PROGRAMS

ISRCTN 42553489

INVESTIGATOR’S HANDBOOK

Revised August 2004
For use with GM-CSF (Leukine ®)
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1) **Recruiting a Baby**

All of the documentation necessary for recruiting babies into PROGRAMS can be found in the *PROGRAMS Neonatal Unit Folder*.

**i) Discussing the study with parents**

Potentially eligible infants may be identified before birth. If possible, try to introduce yourself to the parents before the birth. Briefly explain the study to them and say you will come back to see them again after their baby is born. Remember eligibility can only be determined after birth. Try to speak to both parents together.

Always make an entry in the medical notes (dated & timed) whenever you discuss the study with parents and when you obtain consent.

**ii) Eligibility**

To be eligible for recruitment to PROGRAMS, babies must be **ALL** of the following:

- preterm neonate ≤ 31+0 weeks gestational age (see Section 2i)
- SGA (<10th centile for birthweight) (see Section 2ii)
- within 72 hours of birth
- have written informed parental consent.

Exclusion criteria

- immediately life threatening congenital abnormality  **OR**
- maternal pyrexia exceeding 38.0°C on two consecutive occasions during labour

**iii) Obtaining consent**

After you have confirmed eligibility, discuss the study fully with both parents, if possible. Be prepared to speak to them more than once. Give them the *Parent Information Leaflet* to read and ask them if they have any questions. If the parents are happy for their baby to be randomised into the study, one or both of them must sign the consent form.
iv) After obtaining consent
Make 3 photocopies of the signed Consent Form (i.e. original plus 3 copies).

- Give one copy to the parents
- Place one copy in the notes
- File one copy in your own records
- Place the original in the baby’s PROGRAMS folder (pink folders in the PROGRAMS Neonatal Unit folder).

2) Randomisation

i) Establishing gestational age
To establish gestational age, use scan dates if a scan has been done early in pregnancy (before 13 weeks). If not, go by the LMP if certain. If both are unavailable, go by what the obstetricians have recorded in the notes.

ii) Establish birthweight centile
Use birthweight centile table on back of the Trial Entry Form in the Data Collection Booklet Part 1.

iii) Complete Trial Entry Form Section A
Ensure that Trial Entry Form Section A is completed prior to telephoning the Randomisation Service.

iv) Telephone Randomisation Service
Telephone the Randomisation Service (the telephone number is given on the Trial Entry Form Section A). You should leave a message with the operator giving your name, your hospital’s name and your telephone number. The Randomisation Service will telephone you back and will ask for the information on the Trial Entry Form Section A before giving you the treatment allocation and study number.

Record the allocated treatment and study number in the spaces provided on Trial Entry Form Section A, then fill in the baby’s name and your name.

Record the allocated treatment and study number in the baby’s notes.
3) **After randomisation**

i) **Inform parent(s) of the group to which the baby has been randomised.**
If parents insist on having GM-CSF after randomisation to the control group, they have not understood the study and more time is needed to explain it. Involve the baby’s consultant if necessary.

ii) **Obtain pre-treatment FBC**
Remember to place a sticker from the *PROGRAMS Neonatal Unit Folder* on the haematology request form.
If an FBC sample has already been sent to the laboratory that day, contact the lab. to ensure that a manual white cell differential is done.
The pre-treatment FBC should be recorded on the *Daily Log* in the “Study Day 1” column.

iii) **Label baby’s notes with participation sticker and baby’s cot with participation tag**
These can be found in the *PROGRAMS Neonatal Unit Folder*.

iv) **Administration of GM-CSF, if allocated**
Infants randomised to **Treatment** receive GM-CSF 10µg/kg/day by subcutaneous injection for 5 days. The first dose should be given immediately after randomisation. Doses should be administered 24 hours apart, at the same time each day.

**GM-CSF (Leukine®) is supplied as lyophilised powder (250µg / vial). Diluent is not provided.** The powder should be reconstituted with 2.5mls sterile Water for Injection BP (*without preservative*) to give a final concentration of 10µg in 0.1ml (*eg. a 1000g infant would receive a volume of 0.1ml*). It should be drawn into the syringe immediately prior to injection.

Reconstituted vials of Leukine may be kept at 4°C for a maximum of 6 hours only. Therefore a single vial cannot be used for 2 doses to the same baby. Each treated baby will therefore use 5 vials of Leukine. However, it may be possible to use the same vial for two babies being treated in parallel.

Injections should be given subcutaneously into the anterior aspect of the thigh (we recommend using a 27G or smaller needle).
Please liaise closely with the nurse(s) to make sure that the GM-CSF is administered correctly and at the right dose. If the nurse is unhappy to administer a subcutaneous injection, it should be administered by one of the medical staff.

Calculate and record the dose of GM-CSF to one decimal place. The calculated dose must be formally prescribed on the baby’s drug chart. Write each daily dose individually, AFTER you have checked that day’s white cell count.

If the **TOTAL** white cell count (corrected for nucleated red cells) rises to $>50 \times 10^9/\text{l}$, GM-CSF should cease permanently. However these babies remain in the study and their full data should be collected as usual.

**v) Supply & Stock**

GM-CSF Leukine ® is manufactured by Berlex Laboratories, California. It is imported into the UK specifically for PROGRAMS through IDIS World Medicines.

GM-CSF Leukine ® is supplied in boxes of 5 vials of lyophilised powder (250\( \mu \text{g} / \text{vial} \)). Thus, each treated infant will use one box of Leukine over the 5 treatment days.

Always make sure that sufficient vials are held as stock on the neonatal unit and that there are enough to cover weekends/ bank holidays. Vials must be stored refrigerated.

**vi) Complete Trial Entry Form Section B**

Details of the pregnancy & delivery should be obtained personally from baby’s mother and mother’s notes (try not to use the neonatal admission sheet as this may contain errors).

Check the number and time of administration of doses of antenatal steroids from mother’s drug sheet and not from the obstetric notes, if possible.

**vii) Perform Cranial Ultrasound Scan No 1**

Perform Cranial Ultrasound Scan.

Complete “Trial entry” section of Cranial Ultrasound Scan form (in Data Collection Booklet Part 2). Place hard copy of scan in the baby’s PROGRAMS folder.

Once you have completed Sections A and B of Data Collection Booklet Part 1, forward the booklet in the FREEPOST envelope provided.
viii) Inform GP of baby’s participation in PROGRAMS
Complete GP letter, this can be found in the baby’s PROGRAMS folder, and forward to baby’s/mother’s GP.

4) Daily Data Collection

i) Complete Daily Log forms
The Daily Log forms should be completed each day for the first 28 days after study entry. When the Daily Log forms have been completed for 28 days from study entry, they should be sent to the PROGRAMS Administrator. Check that they are complete and make sure that the baby’s details are included at the top of each form. Return the forms, in the FREEPOST envelope provided in the baby’s PROGRAMS folder.

ii) Haematology requests
Ensure that you have introduced yourself to your haematologist and explained that you are the PROGRAMS co-ordinator. Your haematologist should already have been contacted by one of the principal investigators. If they have not, please contact Dr Carr.

Always label haematology request forms with a PROGRAMS sticker (kept in the PROGRAMS Neonatal Unit folder).

Please notify the haematology laboratory if the baby is receiving GM-CSF. Because GM-CSF produces neutrophil morphology changes similar to those seen in acute sepsis it may affect their blood film interpretation.

iii) Obtaining total white cell count
Always ask the lab. for the corrected white cell count and manual differential on all trial babies (whether Treated or Control) throughout the entire 28 day period of the Daily Log. DO NOT write down the automated (machine) differential counts on the Daily Log form, as they are often inaccurate in preterm babies.

Full blood counts should be requested and recorded daily during study days 1-14, but during study days 15-28 may be measured only when clinically indicated.

iv) Clinical indicators
Enter the events of the previous 24 hours at the next day’s ward round so that you can get an overall picture of what happened during the previous 24 hours.
KEEP UP WITH DAILY DATA COLLECTION. DO NOT ENTER DATA MORE THAN ONE DAY RETROSPECTIVELY.

Never fill out the form solely using verbal information passed down from the nurses or doctors. If you were not present on the day, only use objective sources of information such as nursing and medical observation charts.

Always record the presence of intravenous lines and other invasive devices DAILY. Peripheral drips frequently tissue and are resited.

5) Additional Data Collection
i) At 36 weeks postmenstrual age
Complete “oxygen requirement at 36/40” in Question 1 on Hospital Discharge Form in Data Collection Booklet Part 2.

ii) At term
Perform second Ultrasound Scan, place hard copy in PROGRAMS folder and complete Term section of Cranial Ultrasound Scan Form (in Data Collection Booklet Part 2).

6) At Discharge, Transfer or death
i) At Discharge
Complete Hospital Discharge Form in Data Collection Booklet Part 2.

Perform third Cranial Ultrasound scan, place a hard copy in the PROGRAMS folder and complete Discharge section of Cranial Ultrasound Scan Form at the back of Data Collection Booklet Part 2.

Forward the Data Collection Booklet Part 2 and the PROGRAMS folder (which should include 3 hard copies of Cranial Ultrasound Scans) to the PROGRAMS Co-ordinator.

ii) On transfer to another Unit or Hospital
If a baby taking part in PROGRAMS is transferred to a different hospital please liase closely with the hospital to which the baby is being transferred and follow these procedures:
If it is LESS THAN 28 days since date of study entry:

- Ensure *Daily Log forms* are complete for all the days the baby has been in your hospital.
- Send the *Daily Log forms* with the Transfer Pack (which can be found in the *Neonatal Unit folder*) to the receiving hospital.
- Enter Centre Number, Study Number, Baby’s Name, and Date of Study Entry in *Transfer Hospital Data Collection Booklet* which can be found in the *Transfer Pack* located in Neonatal Unit Box Folder.
- Complete *Hospital Discharge Form* in *Data Collection Booklet Part 2* and return with the *baby’s PROGRAMS folder* to the PROGRAMS Co-ordinator.

A. If it is 28 days or MORE since date of study entry:

- The *Daily Log forms* should have been completed up to Day 28 after study entry, and should be sent to the PROGRAMS Co-ordinator at this time.
- Complete the *Hospital Discharge Form* in *Data Collection Booklet Part 2* and return with the *baby’s PROGRAMS folder* to the PROGRAMS Co-ordinator.
- Enter Centre Number, Study Number, Baby’s Name, and Date of Study Entry in *Transfer Hospital Data Collection Booklet* which can be found in the *Transfer Pack* located in Neonatal Unit Box Folder. Send to receiving hospital with baby.

iii) On Death

Complete *Hospital Discharge Form* in *Data Collection Booklet Part 2*.

Forward the *Data Collection Booklet Part 2* and the *baby’s PROGRAMS folder* (which should include hard copies of Cranial Ultrasound Scans) to the PROGRAMS Co-ordinator at the address below in the FREEPOST envelope provided.

<table>
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<th>Anne Smith</th>
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<tr>
<td>PROGRAMS Co-ordinator</td>
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Serious Adverse Event Reporting

Report all serious or unexpected adverse events in the following way:

1) Phone Dr Modi, or Dr Carr (see 8i) to discuss the adverse events.

2) Complete a Serious Adverse Event Report form, which can be found in the PROGRAMS Neonatal Unit folder.

3) Fax the form to the PROGRAMS Co-ordinator immediately.

8) Contact details

i) Clinical Queries

Dr Neena Modi
Reader in Neonatal Medicine
Imperial College Faculty of Medicine
4th Floor
Chelsea & Westminster Hospital
369 Fulham Road
London SW10 9NH
Tel: 020 8237 5102 Fax: 020 8746 8887
Bleep 5874

Dr Robert Carr
Senior Lecturer/Honorary Consultant in Haematology
Guy’s & St Thomas’ Hospital
London SE1 9RT
Tel: 020 7188 1431

ii) Co-ordinating Centre

Anne Smith
PROGRAMS Co-ordinator
National Perinatal Epidemiology Unit
University of Oxford
Old Road Campus
Oxford OX7 3LF
Telephone: 01865 226762
Fax: 01865 227002
Email: PROGRAMS@perinat.ox.ac.uk

Do not hesitate to telephone if you have any queries at any time, no matter how trivial they might seem.