A multicentre, randomised controlled trial of Prophylactic Granulocyte-Macrophage colony-stimulating factor (GM-CSF) to reduce Sepsis in preterm neonates

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FULL PROTOCOL

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Title
A multicentre randomised controlled trial of prophylactic Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) to reduce systemic sepsis in preterm neonates (PROGRAMS - PROphylactic GRAAnulocyte-Macrophage colony stimulating factor for Sepsis).

Background
Neonatal sepsis is a major cause of death and disability. In preterm newborns receiving intensive care, published rates range from 25-50% and sepsis-related mortality has remained constant over two decades. Sepsis interacts with other pathologies to increase morbidity. Of particular relevance is that the preterm brain appears to be vulnerable to damage arising as a consequence of infection remote from the brain. Sepsis is a prime candidate to cause white matter and other brain injury, including cerebral palsy, as well as chronic lung disease. These conditions are powerful determinants of outcome after preterm birth. Recent strategies to reduce sepsis and related mortality and morbidity have thus far failed to make sufficient impact. Antibiotic resistance is also increasing.

The most important sepsis risk factor is degree of immaturity. Neutropenia, which occurs frequently in infants born before 32 weeks, adds substantially to this risk. When sepsis is associated with severe neutropenia, mortality exceeds 50%. Neutropenia is especially common in infants with intrauterine growth retardation. These infants are at increased risk of sepsis even after recovery from neutropenia. The incidence, severity and duration of neutropenia are related to the degree of intrauterine growth retardation. In addition to immaturity of neutrophil production, preterm infant neutrophils are functionally immature and this contributes to the morbidity attributable to sepsis.

The haemopoietic colony stimulating factor Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF), has the potential to improve antibacterial immunity in preterm infants, through its ability to enhance both neutrophil production and phagocyte function. By preventing postnatal neutropenia, including sepsis-induced neutropenia (see “pilot data” below), prophylactic GM-CSF removes a powerful risk factor for the development of sepsis and abolishes a major predictor of mortality due to sepsis in the newborn period.

Hypothesis to be tested
Prophylactic GM-CSF, administered for a limited period after birth to preterm neonates at high risk of sepsis, will lead to a clinically significant reduction in systemic infection, mortality and later disability.

Review of literature
The applicants (RC & NM) have recently been invited by the Cochrane Neonatal Review Group to undertake a systematic review of colony stimulating factor therapy in neonates. There have been no previous systematic reviews. We have already evaluated the rationale for the use of colony stimulating factors in high risk preterm neonates.

G-CSF and GM-CSF are naturally occurring cytokines which stimulate granulopoiesis and are in routine clinical use in adults and children to accelerate neutrophil recovery following chemotherapy.
GM-CSF has a broader range of activity than G-CSF in that it stimulates proliferation of both neutrophil and monocyte progenitors and increases the functional activity of neutrophils and monocytes. The greater ability of GM-CSF to enhance function in both neutrophils and monocytes makes it a more appropriate agent than G-CSF for prophylactic use in neonates, in whom immaturity of neutrophil function is believed to contribute to the high incidence of bacterial infection, and immaturity of monocyte function to the high incidence of fungal/yeast infection. In addition, this dual activity of GM-CSF gives it the potential to reduce sepsis in infants both with and without neutropenia.

There are few clinical trials examining clinical outcomes using either prophylactic or therapeutic colony stimulating factors.

**Colony stimulating factors as therapy in suspected sepsis**

These trials have investigated the use of G-CSF as intervention rescue therapy in neonates with suspected sepsis and a low neutrophil count. Although most were primarily designed to assess the ability of G-CSF to correct sepsis related neutropenia, six of the published studies, involving a total of 172 infants, have also reported sepsis-related mortality. A reduction in mortality was only observed in one of these studies, a non-randomised trial involving 25 infants. The largest study, as yet unpublished, is a company sponsored, US multi-centre randomised controlled trial of G-CSF for late onset sepsis. Unfortunately this study was closed early after interim analysis of the first 100 infants showed no difference in mortality between the two study groups (treated 14%; control 12%).

Overall, the randomised trials to date do not provide evidence of reduced mortality following G-CSF as intervention rescue therapy in septic, neutropenic neonates (odds ratio for mortality 0.6, 95% CI 0.2, 1.8; p=0.5). However it is important to note that no acute toxicities were identified.

**Colony stimulating factors as prophylaxis against sepsis**

The alternative strategy has been to use CSFs prophylactically, to prevent sepsis by prospectively stimulating neutrophil production and enhancing phagocytic bactericidal function. In rodent models of experimental sepsis, both G- and GM-CSF reduced mortality but were more effective when given prior to bacterial inoculation, which supports the potential benefit of prophylactic use.

**The applicant’s pilot data**

We have recently published the results of a randomised controlled trial of prophylactic GM-CSF in 75 neonates <32 weeks gestation. We elected to use GM-CSF because of its broader stimulation of phagocyte proliferation and function than G-CSF. The study showed that prophylactic GM-CSF, 10µg/kg/day, commenced within 72 hours of birth and administered subcutaneously for 5 days, completely prevented the development of neutropenia, including sepsis induced neutropenia, during the subsequent 4 weeks. In contrast 71% of small for gestation (SGA) infants and 24% of appropriate for gestational age (AGA) infants in the control arm developed neutropenia (<1.7 x 10⁹/l) during the same period. Although not designed to address clinical benefit, there were fewer infants who developed one or more episodes of acute symptomatic, blood culture positive sepsis during 14 days from study entry. This reduction in the incidence of sepsis was most marked in the SGA infants (treated 18%; control 50%) compared to the AGA infants (treated 36%; control 44%).
Other data
Kocherlakota and La Gamma \(^{20}\) administered G-CSF (10µg/kg/day) prophylactically for 3 days to 15 non-infected neonates with pre-eclampsia associated neutropenia and compared clinical outcome with 13 concurrent, case matched controls.
This study also showed a marked reduction in the number of infants developing sepsis. As in our study, sepsis was defined as the acute onset of clinical signs in association with a positive blood culture. In this study 13% of treated infants developed sepsis, compared with 54% of controls.

The effect of prophylactic CSF therapy in appropriately grown, very low birthweight neonates has been tested in only a single, inadequately powered trial. \(^{3}\) The criteria used for the diagnosis of sepsis in this study were less robust than in the above studies and SGA infants were specifically excluded. No difference in sepsis rate was found but the number recruited only had power to detect a 16% reduction in sepsis. If prophylactic therapy reduces sepsis in AGA infants, i.e. infants who are at lower risk of neutropenia, the effect size is likely to be smaller than was detectable by this study, though still clinically important.

In conclusion, the prophylactic studies so far have demonstrated a promising reduction in systemic infection in SGA neonates \(^{5}\) and in neonates with established neutropenia. \(^{20}\) The odds ratio for the effect of prophylactic CSF therapy on the prevention of sepsis in both of these studies combined is 0.2 (95% CI 0.05, 0.84; p=0.03).

Justification for trial
The colony stimulating factors are entering into use for preterm neonates in an uncontrolled way without adequate evidence of either efficacy or safety. This is unsatisfactory as there are no trial data providing adequate evidence of clinical benefit in terms of sepsis, mortality or long term outcomes. The need to address this issue now, in a definitive trial, is supported by trends in clinical practice together with the applicant’s pilot data and other interim data, extending to two year follow up,\(^{26}\) that suggest clinical benefit without apparent toxicity. The study has the potential to influence neonatal practice directly and immediately. Professional consensus has been demonstrated by the number of neonatologists who have expressed support.

Proposed trial design
The study will be an open, multi-centre, randomised controlled trial, comparing the effect of once daily, short-term (5 day) prophylactic GM-CSF in a dose of 10µg/kg/day vs no GM-CSF treatment in preterm neonates at high risk of sepsis.

Justification for the proposed trial design
i) Control infants will not receive placebo injections: The administration of placebo would not blind staff caring for the infant to the treatment allocation, since the effect of GM-CSF in increasing the neutrophil count is apparent within 24-48 hours of first treatment dose.
To avoid bias, sepsis as an outcome measure will be assessed by an independent committee blinded to treatment allocation and white cell counts.

ii) Selection of infants at high risk of sepsis: SGA infants (<10\(^{th}\) centile for birthweight) will be recruited up to 31 weeks as they are a group at greatest risk of both neutropenia and sepsis. SGA status is utilised in this context as a pragmatic criterion to facilitate the capture of infants of mothers with pregnancy induced hypertension, pre-eclampsia and intrauterine growth retardation. These conditions are all recognised associates of increased risk of neutropenia.
However, unlike the definitions and diagnostic criteria for these conditions, SGA status is a simple and unambiguous index.

In our pilot study this approach was shown to be a sensitive method for selecting those infants at increased risk of neutropenia: 71% of SGA babies in the control group developed neutropenia (<1.7x10^9/l) during 14 days from study entry. These infants also have a near universal requirement for invasive clinical intervention.

**Administration of GM-CSF**

Human recombinant GM-CSF (Leukine ®) will be administered subcutaneously, because this route avoids the high peak blood levels seen with intravenous administration. Subcutaneous administration was found to be easy and free of complication during the pilot study. When reconstituted, GM-CSF is a colourless liquid, with a concentration of 10µg in 0.1ml (i.e. a 1000g infant will receive a volume of 0.1ml for each injection). GM-CSF will be prepared for injection and administered by ward staff. As in the pilot study, GM-CSF will be discontinued early if the peripheral white cell count exceeds 50 x 10^9/l.

**Inclusion/exclusion criteria**

**Inclusion**
1. Preterm neonates in whom it is considered appropriate to continue intensive care, admitted to a participating neonatal intensive care unit.
2. SGA (<10th centile for birth weight)
3. ≤ 31 completed weeks gestational age
4. Within 72 hours of birth
5. Written informed parental consent.

**Exclusion**
1. Immediately life threatening congenital abnormality.
2. Evidence of early onset sepsis (maternal pyrexia >38.0°C on two consecutive occasions during labour).

**Outcome measures**

**Primary**
1. Sepsis-free survival at 14 days from trial entry

**Secondary**
1. Survival without moderate/severe disability at 2 years from term
2. Survival to discharge
3. Sepsis: Culture positive systemic infection, to 14 days from trial entry, Culture negative systemic infection, to 14 days from trial entry, Probable (culture positive or negative) systemic infection, to 28 days from trial entry
4. Clinical morbidity: Chronic lung disease (bronchopulmonary dysplasia), Necrotising enterocolitis, Periventricular haemorrhage, Periventricular leucomalacia & Ventriculomegaly
5. Haematological: Culture positive systemic infection associated with neutropenia, to 14 days from trial entry, Culture positive systemic infection associated with neutropenia, to 28 days from trial entry

4. Economic evaluation See appendix 1
Rationale for choice of outcomes

Sepsis-free survival at 14 days from trial entry
This measure, defined as the proportion of infants surviving who have not experienced “culture positive” systemic infection at 14 days from trial entry, will be sensitive to the principal proposed benefit of GM-CSF; namely prevention of sepsis and immediate sepsis-related mortality, as well as to the possibility of early life threatening GM-CSF toxicity.

Survival without moderate/severe disability at 2 years from term
This measure will be sensitive to benefit arising from a reduction in infection related morbidity, as well as any unsuspected GM-CSF toxicity.

Measurement of outcomes
i) Sepsis:
   *Culture positive systemic infection* will be defined as:
   1. microbiologically positive cultures of blood, cerebrospinal fluid, or suprapubic-aspirate of urine; *plus*
   2. acute onset of at least 3 predefined clinical signs of sepsis; *plus*
   3. acute rise in C-reactive protein (CRP).
   “Probable” systemic infection will be defined as (2) and (3), i.e. based on clinical signs and elevated CRP in the absence of a positive culture.
   Sepsis will be monitored for 28 days, to assess whether any effect persists beyond the period of direct GM-CSF influence on cell number and function.

ii) Sepsis-free survival at 14 days from trial entry: This measure, defined as the proportion of infants surviving who have not experienced culture positive systemic infection by 14 days from trial entry, will be sensitive to the principal proposed benefit of GM-CSF, namely prevention of sepsis and immediate sepsis-related mortality. Because of the difficulty of correctly identifying sepsis-related death, this outcome includes all cause mortality. Fourteen days was selected, as the effect of GM-CSF on phagocyte number and function persists for 7-10 days.
   The diagnosis of sepsis episode as an outcome measure will be made by an independent *Sepsis Identification Committee* who will be blind to treatment allocation and blood counts. For each study subject they will assess objective clinical data within three diagnostic categories, microbiological, clinical and immunological.

iii) Moderate/severe disability at age 2 years from term and age 5 years
Follow-up forms part of routine clinical practice for this patient population as they are at high risk of later problems. The focus will be on functional loss or disability.
   The assessments are detailed in appendix 2. Information will also be sought from the local paediatrician providing routine follow-up care if necessary. Children will be described using the standard data set laid out in the document “Disability and Perinatal Care”. Disability is assessed in the following domains: neuromotor function including cerebral palsy, auditory function, communication, visual function, cognitive function, other physical disabilities, malformation and congenital abnormality.
**Randomisation method**
After informed written parental consent has been obtained by a member of the clinical staff at the participating trial site, allocation to study arm will be by central telephone randomisation with minimisation based on gestational age (23-25, 26-28, 29-31 weeks), birthweight (<500, 501-750, 751-1000, >1000 g), and trial site.

**Sample size**
The total sample size will be 320 infants. This includes projected loss to follow-up.

**Justification for the size of the difference that the trial is powered to detect**
During the pilot study the following sepsis-free survival was observed at 14 days from trial entry in the subgroup of babies who conformed to the proposed trial eligibility criteria; i.e. SGA infants ≤31 weeks

<table>
<thead>
<tr>
<th>Sepsis free survival: n (%)</th>
<th>Control</th>
<th>GM-CSF 5 days</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6/14 (43%)</td>
<td>9/11 (82%)</td>
<td>39%</td>
</tr>
</tbody>
</table>

We have calculated (see table below) that a total sample size of 300 infants would have 80% power to detect a 16.1% improvement in the primary outcome measure, sepsis free survival at 14 days (two sided sample size calculations, 5% significance).
A 16% improvement would not only be clinically important but is also a realistic estimate as it is less than half the magnitude of the effect size seen in the pilot study.

<table>
<thead>
<tr>
<th>Total n</th>
<th>14 day sepsis free survival in control group</th>
<th>14 day sepsis free survival in GM-CSF group</th>
<th>difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>43%</td>
<td>67%</td>
<td>24%</td>
</tr>
<tr>
<td>200</td>
<td>43%</td>
<td>63.7%</td>
<td>20.7%</td>
</tr>
<tr>
<td>300</td>
<td>43%</td>
<td>59.1%</td>
<td>16.1%</td>
</tr>
<tr>
<td>400</td>
<td>43%</td>
<td>57%</td>
<td>14%</td>
</tr>
<tr>
<td>600</td>
<td>43%</td>
<td>54.4%</td>
<td>11.4%</td>
</tr>
</tbody>
</table>

**Planned recruitment rate**
Subjects will be recruited over 2½ years. Evidence from the pilot study suggests a recruitment rate of around 70% and from other UK multi-centre trials, around 50%. These figures include failure to recruit because of conflict with other clinical trials. Assuming no more than 50% recruitment, 320 infants could be recruited over 2½ years, within a realistic safety margin.

**Loss to follow up**
Loss to follow up for the first primary outcome measure, 14 day sepsis-free survival will be negligible. Loss to follow-up at 2 years from term will be minimised through the use of standard identifiers, including the NHS number and refresher contact with families through birthday cards at 1 year. The proposed sample size of 320 allows for 5% loss to follow-up.

**Data analysis**
The event rates, relative risks, number needed to treat and 95% confidence intervals will be compared in the two groups. The analysis will be by intention to treat.
Sub-group analyses
Possible interactions with treatment effect will be investigated using logistic regression models for the following potential effect modifiers, although these will have limited power: gestational age, birthweight, neutropenia at trial entry, neutropenia risk at trial entry as indicated by maternal hypertension or pre-eclampsia.

Frequency of analysis
The first interim analysis will be carried out after the first 100 infants have reached the time of primary outcome assessment, i.e. at 14 days. The Data Monitoring and Ethics Committee advise on the frequency of interim analyses thereafter.

Principal Investigators
Dr Neena Modi, Clinical Reader in Neonatal Medicine, Imperial College London
Dr Robert Carr, Senior Lecturer/Honorary Consultant in Haematology, St Thomas’ Hospital
Dr Peter Brocklehurst, Director, National Perinatal Epidemiology Unit, University of Oxford

Trial Manager
Anne Smith, National Perinatal Epidemiology Unit, University of Oxford

Trial Health Economist
Stavros Petrou, National Perinatal Epidemiology Unit, Oxford

Trial Statistician
Caroline Doré, Senior Statistician, MRC Clinical Trials Unit, London

Trial management
Trial management will be the responsibility of the Trial Manager, the Principal Investigators, Trial Statistician, Trial Health Economist and advisors on microbiology (Dr Robert Feldman, Honorary Senior Lecturer in Microbiology, ICSM, Hammersmith Hospital), perinatal haematology (Dr Irene Roberts, Senior Lecturer in Haematology, ICSM, Hammersmith Hospital), and follow-up assessment (Professor Neil Marlow, Professor of Neonatal Medicine, University of Nottingham).

Trial Steering Committee
Lady Sarah Riddell (Chair), Lay member, Imperial College School of Medicine and Hammersmith Hospitals Trust Research Ethics Committee and North Thames Multi-centre Research Ethics Committee, Non-executive member of the Hammersmith Hospitals Trust Board; Professor Malcolm Chiswick, Professor of Child Health, Manchester University; Professor Neil Marlow, Professor of Neonatal Medicine, University of Nottingham; Professor Michael Weindling, Professor of Neonatal Paediatrics, University of Liverpool; Principal Investigators, Trial Statistician.

Data Monitoring and Ethics Committee, primary trial
Professor E Gordon Smith (Chair), Professor of Haematology, St George’s Medical School and Chairman of the MRC Leukaemia Trials Working Party; Dr Barbara Holland, Consultant in Neonatal Paediatrics, The Queen Mother’s Hospital, Yorkhill, Glasgow; Professor David Field, Professor of Neonatology, University of Leicester.
Data Monitoring and Ethics Committee, Follow-up study
Professor David Field (Chair), Professor of Neonatology, University of Leicester; 
Dr Jane Hutton, Reader, Department of Statistics, University of Warwick; 
Dr Saroj Saigal, Professor of Pediatrics, McMaster University, Canada; 
Dr Charlotte Bennett, Neonatal Consultant, John Radcliffe Hospital, Oxford.

Sepsis Identification Committee
Professor C Anthony Hart (Chair), Professor of Microbiology, University of Liverpool; 
Dr Anthony Emmerson, Consultant Paediatrician, St Mary’s Hospital, Manchester; 
Dr Neil Murray, Senior Lecturer in Neonatal Medicine, Hammersmith Hospital, London; 
Dr Neena Modi, Clinical Reader in Neonatal Medicine, Imperial College, London.

ADDITIONAL INFORMATION

“Pro rata” salary contribution (£150 per infant recruited)
This is intended as a contribution towards the salary of the local trial co-ordinator (nursing or medical) with designated responsibility for the trial at each site. The sum is based on experience from the applicants’ pilot study that demonstrated that recruitment and data collection required approximately 4 hours per week for the first 4 weeks. The payment will NOT be made to individuals but to the department concerned. It is in recognition that good quality clinical research requires dedicated time and sustained effort by personnel involved and it is envisaged that this sum might be combined with similar payments from other studies to employ full time research staff.

Continuing Professional Development
Local trial co-ordinators will be invited to attend meetings in central London. These will provide an introduction to clinical research methodology, trial design, evidence based medicine and parental involvement in neonatal research, as well as information relating specifically to PROGRAMS.

Drug costs
GM-CSF (Leukine ®) will be supplied to trial sites by IDIS World Medicines Limited. The principal trial sites’ NHS Trusts (Hammersmith Hospitals Trust and Guy’s and St Thomas’ Trust) have confirmed that it is appropriate for this Treatment Cost (£750 per treated infant) to be met by Trusts as a Patient Care Cost, and any additional laboratory tests met as a Service Support Cost from central NHS Research and Development Funds. This is in accord with the Statement of Partnership issued by the Government [HSG(97)32, 29th May 1997] which guarantees NHS support for R&D funded by Research Charities. A CTA has been granted to cover the use of GM-CSF in this trial.

INITIAL PROCEDURE FOR TRIAL ENTRY AND RANDOMISATION

• Complete first section of “Trial Entry Form” (Section A) confirming eligibility 
• Telephone the National Perinatal Epidemiology Unit, Perinatal Trials Service, (07623 947 508) for allocation of trial number and randomisation to Treatment (GM-CSF) or Control (no GM-CSF) arm
• Complete “Trial Entry Form” (Section B) and return to “PROGRAMS Study Co-ordinator, National Perinatal Epidemiology Unit, University of Oxford, Old Road Campus, Headington, Oxford OX3 7LF”

ADMINISTRATION OF GM-CSF

• Infants randomised to Treatment receive GM-CSF 10µg/kg/day for 5 days; Control infants receive no GM-CSF
• GM-CSF (Leukine ®) is supplied by IDIS World Medicines Ltd, Millbank House, 171-185 Ewell Road, Surbiton, Surrey KT6 6AX. It is recommended that trial sites hold a minimum of 5 vials (sufficient to treat one infant)
• GM-CSF should be commenced in infants allocated to Treatment as soon as possible after randomisation. Doses should be administered 24 hours apart, at the same time each day
• GM-CSF is supplied as lyophilised powder (250µg / vial). It must be reconstituted with 2.5mls Sterile Water for Injection BP (without preservative) to give a final concentration of 10µg / 0.1ml. (i.e. a 1000g infant will receive a volume of 0.1ml). It should be drawn into the syringe immediately prior to injection
• Reconstituted vials may be kept at 4ºC 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 2 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)

Indications for early discontinuation of GM-CSF
If the total WBC* rises to >50 x 10⁹/l GM-CSF treatment should be discontinued, although the infant remains in the study. (* Ensure that the WBC has been corrected for nucleated red cells). Although there is no evidence that a high white cell count induced by colony stimulating factors carries any risk, it is unlikely that further stimulation of granulopoiesis would give additional benefit.
The mean peak neutrophil count observed in treated SGA infants in the pilot study was 14.5 x 10⁹/l and the highest total WBC was 45.0 x 10⁹/l.

Safety Issues
No toxicities attributable to GM-CSF have been identified in neonatal studies to date.
Side effects that have occurred in adults when GM-CSF is administered subcutaneously at a dose of 10µg/kg include mild bone pain, low grade fever and, rarely, vasculitic skin rashes. Any suspected adverse effect in infants receiving GM-CSF should be discussed immediately with one of the principal investigators and an adverse event form completed, if appropriate.

As this is a prophylactic study, it is not intended to recruit infants with acute sepsis at birth. GM-CSF should not be discontinued should sepsis occur during the period of administration as there is no evidence from neonatal observations to date and extensive adult experience that GM-CSF in the presence of active sepsis is detrimental to outcome. GM-CSF has been investigated as adjuvant therapy in sepsis in both adult and neonatal trials.
DATA COLLECTION IN HOSPITAL

- Complete the “Daily Logs” from trial entry (study day 1) to day 28. This is a record of microbiological data, clinical indicators of sepsis, CRP, and FBC data.
- FBCs and CRP should be measured daily at the time of routine blood testing, (commencing prior to first GM-CSF dose in treated subjects) for the first 14 days from study entry and between day 15-28 as clinically indicated. Total WBCs should be adjusted for circulating nucleated red blood cells; neutrophil counts should be based on manual WBC differentials.
- At discharge complete the “Hospital Discharge Form”.

References
22. National Perinatal Epidemiology Unit and Oxford Regional Health Authority. Disability and Perinatal Care: Measurement of Health Status at Two Years. A report of two working groups. 1994
Appendix 1: Economic Evaluation

Study design
An economic evaluation will be integrated into the clinical trial. It will compare a policy of administering prophylactic GM-CSF to high risk preterm neonates with a policy of no GM-CSF treatment. The cost differences between the two groups will be identified, measured, valued and combined with clinical effectiveness data from the trial.

Cost measurement
Data will be collected on the health service resources used and the costs to the parents: i) during the infant’s stay in hospital, and ii) during the period following hospital discharge until the clinical follow up assessment at 2 years corrected age. Data on health service resource utilisation during the hospital stay will be collected by hospital staff and by observational research, as described below. Data on parental costs will be collected through two parent questionnaires.

During the period between randomisation and hospital discharge, trial data collection forms will record the duration and intensity of neonatal care, based on standard criteria for level of care, as well as profile the complications experienced by infants. Observational research will be conducted at each of the clinical centres to provide details of the resources and staff inputs required for the delivery of the intervention, as well as staff time, tests, procedures, drugs and equipment entailed by complications. We propose to use tick charts, which will be completed by health professionals caring for all infants in the trial, to document the key resource inputs not recorded by the trial data collection forms. A similar approach to documenting health service resource inputs has successfully been applied to other economic evaluations conducted alongside clinical trials by the National Perinatal Epidemiology Unit (NPEU), Oxford.

Economic questionnaires completed by parents at hospital discharge (Economic Evaluation Questionnaire I) and at six-month intervals (Economic Evaluation Questionnaire II) up to the age of two will document subsequent health and social care use, as well as wider societal costs.

Valuation of costs
Current UK unit costs will be applied to each resource item to value total resource use in each arm of the trial. Estimates of the unit costs of neonatal services will be partly derived from two studies of neonatal intensive care conducted by NPEU researchers (the Department of Health funded ECMO trial and the Medical Research Council funded ECSURF study). The unit costs of resources unique to the PROGRAMS trial will be obtained from the finance departments of the clinical centres participating in the trial. The unit costs of community services and costs borne by parents and informal carers will be derived from a variety of published sources. These will be obtained towards the end of the trial period to ensure that the unit costs are as current as possible for the final analysis.

Economic evaluation
The economic evaluation will be conducted from a societal perspective and will take the form of an incremental cost-effectiveness analysis. If differences in outcomes between the two trial arms are revealed, the several outcome measures incorporated into the trial will allow us to present the economic evaluation in a number of forms, for example, the incremental cost per additional case of sepsis-free survival at 14 days or the incremental cost per disability-free life year gained.
Data analysis
All analyses will be conducted on the basis of intention to treat. Costs for the intervention and control groups will be compared using relative risks and 95% confidence intervals for dichotomous variables, Mann-Whitney U-tests for ordinal variables, and Student's t-tests for interval variables where parametric assumptions are met. Fieller’s theorem will be used to calculate 95% confidence intervals for incremental cost effectiveness ratios. In the absence of stochastic data for all variables, a series of multi-way sensitivity analyses will be undertaken to explore the implications of uncertainty on the base-case incremental cost effectiveness ratios. In addition, cost-effectiveness acceptability curves will be constructed using the net benefits approach. Actualisation will be performed where necessary using discount rates recommended by the Department of Health. All analyses will be performed with a microcomputer using Statistical Package for the Social Sciences (SPSS) software, version 7.5.

References
Appendix 2: Follow-up Study

The initial protocol for this trial included as an outcome, a comparison of neurodevelopmental status at the age of 2 years from term. Funding was not available at that time for standardised examinations to be carried out by a team of specifically trained clinicians. Information was to have been obtained from local paediatricians who would have seen the children as part of their routine clinical follow-up. Given that these examinations would be performed by multiple observers, they would be unstandardised. This method would provide a broad functional categorisation of moderate/severe disability, in particular motor disability. However it would not be sufficiently sensitive to detect all clinically important deficits across this and other domains. In addition, the detection of many subtle deficits, particularly in the fields of behaviour, attention and cognition, are unreliable at the age of two years. These deficits may have major implications for educational achievement and social functioning.

In order to improve the assessment of neurodevelopmental outcomes, the Wellcome Trust has awarded us additional funding to carry out a detailed, standardised clinical examination and neurodevelopmental assessment at the ages of two and five years. These will be conducted by approximately five pairs of assessors (developmental paediatrician and child psychologist) who will provide cover for the whole of the UK. The assessments will be carried out either in the child’s home or at a local hospital at age 2 years corrected and at age 5 years, the assessment will be carried out at the child’s school. As such an assessment would form a valuable part of the normal clinical follow-up of these extremely preterm children, we would make the results available to the child’s paediatrician. The results will also be made available to the child’s parents if they wish. The neurodevelopmental tools are detailed below.

Neurodevelopmental Tools

Two year assessments: These will be carried out by a developmental paediatrician at a corrected (post-menstrual age) of two years and will comprise:

- A formal clinical and neurological examination, developed and validated for use in infants born preterm
- The Bayley Scales of Infant Development, 2nd edition (BSID-II)
- The Tester’s Rating of Child Behaviour (TRCB), a situational assessment of behaviour that has been widely used with preterm populations.
- A modified Parent Report of Children’s Abilities (PARCA)

Five year assessments (uncorrected for prematurity): These will be carried out by a child psychologist or developmental paediatrician and will comprise:

- A formal clinical and neurological examination for those children unable to perform a full assessment by a psychologist.
- Assessment of motor ability using the Movement Assessment Battery for Children
- Cognitive assessment using the Kaufman Assessment Battery for Children
- Behavioural assessment using the Strengths and Difficulties Questionnaire (Teacher and Parents)
- A detailed neurodevelopmental evaluation (NEPSY) to provide focused assessment of higher executive and attentional function, sensorimotor function, language production, memory and visuo-spatial skills
- A modified Parent Report of Children’s Abilities (PARCA)
References