International Neonatal Immunotherapy Study

PROTOCOL

Non-specific intravenous immunoglobulin (Intragam® P) therapy for suspected or proven neonatal sepsis: an international, placebo controlled multi-centre randomised trial

V2, July 2003 - Australian and New Zealand Version
Supercedes: V1, January 2002 – Australian and New Zealand Version
ISRCTN 94984750
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PROTOCOL SUMMARY

Background
Sepsis is an important, but sometimes undiagnosed, cause of perinatal brain damage and mortality. In term infants, blood concentrations of inflammatory cytokines are elevated in those later diagnosed with cerebral palsy. In preterm infants, infection remote from the brain may predispose to cerebral white matter damage. While effective antibiotic treatment is essential, resistance to antibiotics is increasing. Adjuvant therapies, such as intravenous immunoglobulin (IVIG), therefore offer an important additional strategy.

Newborn babies are deficient in immunoglobulins, which enhance and modulate the immune response to infection. The anti-inflammatory properties of polyclonal IVIG make it of therapeutic benefit in many auto-immune and inflammatory diseases such as multiple sclerosis and chronic demyelinating inflammatory polyneuropathy. In laboratory studies, polyclonal IVIG can modulate the local CNS immune reaction, suppressing phagocytosis and facilitating the re-myelination of damaged oligodendrocytes. Polyclonal IVIG may therefore be of therapeutic benefit in cerebral inflammation due to sepsis.

Three recent Cochrane systematic reviews of randomised controlled trials in nearly 6,000 patients suggest that non-specific, polyclonal IVIG is safe, reduces sepsis by about 15% in prophylaxis and may reduce mortality by 45% in treatment of neonatal sepsis. However, the trials of treatment were small and lacked long-term follow-up data. This protocol is for a large, simple, international trial, to assess reliably whether treatment of neonatal sepsis with IVIG reduces mortality and adverse neuro-developmental outcome. It needs no special expertise and can be conducted simultaneously with other studies.

Research Plan
Infants are eligible if they have proven or suspected serious infection; AND they have at least one of the following, either (i) birth weight of less than 1500 g; or (ii) evidence of infection in blood culture, CSF or usually sterile site body fluid; or (iii) respiratory support via an endotracheal tube; AND they are receiving antibiotics. Infants are excluded if IVIG has already been given or if IVIG is thought to be needed or contraindicated.

The treatment group will receive an infusion of IVIG, 500 mg (8.33 ml) per kg, repeated after 48 hours. The control group will receive an infusion of placebo solution, 8.33 ml per kg, repeated after 48 hours.

The primary measure of outcome is mortality or major disability at two years, corrected for gestational age. Secondary outcomes include hospital mortality, chronic lung disease or major cerebral abnormality before hospital discharge, significant positive culture after trial entry, pneumonia, necrotising enterocolitis, duration of respiratory support, mortality before two years, major disability at 2 years, non-major disability at 2 years, length of hospital stay and number of hospital admissions. Subgroup analyses will stratify by birthweight, gestation, clinical severity, clinical chorioamnionitis, small for gestation, elevated maternal CRP, duration of membrane rupture, type of infection, and type of IVIG.

Recruitment will continue until the end of 2005, with follow-up until early 2008. The total sample of 5,000 infants worldwide will yield over 90% power with a type I error of 5% (two tailed) to detect a difference of 4%, from 25% to 21%, in the rate of primary outcome. A moderate reduction like this would mean that one extra death or disabled survivor could be prevented for every 25 babies treated. Australian and New Zealand centres will recruit 1500 of the total sample. Resources are available to train and support part-time local research nurses to facilitate recruitment and data collection.

Significance
Assessment of neuro-developmental status in survivors is essential if neonatal trials are to contribute fully to evidence-based policy. If this trial confirms benefit, it could establish the most cost-effective indication yet for Intragram® P and for other non-specific, polyclonal IVIG products, changing clinical practice worldwide. If the trial shows no benefit, it will curtail demand for IVIG in neonatal care and avoid unnecessary costs.
INTRODUCTION
This protocol is for a large, simple-in-design, double-blind, placebo-controlled, pragmatic multi-centre randomised trial.

HYPOTHESIS
That, in infants receiving antibiotics for clinical sepsis, the addition of non-specific, polyclonal intravenous immunoglobulin IgG (IVIG) therapy reduces mortality and major disability at 2 years compared with antibiotics alone.

BACKGROUND
Despite advances in perinatal care, neonatal sepsis remains a major cause of mortality and morbidity in the first weeks after birth and has been implicated in the causation of perinatal brain damage and cerebral palsy, both in term and preterm infants.\textsuperscript{1,2} Although antibiotics are the mainstay of therapy, increasing numbers of bacteria are resistant to them.\textsuperscript{3,4} Effective adjunctive strategies are therefore needed.

Incidence of neonatal sepsis, potential impact on mortality and problems in diagnosis
Prospective Australian studies have reported an incidence of neonatal sepsis, defined as clinical evidence of infection confirmed by a positive blood culture, of 6.6 per 1000 live births,\textsuperscript{5} with approximately threefold greater risk in Aboriginal infants.\textsuperscript{6} The ratio of sepsis of early onset (within 48 hours of birth) to late onset sepsis was 1:2 and the overall hospital mortality rate was 10%. In the Australian and New Zealand Neonatal Network cohort in 2000, the incidence of clinically proven systemic infection, including early and late onset infection, was 14%, with 15% all-cause mortality, and 6% mortality due to infection.\textsuperscript{7} Among a North American cohort of very low birth weight infants, late onset sepsis occurred in 16%, with 21% hospital mortality.\textsuperscript{8} Assuming a 15% rate of neurodevelopmental impairment, this translates annually into 250 deaths and 350 disabled survivors in Australia and New Zealand and over 1 million deaths or disabled survivors worldwide. However, even these figures may underestimate the true incidence and impact of clinical sepsis in the newborn, which may often remain undiagnosed.\textsuperscript{9-12} Sepsis-specific mortality rates should therefore be interpreted with caution as the diagnosis may often be inaccurate. More reliable evidence would be provided by randomised comparisons of the effects of specific interventions on all-cause mortality.

Pathophysiology of neonatal sepsis and potential impact of sepsis on the perinatal brain
Recent evidence suggests that sepsis is also important in the pathogenesis of neurodevelopmental impairment of perinatal origin. Neonatal sepsis of early or late onset is associated with cerebral white matter damage and cerebral palsy\textsuperscript{13,14} and neurodevelopmental impairment\textsuperscript{15} or need for special educational resources.\textsuperscript{14,16-18} In preterm infants, chorioamnionitis and neonatal sepsis are each independently associated with a fourfold increase in odds of cerebral palsy.\textsuperscript{2,17} Even in children born at term, cerebral palsy is nine times more likely to develop after antenatal exposure to maternal infection around the time of birth compared with controls.\textsuperscript{1} In another case-control study of term infants, levels of cytokines in neonatal blood spots were consistently higher in children diagnosed with cerebral palsy at 3 years of age than in controls, suggesting that an inflammatory response may be important in the aetiology of cerebral impairment.\textsuperscript{7} Furthermore, early cerebral lesions on magnetic resonance imaging (MRI) are associated with an inflammatory response to chorioamnionitis and prenatal infection in preterm infants,\textsuperscript{20} which may partly reflect their relative deficiency in anti-inflammatory, endogenous immunoglobulin.\textsuperscript{21} As antenatal and postnatal sepsis may predispose to neurodevelopmental impairment and disability in term and preterm infants, these are essential measures of outcome.

In the immature brain, infection may lead to the release of cytokines, chemokines, adhesins, matrix metallo-proteinases, disruption of the blood brain barrier, activation of microglia and astrocytes and transendothelial migration of circulating leukocytes, leading to disruption of oligodendrocyte myelination, disordered migration of precursors and cellular apoptosis. Other mechanisms of neuronal damage in sepsis may include cerebral hypoperfusion and neurotoxicity from hyperbilirubinaemia. Dammann and Leviton have suggested that infection remote from the preterm brain may predispose to cerebral white matter damage with disruption of oligodendroglial
myelination and disordered migration of precursors. The damage could result partly from inadequate endogenous protection from developmentally regulated factors such as oligodifferentiation.

The commonest organisms causing sepsis in neonatal intensive care units (NICUs) in Australia and New Zealand are coagulase negative Staphylococci (CONS), particularly Staphylococcus epidermidis. There is increasing evidence of their pathogenicity. Perinatal CONS infection is associated with subsequent cerebral palsy. Neonatal CONS infection prolongs hospitalisation and increases morbidity and costs. No difference has been reported in the rate of neurodevelopmental impairment after neonatal meningitis associated with S. Epidermidis versus other organisms.

Theoretical and clinical basis for immunoglobulin therapy in neonatal sepsis

Newborn infants, particularly those who are born preterm or very low birthweight, are deficient in IgG. This immunoglobulin can bind to cell surface receptors and has many pro-inflammatory properties such as promoting opsonic activity, fixation of complement, antibody dependent cytotoxicity, neutrophil chemiluminescence, phagocytosis and release of stored neutrophils. IgG also has several anti-inflammatory effects including down-regulation of inflammatory cytokines via Fc receptor blockade, provision of anti-idiotype antibodies and interference with the activation of T-cells, B-cells, the cytokine network and complement. Of particular interest, polyclonal IVIG may modulate the local immune reaction in the CNS and may help prevent or repair damage to oligodendrocytes. Owing to its anti-inflammatory properties, polyclonal IVIG is of therapeutic benefit in many autoimmune and inflammatory disorders, such as Kawasaki Disease and Idiopathic Thrombocytopenic Purpura, and in central nervous system (CNS) inflammatory diseases such as multiple sclerosis and chronic demyelinating inflammatory polyneuropathy and others. In randomised controlled trials, polyclonal IVIG decreased cerebral lesions on serial MRI in relapsing multiple sclerosis and reduced clinical relapses by 30%. The immunomodulatory properties of polyclonal IVIG may also partly explain why it reduces mortality by 36% in adults with sepsis. The data support the hypothesis that polyclonal IVIG may reduce mortality, cerebral inflammatory damage and neurodevelopmental impairment after neonatal sepsis.

Intravenous immunoglobulin (IVIG) is therefore a theoretically attractive strategy, with multiple mechanisms of action. Its potential clinical relevance is confirmed by recent evidence from randomised controlled trials.

Other possible adjunctive treatments

Pentoxifylline
In animal models of sepsis, pentoxifylline, a methylxanthine derivative, inhibits production of Tumour Necrosis Factor (TNF), preserves micro-vascular blood flow, prevents circulatory failure and intestinal vaso-constriction and improves survival. It is well tolerated and decreases TNF production in adults and preterm infants with sepsis. Two randomised controlled trials (RCTs) of pentoxifylline recruited 140 preterm infants with clinical sepsis. Pentoxifylline was associated with an 87% reduction in the risk of mortality (RR 0.13, 95% CI 0.02 to 0.69). Pentoxifylline may be a promising therapy in neonatal sepsis.

Cytokines
Other adjunctive strategies for prophylaxis or treatment of neonatal sepsis are also attractive, such as use of the recombinant cytokines Granulocyte Colony Stimulating Factor (G-CSF) or Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) to prevent neutropenia. However, no systematic reviews of RCTs of these agents are yet available. In four RCTs of G-CSF therapy which recruited 125 infants with neonatal sepsis, there was a trend to reduced mortality which was not statistically significant (OR 0.6, 95% CI 0.2 to 1.8). Two recent RCTs of GM-CSF prophylaxis in a total of 339 high risk infants showed no reduction in sepsis or mortality. However, these findings do not rule out a moderate benefit.
Blood products other than immunoglobulin

White cell (granulocyte) transfusions are also a logical approach. Although preliminary clinical evidence is encouraging, there are potential risks from transmission of infection (e.g. HIV or hepatitis) or from graft-versus-host disease, and the technology is not widely available. Exchange transfusion with fresh whole adult blood appeared effective in one RCT of 22 septicaemic infants, but may also transmit infection. In another RCT, in 776 infants of less than 32 weeks gestation, there was no evidence that prophylactic fresh frozen plasma reduced the risks of mortality from all causes or of disability in survivors at 2 years.

Overall, therefore, the evidence suggests that IVIG therapy is one of the most promising strategies in neonatal sepsis and should be assessed in a definitive RCT.

Results of previous randomised controlled trials (RCTs)

A Cochrane systematic review of the prophylactic use of non-specific, polyclonal IVIG in 15 RCTs with 5,054 preterm or low birthweight infants demonstrated that prophylactic, non-specific IVIG reduced the risk of sepsis (RR 0.85, 95% CI 0.74 to 0.98) and was safe, with no serious adverse effects reported, but did not alter mortality (RR 0.89, 95% CI 0.75 to 1.05).

A Cochrane systematic review of reports of RCTs of IVIG therapy for proven or suspected neonatal sepsis identified nine studies that reported outcomes for 318 infants with suspected infection and 262 infants with proven infection. IVIG therapy appeared to be safe and was associated with approximately a 40% reduction in the risk of mortality for both suspected and proven infection (Tables 1 and 2). However the confidence intervals were wide and the studies included in the analyses were small and not of high methodological quality. Problems identified by the reviewers were lack of allocation concealment, lack of blinding of outcome assessment and high levels of post-randomisation exclusions in some of the trials. The reviewers concluded that: “The reduced mortality following treatment with IVIG for subsequently proven infection, the imprecise estimate of the effect size (number needed to treat 11, 95% CI 5.6, 100) and the borderline statistical significance for the outcome of mortality in neonates with suspected infection justify further research. Researchers should be encouraged to undertake well-designed trials to confirm or refute the effectiveness of IVIG”.

Table 1: Mortality in trials of IVIG for suspected infection in neonates

<table>
<thead>
<tr>
<th>Review: IVIG in neonatal infection</th>
<th>Comparison: IVIG vs placebo or no intervention for suspected infection</th>
<th>Outcome: Mortality from any cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>Expt. n/N</td>
<td>Ctrl. n/N</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Christensen 1991</td>
<td>0/11</td>
<td>0/11</td>
</tr>
<tr>
<td>Erdem 1993</td>
<td>6/20</td>
<td>9/24</td>
</tr>
<tr>
<td>Haque 1988</td>
<td>1/30</td>
<td>6/30</td>
</tr>
<tr>
<td>Samatha 1997</td>
<td>5/30</td>
<td>8/30</td>
</tr>
<tr>
<td>Shenoi 1999</td>
<td>7/25</td>
<td>7/25</td>
</tr>
<tr>
<td>Sidiroopoulos 1981</td>
<td>4/41</td>
<td>8/41</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>23/157</td>
<td>38/161</td>
</tr>
</tbody>
</table>
Table 2: Mortality in trials of IVIG for proven infection in neonates

<table>
<thead>
<tr>
<th>RCT</th>
<th>Exptl n/N</th>
<th>Ctrl n/N</th>
<th>Relative Risk (95% CI Fixed)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 1996</td>
<td>2/ 28</td>
<td>1/ 28</td>
<td>2.00 [0.19, 20.82]</td>
<td>3.8%</td>
</tr>
<tr>
<td>Erdem 1993</td>
<td>5/ 15</td>
<td>7/ 16</td>
<td>0.76 [0.31, 1.89]</td>
<td>25.4%</td>
</tr>
<tr>
<td>Haque 1988</td>
<td>1/ 21</td>
<td>4/ 23</td>
<td>0.27 [0.03, 2.26]</td>
<td>14.3%</td>
</tr>
<tr>
<td>Mancilla-Ramirez 1992</td>
<td>2/ 19</td>
<td>2/ 18</td>
<td>0.95 [0.15, 6.03]</td>
<td>7.7%</td>
</tr>
<tr>
<td>Samatha 1997</td>
<td>0/ 12</td>
<td>4/ 16</td>
<td>0.15 [0.01, 2.46]</td>
<td>14.6%</td>
</tr>
<tr>
<td>Sidiropoulos 1981</td>
<td>2/ 20</td>
<td>4/ 15</td>
<td>0.38 [0.08, 1.78]</td>
<td>17.2%</td>
</tr>
<tr>
<td>Weisman 1992</td>
<td>2/ 14</td>
<td>5/ 17</td>
<td>0.49 [0.11, 2.13]</td>
<td>17.0%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>14/ 129</td>
<td>27/ 133</td>
<td>0.55 [0.31, 0.98]</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Using slightly different selection criteria and methods for analysis, Jenson and Pollock published a systematic review of three RCTs of IVIG in neonatal sepsis in which 55 infants received IVIG and 55 received placebo or no infusion. The odds ratio for mortality in treated versus control infants was 0.17 (95% CI 0.03-0.75). These authors reached a conclusion which many would consider premature, namely that ‘IVIG should be considered as part of the routine therapy of neonatal sepsis’. Nevertheless, it remains true that, among all interventions currently reviewed in the Cochrane Library, IVIG therapy in neonatal sepsis is associated with one of the largest reductions in the odds of death. A further RCT of IVIG in neonatal sepsis in Brazilian neonatal units is being conducted. One of the applicants (K Haque) is an investigator of this trial. Its results will be incorporated into the current meta-analysis as soon as they are available.

Another recent Cochrane systematic review and meta-analysis of IVIG in treating sepsis and septic-shock in all patients (adults, children and neonates) with non-specific, polyclonal IVIG from a variety of sources suggested a beneficial effect on all-cause mortality (OR 0.64, 95% CI 0.51 – 0.80) (Table 3).

Table 3. Mortality in trials of IVIG for proven sepsis/septic shock in adults & children

<table>
<thead>
<tr>
<th>RCT</th>
<th>Exptl n/N</th>
<th>Ctrl n/N</th>
<th>Relative Risk (95% CI Fixed)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polyclonal IVIG vs placebo, adults, ACM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Simone 1988</td>
<td>7/ 12</td>
<td>9/ 12</td>
<td>0.78 [0.44 – 1.39]</td>
<td>8.5%</td>
</tr>
<tr>
<td>Dominioni 1991</td>
<td>11/ 29</td>
<td>22/ 33</td>
<td>0.57 [0.34 – 0.96]</td>
<td>19.3%</td>
</tr>
<tr>
<td>Grundmann 1988</td>
<td>15/ 24</td>
<td>19/ 22</td>
<td>0.72 [0.51 – 1.00]</td>
<td>18.6%</td>
</tr>
<tr>
<td>Just 1986</td>
<td>6/ 13</td>
<td>9/ 16</td>
<td>0.82 [0.40 – 1.70]</td>
<td>7.8%</td>
</tr>
<tr>
<td>Schedel 1991</td>
<td>2/ 27</td>
<td>9/ 28</td>
<td>0.23 [0.05 – 0.97]</td>
<td>8.3%</td>
</tr>
<tr>
<td>Wesoly 1990</td>
<td>8/ 18</td>
<td>13/ 17</td>
<td>0.58 [0.33 – 1.04]</td>
<td>12.6%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>49/ 123</td>
<td>81/ 128</td>
<td>0.62 [0.49 – 0.79]</td>
<td>74.9%</td>
</tr>
<tr>
<td><strong>Polyclonal IVIG vs placebo, neonates, ACM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen 1996</td>
<td>2/ 28</td>
<td>1/ 28</td>
<td>2.00 [0.19 - 20.82]</td>
<td>0.9%</td>
</tr>
<tr>
<td>Erdem 1993</td>
<td>6/ 20</td>
<td>9/ 24</td>
<td>0.80 [0.34 – 1.86]</td>
<td>7.7%</td>
</tr>
<tr>
<td>Haque 1988</td>
<td>1/ 30</td>
<td>6/ 30</td>
<td>0.17 [0.02 – 1.30]</td>
<td>5.6%</td>
</tr>
<tr>
<td>Shenoi 1999</td>
<td>7/ 25</td>
<td>7/ 25</td>
<td>1.00 [0.41 – 2.43]</td>
<td>6.6%</td>
</tr>
<tr>
<td>Weisman 1992</td>
<td>2/ 14</td>
<td>5/ 17</td>
<td>0.49 [0.11 – 2.13]</td>
<td>4.2%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>18/ 117</td>
<td>28/ 124</td>
<td>0.70 [0.42 - 1.18]</td>
<td>25.1%</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>67/ 240</td>
<td>109/ 252</td>
<td>0.64 [0.51 – 0.80]</td>
<td>100%</td>
</tr>
</tbody>
</table>
There was significant heterogeneity between studies, which makes this summary measure difficult to interpret. A sensitivity analysis of studies of good and fair quality, however, did not detect any heterogeneity and also suggested a decreased risk of mortality in septic patients (n=332; RR 0.55 95% CI 0.40-0.79). The same Cochrane review also explored the effect of monoclonal antibodies: the relative risks for both anti-endotoxins and anti-cytokines were similar and were of borderline statistical significance (anti-endotoxins RR 0.93, 95% CI 0.85 to 1.02; anti-cytokines RR 0.92, 95% CI 0.86 to 0.99). The authors concluded that although there was evidence that non-specific IVIG appears to be beneficial, "Large, multi-centre studies are needed to confirm the effectiveness of polyclonal IVIG in reducing mortality in patients with sepsis. These are particularly indicated for neonatal sepsis, where evidence for benefit is still conflicting". Duration of hospitalisation was reported as a secondary outcome measure in seven polyclonal IVIG trials. There was a significant reduction in number of days in hospital in the IVIG group (weighted mean difference -1.36; 95% CI -2.51,-0.22).

Non-specific, polyclonal human IVIG appears to be generically effective, in keeping with multifactorial actions, and its impact does not appear limited to any one IVIG product. As no trial used repeated IVIG treatment for subsequent episodes of neonatal sepsis, repeated treatments are not proposed in this study. While there is evidence that polyclonal IVIG may reduce mortality in neonates, its effects on specific organisms may vary.75 The INIS trial will therefore provide reliable comparisons among subgroups by pathogen. Detailed follow up of survivors is mandatory as there are no reliable data on disability, which is a major determinant of costs. The trial is unique in proposing systematic follow-up in a large sample of survivors to provide reliable comparisons of health status and disability at two years between the treated and control groups.

**Non-specific, polyclonal IVIG versus specific, hyper-immune IVIG**

This trial will use non-specific, polyclonal IVIG (normal human IgG immunoglobulin) (Intragam® P) produced by CSL, Melbourne, Australia, from voluntary donors in each country (Australian donors for Australian IVIG and New Zealand donors for New Zealand IVIG). It was decided that specific, hyper-immune IVIG would not be used and that there was no necessity to characterise the specific antibacterial profile of non-specific, polyclonal IVIG, for several reasons:

(i) Previous RCTs of non-specific, polyclonal IVIG in neonates and adults did not characterise any specific aspects of antibacterial function in the products used. There is therefore no reference laboratory data against which to judge the possible antibacterial efficacy of polyclonal IVIG.

(ii) As the mechanism of action of IVIG is likely to be multifactorial, the precise aspects of antibacterial function that should be assessed are speculative. Much of the therapeutic benefit of polyclonal IVIG may be related to its anti-inflammatory properties, which are multi-factorial and non-specific.

(iii) Despite production of monoclonal antibodies with demonstrable in vitro and in vivo antibacterial function in laboratory studies, they have not been associated with reductions in mortality in RCTs.46 There is no evidence that laboratory studies to characterise specific antibacterial function in IVIG would be more predictive of clinical efficacy than the evidence from RCTs for non-specific, polyclonal IVIG therapy.

The UK Medical Research Council commissioned three referees to examine this issue. They concluded that hyper-immune IVIG for specific pathogens was theoretically preferable but unavailable and unanimously endorsed use of non-specific, polyclonal IVIG in this study.
SAFETY

Safety: Transmission of blood borne viruses and prion disease
The risk of transmissible infection by blood products remains a potent source of anxiety for clinicians and patients. However, Intragam® P, for use in Australia and New Zealand, is produced to the most modern standards of quality control using only plasma donated by healthy, unpaid, local volunteers screened for viruses such as HIV and Hepatitis. The process includes alcohol fractionation, partitioning, microfiltration and two specific virus inactivation steps: pasteurisation (heating at 60°C for 10 hours) and low pH incubation (for 14 days at 27°C). Intragam® P and its predecessor, Intragam®, have an excellent safety record, with no documented cases of transmissible infection. The manufacturer estimates the risk of transmission of a virus, such as Hepatitis or HIV, as less than 1 in 10 million IVIG infusions, approximately 100 times lower than the risk associated with blood transfusions (Australian Red Cross Blood Service, Jan 2001). Leucocytes are the main source of infectivity in Creutzfeld-Jacob disease. Owing to the physico-chemical characteristics of the abnormal prion protein, the process of partitioning and filtration of leucocytes during fractionation of Intragam® P reduces any theoretical risk of prion transmission in IVIG. Fractionation pools are also tested with PCR (polymerase chain reaction) for blood borne viruses. The residual theoretical risk of transmissible infection must be balanced against the estimated actual 25% risk of mortality or major morbidity in infants eligible for the trial and against potential benefits that may include a 30% reduction in mortality.

Safety: Haemolysis in relation to T activation of red cells
Bacteria such as Clostridia can strip neuraminic acid residues from the red cell membrane, exposing the T antigen (T activation). Adult plasma contains anti-T antibodies, so transfusing newborn infants whose red cells are T activated with whole blood, unwashed red cells or unselected plasma may lead to polyagglutination and haemolysis. However, anti-T antibodies are predominantly IgM immunoglobulins, a fraction which is removed from the IVIG products used in this study (CSL Intragam® P product literature). In the published literature, no significant neonatal haemolysis has been noted with IVIG. Neither the Adverse Drug Reactions Advisory Committee in Australia nor the UK Committee on Safety of Medicines have received any reports of haemolysis or other serious adverse reactions in association with neonatal IVIG treatment (personal communication, Sept 1999). T activation is thus not a contraindication for these IVIG products in neonatal sepsis.

SUMMARY
There is good preliminary evidence that IVIG therapy may reduce mortality and cerebral inflammatory damage in neonatal sepsis. However, there is no information on longer term quality of survival, the number of babies included in the existing systematic reviews is small and the effect size seems larger than would be anticipated. As a consequence a reliable multicentre trial is needed to test whether IVIG therapy is of benefit, with survival free from major morbidity in early childhood as the outcome. IVIG is not yet widely used as routine therapy. There remains, therefore, a window of opportunity for a reliable trial before an inadequately assessed intervention may be introduced into practice. The trial results will be generalisable to other IVIG products, commercial and non-commercial. Most importantly, they will provide reliable evidence on whether neonatal sepsis should constitute a new indication for IVIG therapy in Australia and New Zealand.
RESEARCH PLAN

Trial eligibility
Hospitals are eligible to join the International Neonatal Immunotherapy Study (INIS) if they provide neonatal intensive or special care, can achieve satisfactory rates of follow-up at 2 years and would be able to institute the routine use of adjuvant IVIG for babies with sepsis if the trial demonstrates evidence of benefit.

Infants are eligible if:

1. They have proven or suspected serious infection
   AND
2. They have at least one of the following:
   - birth weight less than 1500 g
   OR
   - evidence of infection in blood culture, or CSF or usually sterile body fluid
   OR
   - respiratory support via an endotracheal tube
   AND
3. They are receiving antibiotics and there is substantial uncertainty that IVIG is indicated

Exclusion criteria are:
1. IVIG has already been given
2. IVIG has already been given or is thought necessary or contra-indicated

Over 50 clinical and laboratory criteria have been described for neonatal sepsis,\(^{78-82}\) which may present with subtle changes, so a precise definition is not practicable. A pragmatic approach will therefore be adopted, based on the clinicians’ own judgement that there is serious infection. However, specific, previously validated clinical and laboratory criteria (see Statistical Analysis) will be recorded at trial entry to grade the clinical severity (low, moderate, high) of all infants for subsequent analysis. Clinicians normally have a low threshold for antibiotic treatment, which should begin quickly, as infected infants can quickly deteriorate. However, the threshold for IVIG therapy in this study is greater than for simply starting a course of antibiotics. For entry into INIS there should be a clinical suspicion that the baby has infection and/or be considered at significantly increased risk.\(^{83}\) Once an infant is considered to be eligible, it is important that enrolment takes place as soon as practically possible.

The trial is designed to include all neonatal infections, including bacterial, viral and fungal infections. Both early and late onset infections are also included. Babies remain eligible at any age during their first hospitalisation. If they have been readmitted from home, they are eligible up until their EDD (estimated date of delivery) plus 28 days.

Parental consent
Recruitment will depend on good teamwork, knowledge and confidence among all clinicians, particularly front line nursing and medical staff, so that parents receive appropriate information about the study before entry and throughout their baby's stay. Experience from the ORACLE trials,\(^{84,85}\) which recruited over 11,000 women from 161 centres, suggests that it is helpful if nurses and doctors understand the study background, see clinical research as an integral part of clinical care contributing to future quality, and if a named nurse is appointed and trained as a local trial coordinator. If those caring for the baby are well informed about the study, they can discuss it without transmitting anxiety. Indeed, parents are likely to feel less anxious if given the opportunity to discuss options for their baby’s treatment in the context of the study with knowledgeable staff. The named nursing and medical representative in each unit will therefore receive opportunities for training, regular information and support to enable them to orientate and update new and established nursing and medical staff. The protocol, printed materials and relevant new research will be widely available and staff will be kept informed by newsletters, personal visits and the study website (ANZ: INIS website is being developed at the NHMRC Clinical Trials Centre; UK: www.npeu.ox.ac.uk/INIS).
Parents should routinely be given an Information Sheet about INIS by the nursing staff when their baby is admitted to the neonatal unit, or when appropriate. This will include details of their local medical and nursing contact with whom they can discuss the study. If an infant becomes eligible for INIS it is necessary to gain parental consent and start treatment with the study drug as soon as possible. Therefore, informing the parents about INIS early may help them to be able to decide about participation in INIS quickly, if the need arises. If their baby becomes eligible they will be asked for consent to participate in the study and later follow up, by the most appropriate member of staff available, in person or by telephone. If telephone consent is considered necessary and appropriate by the recruiting clinician, a ‘Telephone consent’ form will be completed and the parent will be asked to sign the consent form on their next visit to the hospital. A copy of the Information Sheet and consent form will be given to parents. Nursing and medical staff will be asked to encourage parents to ask any questions they may still have about the study during their baby’s continuing care and follow up. Regular newsletters will inform parents about the study after discharge and, eventually, about its results.

**Randomisation**
The randomisation will be a stratified block design, stratified by site, with randomly varied block sizes. The computer-generated randomisation lists will be prepared by an independent statistician at the NHMRC Clinical Trials Centre, University of Sydney. The randomisation list will be held by the clinical trials pharmacist or other appropriate third party at each participating hospital, and will be accessed only by authorised staff not involved in the baby’s daily clinical care.

**Treatment**
Infants will be randomly allocated to the treatment and control groups. The treatment group will receive an intravenous infusion of IVIG (Intragam® P), 500 mg/kg (8.3 ml per kg) over 4–6 hours, repeated after 48 hours. The control group will receive 8.3 ml per kg, normal saline (placebo solution) over 4-6 hours, repeated after 48 hours. The study is double-blind, i.e. treatment allocation will be concealed from investigators, clinicians and parents. To maintain the blinding, the pharmacist or other appropriate third party person will prime the extension line, mask the syringe with yellow tape and ensure that no bubbles are present.

**Clinical management**
After the second dose, no further IVIG or placebo, nor open label IVIG should be given, in this or any subsequent episodes of clinical sepsis. Other aspects of management are left to the neonatologist responsible for care. No special investigations and no delays of discharge will be required.

IVIG may lessen the immune response to live virus vaccines (e.g. MMR and polio) up to 3 months after treatment with IVIG. However this will not interfere with the infants’ polio vaccinations (National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, The Children’s Hospital at Westmead, Sydney; and NSW Health; personal correspondence, May 2003).

**OUTCOMES**

**Primary outcome**
1. Mortality or major disability at two years, corrected for gestational age.

**Secondary short term outcomes**
2. Mortality, chronic lung disease or major cerebral abnormality before hospital discharge, significant positive culture after trial entry, pneumonia, necrotising enterocolitis, duration of respiratory support.

**Secondary long term outcomes**
3. Mortality before two years, major disability at 2 years, non-major disability at 2 years.
Health service utilisation

4. Length of hospital stay and number of hospital admissions.

Measurement of Outcomes
All examinations will be blinded to treatment allocation. Hospital mortality, chronic lung disease, major cerebral abnormality and length of stay will be assessed from case notes. Major disability at two years will be assessed by questionnaires sent to the child's parents and health care professionals. Major disability will be defined according to the criteria set out in the National Perinatal Epidemiology Unit (NPEU) and Oxford Regional Health Authority document and will include any major disability in the following domains: neuromotor function, seizures, auditory function, communication, visual function, cognitive function and other physical disability. The parental questionnaire incorporates the parent report component of the Parent Report of Children's Abilities (PARCA), which was used in the 2 year follow up of the MRC funded UKOS trial. This shortened version of the PARCA was acceptable to parents, with a high response rate in UKOS, and is currently being validated by the UKOS team. The PARCA score (both parent report and parent administered components) has been validated and was found to predict performance on the Mental Development Index of the Bayley Scales of Infant Development II (BSID II). The overall score for the modified PARCA will give a measure of verbal and non-verbal cognitive abilities. The parents' questionnaire also includes questions about temperament, which may give an early indication of behavioural and attentional difficulties, and also includes questions about respiratory function, hearing, vision, hospital admissions, relevant diagnoses and current function in a number of domains, allowing categorisation of disability as major or non-major.

In addition a BSID II assessment will be undertaken at 2 years of age in all infants recruited in New Zealand centres and a number of infants recruited in Australian centres. The BSID-II is a gold standard test for evaluating disability and developmental status, administered by a certified psychologist or paediatrician, which can reliably differentiate major, moderate and mild disability and normal development. The Bayley assessments in Australia and New Zealand will allow further validation of the PARCA parent questionnaires, and for the first time in these countries. These data will also be used to perform a sensitivity analysis within the economic evaluation by reliably classifying the surviving infants into major, moderate, mild or no disability at 2 years of age. While parental questionnaires have generally been shown to be predictive of major disability versus no disability, they tend to be less predictive of more subtle disabilities. The Bayley assessments will also enable evaluation of whether IVIG has subtle beneficial effects on cognitive and psychomotor development, by comparing their mean test scores in pre-specified subgroups who are at high risk of a poor outcome, such as preterm infants born after clinical chorioamnionitis, preterm, prolonged rupture of membranes and high maternal CRP.

Loss to follow-up will be minimised by collecting comprehensive contact details, distribution of parent newsletters, contact with the hospital follow-up clinic and use of the Health Insurance Commission address database in Australia where appropriate.

DATA COLLECTION
Data collection will be the responsibility of the local trial coordinator. Data forms will be provided by the INIS Coordinating Centre, to prospectively collect data relating to the baby's baseline factors, clinical condition at trial entry, hospital-based outcomes and comprehensive contact details for follow-up. Data will be collected for the baby's entire stay in hospital, up until discharge to home or death. Infants transferred to other hospitals prior to discharge home will be tracked by the local trial coordinator and data about the baby's care in each unit will be collected to ensure that data regarding outcomes are complete. Ongoing mortality data will be collected from the Australian Institute of Health and Welfare mortality register. Data relating to subsequent health service use and hospitalisations will be collected retrospectively using 1yr and 2yr parent questionnaires. Follow-up data collected at 1 and 2 years of age is the responsibility of the local trial coordinator, although the INIS Coordinating Centre will provide logistical and coordination tasks.
support. Data collection will be subjected to stringent quality control at the ANZ INIS Coordinating Centre, NHMRC Clinical Trials Centre, University of Sydney.

**Serious adverse events**

Unexpected serious adverse events occurring during the period of hospitalisation will be notified to the ANZ INIS Coordinating Centre within 24 hours of the event becoming known to the Investigator. The Aust/NZ Study Coordinating Centre will then notify the UK INIS Coordinating Centre of these events within 24 hours. The UK Coordinating Centre will activate a notification cascade, which includes notifying the Safety and Data Monitoring Committee, Trial Steering Committee, multi-centre research ethics committee, Scottish Blood Transfusion Service and Medicines Control Agency if appropriate. In Australia, the ANZ INIS Coordinating Centre will notify the TGA of reportable unexpected serious adverse events as specified in TGA regulations. The Investigator or delegate at each participating institution is responsible for reporting serious adverse events to their Health Research Ethics Committee (HREC) as specified in each HREC's guidelines. Adverse events will be monitored by the Safety and Data Monitoring Committee (UK) at least once per year.

**STATISTICAL ANALYSES**

An intention to treat analysis will be performed comparing the outcome of all infants allocated IVIG with all those allocated placebo, regardless of what treatment was received, or how complete the treatment was. Statistical analysis will calculate the relative risk of an outcome in the IVIG group compared with the placebo group, with a 95% confidence interval. For subgroup analyses, 99% confidence intervals will be calculated to take account of the number of comparisons.

**Subgroup analyses**

Nine subgroup analyses will also be undertaken, stratifying by the factors described below.

1. Birth weight: Infants of very low birth weight (VLBW: < 1500g) vs infants with birth weight = 1500g.
2. Small for gestational age infants (< 10th centile) vs infants = 10th centile.
3. Gestational age at birth: < 26 weeks, 26+0 to 27+6 weeks, 28+0 to 29+6 weeks, 30+0 weeks or more.
4. Maternal chorioamnionitis: infants born at < 30 weeks gestation to women with clinical chorioamnionitis vs infants born at < 30 weeks gestation with no clinical chorioamnionitis vs infants born at = 30 weeks.
5. Elevated maternal CRP: infants born at < 30 weeks gestation to women with elevated CRP (> 80mg/l) vs infants born at < 30 weeks gestation with no elevated maternal CRP vs infants born at = 30 weeks.
6. Preterm birth and duration of membrane rupture: Born at < 37 weeks and membranes ruptured for < 24 hours, 24-48 hours or > 48 hours vs born at = 37 weeks.
7. Clinical markers of mortality risk:
   (i) Clinical evidence of high mortality risk: looking seriously ill or inactive, and has:
      (a) capillary refill time >3 seconds OR
      (b) bowel perforation or definite necrotising enterocolitis OR
      (c) prolonged bleeding from puncture sites OR
      (d) ventilated, $\text{SaO}_2/\text{FiO}_2$ ratio or $\text{PaO}_2/\text{FiO}_2$ ratio consistent with >15% mortality risk for gestation OR
      (e) pH consistent with >15% mortality risk for gestation.

$[\text{SaO}_2/\text{FiO}_2$ ratio, $\text{PaO}_2/\text{FiO}_2$ ratio and pH consistent with >15% mortality risk will be extrapolated from oxygenation and pH data in a prospective cohort of 14,000 infants (UK Neonatal Staffing Study) by methods similar to that used in the development of the MRC funded CRIB score.]$
(ii) Intermediate mortality risk: not satisfying criteria for high risk, but has:
   (a) Total white cell count < 5 x 10^9/l OR
   (b) CRP above 15 mg/l OR
   (c) platelet count < 50 x 10^9/l OR
   (d) organism(s) isolated in blood or usually sterile site OR
   (e) pneumonia on chest X-ray OR
   (f) CSF consistent with bacterial meningitis.

(iii) Other: not satisfying criteria for high or intermediate risk.

8. Type of infection:

   (i) Early onset infection (non contaminant organisms isolated from culture sent before 48 hours)
      a) group B streptococcal disease
      b) other pathogens
      c) indeterminate aetiology

   (ii) Late onset infection (non contaminant organisms isolated from culture sent after 48 hours)
      a) gram positive organisms except *Staphylococcus epidermidis*
      b) *staphylococcus epidermidis*
      c) other pathogens
      d) indeterminate aetiology

   (iii) Post surgery

9. Type of IVIG. This subgroup analysis will analyse separately babies recruited in hospitals using the different IVIG products included in INIS. This subgroup analysis will include baseline characteristics and treatments after randomisation as well as outcomes.

**Interim analyses: the Safety and Data Monitoring Committee**

For the trial a Data Monitoring and Ethics Committee (DMEC) [Safety and Data Monitoring Committee (SDMC)] has been established. This is independent of the trial organisers and meets at least once per year. During the period of recruitment to the trial, interim analyses will be supplied, in strict confidence, to the DMEC, together with any other analyses the DMEC may request. In the light of interim data, and other evidence from relevant studies (including updated overviews of the relevant randomised controlled trials), the DMEC will inform the Trial Steering Committee, if in their view (i) there is proof beyond reasonable doubt that any part of the protocol under investigation is either clearly indicated or contra-indicated, for all infants or for a particular subgroup of trial participants; or (ii) it is evident that no clear outcome will be obtained. Decision to inform the Trial Steering Committee in either of these circumstances will in part be based on statistical considerations.

Appropriate criteria for proof beyond reasonable doubt cannot be specified precisely. A difference of at least 3 standard deviations in the interim analysis of a major endpoint may be needed to justify halting, or modifying, such a study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, and so no fixed schedule is proposed.93

Unless modification or cessation of the protocol is recommended by the DMEC, the Trial Steering Committee, collaborators and administrative staff (except those who supply the confidential information) will remain ignorant of the results of the interim analysis. Collaborators and all others associated with the study may write through the trial office to the DMEC to draw attention to any concern they may have about the possibility of harm arising from the treatment under study, or about any other matters that may be relevant.

The membership of the DMEC is:
SAMPLE SIZE

The total sample of 5,000 infants worldwide will yield over 90% power with a type I error of 5% (two-tailed) to detect an absolute risk difference of 4%, from 25% to 21%, in the rate of primary outcome. A moderate reduction of this magnitude would mean one death or case of major disability prevented for every 25 children treated. This would provide the most cost-effective clinical indication for IVIG ever reported. The study will also have over 85% power with a type I error of 5% (two-tailed) to detect a 3% difference in permanent disability (from 15% to 12%), and over 80% power and a type I error of 5% (two-tailed) to detect important differences in the primary measure of outcome in each of the three subgroups stratified by clinical severity at presentation (see Table 4).

The estimate of the incidence of the outcome (the event rate) for the trial is imprecise, particularly as the threshold at which clinicians will enter patients cannot be precisely estimated. If clinicians enter babies where the likelihood of serious sepsis is lower then the event rate will also be lower. If clinicians restrict entry to only those babies who are very sick, then the event rate will be high. Either of these two scenarios is reasonable because it will define a population to which the trial result can be generalised. However, it does mean that until the trial has recruited sufficient numbers of babies it will not be possible to determine the optimum trial sample size with any certainty. As a consequence the trial sample size currently represents the minimum size desirable. The DMEC (see above) will review the data and advise the Trial Steering Committee whether the trial has answered the clinical question being addressed. If not, the trial will continue to recruit until 5,000 babies have been recruited, or until funding is exhausted.
Table 4. Sample sizes and power in subgroups randomised into the trial with different levels of severity at presentation (Arcus Quickstat: Longman Software)

<table>
<thead>
<tr>
<th>Clinical severity at entry to the study</th>
<th>No of patients</th>
<th>Rate of primary adverse outcome expected</th>
<th>Difference in outcome between IVIG &amp; control group</th>
<th>Power to demonstrate this difference at $p=0.05$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low clinical risk</td>
<td>2,500</td>
<td>10%</td>
<td>10% vs 6%</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>Moderate clinical risk</td>
<td>1,250</td>
<td>30%</td>
<td>30% vs 22%</td>
<td>&gt; 80%</td>
</tr>
<tr>
<td>Septic shock or high mortality risk</td>
<td>1,250</td>
<td>45%</td>
<td>45% vs 37%</td>
<td>&gt; 80%</td>
</tr>
<tr>
<td>All patients</td>
<td>5,000</td>
<td>25%</td>
<td>25% vs 21%</td>
<td>90%</td>
</tr>
</tbody>
</table>

FEASIBILITY

This study reflects the philosophy that the only practicable way to achieve comparisons which are sufficiently large to minimise the risk of being seriously misled by the play of chance is to design trials that are extremely simple and flexible. Experience in the OSIRIS and ORACLE study suggest that a large, simple trial of this scale of a potentially important intervention is feasible. It is expected that approximately 2500 infants will be recruited in the UK, 1500 infants in Australia and New Zealand, and 1000 infants from other European and Asian centres; making a total of 5000 infants from 150 centres worldwide.

Approximately 25 centres in Australia and New Zealand will participate in the study. Assuming recruitment at the rate of 2 patients per centre per month [24 per centre per year], 600 infants will be recruited in each year of 2004 and 2005. With the addition of the estimated 300 babies recruited in Australia by the end of 2003, the target of 1500 babies is feasible by the end of 2005. The average parental consent rate has been 75% in Australian centres to date. Furthermore, a prospective antibiotic audit conducted in 18 ANZ neonatal units in 2002 showed that 7-8 infants per centre per month on average received antibiotics for 5 or more days (which may indicate a serious infection), further suggesting that the target sample size is feasible.

Funding (as at July 2003) has been obtained from the UK Medical Research Council, Financial Markets Foundation for Children, University of Sydney (Sesqui Grant), NHMRC Clinical Trials Centre, New Zealand Health Research Council, Telstra Foundation, and the Ian Potter Foundation (travel grant). The Australian Red Cross Blood Service and New Zealand Blood Service will distribute the IVIG for free to participating centres, and the Commonwealth Government has guaranteed a free and reserved supply of IVIG (Intragam® P) from the National Reserve for the trial in Australia.

Funding is provided for a part-time local research nurse at each participating centre. Evidence that this strategy is effective comes from several large trials: ORACLE, the UK Neonatal Staffing Study, the LIPID Study, and is recommended by The British Association of Perinatal Medicine (http://www.bapm-london.org/publications/mchtn3.pdf). Experience suggests that a large, simple trial of a potentially important intervention supplied free, with local part-time research nurse co-ordinators in participating centres will be feasible.

ECONOMIC EVALUATION OF IVIG

The methods for the economic evaluation of neonatal intensive care will follow those employed previously in Australia. The cost of IVIG will be varied in a sensitivity analysis from $25 per g to $125 per gram, to simulate non-commercial and commercial prices (2 doses of 3 gram vials are administered). Hospitalisations between discharge and 2 years of age will be added assuming that they cost one third of a patient-day of respiratory support. Up to 2 years specialist care for paediatrics, speech, hearing and physiotherapy outside of hospital admissions will be retrospectively reported and costing where significant differences between trial arms are found. The additional cost of long term care for a child with a severe disability will be assumed to be $50,000 ($A 1997) per year and varied in sensitivity analysis, with ranges to include alternative costs of permanent
disability in Australia. To estimate cost per Quality Adjusted Life Year (QALY) saved, utility weights will be assigned as 0 for dead, 0.4 for severe disability, 0.6 for moderate disability, 0.8 for mild disability and 1 for no disability. Utilities at 2 years will be aggregated for each group and divided by the number of children to calculate quality adjusted survival rates at 2 years. Within study life years differences will be calculated with cumulative life years derived from Kaplan Meier survival curves. For both treatment and control groups, life years gained and quality adjusted life years gained per child after age 2 will be calculated incrementally by multiplying the survival rate and the quality adjusted survival rate at 2 years, respectively, by life expectancy at age 2. The difference between groups will be evaluated. A life expectancy at age 2 of 70 years will be assumed, except for multiply severely disabled children, whose life expectancy at age 2 will be assumed to be 40 years. A discount rate of 5% will be applied and cost effectiveness and cost utility ratios for IVIG will be calculated. To assess the robustness of the conclusions, sensitivity of the incremental cost per QALY saved will be calculated with 95% confidence intervals around the treatment effects using a) the paediatric and PARCA parental reports, and b) the BSID-II assessment, and the underlying assumptions about costs of hospital care, costs of permanent disability, assignment of utilities and life expectancy. A 3% reduction in permanent disability would annually prevent 60 cases in Australia alone (each costing a conservatively estimated $800,000 in discounted lifetime care costs). This would lead to net discounted cost savings of over $48 million, mainly attributable to the lifetime costs of care for the 60 cases of disability prevented. Hence participation in INIS could save Australian Health Services in one year substantially more than the cost of the study.

PUBLICATION POLICY
To safeguard the scientific integrity of the trial, data from this study should not be presented in public or submitted for publication without requesting consent from the Trial Steering Committee. The success of the trial depends on the collaboration of a large number of doctors, nurses and researchers. For this reason, chief credit for the results will be given not to the committees or central organisers but to all who have collaborated in the study. Acknowledgement will include all members of the trial committees, the data coordinating centre, trial staff, and local coordinators at all collaborating centres. Authorship at the head of the paper will take the form: “The INIS Collaborative Group”. This is the preferred option, as it avoids giving undue prominence to any individuals. All contributors to the study will be listed at the end of the report, with their contribution to the study identified. Publications based on trial data collected at individual centres or in subgroups of centres which address ancillary research questions may be authored by the individual investigators responsible, but will not be submitted for publication until after the main trial manuscript has been submitted. All ancillary studies must have prior approval of the Steering Committee to ensure that these studies will not interfere with the main study.

The investigators will acknowledge all sources of support in publications arising from the study. However, the conduct, analysis, scientific interpretation and publication of the results of the study will be independent of the sponsors.

OUTCOMES AND SIGNIFICANCE
This study will establish or refute the role of non-specific, polyclonal, human IVIG as an adjunctive treatment for neonatal sepsis. The trial will demonstrate for the first time whether or not IVIG can reduce the risk of death or severe disability at two years. If the intervention is shown to be effective, it is likely to be the most cost effective indication for IVIG yet described. The results of the trial could be rapidly adopted into clinical practice, as Intragam® P is available in Australia and New Zealand.
REFERENCES


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100. Foster PR. Assessment of the potential of plasma fractionation processes to remove causative agents of transmissible spongiform encephalopathy. [Review]. Transfusion Medicine 1999;9:3-14.


108. The OSIRIS Collaborative Group (open study of infants at high risk of or with respiratory insufficiency--the role of surfactant. Early versus delayed neonatal administration of a synthetic surfactant--the judgment of OSIRIS. 


Serious infection cannot be defined precisely but might include any of:
- inactivity
- white cells <5,000/µl (5 x 10^9/l)
- pneumonia
- unresponsiveness
- platelets <50,000/µl (50 x 10^9/l)
- ileus
- poor perfusion
- CRP >15 mg/l
- bowel perforation or definite NEC
- prolonged bleeding
- will definitely need antibiotics ≥ 5 days

**ELIGIBILITY**
Infants are eligible if:
1. They have proven or suspected serious infection
   **AND**
2. The have at least one of the following:
   - birth weight less than 1500g
   - evidence of infection in blood culture, CSF or in usually sterile body fluid
   - respiratory support via an endotracheal tube
   **AND**
   (i) They are receiving antibiotics and there is substantial uncertainty that IVIG is indicated

**EXCLUSIONS:**
- IVIG has already been given
- IVIG is thought to be needed or contra-indicated

**Consent**
- On or before admission, or when appropriate, all parents receive an Information Leaflet from the neonatal unit staff, outlining this study.
- If a baby becomes eligible, the parents are asked as soon as possible, in person or by telephone, for consent to participate in the study and later follow up.
- Parents who participate will receive a leaflet thanking them, with the name of a senior doctor and research co-ordinator they can contact about the study.

**Randomisation** (study entry)
- Phone pharmacist (or on-call pharmacist after hours) who will randomise baby and draw up 1st and 2nd study infusions
- Short Entry Form to complete.

**Treatment**
- 500 mg/kg (8.33 ml/kg) of Intragem® P or placebo (normal saline) over 4-6 hours, repeated 48 hours later. No more study drug can be given.

**At Discharge**
- Short Discharge Form and Contact Details Form to complete.

**Follow-up**
- 1 year short parental questionnaire, and 2 year parental and paediatrician questionnaires, plus Bayley II Scales assessments (in some units).