School-Age Outcomes of Very Preterm Infants and Antenatal Magnesium Sulphate Therapy – A Randomised Controlled Trial

Aim
The aim of this study is to determine the outcome of survivors of the ACTOMgSO4 study at early school age (7-8 years of age), comparing the outcomes for those exposed to antenatal magnesium sulphate to those not so exposed. Outcomes will concentrate on neurological function, including motor function, cognition, including attention and executive function, academic progress, and behaviour, but will also include a wide-ranging assessment of other aspects of health and growth.

Hypotheses
1. The potentially clinically important beneficial effects of antenatal magnesium sulphate exposure that were found at 2 years of age will translate into substantial clinical improvements in neurobehavioural function at school-age.
2. Any gains in neurobehavioural function will not be at the expense of ill-health in other areas.

Background
Survival and disability in very preterm infants
Survival rates for very preterm or tiny infants have increased dramatically with the advent of modern perinatal and neonatal intensive care; for those of birthweight 500-999 g born in the state of Victoria the long-term survival rate has increased from 1-in-4 in the late 1970s to 3-in-4 in the late 1990s.1 Despite the large increases in survival, unfortunately the rates of neurologic abnormalities in survivors have not diminished. In this birthweight group approximately 1-in-4 had a major neurosensory disability (any of blindness, deafness requiring amplification, a developmental quotient more than 2 SD below the mean for randomly-selected normal birthweight (birthweight > 2499 g) controls, or cerebral palsy of sufficient severity such that the child was not walking) at 2 years of age. In comparison, only 1-in-20 randomly-selected controls had such a disability.1

The burden of illness imposed by neurosensory impairments and disabilities on very preterm survivors is huge. Recent court awards for cases of medical negligence resulting in severe disability have exceeded $10,000,000 per case, which is presumed to reflect the cost to the community at large. In addition to cerebral palsy, blindness, deafness and developmental delay, very preterm children at school age have increased rates of school problems, cognitive deficits, including executive dysfunction, as well as behavioural disorders, such as Attention Deficit Hyperactivity Disorder (ADHD).2 3 4 5

As survival rates are reaching their maximum, the search is focusing on interventions to improve long-term outcomes. Despite many therapeutic attempts, before and after birth, to reduce the rates of cerebral palsy, few appear to have been successful to date.6 The only exception is antenatal corticosteroids to accelerate fetal lung maturation which significantly reduces the rate of cerebral palsy (OR 0.59, CI 0.35, 0.97).7 Antenatal corticosteroids have other proven benefits,8 including large reductions in mortality, and have been considered routine therapy in very preterm labour for many years. Several recent randomised controlled trials (RCTs) of different therapies, launched because of promising data from animal studies or earlier smaller human studies, have proved to be...
unsuccessful at improving long-term outcomes for very preterm infants. One example is antenatal thyrotropin-releasing hormone (TRH), which not only failed to reduce the rate of respiratory distress when it was expected to do so, but it was also associated with adverse longer-term outcomes in the babies exposed to TRH in the uterus. Another example is prophylactic indomethacin which reduced the rate of major intraventricular haemorrhage in an earlier smaller study, but did not improve long-term outcome in a much larger RCT.

**A role for magnesium sulphate?**

Experimental studies suggest that magnesium sulphate may be neuroprotective. In observational studies maternal administration of magnesium sulphate has been associated with a reduction in the risk of cerebral palsy in very low birthweight babies. However, not all observational studies examining risk factors for cerebral palsy have shown protective effects for antenatal magnesium sulphate. Although experimental and observational studies suggested a role for antenatal magnesium sulphate as a neuroprotective agent, there had been no large randomised controlled trials that have addressed this issue until the ACTOMgSO4 (Australasian Collaborative Trial of Magnesium Sulphate) study, funded by the NHMRC (ID 34295) and which reported its results in *JAMA* in November 2003.

**The ACTOMgSO4 study**

**Aim:** The ACTOMgSO4 study was designed to assess whether antenatal magnesium sulphate given to women at risk of preterm birth before 30 weeks’ gestation had important effects on pediatric mortality and/or neurosensory morbidity, particularly cerebral palsy.

**Methods:** In this trial, 1062 consenting women with a pregnancy less than 30 weeks’ gestational age where birth was planned or expected within 24 hours were randomised at 16 centers in Australia and New Zealand to either intravenous magnesium sulphate (n = 535) or normal saline placebo (n = 527). These women had a total of 1255 infants alive at randomisation, and resulted in 1061 survivors to two years’ corrected age, of whom outcomes at that age were known for 1047 (99%) survivors.

**Results:** Total paediatric mortality (13.8% vs 17.1%; adjusted relative risk [RR] 0.83, 95% CI 0.64-1.09), cerebral palsy in survivors (6.8% vs 8.2%; RR 0.83, 95% CI 0.54-1.27) and combined death or cerebral palsy (19.8% vs 24.0%; RR 0.83, 95% CI 0.66-1.03) were less frequent for infants exposed to magnesium sulphate, but none of the differences were statistically significant. Since the majority of preterm children with cerebral palsy are not severely disabled, we considered it essential to find out if the overall rates of neurosensory disability or motor dysfunction were lowered with antenatal magnesium therapy, rather than solely determining the presence or absence of cerebral palsy at 2 years’ corrected age. **Significantly fewer survivors exposed to antenatal magnesium sulphate had substantial motor dysfunction (defined as not walking freely at 2 years of age) (3.4% vs 6.6%; RR 0.51, 95% CI 0.29, 0.91), and the rate of the combined outcome of death or survival with substantial gross motor dysfunction was also significantly reduced with antenatal magnesium sulphate (16.7% vs 22.5%; RR 0.75, 95% CI 0.59, 0.96).**

**Discussion and Implications:** The only other trial of which we are aware that has reported on the prophylactic neuroprotective effects of magnesium sulphate has
published data on childhood neurological outcome only as an abstract. They randomly allocated women in active labour who were >4 cm dilated to either a 4 g loading dose of magnesium sulphate or saline control. The trial was stopped early because of concerns of higher total paediatric mortality in the magnesium sulphate group; paediatric mortality was lower, not higher, in the ACTOMgSO4 trial. Of the 43 survivors assessed at 18 months of age in that study, 15% (3/20) exposed to magnesium sulphate had cerebral palsy compared with 0% (0/23) exposed to saline. The small size of their study, the low follow-up rate of survivors to 18 months of age (77%; 43/56), and lack of reported methodological details make it difficult to compare their results with our trial.

There are several other randomised trials of antenatal magnesium sulphate therapy given to women immediately prior to very preterm birth currently recruiting around the world that may help to confirm the short-term benefits of the ACTOMgSO4 study. Regardless of the results of these studies, however, we need to establish if the potential short-term benefits to 2 years of age of antenatal magnesium sulphate translate into more important long-term neurological benefits. This is particularly important as the diagnosis of cerebral palsy is not 100% accurate in early childhood, especially in preterm children, even when only a few well-trained experts are involved in the diagnosis, and also because there are many important neurologic areas, including cognitive, behavioural and academic outcomes, that cannot be assessed fully before school-age. As any neuroprotective effects of magnesium sulphate might benefit neurons other than just those involved in motor pathways, it is essential to evaluate the central nervous system outcome of children exposed to antenatal magnesium sulphate as completely as possible. Moreover, as any drug given in the perinatal period can have unexpected long-term health problems, we must consider other general health outcomes in any further assessments of these children. Of note, the improvement in the short-term motor function of infants with magnesium sulphate in the ACTOMgSO4 was not accompanied by any important side-effects in either the mother, fetus or infant.

Importance of the proposed study

If antenatal magnesium sulphate is proven to reduce the rate of important long-term neurologic outcomes, without any unexpected adverse side-effects it has the potential to be widely used in the management of very preterm birth, with a consequent reduction in the burden of illness in the community.

Research Plan

Study Design: Long-term follow up of children from a randomized controlled trial

Subjects

Survivors of the ACTOMgSO4 study at 2 years of age (n=542 exposed to magnesium sulphate; n=519 controls) will be offered assessments at ages between 7-8 years.

Outcomes

Given the difficulty in mounting large-scale randomised controlled trials in perinatal care, and the additional difficulties with follow-up into school-age, this study may represent the last opportunity to assess as completely as possible the long-term effects of magnesium sulphate on the very preterm fetus. Therefore we want to assess the health outcomes of these children as completely as possible, without exhausting either them or their families.
The outcomes to be determined include neurobehavioural impairments and disabilities (affecting cognitive ability, vision and visual processing, movement, verbal fluency, behaviour, and academic progress), growth, general health and hospital resource utilisation, and health related quality of life. Children will be assessed without reference to any previous results, as well as blinded to treatment group allocation. The few parents who might know the treatment group allocation will be asked not to reveal this to the assessors. Children will be assessed in the years 2005 to 2007. Children in the ACTOMgSO4 study were born between March 1996 and September 2000. We will commence assessing the oldest children first, at age 8 years at the start of 2005, and gradually see the remainder over the ensuing 3 years, so that the youngest survivors assessed will be 7 years of age at the end of 2007. All ages will be corrected for prematurity as we have shown that even at age 8 years correction for prematurity results in elimination of a small but potentially clinically important bias in cognitive test scores.  

A. Motor Function

A developmental paediatrician will examine the children. A neurological examination will detect the presence of cerebral palsy, the diagnosis of which will comprise non-progressive loss of motor function with disordered tone or tendon reflexes. The severity of gross motor function in children with cerebral palsy will be classified according to the criteria of Palisano et al. In addition, motor function in all children will be assessed by the Movement Assessment Battery for Children (ABC). The Movement ABC is a standardised test of motor function and those who score below the 15th centile compared with the norms are considered to have motor dysfunction. In our Victorian cohort born in 1991-92 we have found motor dysfunction in 25.1% (64/255) of extremely low birthweight (ELBW, birthweight <1000g) or very preterm (<28 weeks’ gestation) children at 8 years of age compared with only 4.3% (9/208) in normal birthweight controls ($\chi^2=37.2$, $P<0.0001$), even excluding those with cerebral palsy (very preterm 20.1% [47/234]; 4.3% [9/208] controls; $\chi^2=24.7$, $P<0.0001$). As we found a lower rate of motor dysfunction at 2 years of age in the ACTOMgSO4 study, if antenatal magnesium sulphate does have any clinically important neuroprotective effects on the motor system they will be detectable by the Movement ABC (see under “Power of the Study”).

B. Psychological Assessments

The psychological assessment will include tests in the following areas:

a. General Cognitive Ability

Cognitive ability will be assessed using the Wechsler Intelligence Scale for Children - Fourth Edition. Full Scale IQ is a measure of general intellectual ability, while the four-factor index scores (Verbal Comprehension, Perceptual Reasoning, Working Memory, Processing Speed) will be used to examine specific elements of cognitive functioning. Each scale/index is age standardised with a mean of 100 (SD 15). The criteria for mild intellectual impairment will be a full-scale IQ between 70 – 84 (from −2 SD to −2 SD), for moderate intellectual impairment will be an IQ between 55 – 69 (-3 SD to <-2 SD), and for severe intellectual impairment will be an IQ below 55 (<−3 SD).

b. Attention & Executive Function
On testing executive function at school-age of 275 ELBW/very preterm children born in Victoria in 1991-92, we have shown that the ELBW/very preterm children exhibited significant executive dysfunction compared with normal birthweight peers in all areas assessed. The cognitive assessment revealed global impairment, rather than deficits in specific executive domains. The ELBW/very preterm children also displayed more behavioural problems indicative of executive dysfunction than the normal birthweight children. Severe impairments were exhibited in only a small minority of ELBW/very preterm children.

Attention and executive function are multi-dimensional constructs incorporating both cognitive and behavioural elements. The psychological assessment will include a battery of tests sensitive to specific attentional and executive processes. All tests have age standardised scores or age-appropriate norms. In addition, parents and teachers of participants will complete a questionnaire regarding behaviours associated with attention problems and executive dysfunction.

**Sky Search.** Sky Search is a subtest from the Test of Everyday Attention for Children (TEACh), which assesses selective attention. Children search for all the ‘target’ spaceships as quickly as possible on a sheet filled with very similar distractor spaceships. Performance will be determined by the number of targets identified, and the time taken to complete the task.

**Score.** Score, a subtest from the TEACh, assesses sustained attention. Over 10 trials children count the number of beeps (which are presented at random intervals) they hear on an audiotape. Given that the task is simple and there are some long gaps between beeps, the child has to self-sustain his or her attention. Performance will be judged by the number of correct trials.

**Sky Search Dual Task.** Sky Search Dual Task involves children completing the above two tasks (Sky Search and Score) concurrently, and assesses divided attention. Performance will be determined by the decrement in performance on Sky Search and Score tasks under the dual task conditions.

**Creature Counting.** Creature Counting, also from the TEACh, assesses working memory. Children have to count the number of aliens in their burrow with random arrows instructing them to count upwards and downwards. Thus, children need to shift between counting upwards and downwards. Performance will be judged by accuracy and time taken.

**Letter-Number Sequencing (LNS).** LNS, from the WISC-IV, assesses verbal working memory. Children are presented with a mixed series of numbers and letters, and required to repeat them with the numbers first in numerical order followed by the letters in alphabetical order. Performance will be judged according to accuracy.

**Tower of London (TOL).** The TOL assesses planning ability. Children are instructed to rearrange a set of three coloured balls on three posts of different height, in a nominated number of moves, so that it matches a specified configuration. Problems on the TOL become more difficult as the number of moves allowed to solve the problem increases, and to be successful children will be required to plan ahead and select the appropriate sequence of moves. Performance will be determined by the number of items correctly solved (maximum score of 12) and the number of failed attempts.
Rey Complex Figure (RCF). The RCF assesses spatial organisation and strategic decision-making. Children are required to copy, as accurately as possible, a complex geometrical figure consisting of a large rectangle, vertical and horizontal centrelines, two diagonals, as well as external attachments and internal sections of the large rectangle. Spatial organisation will be assessed using the accuracy scoring procedure developed by Osterrieth, while strategic decision-making will be judged using the RCF-Organizational Strategy Score.

Behavior Rating Inventory of Executive Function (BRIEF). The BRIEF is a questionnaire that assesses behavioural manifestations of inattention and executive function. Both parent and teacher versions will be administered. The BRIEF provides eight theoretically and empirically derived clinical scales (Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor) and scores are age-gender standardised. Internal consistency for the parent form of the BRIEF has been found to be high, ranging from 0.80 to 0.98. Clinical validity has been supported with a variety of diagnostic groups.

c. Educational Progress

Educational progress will be assessed using the Wide Range Achievement Test (WRAT3), and the Comprehensive Scales of Student Abilities (CSSA). The WRAT3 includes three subtests that assess reading (word recognition and decoding), spelling, and arithmetic. Each scale is age standardised with a mean of 100 (SD 15). Mild impairment in these educational domains will be determined by scale scores from 70-84, while scale scores <70 represented major impairment. CSSA is a teacher-completed questionnaire examining 9 aspects of educational ability including Verbal Thinking, Speech, Reading, Writing, Handwriting, Mathematics, General Facts, Basic Motor Generalizations, and Social Behavior. Each scale is age standardised with a mean of 100 (SD 15).

d. Behavioural Problems

As attention-deficit hyperactivity disorder (ADHD) has been reported more frequently in ex-preterm children, we will include a specific ADHD diagnostic questionnaire namely the Conners' ADHD/DSM-IV Scales (CADS; Psychological Corporation). In addition, the Behavior Assessment System for Children (BASC) includes parent and teacher rating scales of behaviour. The BASC parent rating scale provides a comprehensive assessment of a child’s adaptive and problem behaviours in home and community settings, while the teacher rating scale assesses these behaviours at school. Both scales provide composite indexes for externalising problems, internalising problems, adaptive skills, and overall behavioural symptoms. All indexes are age-sex standardised, providing T scores with a mean of 50 (SD10). For the behavioural indices, T scores 70 and above are considered “clinically significant”, while T scores between 60 and 69 represent the “at-risk range”. For the adaptive index, a T score 30 and below is “clinically significant”, while T scores between 31 and 40 represent the “at-risk range”.

C. General Health, Health Resource Utilisation, Growth, and Quality of Life.

A general history and physical examination will determine the presence of any significant chronic illness, and data regarding hospital readmissions will be confirmed, where necessary, by the admitting hospital or doctor. Visual acuity will be assessed with a standard eye chart. Weight and height will be measured in the standard way, and values for the relevant centile, percent of median, and standard deviation scores will be computed from the British Growth Reference.
Health-related quality of life, which has been reported to show significant differences between children of birthweight < 1001 g and normal birthweight controls at 8 years of age, will be measured by a multiattribute health status (MAHS) classification system, which has been adapted for children.\textsuperscript{40} The MAHS classification system derives from the oncology literature and describes both the type and severity of functional limitations according to seven attributes: sensation, mobility, emotion, cognition, self-care, pain, and fertility. Each attribute has four or five levels of function. The MAHS clearly assesses outcomes other than neurological function. Children will also be assessed with the Australian Authorised Adaptation of the Child Health Questionnaire (CHQ).\textsuperscript{41} The CHQ has recently been normed on over 5000 Australian children aged 5-18 years and provides an assessment of the child’s psychosocial health, physical health and well-being.

\textit{Neurosensory Disability}

The severity of the disability imposed by cerebral palsy will be graded into severe, moderate and mild. Severe disability will comprise children who are non-ambulant and are likely to remain so, moderate disability will comprise those who are ambulant at 7-8 years of age but who have substantial limitation of movement, and mild disability will comprise those children walking with little limitation of movement. Children will be considered blind if vision in both eyes is worse than 6/60. Children will be considered deaf if they require hearing aids. Children will be considered intellectually impaired if the IQ is <-1 SD below the mean. The neurosensory disabilities imposed by the various neurosensory impairments will be classified as severe, moderate, and mild, as follows: Severe disability will comprise any of severe cerebral palsy, an IQ <-3 SD below the mean, or blindness. Moderate disability will comprise moderate cerebral palsy, deafness, or an IQ from –3 SD to <-2 SD below the mean. Mild disability will comprise mild cerebral palsy or an IQ from <-2 SD to < -1 SD below the mean. Children without any neurosensory impairment will be considered to have no neurosensory disability.

\textit{Feasibility and Anticipated Follow-up Rate}

The numbers of survivors traced at 2 years of age at each of the 16 study centres is shown in Table 1.
Table 1. 2-year survivors at each study centre, and within regions.

<table>
<thead>
<tr>
<th>Hospital</th>
<th>N</th>
<th>Region</th>
<th>Number in Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>King Edward Memorial</td>
<td>71</td>
<td>WA</td>
<td>71</td>
</tr>
<tr>
<td>Women's &amp; Children's Hospital</td>
<td>162</td>
<td>SA</td>
<td>162</td>
</tr>
<tr>
<td>Monash Medical Centre</td>
<td>53</td>
<td>VIC</td>
<td>216</td>
</tr>
<tr>
<td>Royal Women’s Hospital, Melbourne</td>
<td>94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mercy Hospital For Women</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>King George V</td>
<td>111</td>
<td>Sydney</td>
<td>154</td>
</tr>
<tr>
<td>Royal Hospital For Women</td>
<td>43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Canberra Hospital</td>
<td>78</td>
<td>Canberra</td>
<td>78</td>
</tr>
<tr>
<td>Royal Women’s Hospital, Brisbane</td>
<td>119</td>
<td>Brisbane</td>
<td>176</td>
</tr>
<tr>
<td>The Mater Hospital</td>
<td>57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kirwan Hospital</td>
<td>47</td>
<td>North QLD</td>
<td>47</td>
</tr>
<tr>
<td>Royal Hobart Hospital</td>
<td>13</td>
<td>Tasmania</td>
<td>13</td>
</tr>
<tr>
<td>Royal Darwin Hospital</td>
<td>3</td>
<td>NT</td>
<td>3</td>
</tr>
<tr>
<td>Christchurch Women's Hospital</td>
<td>45</td>
<td>New Zealand</td>
<td>134</td>
</tr>
<tr>
<td>Waikato Hospital</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>National Women's Hospital</td>
<td>65</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The study centres total 16, but to reduce costs and variability of assessments, we propose to have one team assess the children within geographic regions. Therefore for Australia there would be one team each for WA, SA, Victoria, Sydney, Brisbane, Canberra, North Queensland, and Hobart. The 3 children in the Northern Territory will be assessed by a team from another state who will need to visit Darwin for 2 days to assess the 3 children. For New Zealand, there will need to be 3 separate teams for Auckland, the Waikato region, and the South Island (Christchurch). Therefore, in total we will need 11 teams, including 11 sets of equipment. Children born in one region but who are geographically closer to another assessment team will be assessed at the closest region, with the agreement of all concerned.

We expect that > 90% of the survivors will be assessed fully. We were successful in obtaining data on 99% of the cohort at 2 years of age and we have been in contact with the families since that time, updating them on progress and results of the study. We have been noting changes in contact details so that subsequent tracing of families will be facilitated. Many families have spontaneously indicated a willingness for further follow-up of their children, and none have expressed any reluctance. Since some families live large distances from assessment centres, this will necessitate, in some cases, that we provide expenses for the family to travel to the assessment centre. Alternatively, we may have to send the paediatrician and psychologist to the child's residence or school, if the family cannot attend. We have been able to assess 92% (275/298) of very preterm children in one of our Victorian cohorts born in 1991-92. Of the 23 very preterm children not assessed at 8 years of age in that study, 8 were lost, 11 refused and 4 were inaccessible, usually living in another country. In Australia we achieve follow-up rates into school-age for our very preterm survivors that are consistently higher than those reported elsewhere in the world.42
We have previously reported that those children who are hardest to assess have the highest rate of problems, particularly in cognition. Of the 204 very low birthweight children assessed at 5 years of age, 153 (75%) were followed with ease, and 51 (25%) with difficulty. More children followed with difficulty had a neurosensory disability (41% compared with 19%), predominantly because they had lower IQ scores (mean difference in IQ -12.7, 95% CI -18.0 to -7.4). Therefore if we do not assess at least 90% of children in this study we will seriously underestimate the rate of cognitive dysfunction. A follow-up rate of >90% will only be achieved, however, if we are fully funded for equipment and travel, especially for some families to travel for assessments, or in a small number of cases, for the follow-up teams to travel to the child for assessments, including the one visit to Darwin.

Time required for assessments
As we have used these assessments previously, we know that the child will be with the paediatrician for approximately 1½ hours. A full psychological assessment would take an upper limit of 3 hours. Both health professionals then require a further ½ hour to provide reports and feedback to the families and other health professionals involved in the child’s care. Consequently the time taken for a full assessment of the child face-to-face with assessors would be up to 4½ hours, which means the assessments can all occur on one day. Occasionally we note that children tire and require a break. This often occurs between the psychological assessment, which is usually done first when the child is less tired, and the paediatric assessment. Parents and teachers filling out questionnaires take additional time, but this occurs independently of the direct assessments of the child.

Data Management
Data will be entered onto a personal computer and edited using SAS. Data will be analysed by a statistician independent of the CIs and AIs. Dichotomous outcome data will be contrasted by $\chi^2$ analysis or logistic function regression to adjust for confounding variables, and continuous data by t-test or multiple linear regression to adjust for confounding variables. Confounding variables will comprise sociodemographic variables, such as ethnicity, language spoken at home, family structure, mother’s marital status, social class, and mother’s and father’s education, as well as gender. Adjustment will also be necessary to allow for a small design effect caused by non-independence of children from multiple pregnancies. P-values <0.05 will be considered statistically significant.

Power of the Study
The sample size of this study has already been determined (n=1061 survivors). Table 2 shows the sizes of reductions in event rates (ER) that could be detected with 80% power, with variations in the rate of the outcome in the control group, and with both 90% follow-up (n=478 survivors in each group assessed) and 80% follow-up (n=424 survivors assessed in each group).

Table 2. Size of difference for reduction in dichotomous outcomes for 80% power, varying with rate of outcome in control group, and with 90% and 80% follow-up rates.
As an example, on the basis of our previous experience in assessing motor dysfunction in very preterm children we expect 25% to have substantial motor dysfunction on the Movement ABC. With 90% follow-up we would have 80% power to detect a reduction as small 7.4% (absolute), or 30% (relative) with antenatal magnesium therapy. The reason for calculating event rate reductions for follow-up rates as low as 80% is not because we anticipate a follow-up rate that low, but to demonstrate that a lower follow-up rate would not have a large effect on the reductions in event rates. As we found almost a 50% relative reduction in the rate of substantial gross motor dysfunction at age 2 years with antenatal magnesium sulphate the expectation of at least a 30% relative reduction at 7-8 years of age is realistic.

A more clinically important example is moderate or severe neurosensory disability combined, where we would expect 25% in the control group to have this outcome. A 30% relative reduction in moderate or severe disability would be considered clinically very important. On an Australia-wide basis there would be approximately 1250 survivors in Australia per year <30 weeks’ gestation (250,000 live births survive each year x 0.5% <30 weeks’ gestation). If the rate of moderate or severe disability is reduced by a relative 30% with antenatal magnesium sulphate from an expected rate of 25% (n=312), approximately 94 fewer children < 30 weeks’ gestation would survive with moderate or severe disability in Australia. This will represent a huge saving for Australia as a whole.

For outcome variables that are continuous, and normally distributed, with 90% follow-up (n=478 in each group) the study is able to detect differences between group means as small as 0.181 SD, with 80% power. If the follow-up rate is only 80% (n=424 in each group), then the size of difference able to be detected yet sustaining the 80% power increases only slightly to 0.192 SD. For IQ, 0.2 SD represents 3 IQ points difference between groups, which would be considered clinically important. Of course larger clinically important differences between group means will be able to be detected with greater power. For example a difference in IQ of 0.33 SD (5 IQ points) would be detectable with almost 100% power, whether the follow-up rate is either 90%, or only 80%. The majority of the psychological tests report data that are continuous, rather than dichotomous.

Outcomes and Significance
Despite large improvements in survival of very preterm infants with the advent of modern perinatal and neonatal intensive care the rates of neurologic abnormalities in survivors have not diminished.

Magnesium sulphate, given to mothers just prior to preterm birth, is one of the few therapies to offer any promise of improving neurologic outcome for preterm survivors. However, before it is widely introduced into practice, and in the absence of any other evidence to the contrary, we need to determine if the potential benefits observed at 2 years of age in the ACTOMgSO4 study translate into clinically important neurologic benefits at school-age.

If successful, antenatal magnesium sulphate will lead to an important reduction in the burden of illness in the community caused by being born too early. Although the costs of this study might seem large (approx. $700,000), this cost is dwarfed by the cost of just one child extra with severe disability in the community (>\$10,000,000). If indeed antenatal magnesium sulphate results in 94 fewer very preterm survivors in Australia per year with moderate to severe disability the cost savings could be huge, exceeding tens of millions of dollars per year.

Given the difficulty in mounting large-scale randomised controlled trials in perinatal care, and the additional difficulties with follow-up into school-age, this study may represent the last opportunity to assess as completely as possible the long-term effects of antenatal magnesium sulphate on the very preterm fetus.