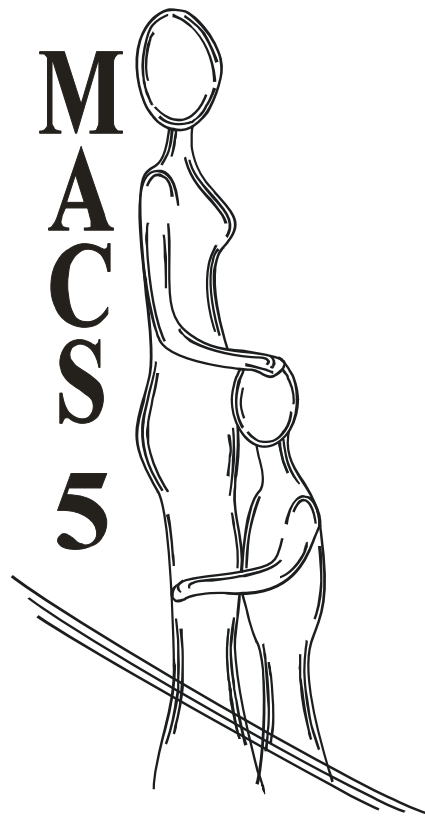


Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study: 5 year Follow-up



Study Protocol

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**MULTIPLE COURSES OF ANTENATAL CORTICOSTEROIDS
FOR PRETERM BIRTH STUDY: **5** YEAR FOLLOW-UP (MACS -5)**

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MULTIPLE COURSES OF ANTENATAL CORTICOSTEROIDS FOR PRETERM BIRTH STUDY: 5 YEAR FOLLOW-UP (MACS-5)

1. BACKGROUND

MACS is a multicentre international randomised controlled trial (RCT) which is enrolling women at 25-32 weeks gestation who received a single course of antenatal corticosteroids (ACS) 14-21 days prior to enrollment and continue to be at increased risk of preterm birth. The objectives of **MACS** are to determine if repeat courses of ACS, every 14 days, reduce the risk of adverse perinatal/neonatal outcome and to determine their effect on neurodevelopmental problems of children at 18-24 months of age.

MACS-5 will determine the effect of repeat courses of ACS on the risk of death or severe disability in neuromotor (non-ambulatory cerebral palsy), neurosensory (blindness, deafness, or need for visual and/or hearing aids), or neurocognitive (abnormal attention, memory, or behaviour) function in children, at 5 years of age. MACS-5 will also determine the effect of repeat courses of ACS on growth, blood pressure, intelligence and specific cognitive (visual motor, visual spatial and language) skills, in children at 5 years of age.

1.1 What is the problem to be addressed?

1.1.1 The problem of preterm birth

Preterm delivery affects 7-10% of births in North America¹ and is responsible for up to 75% of neonatal deaths.² Despite advances in medical technology, the prevalence of preterm birth in Canada has increased.¹ Babies that are born preterm are at increased risk of having respiratory distress syndrome (RDS), intraventricular haemorrhage (IVH), bronchopulmonary dysplasia (BPD) and other neonatal morbidities, which in turn increase the risk of abnormal neurodevelopmental outcome later in life.^{3,4}

1.1.2 Benefits and risks of a single course of ACS for women at increased risk of preterm birth: evidence from RCTs

In 1972, Liggins and Howie published the results of the first RCT evaluating the effects of a single course of ACS.⁵ The study recruited 282 women at increased risk of preterm birth and assigned them to either the ACS group (6 mg of betamethasone phosphate plus 6 mg of betamethasone acetate) or the control group (6 mg cortisone acetate). The treatments were repeated once, 24 hours later, if delivery had not occurred. Among those women who had been in spontaneous preterm labour, ACS reduced the risk of RDS (9.0% vs 25.8%, $p=0.003$) and early neonatal mortality (3.2% vs 15.0%, $p=0.01$).

In 1990, a systematic review and meta-analysis of 12 RCTs by Crowley, involving over 3000 babies, found a reduced risk of RDS, IVH, necrotising enterocolitis and neonatal death with a single course of ACS and no evidence of adverse effects.⁶ The 2004 Cochrane review of 18 RCTs involving over 3700 babies reports a reduced risk of neonatal death, RDS and IVH with a single course of ACS.⁷ In addition to the benefits from a single course of ACS, RCTs have found no evidence of adverse consequences. Indeed, the Cochrane Review has found one course of ACS to be associated with a strong trend towards a reduced risk of abnormal neurodevelopmental outcome on long-term follow-up of the children (Odds Ratio [95%CI]: 0.62 [0.36,1.08]). As a result, since the early 1990's, it has been generally recommended that women receive a single course of ACS if they are at 24 to 34 weeks gestation and at an increased risk of preterm birth.^{8,9}

1.1.3 Benefits and risks of repeat courses of ACS for women at increased risk of preterm birth

Approximately 50% of women given a first course of ACS remain undelivered 7-14 days later.¹⁰ The 2004 Cochrane Review of RCTs of a single course of ACS suggests that the benefits of a single course of ACS may be less if the infant does not deliver within 7-10 days after receiving the first course.⁷ It has been suggested, therefore, that women who remain undelivered after a single course of ACS may benefit by receiving additional or repeat courses of ACS.

A meta-analysis of 8 non-randomised studies comparing repeat courses of ACS with a single course, has found a reduced risk of RDS and patent ductus arteriosus and no increased risk of other adverse outcomes, with repeat courses. However, confounding factors make the findings difficult to interpret and establish the true effects of multiple courses of ACS.¹¹ Over recent years, several large RCTs have been initiated to study the effects of repeat (weekly) courses of ACS (see Table 1.1.3.1). The Guinn RCT found no significant reductions in risk of stillbirth, neonatal death or serious neonatal morbidity with repeat ACS vs placebo (22.5% vs 28.0%, $p=0.16$).¹² The NICHD RCT, which to date has only been presented in abstract form, also found no significant reduction in risk of stillbirth, neonatal death or serious neonatal morbidity with repeat ACS vs placebo (7.7% vs 9.2%, $p=0.67$).¹³ However, subgroup analyses of the NICHD RCT found, that among women delivered before 32 weeks, there was a trend towards a reduction in adverse neonatal outcome in the repeat ACS group (21.3% vs 38.5%, $p=0.083$), and among infants exposed to 4 courses there was a reduction in birth weight in the repeat ACS group (2396 vs 2561 g, $p=0.01$).¹³ The UK and Australian Trials have been closed to further recruitment and their findings have not yet been reported. In summary, the evidence suggests the potential for benefit as well as harm for repeat weekly courses of ACS but the information is inconclusive. *MACS* is the only RCT specifically studying the effects of repeat courses of ACS vs placebo every 14 (as opposed to every 7) days. It is our hope that less frequent dosing of ACS will be associated with similar benefits to weekly coursing but without evidence of harm.

Table 1.1.3.1 RCTs of repeat (weekly) courses of ACS

Study	Country of Origin	Original sample size	Total number recruited
Guinn ¹²	USA	1000	502
NICHD ¹³	USA	2400	495
TEAMS	UK	4000	154
ACTORDS	Australia	980	982

1.1.4 Benefits and risks of Postnatal Corticosteroids (PCS) in human infants

Numerous RCTs have been undertaken to evaluate PCS for the prevention and treatment of chronic lung disease in infants. Although RCTs of PCS vary in their methodology and the findings are not entirely consistent, there is concern that short-term benefits may be offset by long-term problems. In the 2004 Cochrane Review of RCTs of early PCS (< 96 hours), in which 21 RCTs involving over 3000 babies were included, the findings showed significant benefits in terms of earlier extubation, decreased risks of bronchopulmonary dysplasia, patent ductus arteriosus, and severe retinopathy of prematurity with PCS.¹⁴

However, the risk of several adverse outcomes on long term follow-up was increased with PCS. Specifically, in the 9 RCTs that reported late outcomes, survivors receiving PCS had higher risks of developmental delay, cerebral palsy, and an abnormal neurological exam. In addition, a recent evaluation at school age of a cohort of one of the trials showed substantial adverse effects of PCS on neuromotor and cognitive function.¹⁵

Thus the children exposed to early PCS treatment experienced short-term benefits but were also at higher risk of long-term adverse outcomes. The authors of the Cochrane review concluded that ‘there is a compelling need for the long term follow-up and reporting of late outcomes, especially neurological and developmental outcomes, among surviving infants who participated in all randomised trials of early postnatal corticosteroid treatment’.¹⁴ It is similarly important that if repeat courses of ACS are found to be beneficial in the short-term that this is not at the expense of long-term neurodevelopmental problems.

1.1.5 Benefits and risks of ACS in animals

Several RCTs have been conducted in animals to evaluate ACS in increasing doses. Progressive improvement in postnatal lung function has been noted as evidenced by increased lung compliance, surfactant and antioxidant enzyme production, and decreased free radical formation.¹⁶⁻¹⁹

However, these studies have also found a higher risk of adverse effects, with the risk increasing with repeated exposure to ACS. Although the doses used were higher than those used in humans, the adverse effects reported have included delays in growth overall, as well as delays in the growth and development of the central nervous system. Specifically, this has included delay in optic nerve myelination, decreased eye growth, and increased retinal thickening.²⁰⁻²² Other investigators, who have focused on brain development, have noted a decrease in growth of all brain structures, including a reduced number of neurons as well as degeneration of neurons in the hippocampus, with increasing exposure to ACS.^{23,24} The adverse effects found on growth, overall, have included a decrease in birth weight as well as a decrease in lung weight.²⁵⁻²⁷

A systematic review of 19 RCTs involving animals, concluded that the adverse effects noted in these studies are a matter for concern, but that the differences in the animal species and the differences between humans and animals in brain development, sensitivity to glucocorticoid receptors, dosing of ACS, and stages of pregnancy, make it difficult to extrapolate the results of these studies to humans.²⁸

1.1.6 Overall impact of ACS on long-term development of children

There is a well-organized interplay of various hormones to support the developing brain in utero. Too much or too little can cause deviation in development and lead to abnormal function depending on the timing of exposure during development of the brain. Within the developing brain, the limbic system and in particular the hippocampus, is sensitive to both endogenous and exogenous glucocorticoids. The hippocampus has a myriad functions that support cognition, memory and behaviour. For the human, a large percentage of maturation of the hypothalamic-pituitary-adrenal (HPA) axis takes place in utero.²⁹ In addition, during weeks 24-32 of gestation, the developing fetal brain undergoes significant changes related to neuronal migration and organization.³⁰ A growing body of literature suggests that ACS can influence the trajectory of neurodevelopment and that exposure to ACS during this period may adversely program the developing brain. Therefore, maternal ACS can theoretically have an impact on the developing brain, particularly the hippocampus, during critical periods of development.³¹

Three RCTs have studied the long-term effects of a single course of ACS on children.³²⁻³⁴ The 2004 Cochrane review of these RCTs found a strong trend towards a reduced risk of long term neurological abnormality (Odds Ratio [95% CI]: 0.62 [0.37, 1.08]).⁷ The Dutch trial went on to follow the children to 20 years of age and found no adverse effects on long term outcome following one course of ACS.³⁵ Therefore, we can now be fairly confident that benefits outweigh risks for a single course of ACS.

The effect of repeat courses of ACS on the long-term outcomes of children are limited to observational studies (see Table 1.1.6.1).

Table 1.1.6.1 Observational studies of repeat courses of ACS on long-term outcomes

Study	Gestational age at birth	Total number	Length of follow-up	Repeat ACS (betamethasone)	Findings
French et al (1999) ³⁶	23-32 weeks	477	3 years	Exposure to 0-≥3 courses of ACS	No significant effect of repeat courses of ACS on cerebral palsy or neurodevelopmental disability, or on growth parameters
Thorp et al (2003) ³⁷	<34 weeks	299	7 years	Weekly courses of ACS	No effect of repeat courses of ACS on intelligence, achievement, behaviour, or head circumference
French et al (2004) ³⁸	20- 32 weeks	541	6 years	Exposure to 0-≥3 courses of ACS	Repeat courses of ACS were associated with a lower risk of cerebral palsy (2.6% [1 course] and 2.9% [2 courses] vs 5.7% [no courses]; an increased risk of aggressive/destructive behaviour (29 % [2 courses], 28% [≥3 courses] vs 9% [1 course]), an increase in distractible and hyperkinetic behaviour, but no effect on cognition
Kumar et al (2004) ³⁹	24-34 weeks	126	2-2½ years	Exposure to 1-≥3 courses of ACS	No significant effect of repeat courses of ACS on abnormal neurodevelopmental outcome (10% [<2 courses] vs 14% [≥ 2 courses])

The findings from these studies are conflicting; there is some evidence for benefit, some evidence for harm, and some evidence that there is no effect from repeat exposure to ACS. These studies are subject to selection bias and the effects found may be due to the differences in the populations studied rather than due to differences in the number of courses of ACS. Only the findings from RCTs will avoid this selection bias. These studies emphasize the importance of following up the children enrolled in RCTs to determine the true effects of repeat courses of ACS on survival and long-term neurocognitive outcomes.

In summary, although the evidence for a single course of ACS is strong, the risks and benefits of repeat courses are unclear. *MACS* will answer the safety and efficacy question over the shorter term (up to 18-24 months of age), but the effect of repeated exposure of ACS on the critical structures of the developing brain may not become evident until the child is older. Assessment of the older child is required to determine more accurately the impact of repeat courses of ACS on cognitive skills, behaviour, memory, visual spatial and other more complex tasks. The ability to answer the question regarding the effect of repeat courses of ACS on longer term development therefore lies in following the *MACS* children until they are of school age.

1.2 What are the principal research questions to be addressed?

1.2.1 Primary research question

What is the effect of repeat courses of ACS every 14 days, vs placebo, following a single course of ACS 14-21 days prior to enrollment, on the risk of death, or severe disability in neuromotor (non-ambulatory cerebral palsy), neurosensory (blindness, deafness or need for visual and/or hearing aids), or neurocognitive (abnormal attention, memory or behaviour) function, in children at 5 years of age?

1.2.2 Secondary research questions

1. What is the effect of repeat courses of ACS every 14 days, vs placebo, following a single course of ACS 14-21 days prior to enrollment, on height, weight, head circumference, and blood pressure, in children at 5 years of age?
2. What is the effect of repeat courses of ACS every 14 days, vs placebo, following a single course of ACS 14-21 days prior to enrollment, on intelligence and specific cognitive (visual motor, visual spatial, and language) skills, in children at 5 years of age?

1.3 Why is the trial needed now?

Because of the effectiveness of a single course of ACS in enhancing fetal lung maturity and reducing the risk of RDS, and because other complications of prematurity are high for infants born

preterm, some clinicians have suggested that weekly or biweekly courses of ACS should be given to women who are at an increased risk of preterm birth and remain undelivered 7 or more days following the initial course.⁴⁰ Many policies and approaches to care in both obstetrics and neonatology have become standard practice without adequate evidence to support them. Once a policy of clinical management has been accepted and implemented into practice, it is very difficult to undertake research that is designed to determine the safety and effectiveness of the practice. Practice only changes once harm has been noted. This experience has been noted with the use of early PCS in the management of lung disease in high risk neonates.^{14,41}

We do not yet know the true effect of repeat courses of ACS on short term neonatal outcomes. However, if repeat courses of ACS are associated with benefits in the short-term, but with a higher risk of adverse effects in the long-term, repeat courses of ACS should not be used. The body of information regarding the long-term risks and benefits of repeat courses of ACS is generally mixed. Animal studies indicate significant neurodevelopmental influences of ACS, and early PCS, although associated with short-term benefits, show a higher risk of long-term problems.¹⁵ RCTs of repeat courses of ACS are in progress. We believe that it is imperative that the children enrolled in these RCTs are followed until they are older to assess their attention, memory, and behavioural skills as these outcomes are affected by the function of the limbic system of the brain. In other words, if repeat courses of ACS are found to reduce mortality or short-term neonatal morbidity, it will be important to be confident that this has not led to an altered incidence of the commonly seen cognitive difficulties (“hidden disabilities”) that impact significantly on school functioning.⁴²

1.4 Relevant systematic reviews

A Cochrane systematic review of repeat (weekly) courses of ACS, which is principally dependent on the Guinn trial,¹² has found trends towards benefit (less composite serious morbidity with repeat ACS) as well as trends towards harm (lower birth weight) (see Figures 1.4.1, 1.4.2).⁴³ The results of the NICHD trial (see section 1.1.3) show similar trends suggesting these findings may be true.¹³ The more important question, however, is whether long-term outcomes are generally better or worse with repeat courses of ACS. It is our hope that *MACS*, which is evaluating repeat courses every 14 days, will find benefit but without evidence of harm.

Figure 1.4.1: Effect of weekly ACS on composite mortality and morbidity

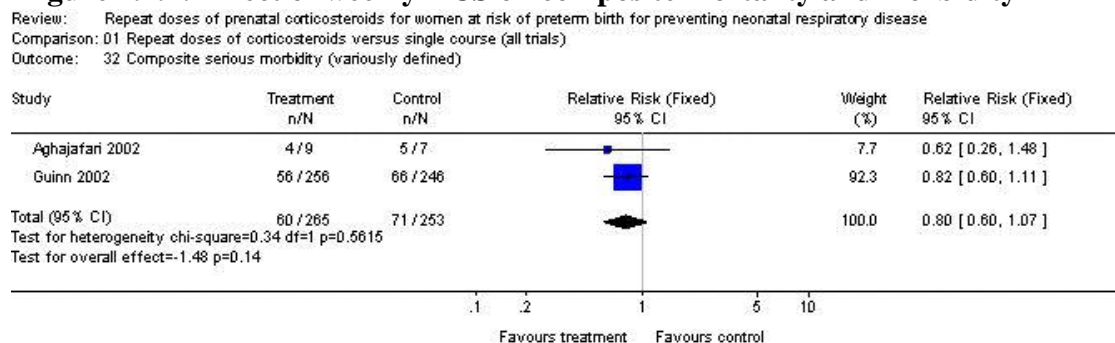
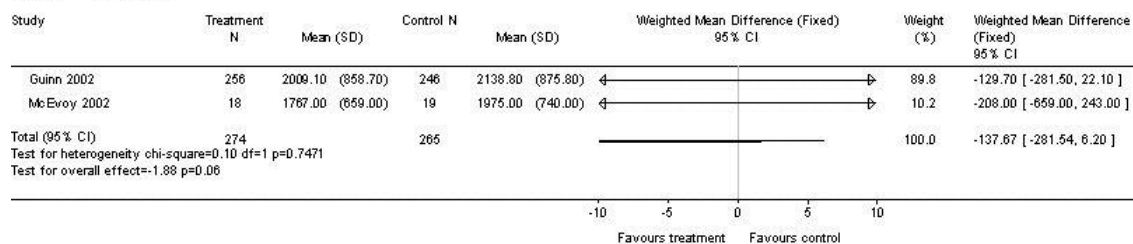


Figure 1.4.2: Effect of weekly ACS on birth weight

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease
 Comparison: 01 Repeat doses of corticosteroids versus single course (all trials)
 Outcome: 03 Birth weight



1.5 How will the results of this trial be used?

MACS-5 will determine the safety of repeat ACS (every 14 days) up to 5 years of age. Policy makers and national specialty societies will use the results of **MACS** and **MACS-5** to develop evidence-based clinical practice guidelines. Obstetricians and other health care providers will use the results to counsel women who are at increased risk and remain at increased risk of preterm birth after receiving one course of ACS. The risks and benefits of repeat courses of ACS can then be discussed so that women can make an informed decision/choice about management and care.

1.6 Risks to the safety of participants involved in the trial.

The initial **MACS** RCT has been approved by Research Ethics Boards at all participating centres and women sign a form indicating their free and informed consent, prior to their participation in **MACS**. In centres planning participation in **MACS-5**, participants have been informed about the study and have been asked to agree to continued contact. The **MACS-5** protocol for the 5 year follow-up assessments will be reviewed by the Research Ethics Boards of collaborating centers participating in **MACS-5**, and all women who were enrolled in **MACS** in these centers will be invited to participate. A Data Safety Monitoring Board is available to review safety concerns if any issues should arise during the conduct of **MACS-5**.

2. PROTOCOL

2.1 Research Design

MACS is a multicentre double-masked RCT with prognostic stratification for gestational age (25-27 weeks, 28-32 weeks) and centre. Women who continue to be at increased risk of preterm birth, 14-21 days after having received one full course of ACS, are allocated to the repeat ACS or placebo groups by a centrally controlled telephone randomisation service.

In **MACS-5**, **MACS** children are followed to 5 years of age to determine the long-term effects of ACS with a particular emphasis on cognitive, behavioural and motor development. All of the children whose mothers were randomised in centres participating in the 5-year follow-up will have a physical examination and questionnaires completed on attention, memory and behavioural skills. In addition, children whose mothers were randomised in English-speaking centres will have an additional in-depth assessment of the child's intelligence and specific cognitive (visual motor, visual spatial, and language skills) skills.

2.2 Trial interventions

In **MACS**, women allocated to the ACS group receive repeated courses of ACS every 14 days until 33^{6/7} weeks gestation (women with ruptured membranes have study medication stopped at 32^{6/7} weeks). Each course consists of two doses of betamethasone (12 mg per dose), given intramuscularly 24 hours apart. The betamethasone formulation is a combination of betamethasone phosphate and

acetate and is supplied by Schering-Plough Corporation, Madison, New Jersey, USA. Women allocated to the placebo group receive repeat courses of placebo. The placebo consists of a dilute concentration of aluminum monostearate. This substance is commonly used as a filler in many pharmaceutical preparations and is considered to be inert. The placebo is supplied by Eminent Services Corporation, Gaithersburg, Maryland, USA.

2.3 Practical arrangements for allocating participants to the trial groups

Women are randomised in *MACS* using the centrally controlled computerised telephone randomisation service at the University of Toronto Maternal, Infant & Reproductive Health Research Unit (MIRU). The treatment number issued at randomisation corresponds to a study box at the centre, which contains vials of betamethasone or similarly appearing placebo (see section 2.1).

2.4 Methods for protecting against other sources of bias

MACS is a double-masked RCT. Thus selection bias is avoided. Parents and caregivers remain masked to treatment group until all follow-up assessments are completed, unless they specifically request unmasking. Thus outcome assessments for *MACS-5* will be unbiased.

2.5 Inclusion/Exclusion criteria

Inclusion criteria for *MACS*: a) 25-32 weeks gestation, b) received a completed course of ACS 14-21 days ago, c) are at continued increased risk of preterm birth, and d) all fetuses are alive at randomisation. Exclusion criteria for *MACS*: a) requiring corticosteroids secondary to a medical condition, b) contraindication to corticosteroids, c) clinical evidence of chorioamnionitis, d) known lethal anomaly, e) first course of ACS prior to 23 weeks, or f) previous participation in *MACS*. For *MACS-5*, all children are included if their mothers were randomised in centers participating in the 5-year follow-up.

2.6 Duration of treatment period

In *MACS*, women receive repeat courses of ACS (or placebo) every 14 days, from randomisation until either delivery or 33 weeks gestation, whichever is sooner. Children are assessed for neonatal morbidity prior to discharge from hospital, and then for mental and motor development (Bayley Scales of Infant development-II [BSID-II]), cerebral palsy, and vision and hearing impairment at 18-24 months of age.

In *MACS-5*, children have one visit at 5 years of age. All children are assessed for neuromotor (non-ambulatory cerebral palsy), neurosensory (blindness, deafness or need for visual and/or hearing aids), and neurocognitive (abnormal attention, memory, or behavioural skills) function, growth, and blood pressure. Children from English-speaking centres have assessments for intelligence and specific cognitive (visual motor, visual spatial and language) skills.

2.7 Frequency and duration of follow-up

All the assessments for *MACS-5* will be conducted at one visit when the children are 5 years chronological age (with a window of 4 months past the 5th birthday, to allow for some leeway in arranging appointments). Study centres will maintain regular contact with the families, by mail, telephone, or by outpatient visits, every 3-6 months, to ensure contact details are correct and thus prevent and minimise loss-to-follow-up. Centres use their judgement as to the best frequency of contact for individual mothers.

2.8 Primary and Secondary Outcomes

2.8.1 Primary outcome for *MACS-5*: The primary outcome, to be assessed in all children at 5 years of age, is death or survival with a severe disability in at least one of the following domains:

neuromotor (non-ambulatory cerebral palsy), neurosensory (blindness, deafness, or need for visual and/or hearing aids), or neurocognitive (abnormal attention, memory or behaviour) function. Although the principal goal of **MACS-5** is to evaluate neurocognitive function at 5 years of age, as most surviving children with neuromotor and neurosensory disability will be identified before this time, it is important that the primary outcome is comprehensive, thus categorising all children with severe disability as abnormal.

1. *Death* is defined as any death prior to 5 years of age
2. *Neuromotor disability* is non-ambulatory cerebral palsy, to be determined by physical examination and the Gross Motor Function Classification System (GMFCS).⁴⁴ The GMFCS is a functional as opposed to a physiological or anatomical measure of cerebral palsy based on the child's ability to achieve independent ambulation. Non-ambulatory cerebral palsy is cerebral palsy that is at a GMFCS level of III, IV or V.
3. *Neurosensory disability* is defined as blindness, deafness or the need for visual and/or hearing aids.
4. *Neurocognitive disability (abnormal attention, memory or behaviour)* is defined as an abnormal score on either the BRIEF-P^{45,46} or the CBCL^{47,48} (see 4i and 4ii below).

4i) *Behavior Rating Inventory of Executive Function (BRIEF)- Preschool version (BRIEF-P)*: Executive functioning incorporates four discrete but inter-related domains: cognitive flexibility, goal setting, attentional control and information processing. The BRIEF-P is used to assess and estimate executive function, attention and memory.^{45,46,51} It is the first standardized rating scale designed specifically to measure the range of behavioural manifestations of executive function in pre-school aged children. It provides an overall Global Executive Composite score, two broad Behavioral Regulation and Metacognition Indices, as well as individual scales assessing Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, and Monitor abilities. The psychometric properties include high internal consistency of .80 to .98, test-retest reliability of .82 to .88, and validity estimates from .64 to .90. Evidence supporting the valid interpretation of BRIEF-P scores is based on a) content of the items; b) convergence and divergence of BRIEF-P scores with those of other measures; and c) the internal structure of the BRIEF-P. Because no other scales existed similar to BRIEF-P, BRIEF-P was compared to other measures of behavioral functioning from other scales including the ADHD Rating Scale-IV, Preschool Version (ADHD-IV-P),⁵² the Child Behavior Checklist/1½-5 (CBCL-1½-5),^{47,48} and Behavior Assessment System for Children (BASC).⁵³ The overall Global Executive Composite score contributes to the primary outcome; individual scale scores are evaluated as other outcomes. An abnormal outcome is defined as a score that is 1.5 SD above the mean of the normative control sample; a higher score reflects abnormality.

4ii) *Child Behavior Checklist (CBCL)-Parent Form*: The Parent Form for ages 1½-5 years is used as an additional measure of both attention and behavioural skills.^{47,48} This is one of the most commonly used tools to measure behaviours in children and has been used in studies evaluating behaviours in preterm children. The psychometric properties include high test-retest reliability (0.95-1.0), inter-rater reliability (0.93-0.96), and internal consistency (0.78-0.97) and validity estimates from .55 to .75. The CBCL has undergone numerous studies to assess content and construct validity. Comparisons with clinical status (referred/non-referred) also support the validity of the instrument.^{47,48} The Total Behaviors Problems T scores contributes to the primary outcome. An abnormal outcome is defined as a score that is 1.5 SD above the mean of the normative control sample; again, a higher score reflects abnormality.

The CBCL and BRIEF-P will be made available in all of the languages that are required for the study.

2.8.2 Secondary outcomes for MACS-5:

Secondary outcomes to be assessed in all children include *measures of growth and blood pressure*:

- 1i) height (cm)
- 1ii) weight (kg)
- 1iii) head circumference (cm)
- 1iv) systolic and diastolic blood pressure (mmHg)

Secondary outcomes to be assessed in children in English speaking centres include *intelligence and specific cognitive skills (visual motor, visual spatial, and language skills)*: For logistical reasons, only English-speaking centers that have trained psychologists or psychometrists that are available to administer these more specific psychological tests will participate in these assessments:

2i) *WPPSI-III (Wechsler Preschool and Primary Intelligence Scale for Children-III edition)* is an individually administered clinical measure for assessing the intelligence of children aged 2 years 6 months to 7 years 3 months.^{52,53} The measure provides subtest and composite scores that represent intellectual functioning in verbal and performance cognitive domains as well as a composite score representing a child's general intellectual ability (IQ). Being the criterion test of preschool intelligence, the WPPSI-III has an overall reliability index of .96 and validity estimates from .78 to .89. Validity comparisons with numerous other measures have been conducted as have studies with various special groups including those with intellectual disability, developmental delay, language disorders (expressive and receptive), and with children at risk, with motor impairment and with Attention Disorder/Hyperactive Disorder (ADHD).^{54,55}

2ii) *Beery: The Developmental Test of Visual Motor Integration –5th edition (VMI)* is a sensitive, unbiased standardised instrument for measuring the development of visual and motor abilities and their integration. The VMI contains a series of 24 geometric forms that the child is required to copy until a criterion performance is reached.^{56,57} The psychometric properties include high overall reliability of .92, with strong internal consistency of .96, interscorer consistency of .94, and time sampling of .87. The VMI is considered the most valid instrument of its kind and is highly predictive in identifying children at risk for learning disabilities.

2iii) *Peabody Picture Vocabulary Test- 3rd Edition (PPVT-III)* is an individually administered, untimed, norm-referenced test that evaluates children's vocabulary knowledge development and is the hallmark tool for assessing receptive language abilities.^{58,59} The PPVT-III demonstrates high internal consistency of .95 and stability in time sampling of .91/.92. It is a valid screener with correlation coefficients for intellectual functioning (.90) and moderately predicts school achievement (.33-.80), language abilities (.42-.75), and written language (.77).⁵⁸

2.9 How will the outcome measures be measured at follow-up?

In MACS-5, clinicians who specialise in the follow-up of at-risk children are responsible for completing all assessments. They will determine the presence of cerebral palsy or other neurologic deficit, visual or hearing impairment (new or previously diagnosed), and undertake measures of growth (weight, height, head circumference) and blood pressure. The local research staff co-ordinate the visits and ensure that appropriately qualified clinicians are available to assess the children. Parents complete the BRIEF-P and the CBCL–Parent Form prior to or at the time of the visit, assisted by local research staff when necessary (see section 2.8.1).

For children in English-speaking centres, certified psychologists/psychometrists will test the children directly for the WPPSI-III, the Beery, and the Peabody Picture Vocabulary Test (see section 2.8.2).

2.10 Will health service research issues be addressed?

An economic analysis will be undertaken as part of *MACS* but is not planned as part of *MACS-5*.

2.11 Sample size and what is the justification for the assumptions underlying the power calculations

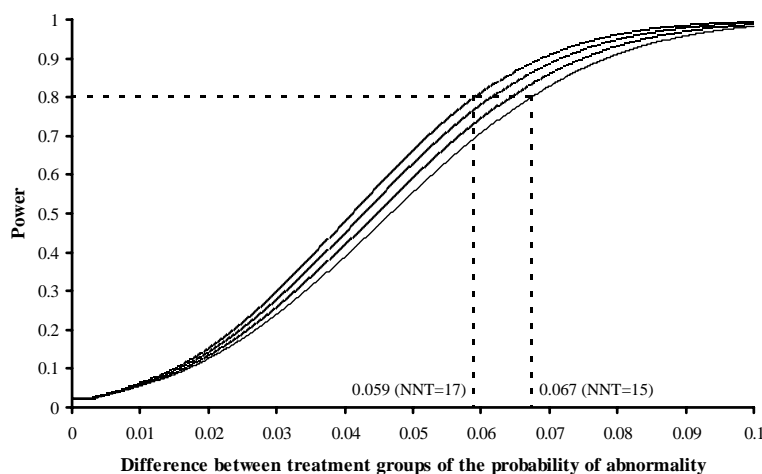
2.11.1 Sample size for primary outcome: death or survival with a severe disability in at least one of the following domains: neuromotor (non-ambulatory cerebral palsy), neurosensory (blindness, deafness, or need for visual and/or hearing aids), or neurocognitive (abnormal attention, memory or behaviour) function

The sample size of *MACS* is 1900 women. This sample size has an 80% power of finding a 33.3% reduction in the risk of RDS from 12% to 8% (2-sided Type I error of 5%), and greater than 80% power to detect an increase in the incidence of death or neurologic impairment from 5% to 9% at 18 to 24 months corrected age, if such a difference exists (2-sided Type I error of 5%).

We estimate that the children of 55% to 70% of mothers recruited to *MACS* will actually be followed to 5 years of age (or known to have died before this age) (N=1045-1330). This is based on an estimate that 70% to 90% of mothers in *MACS* will be recruited in centres participating in the 5 year follow-up, and that 80% of the children of these mothers will be followed to 5 years of age.

The primary outcome is a single binary variable, which is “abnormal” for a pregnancy if any child from that pregnancy meets any of the criteria given in Section 2.8.2. We do not know what the risk of an abnormal outcome will be in the placebo group at 5 years of age. However, the Cochrane Review of RCTs of a single course of ACS reports that in the treatment groups, the risk of neonatal death in babies treated after 1980 was 0.084 and the risk of long-term neurological abnormality among survivors was 0.057.⁷ Therefore, we assume that the risk of death or neurodevelopmental morbidity or abnormal cognitive skills (primary outcome) in the placebo arm at 5 years of age is 0.14. Four power curves for the primary outcome, assuming 55%, 60%, 65% or 70% follow-up, are given in Figure 2.11.1. A 2-sided type I error of 5% is used. The range of differences for which we would have an 80% power is 0.059 to 0.067, corresponding to a number needed to treat of 17 to 15. Since we expect to get more than 55%, and perhaps as much as 70%, follow-up at 5 years, we have adequate power for a difference in the range of 0.059 to 0.067, meaning that if physicians are willing to treat up to 15 or 17 patients to prevent an abnormal outcome, then we have sufficient power.

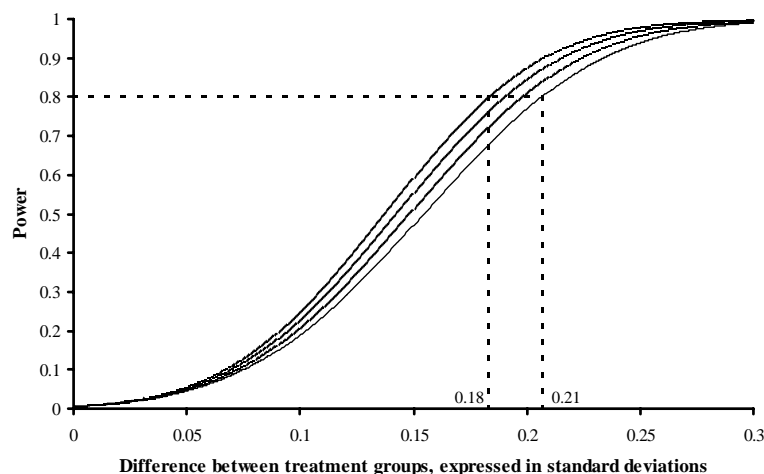
Figure 2.11.1 Power Curves for Primary Outcome



2.11.2 Sample size for secondary outcomes: growth measures and blood pressure

Four power curves for the secondary outcomes of growth measures and blood pressure, assuming 55%, 60%, 65% or 70% follow-up, are given in Figure 2.11.2. A 2-sided type I error of 5% is used. (A nominal value of $0.05/4 = 0.0125$ was used to control type I error because there are 4 outcomes in this category.) The range of differences for which we have an 80% power is 0.18 to 0.21 standard deviations.

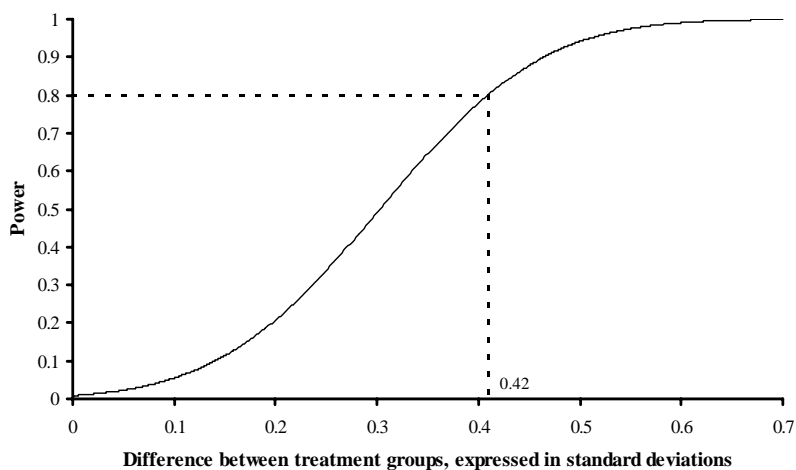
Figure 2.11.2 Power Curves for Growth Measures and Blood Pressure



2.11.3 Sample size for secondary outcomes: intelligence and specific cognitive skills

We estimate that over 300 women will be recruited in English-speaking centres and that approximately 250 of the children will be followed until 5 years of age. Thus the children of 250 women from participating English-speaking centers will be available to evaluate these outcomes. The power curve for this sample size is given in Figure 2.11.3. The difference for which we have an 80% power is 0.42 standard deviations. For the WPPSI, this corresponds roughly to absolute differences of 5-7 points on the scale.³² (A nominal value of $0.05/3 = 0.0167$ was used to control type I error because there are 3 outcomes in this category.)

Figure 2.11.3 Power Curves for Intelligence and Specific Cognitive Skills



2.12 Recruitment rate

MACS children begin turning 5 years of age in the spring of 2006 and we anticipate that the 5-year follow-up will be completed by December 2011.

2.13 Are there likely to be any problems with compliance?

In *MACS* we regularly assess the rate of compliance with the eligibility criteria and the timing of initial administration of the study drugs for each site and overall. These compliance reports are sent to centres every six months. The most recent overall compliance rate was 92.5%. Additionally, as part of the interim analysis, we looked in depth at the interval between each administration of study drug courses by patient and found a compliance rate of 80.1%.

2.14 Rate of loss to follow-up

We do not anticipate a big problem with loss to follow-up for *MACS-5*, as the follow-up rate for the 18-24 month assessments is 98.6% for children born in 2001. Centres are asked to contact the mothers every 3-6 months, using their judgement as to the best frequency for individual mothers. Only centres committed to the 5-year follow-up are invited to participate in *MACS-5*.

Although this will be the first study of this magnitude to follow children to 5 years of age in so many countries, other studies have also achieved high rates of follow-up for children into school age. Recently, Yeh reported on the outcome at 8 years of age on a cohort of infants who were in their original dexamethasone trial, of whom 61% survived to school age.¹⁵ Of these infants, they were able to report on 92%, reflecting an 8% lost-to follow-up rate. We have based our power calculations on an assumption that we would have outcome information on 55% - 70% of the original sample.

2.15 Analysis

2.15.1 Analysis of primary outcome

Since the pregnancies used for the 5-year follow-up will be a sub-sample of the original *MACS* pregnancies, they will be compared to those not included with respect to the baseline variables: premature rupture of membranes (PROM), multiple birth (1 fetus versus 2+) and gestational age at randomisation. In addition, in the sample used for the 5-year follow-up, the treatment arms will be compared with respect to the same baseline variables. Fisher's exact tests will be used for PROM and multiple birth, and t-tests (or Mann-Whitney U test, if data are skewed) for gestational age. A two-sided Type I error of 0.05 will be used.

The primary outcome will be compared between treatment arms using a Fisher's exact test with a two-sided Type I error of 0.05. The relative risk and its corresponding 95% confidence interval will be calculated. In addition, a logistic regression analysis will be performed to compare treatment arms while controlling for PROM, multiple birth and gestational age. A multi-level model will be applied to the data using WinBUGS (version 1.4.1, see www.mrc-bsu.cam.ac.uk/bugs/welcome.shtml) to allow for random effects (intercept and slope) due to centres while also controlling for baseline variables. Using a similar analytic approach, a supportive analysis as described in the above four sentences will compare treatment arms with respect to the four domains comprising the primary outcome (death, neuromotor disability [non-ambulatory cerebral palsy], neurosensory disability [blindness, deafness, or need for visual and/or hearing aids], and abnormal cognitive score). Since pregnancy is the unit of analysis, if any child of a multiple birth has an abnormal outcome, the pregnancy will be considered to have had an abnormal outcome. If some of the data are missing, the child will only be considered to have an abnormal outcome if he or she is abnormal based on the data that are not missing.

2.15.2 Analysis of secondary outcomes: growth measures and blood pressure

These secondary outcomes are continuous and will be compared between treatment arms using two-sample t-tests. Multiple linear (least-squares) regression will be used to adjust for the baseline variables. Transformation or ranking procedures will be used if the data are observed to be skewed. A nominal Type I error of 0.0125 will be used to maintain an overall Type I error of 0.05. Since pregnancy is the unit of analysis, the worst value for the children of multiple births will be used.

2.15.3 Analysis of secondary outcomes: intelligence and specific cognitive skills

Since the pregnancies used for these outcomes will be an even smaller sub-sample of the original *MACS* pregnancies, they will be compared to those not included with respect to the baseline variables PROM, multiple birth and gestational age at randomisation. In addition, in the sample used for these outcomes the treatment arms will be compared with respect to the same baseline variables. Fisher's exact tests will be used for PROM and multiple birth and t-tests (or Mann-Whitney U test, if data are skewed) for gestational age. A two-sided Type I error of 0.05 will be used.

These secondary outcomes are continuous and will be compared between treatment arms using two-sample t-tests. Multiple linear (least-squares) regression will be used to adjust for the baseline variables. Transformation or ranking procedures will be used if the data are observed to be skewed. A nominal Type I error of 0.0125 will be used to maintain an overall Type I error of 0.05. Since pregnancy is the unit of analysis, the worst value for the children of multiple births will be used.

2.16 Frequency of analyses?

There will be one final analysis, which will take place after all the 5-year assessments have been completed. One interim analysis of initial *MACS* outcome data was undertaken after data had been received for the first 800 women enrolled. No interim analyses of *MACS-5* data are currently planned.

2.17 Are there any planned subgroup analyses?

No subgroup analyses are planned.

3. DETAILS OF TRIAL TEAM

3.1 Trial Management

MIRU will coordinate *MACS-5* in close collaboration with the principal investigator. A trial coordinator will be responsible for overseeing the data management and the day-to-day activities.

3.2 Applicants

The principal applicant, Asztalos, is an academic neonatologist and the Medical Director of one of the larger follow-up programs in Canada with considerable experience in neurodevelopmental follow-up in large scale neonatal RCTs including the Trial of Indomethacin Prophylaxis in Preterms (TIPP), Caffeine for Apnea of Prematurity (CAP), and Preterms in Need of Transfusion-Outcome Study (PINT-OS). She is a co-investigator/co-applicant for PINT-OS and for the 5 year follow-up of the CAP trial. She is on the Steering Committees as the individual responsible for the follow-up component for these trials as well as for *MACS* and the Twin Birth Study.

The co-principal applicants include Rovet, Sananes, Murphy, and Hannah. Rovet is a Senior Scientist in the Brain and Behaviour Program at the Hospital for Sick Children, Toronto, Canada and has done extensive research in the neuropsychological follow-up of congenital hypothyroidism and other prenatal thyroid hormone insufficiencies. Rovet and Asztalos have worked extensively, since 2000, on projects related to hypothyroxemia of prematurity, which have involved 4-5 year follow-up of

preterm children. Sananes is a senior psychologist at the Hospital for Sick Children with experience in long term psychological studies involving preterm children and children with major learning difficulties. Murphy is the principal investigator of the initial **MACS** trial and Hannah has extensive experience in international RCTs.

The remaining co-applicants include Ross, Ohlsson, Saigal, Kelly, Matthews, Delisle, Amankwah, Willan, Lee, Gafni, and a consumer member, Guselle. The principal applicant Asztalos is responsible for the overall progress and timely completion of **MACS-5**, is the principal liaison with the centres in the field, and responds to questions regarding the protocol. Rovet and Sananes are responsible for reviewing back translations of the BRIEF-P to ensure that the translations are valid prior to their use in participating countries. They are also responsible for the collection and interpretation of the psychological data and for providing advice to field testers with respect to the psychological assessments being used.

Hannah assists with advice on the overall management of the trial, including liaison with study centres. Ohlsson, Kelly, Lee, and Saigal assist in providing advice from the neonatal and neurodevelopmental perspective. Murphy is instrumental in maintaining a liaison with the original study centres and the obstetrical contacts, along with Amankwah and Delisle. Matthews provides input at the level of molecular and developmental neuroscience. Willan is responsible for the statistical analyses and works closely with the principal and co-principal investigators. Gafni provides input on health economic issues if needed and Guselle provides input from a consumer perspective. All applicants are responsible for encouraging high rates of recruitment to the initial study, maintaining compliance with the interventions and tests, and for encouraging high rates of follow-up.

3.3 Committees

The Steering Committee, which consists of all the applicants and the trial research staff, meets every 3-4 months. This committee is responsible for decisions related to the organisation and conduct of the trial. A smaller working group, including Asztalos, Murphy, the MIRU Director, the MIRU Research Manager, and the trial staff, meets weekly to oversee the day-to-day running of the study.

An independent Data Safety Monitoring Board (DSMB) is in place. Members are: *Professor Michael B. Bracken* (Chair of DSMB), Center for Perinatal Pediatric and Environmental Epidemiology, Yale University School of Medicine; New Haven CT, USA; *Dr Patricia Crowley*, Dept of Obstetrics & Gynaecology; Coombe Women's Hospital, Dublin, Ireland; *Professor Allan Donner*, Chair, Department of Epidemiology and Biostatistics; University of Western Ontario, London ON, Canada; *Dr Lelia Duley*, Resource Centre for Randomised Trials; Institute of Health Sciences, Oxford, UK; *Dr Jon Tyson*, Center for Population and Evidence-Based Medicine; University of Texas. During **MACS-5**, the DSMB will be asked to review data or reports, internal or external to **MACS**, if the Steering Committee has concerns; otherwise, there is no plan for the DSMB to review data for **MACS-5**.

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