 and on day 2 and day 4 week 12 [given 4 hrs after last cytarabine infusion]
f) **Bactrim** given twice daily on two consecutive days per week, week 11, week 12 and week 15.

**Week 13**
Stop Bactrim

**Week 14**
This phase of intensification starts as soon as the child is able to tolerate it. The ANC should be > 0.5 x 109/l and the platelets > 50 x 109/l, with evidence of count recovery and the child should be clinically well.

a) **Intrathecal Methotrexate** On day 1 of week 14.
   
   *Dose by age:*
   
   < 2yrs: 8mg
   
   2 yrs: 10mg
   
   ≥ 3yrs: 12 mg
   
   This is ideally given prior to starting the IV Methotrexate infusion or immediately after. If it needs to be given during the infusion, on no account should the infusion be stopped

b) **Methotrexate** On day 1, week 14, 1000 mg/m2 IV. 10% of this is given as an IV bolus and the remaining 90% as a continuous infusion from d 1 for 36 hours, with concomitant hydration (see Appendix 3).

c) **Leucovorin** 15 mg/m2 per dose intravenously. Starts 48 hours after the beginning of the infusion, and given at 48 and 54 hours (see Appendix 3).

d) **Erwinase** Erwinase 20,000 units/m2 IM on day 2 week 14 [4hours post Methotrexate]

**Week 15:**

**Bone marrow aspirate for MRD at week 15**

Intrathecal Methotrexate on d1, week 3. <2yrs 8mg; 2yrs 10 mg; ≥3 yrs 12 mg
RALL-14
Pre SCT Cytoreduction – Phase IV FLAD

Phase IV - FLAD
Days: 1 2 3 4 5

NB. Only those patients who are MRD ≥10-3 at week 13 are eligible for this phase of treatment.
This phase of intensification starts as soon as the child is able to tolerate it.
The ANC should be ≥0.5 x 109/l and the platelets ≥50 x 109/l, with evidence of count recovery and the child should be clinically well.
a) Fludarabine 25mg/m2 daily, as a 30 minute IV infusion, 4 hours prior to Cytarabine, on days 1-5.
b) Cytarabine 2000mg/m2 daily, as a 4 hour infusion. Starting 4 hours after the start of the Fludarabine infusion, on days 1-5.
c) Daunorubicin 25mg/m2 as a 2 hour infusion on day 1, starting 4 hours after the start of the Cytarabine infusion. (Accumulative anthracyclin should be equal or less than 400 mg/ m2)
G-CSF 5mcg/kg daily from day+7 until count recovery.	Subcutaneous or IV depending on inpatient or outpatient status.
Patients should be prescribed dexamethasone eye-drops 2 hourly on days 1-10.
NB. The sequence of chemotherapy is important. Fludarabine should precede Cytarabine by 4 hours, which in turn precedes daunorubicin by a further 4 hours.
APPENDICES

Appendix 1: Antifungal Prophylaxis

The approach to these children should be similar to that of induction in a child with Acute Myeloid Leukemia. They are high risk relapses potentially at risk of chemotherapy induced toxicity and infection and should be kept in hospital until count recovery is seen post-induction.

All children should receive antifungal prophylaxis during the phases I - III.

During induction:
Liposomal Amphotericin 1mg/kg should be given three times weekly until count recovery.

Post count recovery after induction:
Continue with Liposomal Amphotericin 1mg/kg

OR

Voriconazole:
Ages 2-<12yrs Treatment and Prophylaxis
Intravenous:
Loading dose: 7mg/kg every 12 hours for 2 doses, then
Maintenance dose: 4mg/kg every 12 hours
Oral:
200mg every 12 hours

Adult Dosage Information (ages >12yrs) Treatment and Prophylaxis
Intravenous:
Loading dose: 6mg/kg every 12 hours for 2 doses, then
Maintenance dose: 4mg/kg every 12 hours
Oral:
Patients 40kg and over:
Loading dose: 400mg every 12 hours for 2 doses, then
Maintenance dose: 200mg every 12 hours
Patients <40kg:
Loading dose: 200mg every 12 hours for 2 doses, then
Maintenance dose: 100mg every 12 hours

Notes
• For oral administration, give tablets at least one hour before, or one hour after a meal
• Duration of treatment depends on patient’s clinical response
• No dose adjustment for renal impairment for patients receiving oral voriconazole. However, for patients with moderate to severe renal impairment, consideration should be given to avoiding the iv formulation as the intravenous vehicle may accumulate
Appendix 2: Guidelines for intermediate dose intravenous administration of Methotrexate:

Bactrim should be stopped 7 days before the start of the intravenous methotrexate infusion and can be recommenced 7 days after.

**Prehydration**

**Time:** Start hydration at least 6 hours prior to the commencement of the intravenous methotrexate.

**Infusion rate:** 125 mls/m2/hr (3 L/m2/day)

**NB:** Adjust the sodium bicarbonate concentration to maintain the urinary pH between 7 and 8. Do not start the infusion until a urinary pH of at least 7 has been achieved.

**Dose of Methotrexate:**

Dilute the methotrexate in an appropriate volume of saline (0.9%). Infuse 100 mg/m2 of methotrexate bolus and then 900 mg/m2 of methotrexate to be infused over 36 hours. Note, even if the infusion is not complete at this time point, it must be stopped.

**Hydration during Methotrexate infusion:**

**Infusion rate:** Hydration needs to continue during the 36 hours of methotrexate infusion to maintain a combined infusion rate of 125 mls/hr. This may be achieved either by using a Y extension set or using both lumens of the central venous line.

**Post Methotrexate Hydration:**

Continue hydration until Leucovorin rescue is completed

**Infusion rate:** 125 mls/m2/hr (3 L/m2/day)

**Methotrexate levels:** Check plasma methotrexate level at 48 hours after start of the methotrexate infusion. If the level is ≤0.5 micromol/L (< 1 x 10^-6 M or 0.227 μg/ml), then do not give more than two doses of Leucovorin (48 and 54 hours). If MTX levels at 48 hours are > 0.5 micromol/L, then continue hydration and Leucovorin rescue every 6 hours until MTX levels are < 0.25 micromol/L.

**Leucovorin rescue:** 15 mg/m2 intravenously at 48 and 54 hours and subsequently only if the plasma methotrexate level is high (see above). Subsequent doses may be given orally if necessary. Intravenous hydration is stopped when the last dose of Leucovorin is given.

**Intrathecal Methotrexate:** This can be given before the start of the methotrexate infusion. Where necessary, to fit in with local practice, it can be given during the methotrexate infusion. If this is the case, the infusion must not be discontinued. Intrathecal methotrexate should not be given once the intravenous methotrexate infusion has been stopped at 36 hrs.

**Note:** Maintain output at 400 mls/m2 for any 4 hour period.

**Glucarpidase (formerly Carboxypeptidase) and Methotrexate Nephrotoxicity**

Nephrotoxicity is an infrequent but potentially life-threatening complication of high-dose methotrexate because it can lead to delayed methotrexate (MTX) excretion and a marked enhancement of MTX-induced myelosuppression, mucositis, hepatitis, and dermatitis. It occurs probably by a combination of precipitation and direct effects on the tubule. This can result in delayed renal excretion of methotrexate and therefore sustained elevated plasma methotrexate concentrations. Leucovorin ‘rescue’ in this setting (high plasma methotrexate concentrations) is often inadequate as both methotrexate and Leucovorin compete for the same cellular uptake pathway. Also Leucovorin is insoluble in acid urine and high doses have been associated with cardiac disturbances secondary to electrolyte disturbances. If there is a rising creatinine (>100% in 24 hours) or the 48 hour methotrexate level is >10 μ/l consider using glucarpidase. The glucarpidase enzyme cleaves the terminal glutamate from folate and folate analogues such as methotrexate. In the case of methotrexate nephrotoxicity, glucarpidase action results in the production of an inactive metabolite (DAMPA). Stop Leucovorin 2 hours before administering glucarpidase as it is a competitive substrate and may compete with MTX for glucarpidase binding sites. Dose of glucarpidase: 50 units/kg administered by
intravenous bolus over 5 minutes. Reconstitute each vial with 1ml sodium chloride 0.9% (do not further dilute). Each vial contains 1000units/ml (after reconstitution) and round dose up to vial size. No further dose is required.

Maintaining alkalisation of urine with sodium bicarbonate is essential to maintain urinary pH>7. It is essential that patients are NOT co-prescribed the following medicines which reduce MTX excretion: NSAIDS, aspirin, ciprofloxacin, co-trimoxazole, penicillin, probenecid, omeprazole. Leucovorin should not be administered in the 2 hours prior to or the 2 hours following the administration of glucarpidase. 2 hours after administration of glucarpidase, Leucovorin should be administered at a dose of 250mg/m2 every 6 hours by IV bolus (maximum rate: 160mg/min) for up to 48 hours and then decreased based on plasma MTX concentrations to 15mg/m2 intravenously or orally every 6 hours until the plasma MTX concentration is less than 0.2 μmol/l.
Appendix 3: Mercaptopurine and methotrexate dose alterations

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

Start at 100% MP (75 mg/m2/day) and MTX (20 mg/m2/week) and do not escalate. Follow dose reduction guidelines as described below.

Reductions of mercaptopurine and methotrexate during continuing maintenance

If the neutrophil count falls to between 0.5 and 0.75 x 10^9/l HALVE the dose of mercaptopurine and methotrexate. If the neutrophil count falls to < 0.5 x 10^9/l STOP mercaptopurine and methotrexate. ONLY RESTART when the count is over 0.75 x 10^9/l. Restart at 100% of protocol dose (not dose at which counts fell) when neutrophils > 0.75 x109/l.

i) The same dose modifications apply to falling platelet counts. If the count is less than 75 but more than 50 x 10^9/l HALVE dose as above; if less than 50 x 10^9/l, STOP mercaptopurine and methotrexate. REINTRODUCE as above when the count is greater than 75 x 10^9/l.

ii) If counts fluctuate wildly when restarting @ 100% dose after cytopenias, starting at 50% and titrating upwards is permissible to avoid frequent interruptions to mercaptopurine exposure. (This manoeuvre is not often necessary). Escalation of mercaptopurine and methotrexate during continuing maintenance therapy. The aim is to adjust doses to maintain the ANC between 0.75 and 1.5 x 10^9/l and the platelet count between 75 and 150 x 10^9/l. If during interim maintenance the ANC > 1.5 x 10^9/l (and platelets >75 x 10^9/l) the dose of mercaptopurine should be escalated by 25% (from 75 mg/m2/day). If the subsequent monthly ANC is:

1) ANC > 1.5 x 10^9/l (and platelets > 150 x 10^9/l) for 8 weeks, keep mercaptopurine at the 125% dose and increase methotrexate by 25% to 25 mg/m2/dose.

2) Continue to increase the mercaptopurine and methotrexate dose in 25% steps alternately every eight weeks as outlined above if ANC > 1.5 x 10^9/l and platelets > 150 x 10^9/l persists. There are no maximum doses for mercaptopurine and methotrexate.

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

**Dose Reduction**

If ANC < 0.5 or platelets < 30

- Stop both thiopurines and oral methotrexate
- Weekly FBC

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

If ANC > 0.5 and < 0.75 or platelets > 30 and < 75

- Reduce dose of both thiopurines and methotrexate to 50% of protocol (NOT TOLERATED) dose
- Weekly FBC
- ANC > 0.75 and platelets > 75
- Increase dose to 100%

**Dose Escalation**

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

- Increase the mercaptopurine dose by 25%

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

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

(see protocol guidance for those with persistent neutropenia or those with wildly see-sawing counts)
Appendix 4: Guidance on the use of Erwinia

Erwinase® should be used in place of Pegylated E. Coli Asparaginase in the following circumstances:

- Systemic hypersensitivity reactions to native (Medac asparaginase) or Pegylated E.Coli Asparaginase (Oncaspar). This includes patients with generalized rash with or without anaphylactic symptoms, but not those with only local pain or redness at the site of injection.

- Patients with previously documented systemic reactions to E.Coli Asparaginase should receive Erwinase® in any remaining Asparaginase containing courses.

a. Each dose of Pegylated Asparaginase (Oncaspar) should be replaced with 6 doses of 20,000 Units/m2 Erwinase®.
b. Erwinase® should be administered by intra-muscular injection. For older patients requiring large volumes, the individual dose may be split between two injection sites.
c. Please note that in Phase III, the Asparaginase recommended is Erwinase.
<table>
<thead>
<tr>
<th></th>
<th>PEG Asparaginase</th>
<th>Erwinase</th>
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<tbody>
<tr>
<td><strong>INDUCTION</strong></td>
<td>SR/IR</td>
<td>Peg Asparaginase 1000 units/m² IM on day 3 of week 1 on day 3 of week 3</td>
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<tr>
<td></td>
<td>HR</td>
<td>Peg Asparaginase 1000 units/m² IM on day 15</td>
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<tr>
<td><strong>CONSOLIDATION</strong></td>
<td>SR/IR</td>
<td>Peg Asparaginase 1000 units/m² IM on day 2 of week 6, 4 hrs after end of MTX infusion</td>
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<tr>
<td></td>
<td>HR</td>
<td>Peg Asparaginase 1000 units/m² IM on day 3 of week 6, week 7 and week 9</td>
</tr>
<tr>
<td><strong>INTENSIFICATION</strong></td>
<td>SR/IR</td>
<td>week 9, 10 and 12 Erwinase 20,000 units/m² IM on day 2 and day 4 week 9 and on day 2 and day 4 week 10 Erwinase 20,000 units/m² IM on day 1 (week 12), 4 hours post MTX.</td>
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<tr>
<td></td>
<td>HR</td>
<td>week 11, 12 and 14 Erwinase 20,000 units/m² IM on day 2 and day 4 week 11 and on day 2 and day 4 week 12. Erwinase 20,000 units/m² IM on day 1 (week 14) 4 hours post MTX.</td>
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APPENDIX 5: GUIDELINES FOR THE INVESTIGATION AND MANAGEMENT OF THROMBO-EMBOLIC EVENTS

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

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

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

Catheter (CVL) Related Thrombosis

Loss of CVL patency
Inability to withdraw blood with or without inability or impaired ability to infuse. If there is no evidence to suggest displacement of the catheter tip and there are no signs to suggest the presence of an occlusive thrombus, proceed with urokinase lock:
Urokinase 2,500 units each lumen for 2-4 hours.

Failure to restore patency or recurrent loss of patency
Perform a chest roentgenogram to check the position of the catheter tip. A linogram will be required to assess CVL patency. If the linogram demonstrates the presence of a fibrin sheath with no evidence of significant clot formation around the tip, proceed to urokinase infusion.
Urokinase 150 units/kg/hr via each lumen for 12-24 hours.

Monitor coagulation prior to and every 8 hours during infusion
Low dose Alteplase (0.1mg/kg/hr for 4 – 6 hrs) may be considered as an alternative thrombolytic agent. Repeat linogram following infusion to confirm resolution. If the linogram demonstrates (or is suspicious of) the presence of significant clot formation around the catheter tip, of vessel thrombosis, proceed with further imaging studies.
Imaging: consider doppler or MR venography. Linograms have been shown to be relatively insensitive for the detection of large vessel CVL related thrombosis. In the presence of persistent line dysfunction despite a normal linogram, further imaging is indicated. Doppler is a sensitive technique for imaging jugular veins, but has poor sensitivity for central intrathoracic veins. MRV is less well evaluated but is likely to provide good sensitivity. Some children are likely to require a GA for this technique.

**Problem:**

1. **Doppler or Venography confirms the presence of large vessel thrombosis**
2. **Clinical symptoms/signs of CVL related thrombosis:**
   Imaging: Doppler, venography or MR venography to confirm the presence and extent thrombosis

**Treatment:**

If the CVL is no longer required or is non-functioning it should be removed. If CVL access is required and the CVL is still functioning then the CVL can remain in situ. Unless otherwise contraindicated, anticoagulant therapy should be commenced. Low molecular weight heparin (LMWH) is probably the anticoagulant of choice for initial therapy in most cases.

LMWH dosing: Enoxaparin (Clexane) 1mg/kg/bd by s/c injection. Monitor using anti-Xa levels taken at 4 hours post dose, therapeutic range 0.5-1.0 iu/ml. (LMWH pharmacokinetics for children have only been established for enoxaparin and reviparin [not available in the UK] but the use of other LMWH may be acceptable with monitoring. For pulmonary thrombus, dalteparin has been recommended. Prior to a lumbar puncture, or any other invasive procedure, the preceding two doses of LMWH should be omitted.

If there is an occlusive thrombus in a major vessel e.g. IVC, consider local thrombolytic therapy prior to anticoagulation and/or catheter removal. Low-dose Alteplase (0.1mg/kg/hr) may be administered locally via the CVL but higher doses (0.5mg/kg/hr) are required for systemic therapy. Alteplase should be administered for 4 – 6 hours, followed by re-imaging. Maximum dose for Alteplase treatment is 100mg/day.

Following the initial 3 months of therapy for children with a first CVL-related DVT, prophylactic doses of oral anticoagulants (INR 1.5 to 1.8) or LMWH –(anti-factor Xa levels of 0.1-0.3) is an option until the CVL is removed. Children with recurrent CVL related DVT should have prophylactic anticoagulation until the removal of the CVL. Some children will be scheduled to receive Asparaginase as per protocol having had an earlier catheter-related thrombotic event. Consideration should be given to removal of the CVL but those children receiving Asparaginase with a CVL in-situ should receive prophylactic anticoagulation for the duration of their Asparaginase therapy.

Thrombophilia screening should be performed following completion of anticoagulant therapy and should include Protein C, Protein S, AT, FV Leiden, lupus screen, anticardiolipin antibodies and prothrombin gene 20210A.

Use of anticoagulants for treatment of the acute phase is contentious. Asparaginase should be suspended from that particular course but can be given in subsequent courses under prophylactic anticoagulant cover as described above.
Appendix 6: Drug Toxicities and Dosage Modifications

Dexamethasone:

Note maximum daily dose during induction is 40mgs

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

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

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

Pancreatitis: Do not modify dose.

Psychosis: Administer half dosage of steroid.

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

Avascular necrosis: Contact trial coordinators if AVN develops before continuing therapy has begun. Omit further steroids if AVN develops during maintenance.

Varicella Zoster: Steroids should be held during active infection except during Induction. They should not be given during the incubation period following exposure to varicella.

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

Vincristine:

Seizures: Hold 1 dose, then reinstitute.

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

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

Hyperbilirubinemia: Withhold if total bilirubin > 40. Administer 50% of dose if total bilirubin 25 - 40. Do not alter doses for raised transaminases.

Asparaginase:

Anaphylaxis or anaphylactoid reactions:

PEG-asparaginase should be discontinued if the patient develops a systemic allergic reaction (urticaria, wheezing, hypotension, etc.). Investigators may substitute Erwinia Asparaginase, 20,000 u given every 48 hours for 6 doses.

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

Hyperglycemia: Do not modify dose. Insulin can be administered for hyperglycemia.

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

Coagulopathy: When significant coagulopathy occurs, withhold L-asparaginase until resolved. Coagulopathy without bleeding is not an indication to withhold L-asparaginase. Routine clotting screens are not recommended. Management of Asparaginase associated thrombosis is described in Appendix 8.

Liver Dysfunction: For increase in hepatic transaminases (SGPT/ALT or SGOT/AST) to greater than 200, obtain total bilirubin. Withhold Asparaginase if total bilirubin > 40. Administer 50% dose if total bilirubin >25 and ≤40. Do not alter dose for abnormal transaminases.

Clofarabine:

Erythrodysaesthesia and SIRS can usually be prevented by the concomitant use of steroids.

Contraindicated if:

Serum creatinine > 2 x ULN and Bilirubin > 1.5 x ULN with AST & ALT > 5x ULN.
Mitoxantrone:
Each dose of mitoxantrone of 10 mg/m² should be tabulated as the isotoxic equivalent of 50 mg/m² of daunorubicin or Adriamycin toward the lifetime maximum of 550 mg/m² in patients with no prior cardiac irradiation. An echocardiogram should precede anthracycline therapy. Prior anthracycline exposure and the initial baseline echocardiogram obtained prior to any anthracycline exposure should be reviewed.

Cardiac re-evaluation is recommended at a cumulative exposure of 270 mg/m² and each 50 mg/m² following. If the maximum cumulative dose is achieved or the shortening fraction on ECHO decreases to < 25% or the ejection fraction decreases to < 55%, inform Trial Coordinator.

**Hyperbilirubinemia** If total bilirubin > 120 omit dose; if > 90 but ≤ 120 give 25% of dose. If > 50 but ≤ 90 give 50% of dose, and if ≤ 50 give full dose.

Note: The use of Itraconazole as an anti-fungal prophylaxis during the first 4 weeks may potentiate anthracycline toxicity.

Intrathecal Methotrexate
Any significant neurotoxic reactions not due to lumbar puncture syndrome (low opening pressure, slow CSF flow, orthostatic symptoms) should be reported.

**Systemic toxicity** The dosage for IT methotrexate will not be reduced for systemic toxicity (myelosuppression, mucositis, etc.).
Uric acid > 0.4, phosphorus > 2.25, or creatinine > 90 -- DURING INDUCTION ONLY: Omit intrathecal methotrexate and substitute with intrathecal Ara-C 30mg <2yrs; 50mg 2-3yrs; 70mg >3yrs.

**Hydrocephalus, microcephaly or known abnormality of CSF flow** – inform Trial Coordinator

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

**Seizure, paresis or organic brain syndrome** attributed to intrathecal methotrexate. Omit intrathecal methotrexate and substitute with intrathecal Ara-C 30mg <2yrs; 50mg 2-3yrs; 70mg >3yrs.

Intravenous Methotrexate

**Liver Dysfunction (Grade 3-4)** Omit IV MTX until toxicity grade 0-2. **Check LFT’s only if patient jaundiced.**

**Kidney Dysfunction (Grade 3-4)** Omit IV MTX until grade 0 toxicity (resolved). Resume at 100% dose.

**Mucositis** For grade 2 stomatitis of > 3 days duration: decrease next dose by 30%. For grade 3-4 stomatitis, withhold IV MTX until resolved; give next dose at 50% of the last given dose.
Consider culturing lesions for herpes simplex if mucositis persists or recurs and treating with Aciclovir.

Oral High Dose Methotrexate

**Liver Dysfunction (Grade 3-4)** Omit oral high dose MTX

**Kidney Dysfunction (Grade 3-4)** Omit oral high dose MTX

**Mucositis** For grade 3-4 stomatitis, omit oral high dose MTX
Consider culturing lesions for herpes simplex if mucositis persists or recurs and treating with Aciclovir.

Cyclophosphamide
Prior history of gross haematuria or microscopic haematuria: Hydrate at 125 ml/m²/hr for 24 hours after dose and use Mesna 360 mg/m² pre, and 4, 7, 11 hours post dose.
Acute fluid retention treat with frusemide and saline; do not modify cyclophosphamide administration.

**High Dose Cytarabine (Ara-C)**
Ara-C Syndrome For fever, do not withhold Ara-C as this is likely with Ara-C. Obtain blood culture if central line present. For rash or conjunctivitis, withhold for grade 3-4 toxicity until resolved. If all 8 doses of Ara-C cannot be completed please report.

Liver Dysfunction For increase in hepatic transaminases (SGPT/ALT or SGOT/AST) to greater than 200 U/L, obtain total bilirubin. Monitor SGPT/ALT or SGOT/AST and total bilirubin, before each course of Ara-C. Continue full dose therapy unless either of the following occur: (1) Bilirubin > 40; (2) SGPT/ALT or SGOT/AST > 1000 on two determinations at least one week apart. If either of these occur, hold therapy with Ara-C and monitor as above, weekly. Restart at full dose therapy when the transaminase is less than 200 U/L if bilirubin is normal. Notify if the elevations persist for greater than 2 weeks. Exclude infectious hepatitis (A, B, C) for persistent (>1month) elevations in SGPT/ALT or SGOT/AST above 200).

Etoposide
Kidney Dysfunction (Grade 3-4) Reduce dose to 75%
NB: For Liver Toxicity: Dosage adjustments are not required for elevated transaminase levels alone. Dosage adjustments are based on bilirubin levels, as defined for each drug. For a child with pre-existing liver disease, please speak to one of the coordinators.

Mercaptopurine
Hyperbilirubinaemia and Mucositis: As for oral methotrexate.

**Appendix 7: Radiotherapy**

**CNS Disease at relapse and proceeding to chemotherapy alone:**
Patients with CNS disease at diagnosis (the presence of >5/cumm unequivocal lymphoblasts in the CSF) should receive weekly intrathecal methotrexate until two consecutive clear CSF’s have been obtained. Patients not being transplanted should receive cranial irradiation 24 Gy in 15 fractions of 1.6 Gy each of cranial radiotherapy starting week 14. Following radiotherapy they should not receive any further intrathecal methotrexate.

There is evidence to suggest that the use of thiopurines during cranial irradiation may predispose to the occurrence of brain tumors. Therefore during cranial radiotherapy, only the use of vincristine and dexamethasone is recommended.

**NB: Children under 2 years of age with CNS disease at diagnosis are not eligible for cranial radiotherapy.** We anticipate that this will be a rare occurrence. If you do have this problem, please discuss it the leukemia team.

**Formulation of IT MTX and post-LP care:**
Some centres may be using a highly concentrated formulation of Methotrexate which results in insufficient volume to fill the dead space and reach ventricular spaces. Methotrexate for intra-thecal use should be made up at a maximum concentration of 2.5mg/ml so as to provide an adequate volume of distribution across the CNS.

We recommend laying the patient supine for at least 1 hr after the intra-thecal procedure. Experiments in primate models indicate better ventricular distribution of intra-thecal chemotherapy if the subject lies supine for this period after the procedure.
A. Cranial radiotherapy guidelines:
These guidelines only apply to patients with CNS disease at presentation. Children under 2 years of age do not receive cranial irradiation.

a) Megavoltage Apparatus should be used, preferably a linear accelerator.
b) All fields should be treated on each treatment day.
c) Midplane dose 24 Gy in 15 fractions of 1.6 Gy each, in 15-21 days. (Treatment may start on any day except Friday).
d) Lateral opposed fields are used to involve all cranial meninges including those surrounding the optic nerve in the retro-orbit, and extending down the spinal cord to level of C2. Field margins should extend at least 2 cm beyond the meninges in all directions to avoid under dosage at the edges of the beam. The dose of 24 Gy has been chosen rather than 18 Gy, as this therapy is for patients with overt CNS disease and hence is an essential part of the treatment, rather than being “prophylactic” in nature. The preferred technique is one which ensures adequate coverage of the whole of the cranial meninges while ensuring that the lens dose is kept as low as possible. The patient should be treated immobilized in a supine shell. A technique that centres on the orbit and uses customized lead blocks to minimise beam divergence is therefore preferred.
A treatment area is selected clinically which is symmetrical and lies 15 mm behind the cornea on each side. Using a simulator these 2 points are opposed and a simulator film taken for the production of customised lead blocks. These should be designed so as to treat the cervical cord down to the level of C2 and to ensure adequate treatment to the origin of the facial nerve. The use of this technique necessitates either the use of asymmetric jaws to block the lower part of the neck or else the use of a very large amount of lead. It may therefore not be possible at all centres and in such cases a similar blocking arrangement using field centred in the midcranium are acceptable. A third alternative is to use a rectangular field with one edge running parallel to Ried’s baseline.
e) Treatment to additional fields, eg nasal electrons to the cribiform plate may be used at the discretion of the clinician. If such modifications are used they should be specified on the enquiry sheet and the reason they were considered necessary in giving.
f) Dose to the lens. Although there is uncertainty as to whether thermoluminescent dosimetry (TLD) can adequately estimate the dose to the lens, it is nonetheless recommended that such dosimetry be performed and the results recorded, as it is intended to use the data collected to study cataractogenesis in long term survivors. TLDs should be placed on the patient underneath the shell, both on the eyelid in front of the position of the lens, and at the outer canthus of the eye. If possible the dose to the lens should be less than 10% of the mid-plane dose, although it is recognised that this may not always be achievable with adequate treatment of the cribiform plate. Where estimated doses are high, they should be discussed with the radiotherapy coordinator.
g) Quality control. An initial simulator film should be taken for planning purposes. Shielding block positions should where possible be checked at a second simulator session. Beam films should be taken on the treatment set to verify block positions. Simulator and beam films will be requested for review following the completion of treatment.
h) Interruptions to radiotherapy should be kept to a minimum. Treatment need not be interrupted for cytopenia unless the patient is unwell. In such cases, treatment should be re-commenced as soon as possible. Interruptions longer than 48 hours should be discussed with one of the trial coordinators.
Note: There is evidence to suggest that the use of thiopurines during cranial irradiation may predispose to the occurrence of brain tumours. Therefore, during the cranial radiotherapy, only the use of vincristine and dexamethasone is recommended and the use of thiopurines and methotrexate is to be avoided.

Those who receive cranial radiotherapy will not receive any further intrathecal methotrexate. This will be replaced by once weekly oral methotrexate, 20 mg/m2 in the week that intrathecal methotrexate would have been scheduled in phases V and VI.

B. Testicular radiotherapy guidelines:

Testicular disease at relapse and proceeding to chemotherapy alone:
Boys with testicular infiltration at presentation should follow the protocol. Those not being transplanted should have 24Gy in 12 daily fractions of irradiation to both testes starting week 14. Other treatment should continue uninterrupted during the period of Radiotherapy.
  a) Megavoltage or Orthovoltage apparatus may be used.
  b) As in previous MRC studies, the volume should include the testes and the spermatic cord to the level of the deep inguinal ring with lead shielding to surrounding tissues including the penis. An applied field is used. The use of bolus should be considered depending on the energy of the radiation and the size/age of the child.
  c) The dose will be 24 Gy in 12 daily fractions of 2 Gy. This should be given during weeks 14-16 (post Intentensification). In patients receiving cranial RT, testicular irradiation should be given concomitantly with cranial irradiation.

Interruptions to radiotherapy should be kept to a minimum. Treatment need not be interrupted for cytopenia unless the patient is unwell. In such cases treatment should be recommenced as soon as possible. Interruptions longer than 48 hours should be discussed with one of the trial coordinators.

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

C. Total Body Irradiation (TBI)

There is no universally recognised technique, and different centres will have their own local variations dictated by the equipment available. These guidelines do not apply to children under 2 years of age. If general anaesthesia is required the technique may need to be modified further.
  a) Megavoltage apparatus should be used. The potential field size at extended distance should be large enough to cover the majority of patients comfortably.
  b) A single field is treated in most sessions. The chosen fields should result in an even distribution of dose throughout the body by the end of treatment. Bolus bags, compensators and shielding may be used to achieve this, according to local technique.
Doses should not vary by more than +/- 5%.
  c) The dose is 14.4 Gy in 8 fractions administered twice daily on consecutive days with a minimum interval of 6 hours between fractions. The dose is prescribed in the midplane of the lungs (density corrected) at the level of the nipples.
  d) Treatment should be planned with CT scans. Alternatively, test doses can be carried out for critical areas.

During treatment, actual doses should be measured at entrance and exit points representative of lung, brain and kidneys (other sites optional). This may be done using diodes or thermo-luminescence dosimeters. There should also be monitoring of the machine output at the extended treatment distance.
e) The value of CNS and testicular boosts remains controversial. The rationale for boosting is to achieve a radiation dose more nearly equivalent in radio-biological terms to that which would have been given had the patient not been receiving TBI. There have been no randomised controlled trials to test the benefits or otherwise of this approach. Some centres prefer to avoid boosts because of concerns about late toxicity. It is therefore up to each centre to decide on its policy in the absence of clear evidence, and to remain consistent in its approach.

If boosts are used, the recommended doses are: cranial boost – 6 Gy in 4 daily fractions; testicular boost - 6Gy in 3-4 daily fractions (can be given concurrently). The boosts are given in the week before TBI.
ROADMAPS FOR STANDARD RISK AND INTERMEDIATE RISK PATIENTS
### Risk Stratification of Relapsed ALL patients

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<td><strong>Late off Rx &gt; 6M</strong></td>
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*To consider BMT if the patient has a full matched donor (family related/MUD).*

**Date of Initial Diagnosis:**

**Date of initial Therapy completed:**

Standard Risk= Chemotherapy + Targeted XRT.

High Risk= Chemotherapy+ Allo SCT

Intermediate Risk= Chemotherapy ± Allo SCT based on MRD post induction week 5.
Relapsed Acute Lymphoblastic Leukemia 2014 (RALL-14)

**Standard and Intermediate Risk Only**

**Phase I - Induction (Wks. 1 & 2)**

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<th>Mitoxantrone 10mg/m²</th>
<th>PEG Asparaginase 1000 units/m² IV</th>
<th>Methotrexate IT*</th>
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- **Vincristine on Day 3 of Wk. 1+ Day 3 of Wk. 2 (1.5mg/m²) IVPB MAX 2mg as a single dose.**
- **Intrathecal Methotrexate on Day1, Wk1 and Day1, Wk2. <2yrs 8mg; 2-3 yrs. 10 mg; ≥3 yrs. 12 mg**
- *(Patients who have CNS disease at presentation should receive weekly doses until two clear CSF samples are obtained).*
- **Mitoxantrone on Day 1 and 2, wk1. (10mg/m²) IV infusion over 1 hour.**
- **Dexamethasone on Day 3 of Wk 1-5 (20 mg/m²) orally in 2 divided doses per day (max 40mg/day).**
- **PEG Asparaginase on Day 3, wk. 1. (1000 units/m² IV)**
- **Bactrim twice daily on two consecutive days from Day 1 of weeks 1-4**

*If allergic to E.Coli Asparaginase; Erwinia (20,000 units/m²) IM on day 3 of week 1 and then alternate days for 12 doses in total.*
**Relapsed Acute Lymphoblastic Leukemia 2014 (RALL-14)**

**Standard and Intermediate Risk Only**
Phase I - Induction (Wks. 3 & 4)

- **Ht.:**
- **Wt.:**
- **BSA:**

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- Vincristine on Day 3 of Wk. 3, and Day 3 of Wk. 4 (1.5mg/m²) IVPB MAX 2mg as a single dose.
- Dexamethasone on Day 1-5, wk1 and Day 1-5, wk3. (20 mg/m²) orally in 2 divided doses per day (max 40mg/day).
- PEG Asparaginase on Day 3 wk. 3. (1000 units/m² IV)
- If allergic to E.Coli Asparaginase; Erwinia (20,000 units/m²) IM on day 3 of week 1 and then alternate days for 12 doses in total.
- Bactrim twice daily on two consecutive days from Day 1 of weeks 1-4

*(Patients who have CNS disease at presentation should receive weekly doses until two clear CSF samples are obtained).*
### Relapsed Acute Lymphoblastic Leukemia 2014 (RALL-14)

#### Standard and Intermediate Risk Only
Phase II - consolidation (Wks. 5 & 6)

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*Bone marrow Aspirate and Biopsy + MRD*

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|          |            |       | 8   |                      |                         |                             |                 |                         |

- Dexamethasone, Day1-5, Wk 5. (6 mg/m²) orally in 2 divided doses.
- Vincristine on Day3, Wk 5. (1.5mg/m² IV) bolus **MAX 2mg as a single dose**

*Proceed to week 6 only when count is recovering and ANC ≥ 0.5 x 10⁹/l and platelets ≥ 50 x 10⁹/l.*

- Intrathecal Methotrexate on Day1, Wk 6. (<2yrs 8mg; 2 yrs. 10 mg; ≥3 yrs 12 mg)
- Methotrexate, Day 1, Wk 6. (1000 mg/m² IV) infusion over 36 hours
- PEG Asparaginase, Day 2 Wk 6, 4 hours **after the end** of the methotrexate infusion. (1000 u/m²) IV
- **If allergic to E. Coli Asparaginase Erwinia (20,000 units/m²) IM on day 2 of week 6, 4 hrs after end of MTX infusion and then alternate days for 6 doses in total.**
- Leucovorin 48 hrs after the beginning of methotrexate infusion. (15 mg/m²) IV bolus at 48 and 54 hours. (If MTX levels at 48 hours are > 0.5 micromol/L, then continue hydration and Leucovorin rescue every 6 hours until MTX levels are < 0.25 micromol/L.)
- **No Bactrim, the week prior to and the week of IV methotrexate.**
Relapsed Acute Lymphoblastic Leukemia 2014 (RALL-14)

Standard and Intermediate Risk Only
Phase II - consolidation (Wks. 7 & 8)

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<th>Date Due</th>
<th>Date Given</th>
<th>Week</th>
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*Proceed to week 7 only when count is recovering and ANC ≥ 0.5 x 10⁹/l and platelets ≥ 50 x 10⁹/l.

- Cyclophosphamide, Day 1-5, Wk 7. (440 mg/m²) IV infusion over 30 minutes.
- Etoposide, Day 1-5 Wk 7. (100 mg/m²) IV infusion over 4 hours.
- Bactrim twice daily on two consecutive days Wk 7, 8
- Mesna is not required unless there is a microscopic hematuria or past history for gross hematuria.
# Relapsed Acute Lymphoblastic Leukemia 2014 (RALL-14)

**Standard and Intermediate Risk Only**

**Phase III - Intensification (Wks. 9 & 10)**

**ANC ≥ 0.5 x 10⁹/l and platelets ≥ 50,000**

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- Dexamethasone, Day 1-5, Wk 9. (6 mg/m²) orally in 2 divided doses.
- Vincristine on Day 3, Wk 9. (1.5mg/m²) IV bolus MAX 2mg as a single dose.
- Intrathecal Methotrexate on Day 1, wk 9. (<2yrs 8mg; 2yrs 10 mg; ≥3 yrs 12 mg).
- Cytarabine (3000 mg/m²) as IV infusion over 3 hours, every 12 hours, Day 1 and 2 Wk. 9 and Day 1, and Day 2 Wk10.
- Erwinia (20,000 units/m²) IM on d 2 and d 4 of Wk 9 and on d 2 and d 4 of Wk. 10, to be given 4 hrs. After last Cytarabine infusion.
- Bactrim twice daily on two consecutive days Wks 9 &10.
- Dexamethasone eye drops every 2 hours from Day 1, wk9 and stopped 5 days after the last Cytarabine infusion.
Relapsed Acute Lymphoblastic Leukemia 2014 (RALL-14)
Standard and Intermediate Risk Only
Phase III - Intensification (Wks. 11 - 13)

Ht.:_______________ Wt.:_______________ BSA:_______________

**ANC ≥0.5 x10⁹/l and platelets ≥50.000**

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Bone Marrow sample to be sent to the MRD laboratory.

*Start Week 12 when marrow is recovering and ANC ≥0.5 and platelets ≥50*

- Intrathecal Methotrexate on Day 1 wk. 12. (<2yrs 8mg; 2yrs 10 mg; ≥3 yrs 12 mg).
- Methotrexate, Day 1 Wk12. ( 1000 mg/m² )IV infusion over 36 hours.
- Leucovorin 48 hrs after the beginning of methotrexate infusion. (15 mg/m²) IV bolus at 48 and 54 hours. (If MTX levels at 48 hours are > 0.5 micromol/L, then continue hydration and Leucovorin rescue every 6 hours until MTX levels are < 0.25 micromol/L.)
- Erwinia (20,000 units/m²) IM on Day 2 of Wk 12, **4hrs after the end of the methotrexate infusion.**
### Relapsed Acute Lymphoblastic Leukemia 2014 (RALL-14)

#### INTERIM MAINTENANCE

Phase V - Interim Maintenance - Cycle 1

**WEEK(14-19)**

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<th>Leucovorin 10mg/m²</th>
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- Dexamethasone, Day 1-5, wk14. (6 mg/m²) orally in 2 divided doses.
- ORAL Methotrexate once weekly, wk 15, 16 and 18, 19. (20 mg/m²) orally.
- Intrathecal Methotrexate on Day 1, wk 14. (<2yrs 8mg; 2 yrs 10 mg; ≥3 yrs 12 mg).
- Vincristine on Day 3, wk14. (1.5mg/m²)IV bolus MAX 2.0 mg as a single dose.
- HD ORAL Methotrexate Day 1, wk. 17. (25 mg/m²) every 6 hours for 4 doses orally.
- Leucovorin, Day 3, wk17. (10 mg/m²) every 6 hours for 2 doses orally.
- Mercaptopurine daily, wk 14-19. (75 mg/m2/day) orally.
- Bactrim twice daily on two consecutive days Wks 14-15, 17-21 (give the Bactrim on wk17 after the Leucovorin)

*Note, children who have received cranial radiotherapy do not receive Intrathecal methotrexate during this phase and should receive oral methotrexate on Day 1, wk 14 (20 mg/m²)
Relapsed Acute Lymphoblastic Leukemia 2014 (RALL-14)

INTERIM MAINTENANCE

Phase V - Interim Maintenance - Cycle 1
(weeks 20 & 21)

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- Intrathecal Methotrexate on Day 1, wk 20. (<2yrs 8mg; 2 yrs 10 mg; ≥3 yrs 12 mg).
- Thioguanine Day 1-7, wk 20, (40mg/m²/day) orally.
- Etoposide, Day 1 wk20 and Day 1 wk21. (150 mg/m²) IV infusion over 4 hours.
- Cyclophosphamide, Day 1, wk20 and Day 1, wk21 (300 mg/m²) IV infusion over 30 minutes.
- Cytarabine Day 2-5 wk20, Day2-5, wk 21. (50 mg/m²) IV per dose for total 8 doses, in two pulses 4 days each Day 2-5 wk20, & Day2-5, wk. 21.
- Bactrim given twice daily on two consecutive days per week
- *Note, children who have received cranial radiotherapy do not receive Intrathecal methotrexate during this phase.
Relapsed Acute Lymphoblastic Leukemia 2014 (RALL-14)

INTERIM MAINTENANCE

Phase V - Interim Maintenance - Cycle 2

Weeks (22-27)

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• Dexamethasone, Day 1-5, wk22. (6 mg/m²) orally in 2 divided doses.
• **ORAL** Methotrexate once weekly, wk 23, 24 and 26, 27. (20 mg/m²) orally.
• Intrathecal Methotrexate on Day 1, wk 22{ <2yrs 8mg; 2 yrs 10 mg; ≥3 yrs 12 mg}.
• Vincristine on Day 3, wk22. (1.5mg/m²) IV bolus MAX 2.0 mg as a single dose.
• HD **ORAL** Methotrexate Day 1, wk. 25. (25 mg/m²) every 6 hours for 4 doses orally.
• Leucovorin, Day 3, wk25. (10 mg/m²) every 6 hours for 2 doses orally.
• Mercaptopurine daily, wk 22-27. (75 mg/m2/day) orally.
• Bactrim given twice daily on two consecutive days per week, weeks 22, 23 and weeks 25-29, Omit Bactrim on week 24.

*Note, children who have received cranial radiotherapy do not receive Intrathecal methotrexate during this phase and should receive oral methotrexate on Day 1, wk 22 (20 mg/m²)*
**Relapsed Acute Lymphoblastic Leukemia 2014 (RALL-14)**

**INTERIM MAINTENANCE**

**Phase V - Interim Maintenance - Cycle 2**

**Weeks (28 & 29)**

**Ht.:**----------- **Wt.:**----------- **BSA:**-----------

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- Intrathecal Methotrexate on Day 1, wk 28. (<2yrs 8mg; 2 yrs 10 mg; ≥3 yrs 12 mg).
- Thioguanine Day 1-7, wk 28, (40mg/m²/day) orally.
- Etoposide, Day 1 wk28 and Day 1 wk29. (150 mg/m²) IV infusion over 4 hours.
- Cyclophosphamide, Day 1, wk28 and Day 1, wk29 (300 mg/m²) IV infusion over 30 minutes.
- Cytarabine Day 2-5 wk20, Day2-5, wk 21. (50 mg/m²) IV per dose for total 8 doses, in two pulses 4 days each Day 2-5 wk20, & Day2-5, wk. 21.
- Bactrim, given twice daily on two consecutive days per week

*Note, children who have received cranial radiotherapy do not receive Intrathecal methotrexate during this phase.*
Relapsed Acute Lymphoblastic Leukemia 2014 (RALL-14)

Phase VI- Maintenance

Ht.:-----------------  Wt.:-----------------  BSA:-----------------

**Cycle #1**

ANC ≥ 0.75 x10⁹/l and platelets ≥ 75.000

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</table>

- Intrathecal Methotrexate on day 1, week 1. (<2yrs 8mg; 2yrs 10 mg; ≥3 yrs 12 mg).

*Note, children who have received cranial radiotherapy in R3 do not receive intrathecal methotrexate during this phase and patient should receive oral methotrexate on week 1

- Dexamethasone, day 1-5 Week 1, 5, 9. (6 mg/m²) orally in 2 divided doses
- Vincristine on d 1, Wk 1, 5, 9. (1.5mg/m2) IV bolus **MAX 2mg as a single dose**
- Mercaptopurine every day. (75 mg/m2/day) orally.
- Oral Methotrexate once weekly. (20 mg/m2) **(except on week of Intrathecal methotrexate; week 1)**
- Bactrim twice daily on two consecutive days every week
Relapsed Acute Lymphoblastic Leukemia 2014 (RALL-14)

Phase VI- Maintenance

Ht.:----------------- Wt.:----------------- BSA:-----------------

**Cycle #2**

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</table>

- Intrathecal Methotrexate on day 1, week 1. (<2yrs 8mg; 2yrs 10 mg; ≥3 yrs 12 mg).

*Note, children who have received cranial radiotherapy in R3 do not receive intrathecal methotrexate during this phase and patient should receive oral methotrexate on week 1*

- Dexamethasone, day 1-5 Week 1, 5, 9. (6 mg/m²) orally in 2 divided doses
- Vincristine on d 1, Wk 1, 5, 9. (1.5mg/m2) IV bolus **MAX 2mg as a single dose**
- Mercaptopurine every day. (75 mg/m2/day) orally.
- Oral Methotrexate once weekly. (20 mg/m2) (except on week of Intrathecal methotrexate; week 1)
- Bactrim twice daily on two consecutive days every week
Relapsed Acute Lymphoblastic Leukemia 2014 (RALL-14)

Phase VI- Maintenance

Ht.:-----------------  Wt.:-----------------  BSA:-----------------

**Cycle #3**

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- Intrathecal Methotrexate on day 1, week 1. (<2yrs 8mg; 2yrs 10 mg; ≥3 yrs 12 mg).

**Note, children who have received cranial radiotherapy in R3 do not receive intrathecal methotrexate during this phase and patient should receive oral methotrexate on week 1**
- Dexamethasone, day 1-5 Week 1, 5, 9. (6 mg/m²) orally in 2 divided doses
- Vincristine on d 1, Wk 1, 5, 9. (1.5mg/m²) IV bolus MAX 2mg as a single dose
- Mercaptopurine every day. (75 mg/m2/day) orally.
- Oral Methotrexate once weekly. (20 mg/m²) **(except on week of Intrathecal methotrexate; week 1)**
- Bactrim twice daily on two consecutive days every week
Relapsed Acute Lymphoblastic Leukemia 2014 (RALL-14)

Phase VI- Maintenance

Ht.:----------------- Wt.:------------------ BSA:-----------------

**Cycle #4**

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- Intrathecal Methotrexate on day 1, week 1. (<2yrs 8mg; 2yrs 10 mg; ≥3 yrs 12 mg).

*Note, children who have received cranial radiotherapy in R3 do not receive intrathecal methotrexate during this phase and patient should receive oral methotrexate on week 1
- Dexamethasone, day 1-5 Week 1, 5, 9. (6 mg/m²) orally in 2 divided doses
- Vincristine on d 1, Wk 1, 5, 9. (1.5mg/m2) IV bolus **MAX 2mg as a single dose**
- Mercaptopurine every day. (75 mg/m2/day) orally.
- Oral Methotrexate once weekly. (20 mg/m2) (except on week of Intrathecal methotrexate; week 1)
- Bactrim twice daily on two consecutive days every week
Relapsed Acute Lymphoblastic Leukemia 2014 (RALL-14)

Phase VI - Maintenance

Ht.:_______________ Wt.:_______________ BSA:_______________

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• Intrathecal Methotrexate on day 1, week 1. (<2yrs 8mg; 2yrs 10 mg; ≥3 yrs 12 mg).

*Note, children who have received cranial radiotherapy in R3 do not receive intrathecal methotrexate during this phase and patient should receive oral methotrexate on week 1

• Dexamethasone, day 1-5 Week 1, 5, 9. (6 mg/m²) orally in 2 divided doses
• Vincristine on d 1, Wk 1, 5, 9. (1.5mg/m²) IV bolus MAX 2mg as a single dose
• Mercaptopurine every day. (75 mg/m2/day) orally.
• Oral Methotrexate once weekly. (20 mg/m2) (except on week of Intrathecal methotrexate; week 1)
• Bactrim twice daily on two consecutive days every week
Relapsed Acute Lymphoblastic Leukemia 2014 (RALL-14)

Phase VI- Maintenance

Date Due | Date Given | Week | Day | Vincristine 1.5mg/m² | Dexamethasone 6mg/m² BID x 5 days | Methotrexate *IT | Methotrexate 20mg/m2 PO | Mercaptopurine 75mg/m2 PO
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3 | 1 | | | X | ↓ | ↓ | ↓ | ↓
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5 | 1 | X | X | | X | ↓ | ↓ | ↓
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9 | 1 | X | X | | X | ↓ | ↓ | ↓
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12 | | | | | | | | |

- Intrathecal Methotrexate on day 1, week 1. (<2yrs 8mg; 2yrs 10 mg; ≥3 yrs 12 mg).

*Note, children who have received cranial radiotherapy in R3 do not receive intrathecal methotrexate during this phase and patient should receive oral methotrexate on week 1

- Dexamethasone, day 1-5 Week 1, 5, 9. (6 mg/m²) orally in 2 divided doses
- Vincristine on d 1, Wk 1, 5, 9. (1.5mg/m2) IV bolus MAX 2mg as a single dose
- Mercaptopurine every day. (75 mg/m2/day) orally.
- Oral Methotrexate once weekly. (20 mg/m2) (except on week of Intrathecal methotrexate; week 1)
- Bactrim twice daily on two consecutive days every week
## Relapsed Acute Lymphoblastic Leukemia 2014 (RALL-14)

### Phase VI- Maintenance

Ht.:-------------------  Wt.:-------------------  BSA:-------------------

**Cycle #7**

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- Intrathecal Methotrexate on day 1, week 3. (<2 yrs: 8 mg; 2 yrs: 10 mg; ≥3 yrs: 12 mg).
- **NB** Intrathecal Methotrexate on day 1, week 1. (<2 yrs: 8 mg; 2 yrs: 10 mg; ≥3 yrs: 12 mg).

*Note, children who have received cranial radiotherapy in R3 do not receive intrathecal methotrexate during this phase and patient should receive oral methotrexate on week 1.*

- Dexamethasone, day 1-5 Week 1, 5, 9. (6 mg/m²) orally in 2 divided doses
- Vincristine on d 1, Wk 1, 5, 9. (1.5mg/m²) IV bolus **MAX 2mg as a single dose**
- Mercaptopurine every day. (75 mg/m²/day) orally.
- Oral Methotrexate once weekly. (20 mg/m²) **(except on week of Intrathecal methotrexate; week 1)**
- Bactrim twice daily on two consecutive days every week
Relapsed Acute Lymphoblastic Leukemia 2014 (RALL-14)

Phase VI- Maintenance

Ht.:-------------------  Wt.:-------------------  BSA:-------------------

Cycle #8

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End of Treatment

- Dexamethasone, day 1-5 Week 1 (6 mg/m²) orally in 2 divided doses
- Vincristine on d 1, Wk 1 (1.5mg/m2) IV bolus **MAX 2mg as a single dose**
- Mercaptopurine every day. (75 mg/m2/day) orally x 4 weeks
- Oral Methotrexate once weekly. (20 mg/m2) **x 4 weeks**
- Bactrim twice daily on two consecutive days every week
### Risk Stratification of Relapsed ALL patients

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*To consider BMT if the patient has a full matched donor (family related/MUD).*

**Date of Initial Diagnosis:**

**Date of initial Therapy completed:**

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Standard Risk = Chemotherapy + Targeted XRT.

High Risk = Chemotherapy+ Allo SCT

Intermediate Risk = Chemotherapy ± Allo SCT based on MRD post induction week 5.
### Relapsed Acute Lymphoblastic Leukemia 2014 (RALL-14)

**Phase I – Induction**

**High Risk Only**

**Weeks (1-4)**

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<th>Cyclophosphamide 440mg/m2</th>
<th>Etoposide 100mg/m2</th>
<th>*Pegasparaginase 1000unit/m2 IV</th>
<th>Dexamethasone 10mg/m2 PO</th>
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- Intrathecal Methotrexate on day 1, wk1. (<2yrs 8mg; 2 yrs 10 mg; ≥3 yrs 12 mg)
- *(Patients who have CNS disease at presentation should receive weekly doses until two clear CSF samples are obtained).*
- Dexamethasone, Day 1-7, Wk 1 and 3. (10 mg/m2 orally in 2 divided doses for 7 days with a maximum daily dose of 20mg)
- Clofarabine 40mg/m2 iv infused over 2 hours once daily, day 1-5
- Cyclophosphamide 440 mg/m2 iv infusion over 30 - 60 minutes once daily, day 1-5
- Etoposide 100 mg/m2 iv infusion over 4 hours once daily, day 1-5
- PEG Asparaginase 1000 Units/m² IV on day 15.
  - *If allergic to E. Coli Asparaginase; Erwinase (20,000 Units/m²) IM on day 15 and alternate days for 6 doses every other day.*
- Bactrim twice daily on two consecutive days Wk 1-4
Relapsed Acute Lymphoblastic Leukemia 2014 (RALL-14)

Phase II – Consolidation

High Risk Only

Weeks (5 & 6)

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Bone Marrow sample to be sent to the MRD laboratory.

**Proceed to week 6, only when marrow is recovering and ANC >0.5 x 10⁹/l and platelets >50 x 10⁹/l**

- Dexamethasone 6 mg/m2 orally in 2 divided doses on d 1-5, wk. 5
- Vincristine on d3 of wk5 (1.5mg/m2) iv bolus MAX 2mg as a single dose.
- Intrathecal Methotrexate on d1, wk6, (<2yrs 8mg; 2 yrs 10 mg; ≥3 yrs 12 mg)
- Methotrexate on d1, wk6. 1000mg/m2 iv infusion over 36 hours
- Leucovorin 48 hrs after the beginning of methotrexate infusion. 15 mg/m2 iv bolus at 48 and 54 hours
  (If MTX levels at 48 hours are > 0.5 micromol/L, then continue hydration and Leucovorin rescue every 6 hours until MTX levels are < 0.25 micromol/L.)
- PEG Asparaginase on d3, wk6, (1000 Units/m²) IV
  If allergic to E. Coli Asparaginase; Erwinase (20,000 units/m2) IM on day 3 of week 6 and then alternate days for 12 doses in total
- Do not use Bactrim during week 5.
Relapsed Acute Lymphoblastic Leukemia 2014 (RALL-14)

Phase II – Consolidation

High Risk Only Weeks (7-10)

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<th>Date Due</th>
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<th>Week</th>
<th>Day</th>
<th>Vincristine 1.5mg/m2</th>
<th>Mitoxantrone 10mg/m2</th>
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- Dexamethasone 6 mg/m2 orally in 2 divided doses on d 1-5, wks 7 and 9
- Vincristine on d3 of wk 7, d3 of wk8, d3 of wk 9. (1.5mg/m2 ) IV bolus **MAX 2mg as a single dose**
- Mitoxantrone on d 1 and 2, wk7. (10mg/m2) iv infusion over 1 hour.
- PEG Asparaginase on d3, wk7 and d3 wk 9. (1000 u/m2) IV
  *If allergic to E. Coli Asparaginase; Erwinase (20,000 units/m2) IM on day 3 of week 6 and then alternate days for 12 doses in total*
- Bactrim twice daily on two consecutive days from d 1 of weeks 7 to 10.
Relapsed Acute Lymphoblastic Leukemia 2014 (RALL-14)

Phase III – Intensification

High Risk Only  Weeks (11-15)

**Start Week 14 when marrow is recovering and ANC ≥0.5 and platelets ≥50**

- **Bone marrow aspirate for MRD at week 11.**
  - Dexamethasone, d1-5, Wk 11. (6 mg/m2)orally in 2 divided doses
  - Vincristine on d3, Wk 11. (1.5mg/m2) iv bolus MAX 2mg as a single dose
  - Intrathecal Methotrexate on d1, wk 11. <2yrs 8mg; 2yrs 10 mg; ≥3 yrs 12 mg
  - Cytarabine 3000 mg/m2 as iv infusion over 3 hours, every 12 hours, d1 and 2 Wk11 and d1, 2 Wk12
  - Erwinase 20,000 units/m2 IM on d 2 and d 4 of Wk 11 and on d 2 and d 4 of Wk 12; **to be given 4hrs post Cytarabine infusion**
  - Bactrim twice daily on two consecutive days Wks 11-12 , 15, **No Bactrim, the week prior to and the week of IV methotrexate**

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<th>Date Due</th>
<th>Date Given</th>
<th>Week</th>
<th>Day</th>
<th>Vincristine 1.5mg/m2</th>
<th>Methotrexate 1000 mg/m2</th>
<th>Cytarabine 3000 mg/m2</th>
<th>Erwinia IM 20,000 u/m2</th>
<th>Dexamethasone 6 mg/m2 PO</th>
<th>Intrathecal Methotrexate</th>
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* Bone marrow aspirate for MRD at week 11.

**Start Week 14 when marrow is recovering and ANC ≥0.5 and platelets ≥50**

- Intrathecal Methotrexate on d1 wk14. <2yrs 8mg; 2yrs 10 mg; ≥3 yrs 12 mg
- Methotrexate, d1 Wk14. 1000 mg/m2 IV infusion over 36 hours
- Leucovorin 48 hrs after the beginning of methotrexate infusion. 15 mg/m2 iv bolus at 48 and 54 hours (If MTX levels at 48 hours are > 0.5 micromol/L, then continue hydration and Leucovorin rescue every 6 hours until MTX levels are < 0.25 micromol/L.)
- Erwinase 20,000 units/m2 IM on d 2 of Wk 14, 4hrs after the end of the methotrexate infusion starts as soon as the child is able to tolerate it.
- **Vincristine and Dexamethasone may be given if the counts have not recovered, The day Cytarabine is first given will be counted as the beginning of week 11.**
FLAD
Relapsed Acute Lymphoblastic Leukemia 2014 (RALL-14)

Pre SCT Cytoreduction – Phase IV FLAD
High Risk Only

Ht.:-----------------  Wt.:-----------------  BSA:-----------------  EF%:-----------------

ANC ≥0.5 and platelets ≥50  Anthracycline accumulative dose: ---

Anthracycline accumulative dose should be ≤400mg/m²

<table>
<thead>
<tr>
<th>Date Due</th>
<th>Date Given</th>
<th>Day</th>
<th>Fludarabine 25mg/m²</th>
<th>Cytarabine 2000mg/m²</th>
<th>Daunorubicin 25mg/m²</th>
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NB. Only those patients who are MRD ≥10-3 at week 13 are eligible for this phase of treatment.

Echocardiogram is required before starting daunorubicin
a) Fludarabine 25mg/m2 daily, as a 30 minute IV infusion, 4 hours prior to Cytarabine, on days 1-5.
b) Cytarabine 2000mg/m2 daily, as a 4 hour infusion. Starting 4 hours after the start of the Fludarabine infusion, on days 1-5.
c) Daunorubicin 25mg/m2 as a 2 hour infusion on day 1, starting 4 hours after the start of the Cytarabine infusion. (Accumulative anthracycline should be equal or less than 400 mg/ m2)
G-CSF 5mcg/kg SC daily from day+7 until count recovery.
Patients should be prescribed dexamethasone eye-drops 2 hourly on days 1-10.