This supplement contains the following items:

1. Original protocol, final protocol, summary of changes
2. Original statistical analysis plan, final statistical analysis plan, summary of changes

Childhood Cognitive Function in a Birth Cohort after a Randomized Trial of Antenatal Corticosteroids: the ALPS Neurocognitive Follow-Up Study

Protocol

ALPS FSN

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1 Introduction

1.1 Study Abstract

In a recently completed trial, Antenatal Late Preterm Steroids (ALPS): A Randomized Placebo-Controlled Trial, conducted between 2010-2015 by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network, antenatal betamethasone treatment of pregnant women at risk for late preterm delivery was found to decrease the primary neonatal respiratory composite outcome of treatment in the first 72 hours and other related outcomes.[1] These findings have already changed practice in obstetrics. However, there is strong interest in the community to ascertain whether neurodevelopmental outcome is reassuring. Therefore a follow-up study is proposed of the index children born to women who participated in the MFMU ALPS trial.

In addition to the respiratory benefit there was an increase in neonatal hypoglycemia in the betamethasone arm. Although the hypoglycemia appeared to be self-limited and was not associated with a longer neonatal length of stay, it is important to follow up with these infants because of the association between prolonged hypoglycemia and neurodevelopmental outcome. This follow-up study also allows for the evaluation of whether hypoglycemia and earlier gestational age within the late preterm to term period have long-term consequences on neurodevelopment.

1.2 Primary Hypothesis

Children of mothers at risk for late preterm delivery who were randomly assigned to antenatal betamethasone will have a lower frequency of cognitive function one standard deviation below the mean at age 6 years compared with the children of mothers who were randomly assigned to a matching placebo. Cognitive function will be measured by the Differential Ability Scales - 2nd Edition (DAS-II) core components of the general conceptual ability (GCA) that includes verbal ability, non-verbal reasoning ability, and spatial ability.

1.3 Purpose of the Study Protocol

This protocol describes the background, design and organization of the follow-up study and may be viewed as a written agreement among the study investigators. The Network Advisory Board reviews the protocol. Before recruitment begins, the protocol is approved by the NICHD MFMU Network Steering Committee and the Institutional Review Board (IRB) of each clinical center. Any changes to the protocol during the study period require the approval of the Steering Committee and the IRBs. A manual of operations supplements the protocol with detailed specifications of the study procedures.

2 Background

2.1 Introduction

It is well-established that late preterm (34-36 weeks gestation) birth leads to increased neonatal morbidity, primarily respiratory, compared with delivery at term (≥37 weeks).[2-5] Several studies have demonstrated that morbidity and mortality increase with decreasing gestational age below 39 weeks gestation.[3,5,6] It is also believed that many late preterm morbidities are transient, resolving after discharge. Because late preterm infants were only relatively recently identified as an at-risk group, their long term outcomes are poorly defined, particularly as they relate to neurodevelopment.[7] In 2016 the results of the Antenatal Late Preterm Steroids (ALPS) trial were published.[1] The ALPS trial showed that antenatal corticosteroids decreased several respiratory morbidities including the composite primary outcome of requirement of respiratory support, transient tachypnea of the newborn, bronchopulmonary dysplasia, and the need for immediate resuscitation and postnatal surfactant in offspring of participants exposed to betamethasone. However, the ALPS trial also found a higher rate of hypoglycemia in infants of women who were randomized to receive betamethasone compared with placebo. With the subsequent recommendations from the Society for Maternal-Fetal Medicine and the American College of Obstetricians and Gynecologists, late preterm administration of corticosteroids is becoming the new standard of care.[8,9] Long-term effects of late preterm steroid exposure are poorly understood because administration in this period is newly recommended, and clinical data are scant on the effect of late preterm steroid exposure on the developing brain. However, emerging evidence suggests that late preterm birth has an a priori risk of neurocognitive delay.[10-12] The purpose of this follow-up study is to assess the potential long-term risk or benefit of antenatal corticosteroids on neurocognitive functioning and the long-term consequence of hypoglycemia and earlier gestational age within the late preterm to term period.

2.1.1 Late Preterm Birth and Neurodevelopment

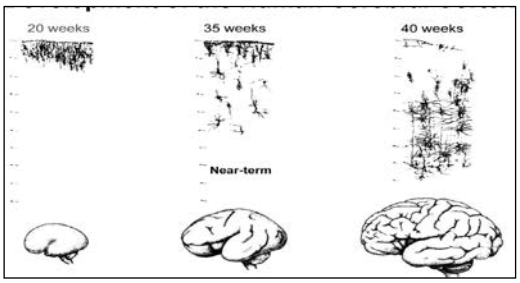
The data on neurodevelopment after late preterm delivery are limited primarily because these infants were only recently recognized as a high risk group.[13] However, since 2006 there have been several studies suggesting that neuro-development is negatively altered by late preterm birth.[11,12,14-16] The available observational cohort studies are limited in that some have used proxies, such as school grades and performance, rather than rigorous methods, such as IQ scores, to measure neurodevelopment; thus, much work is needed in this area. Morse and colleagues found an increase in developmental delay and in school non-readiness in a large cohort of "healthy" former late preterm children in Florida.[12] Former late preterm infants were designated as "healthy" on a review of birth certificate data if they were discharged by day 3. These children were more likely to have developmental delay and require special needs education when compared with children born at term (Table 1).

Table 1. Early School Age Outcomes of Late Preterm Infants[12]

Early school-age outcome	Healthy Late Preterm (%)	Term (%)	Adjusted RR
Developmental delay/disability	4.24	2.96	1.36 (1.29-1.43)
Disability in pre-kindergarten	7.40	6.60	1.10 (1.05-1.14)
Not ready to start school	5.09	4.40	1.04 (1.00-1.09)
"Special needs" education	13.30	11.88	1.10 (1.07-1.13)
Retention in kindergarten	7.96	6.17	1.11 (1.07-1.15)
Suspension in kindergarten	1.80	1.22	1.19 (1.10-1.29)

Similarly, Williams and Jain found an increase in school failure among former late preterm children compared with their term counterparts.[15] After adjusting for maternal and child characteristics, they found a significant increase in failure of reading, math, and English/language arts for former late preterm children compared with those born at term. Using linked national registries from Norway, investigators were able to demonstrate increased rates of cerebral palsy (RR 2.7, 95% CI 2.2-3.3) and psychosocial disorders (RR 1.5, 95% CI 1.2-1.8) in children born from 34 0/7 to 36 6/7 weeks compared to those born at ≥37 weeks.[11]

Figure 1. Development of the human cerebral cortex



A review of studies of school outcome, cognitive functioning and behavior problems in former moderate and late preterm infants (which included both the study by Morse et al. and the Norwegian study) concluded that overall more school problems, less advanced cognitive functioning, more behavioral problems and psychiatric problems occur in moderate and late preterm infants.[17] However, in many of the studies, the data were not presented separately for moderate versus late preterm. In those studies that assessed IQ in childhood, two found no difference in late preterm versus term children[18,19] whereas another found worse IQ only in former late preterm infants with a complicated neonatal course.[20] However, Talge et al did find that the proportion of children at age 6 with IQ<85 was higher in the late preterm group than in the term group, after adjusting for potential confounders (adjusted OR 2.35, 95% CI 1.2 -4.61).[18]

It is accepted that a late preterm brain is less mature with important processes such as formation of gyri and sulci as well as differentiation and proliferation occur near the end of gestation (Figure 1). While less is known about whether exposure to betamethasone enhances brain maturity, what is recognized is that glucocorticoid exposure can promote maturation of the brain my increasing myelination and functional maturation in an animal model.[21,22]

2.2 Steroids and Neurodevelopment

A single course of antenatal corticosteroids has been shown consistently to either have no effect or improve childhood neurocognitive outcomes over no steroids for infants in pregnancies at risk of preterm delivery.[23,24] The landmark clinical trial by Liggins and Howie describing the benefits of antenatal corticosteroid administration included women at risk for late preterm delivery from 24-36 completed weeks of gestation.[25] In 1972 when the study was first published, 28 weeks gestation was considered the limit of viability. In fact, there were no survivors enrolled in the landmark trial at <26 weeks gestation. Therefore, this study was skewed towards moderate and late preterm pregnancies, including those at risk from 34-36 weeks. The study has rigorous long term outcome data, including 30-year neurodevelopmental follow-up.[24] The investigators found no difference in intelligence using the Weschler scales, memory and attention, psychiatric illness, or quality of life by steroid exposure. The median gestational age at delivery for follow-up participants initially in the betamethasone group was 35 weeks, 0 days (IQR 33 weeks, 4 days to 38 weeks 0 days), similar to participants in the ALPS trial. These findings were most recently described in a meta-analysis by Sotiriadis et al, which included randomized and non-randomized prospective studies of women delivering preterm who received a single course of antenatal corticosteroids. While most studies included steroid exposure at up to 34 weeks, this analysis[23] included the initial Auckland cohort from Liggins and Howie[25] with steroid exposure up to 36 6/7 wks. The authors concluded that antenatal corticosteroids decreased the risk of severe disability and increased intact survival.[23] Clinical studies of multiple course steroids have generally found worse neurodevelopmental outcomes compared with those who had a single course and delivered at term, but multiple course steroids have fallen out of favor in most of the world.[26,27]

Despite reassuring clinical data, there is older evidence for potential harm derived from animal data. Huang and colleagues showed a decrease in cerebral length and depth, but not in whole-brain weight in sheep delivered after a single course of antenatal corticosteroids.[28] Other investigators showed that a single dose of dexamethasone administered to pregnant rats can disrupt brain cell differentiation.[29] Some experts however raise caution when evaluating the effect of antenatally administered steroid in animal models since the timing of peak growth in the fetal brain varies by the choice of model.[30] While animal models have suggested a relationship between antenatal corticosteroids and adverse neurodevelopment, this relationship has never been noted from human randomized clinical trials evaluating a single course of steroids.

Clinical data on neurodevelopment after late preterm steroids is currently limited to the initial Auckland cohort.[25] However, there are more recent data from a randomized trial of exposure to open-label betamethasone compared with usual care in women undergoing term scheduled cesarean, the Antenatal Steroid for Term Elective Cesarean Trial (ASTECS).[31] The trial's follow-up study (ASTECS-2) was not pre-planned and used questionnaires completed by parents as well as school assessment data.[32] At the time of assessment, the children were ages 8-15 years; data were available for 407 children (41% of the offspring from the trial). No differences were observed between the offspring of mothers randomized to antenatal betamethasone compared with the offspring of mothers randomized to usual care in the total difficulties score of the strengths and difficulties questionnaire (SDQ) (mean of 8.03±6.83 compared with mean of 7.85±6.49, respectively) or in any of the subscales. No significant differences were observed between the betamethasone and usual care groups for standard assessment tests, with level 4 achievement observed in 86% and 88% for mathematics, 91% and 94% for science, and 87% and 93% for English, respectively. The only difference in outcomes between groups was in the school assessment of quartile by ability, a subjective measure, which showed a higher precent of children in the lower quartile of academic ability in the betamethasone group (18%, compared with 9% in the usual care group; p=.03). The authors of the study concluded *"no adverse effect was seen on health, behaviour and academic achievement of children born following a single course of antenatal betamethasone at term."* Despite the lack of difference in multiple cognitive measures and the risk of a Type 1 error with multiple comparisons, this isolated finding has been used to suggest a signal for harm after steroid exposure at term.

2.3 Hypoglycemia and Neurodevelopment

While a link between hypoglycemia and brain injury exists, there is no agreement on a value that defines pathologic hypoglycemia, nor is there a value below which the brain is absolutely affected.[33] Low neonatal glucose concentrations can lead to brain injury via the glucose transporters, namely GLUT-1 and GLUT-3.[34] In cases where there is deficiency of these transporters, the brain switches to alternate pathways to create fuel, which can lead to brain injury.[35] These controversies were addressed in a NICHD Workshop held in 2008. The group acknowledged that many previously defined thresholds for hypoglycemia do not necessarily reflect "dangerous" levels. Participants also recognized that as many as 5% to 15% of normal newborn infants will have a low plasma glucose, usually noted as <40 to 45 mg/dL, and called for more research to define pathologic hypoglycemia and establish normograms.[33]

The ALPS trial found a higher frequency of hypoglycemia (defined as <40 mg/dl) in infants of women who were randomized to receive betamethasone compared with placebo, 24.0% versus 15.0% (RR 1.60, 95% CI 1.37-1.87).[1] Exposure to betamethasone was also associated with shorter special care nursery stays. Unpublished data also show that infants with hypoglycemia had short randomization to delivery times compared with those without hypoglycemia: 29.7 hours (IQR 16.8-48.8) versus 34.6 hours (IQR 14.5-141.3). The data collected were only binary; information on actual glucose levels was not captured.

2.4 Rationale for the Follow-Up Study

It is unknown whether late preterm antenatal betamethasone treatment is associated with long-term neurocognitive functioning. Some animal models suggest potential for harm since the brain is rapidly developing during this period. However, both limitations in animal models and reassuring clinical data suggest that the potential for adverse outcomes related to betamethasone treatment are unlikely. The ALPS cohort provides a unique opportunity to assess the potential long-term risk or benefit of antenatal corticosteroids in the late preterm period on neurocognitive functioning and whether there are any long-term consequences of what is believed to be transient neonatal hypoglycemia.

3 Study Design

3.1 Primary Research Question

This study will address the following primary research question: In women at risk for late preterm delivery, does administration of antenatal betamethasone treatment in the late preterm period of 34 to 36 weeks gestation have an effect on the cognitive function of their children aged 6 years? Cognitive function will be measured by the DAS-II core components of the general conceptual ability (GCA) that includes verbal ability, non-verbal reasoning ability, and spatial ability.

3.2 Secondary Research Questions

This study will address the following secondary research questions.

- Does antenatal betamethasone at 34 to 36 weeks gestation compared with placebo have an effect on any sub component of the DAS-II (verbal ability, non-verbal reasoning ability, and spatial ability)?
- Does antenatal betamethasone at 34 to 36 weeks gestation have an effect on the frequency of screening positive on the SRS for autism spectrum conditions at age 6?
- Does antenatal betamethasone at 34 to 36 weeks gestation have an effect on childhood behavioral and emotional problems as measured by the child behavior checklist at age 6?
- Does antenatal betamethasone treatment at 34 to 36 weeks gestation compared with placebo have an effect on child height, weight, and BMI at age 6?
- Is neonatal hypoglycemia, and its duration and severity, associated with cognitive function in 6 year old children?
- Does neonatal hypoglycemia mediate a treatment effect of antenatal betamethasone on cognitive function?
- Is earlier gestational age at delivery within the late preterm to term period associated with cognitive function in 6 year old children? And, if such an association is present, does treatment with antenatal betamethasone modify the association?
- Is small birthweight for gestational age or large birthweight for gestational age associated with cognitive function in 6 year old children (among those from the placebo group)?

3.3 Design Summary

This study is a follow-up cohort study of the ALPS trial. Assuming 82%-83% follow-up, approximately 2000 children whose mothers were enrolled in ALPS will undergo one two-hour study visit in which the DAS-II will be administered. Information about the child's health will be obtained, and the Social Responsiveness Scale and Child Behavior Checklist will be administered.

3.4 Eligibility Criteria

3.4.1 Inclusion Criteria

1. Mother enrolled in ALPS
2. Mother enrolled at one of the thirteen centers that participated in the MFMU Network for the 5-year cycle 2011-2016 and agreed to take part in the follow-up study.

3. At least six years of age; the intention is to enroll all children at age six; however, if a child is found at a later age he/she will still be eligible

3.4.2 Exclusion Criteria

1. Death of the child
2. Refusal of the family or inability of the child to take part in a study visit at the clinical center or at home

3.5 Informed Consent Criteria

Written informed consent must be obtained from the parent or guardian as well as the child's assent to participate, as required by the local IRB. Study staff will explain in concrete, age-appropriate terms the purpose of the project, what the child will be asked to do, and what procedures they will undergo. The child will be allowed to ask questions about the process. If the child provides assent to participation, the research staff will ask the child to write his/her name on a separate form.

Each center will develop its own consent forms according to the requirements of its own institutional review board using the model consent forms in Appendix B. Each center will also develop its own patient research authorization documents, as required by the HIPAA Privacy Rule, following the guidelines of its own institution. A copy of the signed consent form(s) will be provided to the parent or guardian and a copy of the assent form to the child.

If feasible, families who are not fluent in English will be enrolled by a person fluent in their language. Both verbal and written informed consent and authorization will be obtained in that language; if this is not possible, the child will be excluded.

The parents/guardians will also be asked if they are willing to be contacted at a later date for a potential longer-term follow-up study of their children. A check box will be provided on the consent form that will need to be checked separately for permission to contact study participants at a later date.

4 Study Procedures

4.1 Locating and Contacting Participants

Locating and contacting participants will be conducted through the parallel ALPS FS Pulmonary study. Each center will be provided with a list of children (identified by their unique Network code) whose mothers were in the ALPS trial, agreed in the informed consent for the primary trial to future contact and who would satisfy the inclusion criteria once they reach six years of age. Mothers who declined future contact during the ALPS trial may also be contacted according to the regulations of the center's IRB. Study staff will start with and give priority to the oldest children first using contact information available from the original study, including identifiers such as social security number from the medical records. Other sources will include services the family may be using, as well as hospital admissions and county agencies. Public search software can also be used. An attempt will be made to locate as many women as possible within the first year of the study, even if their children are not yet old enough to participate.

4.2 Screening for Eligibility and Consent

Once a potentially eligible child is located, research study staff will confirm the identity of the child, explain the purpose of the pulmonary follow-up study to the parent(s) or guardian and invite the family to participate. Any questions will be answered. Interested families will be asked to attend a single follow-up visit with their index child at the original ALPS clinical center. A more convenient center may be chosen if the family has relocated since the delivery of the index child. If the family plans on participating in the pulmonary follow-up, the neurocognitive follow-up can also be explained to the parent or guardian, and they can be invited to participate in the neurocognitive follow-up.

- Initial verbal consent to participate is requested using a standardized script.
- The visit will be scheduled during the year that the child is six.
- The neurocognitive follow-up should take place following the pulmonary assessment but after a sufficient rest and food, so that the cognitive testing is not adversely affected by the prior spirometry testing. It is also permitted to conduct the neurocognitve assessment before the pulmonary assessment depending on the availability of the examiner. Alternately, the child can return for a second visit to complete the neurocognitive follow-up.
- If a family has moved and is unwilling to travel, a home visit may be arranged.

4.3 Baseline Procedures

As an extension to the ALPS trial, additional details related to neonatal hypoglycemia will be abstracted from the neonatal medical records. Glucose values and the duration, severity, and treatments for hypoglycemia will be obtained. Height and weight are measured as part of the parallel ALPS FS Pulmonary study.

4.4 Study Visit Procedures

The neurocognitive follow-up visit is expected to take approximately two hours. The following events and procedures will be conducted specifically for this during the single study visit:

- Written informed consent (and assent if appropriate) obtained.

- A break that can include a meal (if the neurocognitive assessment is conducted on the same day as the pulmonary follow-up).
- Administration of the DAS-II by a study certified psychologist
- The Gross Motor Function Classification System

While the DAS-II is being administered to the child, the parent or guardian will complete the following questionnaires.

- Questions about the index child's health
- Social Responsiveness Scale (SRS) for autism screening. Any child screening positive will be referred for more formal clinical evaluation.
- Child Behavior Checklist (CBCL).

4.5 Patient Management and Follow-Up

Approximately two to four weeks following the visit, the parents/guardians will be sent a letter with pertinent neurodevelopment data as follows:

- DAS-II score and the range in scores that are within age expectation for learning/cognitive abilities.
- SRS score and the range in scores that are within age expectation for social abilities.
- CBCL score and the range in scores that are within age expectation for social and behavioral abilities

The letter will inform the parent/guardian that the assessments were for the purposes of research, and do not provide a complete assessment of the child's learning and emotional strengths and weaknesses and recommend that is the parent/guardian has any concerns that they can share the results with their child's school, psychologist, or physician for planning an evaluation that fits their child's individual needs.

4.6 Adverse Event Reporting

Detailed information concerning adverse events assessed to be definitely, probably or possibly related to study procedures will be collected and evaluated throughout the conduct of the study. Death or any life threatening event will be reported regardless of relatedness to study procedures. The NICHD Project Scientist and the BCC will be informed within 24 hours of being notified of any death or life-threatening event of an enrolled child by secure e-mail/phone/fax. Adverse events will be reported to the Data and Safety Monitoring Committee.

4.7 Study Outcome Measures and Ascertainment

4.7.1 Primary Outcome

The primary outcome is defined as general conceptual ability score (GCA) < 85 (one standard deviation below the mean) evaluated on the DAS-II core components that include verbal ability, non-verbal reasoning ability, and spatial ability at 6 years of age or greater. The DAS II GCA correlates well with full scale IQ as measured by the WPPSI (0.89).

4.7.2 Child Secondary Outcomes

1. Sub components of the DAS-II (verbal ability, non-verbal reasoning ability, and spatial ability)
2. Screening positive on the SRS for autism spectrum conditions (Score ≥ 65)

3. Score on GMFCS
4. Child Behavior Checklist subscales

5 Statistical Considerations

5.1 Data Relevant to the Primary Outcome

Talge et al published an analysis of 168 former late preterm (34-36 weeks of estation at birth) children matched on birth weight z-score with 168 term children.[18] The children were followed up with neurocognitive testing at age 6 using the Wechsler Intelligence Scale for Children Revised. Twenty-one percent of the children who were born in the late preterm period had an IQ less than 85 compared with 12% in the term group. About 84% of the infants in the ALPS trial were born late preterm. Therefore it is reasonable to assume that the proportion of children in the placebo group with IQ < 85 is about 20%.

5.2 Sample Size and Power

The ALPS clinical trial included 2831 mother-infant pairs. After excluding those who did not consent to future contact, deaths, and sites no longer participating in the MFMU Network, and assuming an enrollment rate of 82-83%, the available sample size for this study is 2000. These mothers already consented to future contact, and a previous unplanned follow-up study (Progesterone Follow-up) achieved a similar rate.[36]

With a sample size of approximately 1000 per group and a two-sided type I error of 5%, there is 83% power to detect a 25% reduction in the proportion of children with DAS GCA < 85 in the betamethasone group (from 20% in the placebo group to 15% in the betamethasone group) There is 76% power to detect a 25% increase in the proportion of children with DAS GCA < 85 in the betamethasone group (from 20% in the placebo group to 25% in the betamethasone group).

5.3 Analysis Plan

The primary analysis and secondary analyses involving dichotomous outcomes will consist of a comparison of binomial proportions. The relative risk and confidence interval will be reported. All analyses that examine whether prenatal treatment with betamethasone (vs. placebo) confers long-term benefit will follow the intention-to-treat approach. Betamethasone treatment was randomly assigned and was successful in producing well-balanced groups with regards to baseline patient characteristics. However, a comprehensive comparison of the baseline attributes of the patient treatment groups will serve as a basis for understanding whether any baseline variables should be examined as potential confounders in multivariable models. Socioeconomic status influences child cognitive function, therefore the analysis will be adjusted for maternal education or medical insurance status. An evaluation of treatment by center will be included and analyses will account for center, either by adjusting for center in a multivariable model or by using mixed models.

For logistic regression models, the Hosmer-Lemeshow test will assess goodness of fit and over-dispersion using the tolerance limits on the ratio of the Pearson Chi-square to its degrees of freedom. If the model assumptions are violated, the robust estimate of the covariance matrix of the estimates will serve as the basis for confidence intervals and tests of significance. Partial Wald or score tests will be used to test covariate effects and Madalla's R^2 used to describe the strength of effect for each covariate.

General linear models including analysis of variance will be used to test for differences in continuous outcomes. Model assumptions such as normally distributed residuals will be tested.

5.3.1 Non-participation and loss to follow-up

There are several levels of missing outcome defined: 1) inability to contact the family 2) refusal of consent to participate and 3) loss to follow-up. Baseline characteristics will be compared between participants and non-participants. Loss to follow-up will be defined for those children where consent for

the study has been obtained but it was not possible to administer the DAS-II. A sensitivity analysis including participants lost to follow-up will be applied with different assumptions regarding their outcome, to determine whether the results are robust.

6 Data Collection

6.1 Data Collection Forms

Data will be collected on standardized forms on which nearly all responses have been pre-coded. Each form is briefly described below:

- AF06 Study Visit Form includes information regarding informed consent and the child's health and motor function.
- AF07 DAS-II Form includes all scores for each component of all three core components of the general conceptual ability (GCA) that includes verbal ability, non-verbal reasoning ability, and spatial ability.
- AF08 Social Responsiveness Scale
- AF09 Child Behavior Checklist
- AF12 Adverse Event Form

The following forms will be used to collect data regarding neonatal hypoglycemia:

- LP17 Hypoglycemia Form includes information regarding duration, severity, and treatments for neonatal hypoglycemia
- LP18 Glucose Log includes neonatal glucose measurements

6.2 Web Data Entry System

For this protocol, web-based data entry screens corresponding to the study forms listed above will be developed and maintained by the staff of the BCC. Clinical center staff will enter data into the MySQL database located at the BCC through a web-based data management system (MIDAS). A Users' Manual documenting this system is provided to the centers by the BCC.

6.3 Centralized Data Management System

Daily data conversions from the MySQL database create up-to-date SAS datasets. Data are reviewed weekly using edit routines similar to those implemented on-line during data entry, as well as additional checks for data consistency within or across forms. A database of resulting potential data problems is generated in MIDAS for initial review by BCC staff, who will then evaluate the comments keyed in association with edits on missing or unusual values. Valid edits will be flagged in MIDAS for resolution at the clinical centers.

At regular intervals, specialized data reviews comparing data availability and consistency across forms are run by the BCC staff on the entire database or on a specific subset of data. These reports are also submitted to the centers for correction or clarification.

An audit trail, consisting of all prior versions of each data form as entered in the computer for each participant, is maintained so that the succession of corrections can be monitored.

6.4 Performance Monitoring

The BCC will present regular reports to the ALPS Neurocognitive Follow-Up Study Subcommittee and the Steering Committee. These include:

- Monthly Enrollment Reports- reports of the number of children enrolled by month and clinical center are provided monthly to the ALPS FS Neurocognitive Subcommittee and all other members of the Steering Committee. Weekly or bi-weekly reports are provided electronically if needed.
- Quarterly Steering Committee Reports- reports detailing enrollment, data quality, incidence of missing data and adherence to study protocol by clinical center, are provided quarterly to the ALPS FS Neurocognitive Subcommittee and all other members of the Steering Committee.

7 Study Administration

7.1 Organization and Funding

The study is funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). The study is conducted by the NICHD Maternal-Fetal Medicine Units (MFMU) Network, consisting of fourteen clinical centers, the Biostatistical Coordinating Center (BCC) and the NICHD, and is administered under cooperative agreements between each of the centers and the NICHD. Each of the funded institutions is represented by a Principal Investigator. A complete description of the organization of the MFMU Network is provided in the MFMU Network Policy Manual.

For this study, 13 of the 14 centers that were part of the Network from 2011 to 2016 will participate, which includes three centers that are not currently in the MFMU Network.

7.1.1 MFMU Clinical Centers

Each of the funded institutions is represented by a Principal Investigator. A complete description of the organization of the MFMU Network is provided in the MFMU Network Policy Manual. The participating Principal Investigators of the MFMU Network clinical centers have agreed to abide by the study protocol, to have comparable staff, facilities and equipment and to ensure the proper conduct of the study at each of their centers including: recruitment and study procedures as specified in the protocol, accurate data collection and the transmission of information to the Steering Committee.

7.1.2 Biostatistical Coordinating Center

The BCC is responsible for all aspects of biostatistical design, data management, interim and final statistical analyses, and preparation of publications based on the study results. The Principal Investigator of the BCC reports to the Steering Committee.

7.1.3 NICHD

In addition to its role as funding agency, the NICHD participates in the activities of the Network, including the development of protocols, administration and conduct of the studies, and preparation of publications.

7.1.4 Network Advisory Board

Appointed by the NICHD, the members of the Network Advisory Board consist of a group of experts who are not affiliated with research conducted by the Network and represent the disciplines of maternal-fetal medicine, neonatology and biostatistics/epidemiology. The role of the board includes the review and prioritization of proposed studies, in addition to the identification of scientifically and clinically important questions and ideas that might be conducted by the Network. The NICHD Program Scientist convenes and attends the meetings.

7.2 Committees

7.2.1 Steering Committee

This committee consists of fifteen members. The Principal Investigator from twelve clinical centers, the Principal Investigator from the BCC, and the NICHD MFMU Network Project Scientist are all voting members. The Chair of the Steering Committee may vote to break a tie. The Chair, a person independent of the participating institutions, is appointed by NICHD. The Steering Committee has the responsibility for identifying topics for Network studies, designing and conducting study protocols and monitoring study implementation, recruitment, and protocol adherence. The committee receives recommendations from the Data and Safety Monitoring Committee and the Network Advisory Board.

7.2.2 Protocol Subcommittee

The subcommittee will consist of the Chair of the ALPS Subcommittee, the other MFMU Network investigators on the ALPS subcommittee, the BCC PI, nurse coordinators, designated external consultants, and the NICHD MFMU Network Project Scientist. The Protocol Subcommittee is responsible for the preparation and conduct of the study, and reporting the progress of the study to the Steering Committee.

7.2.3 Publications Committee

The Publications Committee is a standing committee of the Steering Committee. The functions of this committee are to develop publication policies and to review all manuscripts and abstracts prior to submission. The goals of this committee are fair and appropriate authorship credit and high quality publications.

Data and Safety Monitoring Committee

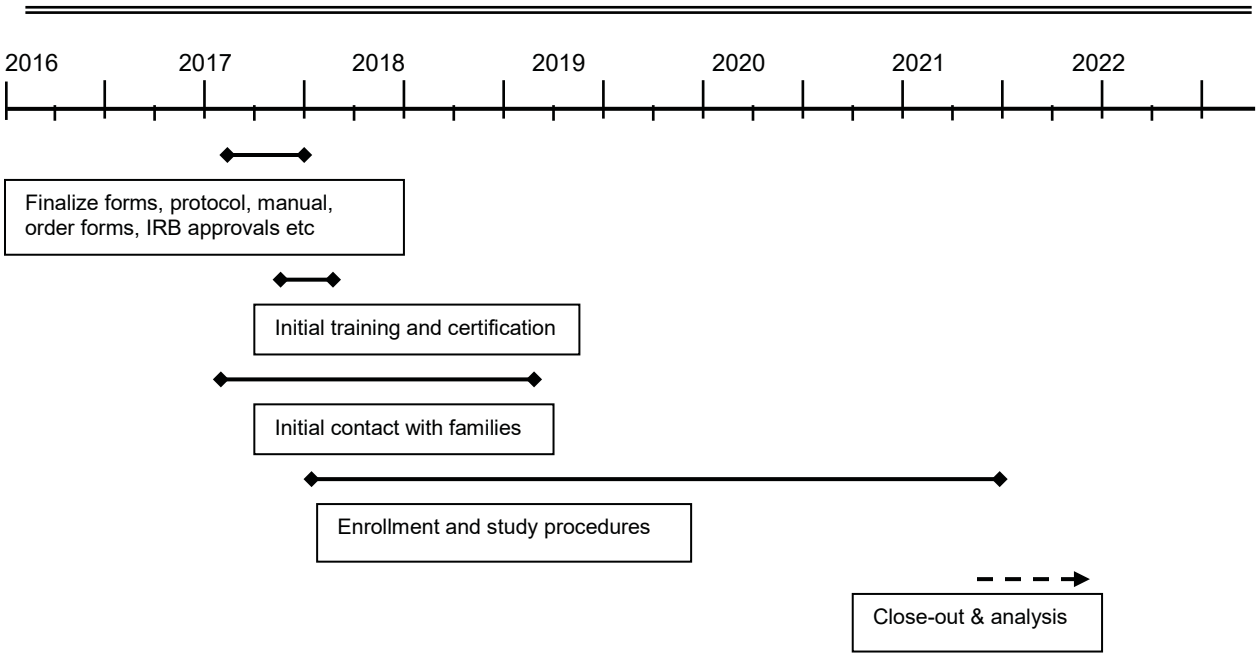
The Data and Safety Monitoring Committee (DSMC), a group of individuals not affiliated with any of the participating institutions, was established by the NICHD to monitor MFMU Network studies. For this study, the committee is charged with monitoring safety only. Recommendations are made to the NICHD and disseminated to the Steering Committee.

8 Study Timetable

8.1 Timetable

The study timetable is depicted below.

Figure 2. Timetable



The oldest child reached 6 at the end of October 2016 and study visits will start in August 2017. For some sites (centers that joined the Network in 2011 and sub-sites that started later) the oldest child will not turn 6 until later in 2017. The youngest child will reach 6 in March 2021.

The staff at each participating center must be trained, certified and have IRB approval to conduct the study before recruitment at that center can begin. The forms, protocol, and manual of operations will be finalized and IRB approval obtained at the centers before enrollment begins. Training on study procedures and conduct of the DAS-II took place in April and May 2017. Certification of a clinical center will include IRB approval, an approved consent form, HIPAA authorization, and institutional approval for the ultimate release of the dataset in addition to an acceptable video of a DAS-II exam on a test subject.

Initial contact with the families will begin as soon as IRB approval is received for the ALPS pulmonary follow-up and it is planned that the main effort of searching and locating families will be concluded after about a year.

Enrollment will continue through March 2021 at least. After completion of the follow-up visit, a two-month period will be dedicated to complete data entry and close-out. Approximately 6 months will be required to complete the final report to the Steering Committee and to submit the study's report on follow-up for publication.

Appendix A Design Summary

Childhood Cognitive Function in a Birth Cohort after a Randomized Trial of Antenatal Corticosteroids: the ALPS Neurocognitive Follow-Up Study

OBJECTIVE: To examine whether children of mothers who were at risk of a late preterm delivery and treated with corticosteroids have better cognitive function compared with children whose mothers did not receive corticosteroids.

ORGANIZATION

Clinical Centers: UAB, Ohio State, Utah, Brown, Columbia, UTMB, Case Western, UT-Houston, UNC, Northwestern, Stanford, U Colorado, Duke

Subcommittee: Dr. Cynthia Gyamfi-Bannerman (Chair)

DESIGN

Major Eligibility Criteria:
- Mother enrolled in ALPS
- Child is 6 years of age or older

Sample Size:
- 2000 ALPS children

Assumptions:
- Outcome event = GCA < 85
- Placebo group event rate = 20%
- Betamethasone group event rate = 15%
- Type 1 error = 5% 2-sided
- Power =83%

SCHEDULED EVALUATIONS/DATA COLLECTION
- Neonatal glucose values
- Duration and type of treatment for hypoglycemia
- Height and weight (
- DAS-II
- General health of the child
- Gross Motor Function Classification System (GMFCS)
- Social Responsiveness Scale (SRS)
- Child Behavior Checklist (CBCL)
-

OUTCOME MEASURES

Primary:
- General Conceptual Ability (GCA)

Secondary
- Verbal ability, non-verbal reasoning ability, and spatial ability component scales of the DAS II
- Screen positive on the SRS for autism spectrum disorder
- Child Behavior Checklist subscales

TIMETABLE
- April 2017 - June 2017: Training/Certification
- June 2017 - May 2021: Enrollment
- May 2017 - July 2021: Data processing
- July 2021 - Dec 2021: Final analysis

Appendix B Sample Informed Consent Form

B.1. Sample Informed Consent Form

Research Study Title: The ALPS Neurocognitive Follow-Up Study

Sponsor*:* The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health

Principal Investigator: _____Phone (____) ___ - ____

Introduction

You and your child are invited to take part in a research study. This consent form provides the information about the risks and benefits of the study. A member of the research team is available to answer your questions and to provide further explanations. You are free to choose whether or not you and your child will take part in the study. If you agree to take part in the research, you will be asked to sign this consent form. This process is known as informed consent.

You are being approached to participate in this study because you participated in the Antenatal Late Preterm Steroids (ALPS): A Randomized Placebo-Controlled Trial to determine if giving steroids to women who are at risk for late preterm delivery will decrease the likelihood that the baby will need respiratory (breathing) support like a ventilator or oxygen soon after birth. The current study is a follow-up study to determine the effect of giving steroids to women who participated in this original study and whether this treatment leads to benefit in terms of cognitive function in your child at 6 years of age.

Thirteen medical centers across the country are participating in this follow-up research study. In all, 2000 children will be enrolled in this follow-up research study.

Length of the Follow-up Research Study

Your participation in this follow-up research study will occur just today and will last approximately two hours.

Information on Research Procedures

If your child participates in this follow-up research study, you and the child will be asked to allow the following measurement and assessment to be obtained from the child. This will take around one hour:

- Assessment of your child's cognition and learning abilities, measured by the Differential Ability Scales-II (DAS-II)

You will be asked questions about your child. These questions will take around 30 minutes to complete:

- Your child's health and motor function
- Your child's social abilities, using the Social Responsiveness Scale (SRS)
- Your child's social and behavioral abilities , using the Child Behavior Checklist (CBCL)

Even if you consent to participate in this follow-up research study, you may refuse any part of the follow-up research study or not answer any questions that make you feel uncomfortable.

Possible Risks

A risk of taking part in this study is the possibility of a loss of confidentiality. Loss of confidentiality includes having your personal information shared with someone who is not on the study team and was not

supposed to see or know about your information. The study team plans to protect your confidentiality. The plans for keeping your information private are described in the 'confidentiality' section of this consent form.

The cognitive assessment should be fun for your child, but s/he may get tired of sitting or being asked questions.

Benefits

If you decide to take part in this follow-up research study, you and your child may not directly benefit from participation. However, you and your child may benefit from receiving the results of the neurocognitive assessments. The results of the assessments will be shared with you and a letter will be sent to you that you can share with your physician or your child's pediatrician. These assessments will be provided free of charge.

Alternative Procedures

The alternative to this follow-up research study is not to participate.

Costs

There will be no cost to you for the study visit.

Compensation

(THIS SECTION WILL BE CENTER SPECIFIC.) You will be paid $XX to compensate you for the time and travel associated with the research study.

Payment for Injury or Harm

(THIS SECTION WILL BE CENTER SPECIFIC.) This hospital is not able to offer financial compensation or absorb the costs of medical treatment in the event of injury resulting from the research. In the event of such injury, treatment will be provided but it is not provided free of charge. Since this is a research study, payment for any injury resulting from your participation in this research study may not be covered by some health insurance plans.

Right to Withdraw From the Research Study

This study is voluntary and it is up to you to decide whether or not you want to participate. You are free to withdraw your consent and stop taking part in this research study at any time without giving a reason. Refusal to take part or the decision to withdraw from the study will involve no penalty or loss of benefits to which you are otherwise entitled. Your refusal will not affect your legal rights or quality of health care that you will receive at this hospital.

Any significant new information which becomes available during your participation in this research, and which may affect your health, safety, or willingness to continue in this research study, will be given to you.

Right of the Investigator to Withdraw

The researchers of this institution or the National Institutes of Health can withdraw you from this study without your approval. A possible reason for withdrawal could be the early termination of the study by the National Institutes of Health.

Confidentiality

You have the right to privacy. All information obtained from this research that can be identified with you will remain confidential within the limits of the law.

If we lose track of you, study staff may collect information from the internet including social network sites in order to find your contact information.

The information collected for this research study will be held at the data coordinating center (George Washington University Biostatistics Center in Rockville, Maryland) in a database consisting of information from all of the participants in this study. Your information in the database will **only** be used for statistical analysis and may appear in scientific publications but will not identify you. The information at the data coordinating center will include your current and previous zip codes but does **not** include names, addresses, social security numbers, hospital numbers, or other personal identifiers.

Instead the data coordinating center will use a unique code for each participant consisting of a number and the first letter of your first name. The key to the code linking it to you will be kept here in a locked file. Only the research study staff employed for this study at this hospital will have access to the key to the code.

The following individuals and/or agencies will be able to look at and copy your research records:

The investigator (study doctor), study staff and other medical professionals who may be evaluating the study. Authorities from this institution, including the Institutional Review Board (IRB)

The Office of Human Research Protections (OHRP)

The National Institute of Child Health and Human Development (NICHD) which sponsors this study, including persons or organizations working with the sponsors, such as the data coordinating center, George Washington University Biostatistics Center in Rockville, Maryland.

The results of this research study will be provided to the sponsor, NICHD (and/or their representatives). In addition, data from this study will be put in a public data set that will be available to other research investigators. This public data set will not contain any identifying patient data and will not be used for commercial purposes.

A description of the ALPS clinical trial and this follow-up study is available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

This permission does not end unless you cancel it, even if you leave the study. You can cancel this permission any time except where a healthcare provider has already used or released your child's health information or relied on your permission to do something. Even if you cancel this authorization, the researchers may still use and disclose protected health information (PHI) they already have obtained about you as necessary to maintain the integrity or reliability of the research. However, no new protected health information or new biological specimens will be collected from you after you revoke your authorization.

To cancel your authorization, you will need to send a letter to < > stating that you are canceling your authorization. This letter must be signed and dated and sent to this address: < >. A copy of this revocation will be provided to the study doctor and his or her research team. Not signing this form or later canceling your permission will not affect your health care treatment outside the study, payment for health care from a health plan, or ability to get health plan benefits.

Your protected health information will be treated confidentially to the extent permitted by applicable laws and regulations. Federal law may allow someone who gets your health information from this study to use or release it in some way not discussed in this section and no longer be protected by the HIPAA Privacy Rule.

By signing this form you authorize the study doctor and members of the research team to use and share with others (disclose) your PHI for the purpose of this study. If you do not wish to authorize the use or

disclosure of your PHI, you cannot participate in this study because your PHI is necessary to conduct this study.

Questions

The researchers are available to answer your questions about this research. A representative of the Institutional Review Board is also available to answer questions about your child's rights as participants in research or to answer your questions about an injury or other complication resulting from your or your child's participation in this research study.

If you have questions or if your child is hurt while taking part in this research study, you should contact _____ at (___) ___-____.

If you have any questions about the informed consent process or any other rights as a research subject, please contact _____, at (____) ___-____. _____ .

Signatures

By signing below, you indicate that you have read this consent form, the study has been explained to you, your questions have been answered, and you agree to take part in this study. You do not give up any of your legal rights by signing this form. A copy of this consent form will be given to you

Study Participant

Print Name_____Signature_____Date _____

Person Obtaining Consent

Print Name_____Signature_____Date _____

The investigator or study team may wish to contact you in the future to request permission for additional research. Please initial the appropriate statement to indicate whether or not you give permission for future contact.

(Initial) YES_____ NO_____ I give permission to be contacted in the future for research purposes.

Investigator Statement

I certify that the research study has been explained to the above individual by me or my research staff including the purpose, the procedures, the possible risks and the potential benefits associated with participation in this research study. Any questions have been answered to the individual's satisfaction.

_____	_____	_____
Investigator Name *(Print Name)*	Signature	Date

B.2 Sample Assent Form

Research Purpose

We are asking you to be in a research study. This paper will tell you all about the study and help you decide whether or not to be in the study. Read this paper carefully and ask any questions you have.

You might have questions about

* what you will be asked to do,
* how long it will take,
* if the study is scary or dangerous, or
* if anyone will find out what you did.

When we have answered all of your questions, you can decide whether or not to be in the study. You can talk to your family about it before deciding.

Information on Research

What is a research study?

A research study is when doctors and nurses collect a lot of information to learn more about something. We are doing a study to learn more about the health of children. After we tell you about it, we will ask if you'd like to be in this research study or not.

Why are you being asked to be part of this research study?

When you were a baby, you were part of a research study. This is the second part of that study. We want to find out about your health now. So we are getting information from boys and girls like you who were in the first part of the study.

About 2,000 children will be in this study.

Why is the study being done?

The study may help to find out how a mom's and baby's health is related to the child's health a few years later.

What will happen to you if you are in this study?

Only if you agree, two things will happen:

1.) A nurse will ask your mom or dad questions.

2.) You will be asked to look at pictures, answer questions, work with cards and blocks and draw with a pencil.

Risks

Will any part of the study hurt or cause problems?

The study should be fun for you, but you may get tired of sitting or being asked questions.

Benefits

Will the study help you or others?

This study won't make you feel any different. But the doctors might find out something that will help other children like you stay healthy. By being part of this study, your family can get your results and better understand how healthy you are.

Alternative Procedures

What happens if you say no to this study?

*Nothing will happen. **You** will just go back home with your family.*

Confidentiality

Who will see the information collected about you?

The information collected about you during this study will be kept safely locked up. Nobody will know it except the people doing the research.

Compensation

What do you get for being in the study?

< >

Voluntary Participation

Do you have to be in the study?

You do not have to be in the study. No one will be upset if you don't want to do this study. If you don't want to be in this study, you just have to tell us. It's up to you.

Additional Information

Do your parents know about this study?

This study was explained to your parents and they said that we could ask you if you want to be in it. You can talk this over with them before you decide.

Do you have any questions?

You can ask questions any time. You can ask now. You can ask later. You can call any of the people whose names and phone numbers are listed on the first page. You can take more time to think about being in the study and talk some more with your parents about being in the study.

Other information about the study.

You can change your mind and stop being part of it at any time. All you have to do is tell one of the people in charge of the study.

You will be given a copy of this paper to keep.

If you decide to be in the study, please write your name below.

Signature

Child

Print Name_____Signature_____Date _____

Person Obtaining Assent

Print Name_____Signature_____Date _____

Check which applies (to be completed by the person conducting assent discussion).

☐ The subject is capable of reading and understanding the assent form and has signed above as documentation of assent to take part in this study.

☐ The subject is not capable of reading the assent form, however, the information was explained verbally to the subject who signed above to acknowledge the verbal explanation and his/her assent to take part in this study.

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April 1, 2019

Childhood Cognitive Function in a Birth Cohort after a Randomized Trial of Antenatal Corticosteroids: the ALPS Neurocognitive Follow-Up Study

Protocol

ALPS FSN

Eunice Kennedy Shriver
National Institute of Child Health and Human Development
Maternal-Fetal Medicine Units Network

Prepared by the

Biostatistical Coordinating Center for the NICHD MFMU Network

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Rockville, MD 20852
(301) 881-9260

April 1, 2019

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Tables and Figures

1 Introduction

1.1 Study Abstract

In a recently completed trial, Antenatal Late Preterm Steroids (ALPS): A Randomized Placebo-Controlled Trial, conducted between 2010-2015 by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network, antenatal betamethasone treatment of pregnant women at risk for late preterm delivery was found to decrease the primary neonatal respiratory composite outcome of treatment in the first 72 hours and other related outcomes.[1] These findings have already changed practice in obstetrics. However, there is strong interest in the community to ascertain whether neurodevelopmental outcome is reassuring. Therefore a follow-up study is proposed of the index children born to women who participated in the MFMU ALPS trial.

In addition to the respiratory benefit there was an increase in neonatal hypoglycemia in the betamethasone arm. Although the hypoglycemia appeared to be self-limiting and was not associated with a longer neonatal stay, it is important to follow up the infants because of the association between prolonged hypoglycemia and neurodevelopmental outcome. This follow-up study also allows for the evaluation of whether hypoglycemia and earlier gestational age within the late preterm to term period have long-term consequences on neurodevelopment.

1.2 Primary Hypothesis

Children of mothers at risk for late preterm delivery who were randomly assigned to antenatal betamethasone will have a lower frequency of cognitive function one standard deviation below the mean at age 6 years compared with the children of mothers who were randomly assigned to a matching placebo. Cognitive function will be measured by the Differential Ability Scales-II (DAS-II) core components of the general conceptual ability (GCA) that includes verbal ability, non-verbal reasoning ability, and spatial ability.

1.3 Purpose of the Study Protocol

This protocol describes the background, design and organization of the follow-up study and may be viewed as a written agreement among the study investigators. The Network Advisory Board reviews the protocol. Before recruitment begins, the protocol is approved by the NICHD MFMU Network Steering Committee and the Institutional Review Board (IRB) of each clinical center. Any changes to the protocol during the study period require the approval of the Steering Committee and the IRBs. A manual of operations supplements the protocol with detailed specifications of the study procedures.

2 Background

2.1 Introduction

It is well-established that late preterm (34-36 weeks gestation) birth leads to increased neonatal morbidity, primarily respiratory, compared with delivery at term (≥37 weeks).[2-5] Several studies have demonstrated that morbidity and mortality increase with decreasing gestational age below 39 weeks gestation.[3,5,6] It is also believed that many late preterm morbidities are transient, resolving after discharge. Because late preterm infants were only relatively recently identified as an at-risk group, their long term outcomes are poorly defined, particularly as they relate to neurodevelopment.[7] In 2016 the results of the Antenatal Late Preterm Steroids (ALPS) trial were published.[1] The ALPS trial showed that antenatal corticosteroids decreased several respiratory morbidities including the composite primary outcome of requirement of respiratory support, transient tachypnea of the newborn, bronchopulmonary dysplasia, and the need for immediate resuscitation and postnatal surfactant in offspring of participants exposed to betamethasone. However, the ALPS trial also found a higher rate of hypoglycemia in infants of women who were randomized to receive betamethasone compared with placebo. With the subsequent recommendations from the Society for Maternal-Fetal Medicine and the American College of Obstetricians and Gynecologists, late preterm administration of corticosteroids is becoming the new standard of care.[8,9] Long-term effects of late preterm steroid exposure are poorly understood because administration in this period is newly recommended, and clinical data are scant on the effect of late preterm steroid exposure on the developing brain, though the available data are reassuring.[10] However, emerging evidence suggests that late preterm birth has an a priori risk of neurocognitive delay compared with birth at term.[11-13] The purpose of this follow-up study is to assess the potential long-term risk or benefit of antenatal corticosteroids on neurocognitive functioning and the long-term consequence of hypoglycemia and earlier gestational age within the late preterm to term period.

2.1.1 Late Preterm Birth and Neurodevelopment

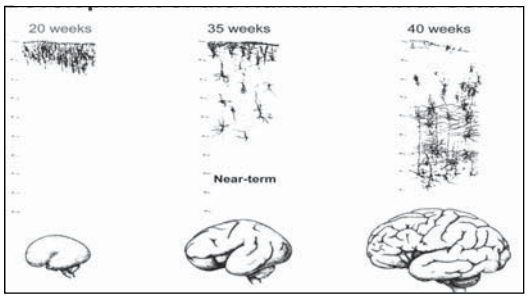
The data on neurodevelopment after late preterm delivery are limited primarily because these infants were only recently recognized as a high risk group.[14] However, since 2006 there have been several studies suggesting that neuro-development is negatively altered by late preterm birth.[12,13,15-17] The available observational cohort studies are limited in that some have used proxies, such as school grades and performance, rather than rigorous methods, such as IQ scores, to measure neurodevelopment; thus, much work is needed in this area. Morse and colleagues found an increase in developmental delay and in school non-readiness in a large cohort of "healthy" former late preterm children in Florida.[13] Former late preterm infants were designated as "healthy" on a review of birth certificate data if they were discharged by day 3. These children were more likely to have developmental delay and require special needs education when compared with children born at term (Table 1).

Table 1. Early School Age Outcomes of Late Preterm Infants[13]

Early school-age outcome	Healthy Late Preterm (%)	Term (%)	Adjusted RR
Developmental delay/disability	4.24	2.96	1.36 (1.29-1.43)
Disability in pre-kindergarten	7.40	6.60	1.10 (1.05-1.14)
Not ready to start school	5.09	4.40	1.04 (1.00-1.09)
"Special needs" education	13.30	11.88	1.10 (1.07-1.13)
Retention in kindergarten	7.96	6.17	1.11 (1.07-1.15)
Suspension in kindergarten	1.80	1.22	1.19 (1.10-1.29)

Similarly, Williams and Jain found an increase in school failure among former late preterm children compared with their term counterparts.[16] After adjusting for maternal and child characteristics, they found a significant increase in failure of reading, math, and English/language arts for former late preterm children compared with those born at term. Using linked national registries from Norway, investigators were able to demonstrate increased rates of cerebral palsy (RR 2.7, 95% CI 2.2-3.3) and psychosocial disorders (RR 1.5, 95% CI 1.2-1.8) in children born from 34 0/7 to 36 6/7 weeks compared to those born at ≥37 weeks.[12]

Figure 1. Development of the human cerebral cortex



A review of studies of school outcome, cognitive functioning and behavior problems in former moderate and late preterm infants (which included both the study by Morse et al. and the Norwegian study) concluded that overall more school problems, less advanced cognitive functioning, more behavioral problems and psychiatric problems occur in moderate and late preterm infants.[18] However, in many of the studies, the data were not presented separately for moderate versus late preterm. In those studies that assessed IQ in childhood, two found no difference in late preterm versus term children[19,20] whereas another found worse IQ only in former late preterm infants with a complicated neonatal course.[21] However, Talge et al did find that the proportion of children at age 6 with IQ<85 was higher in the late preterm group was higher than in the term group, after adjusting for potential confounders (adjusted OR 2.35, 95% CI 1.2 -4.61).[19]

It is accepted that a late preterm brain is less mature with important processes such as formation of gyri and sulci as well as differentiation and proliferation occur near the end of gestation (Figure 1). While less is known about whether exposure to betamethasone enhances brain maturity, what is recognized is that glucocorticoid exposure can promote maturation of the brain my increasing myelination and functional maturation in an animal model.[22,23]

2.2 Steroids and Neurodevelopment

A single course of antenatal corticosteroids has been shown consistently to either have no effect or improve childhood neurocognitive outcomes over no steroids for infants in pregnancies at risk of preterm delivery.[10,24] The landmark clinical trial by Liggins and Howie describing the benefits of antenatal corticosteroid administration included women at risk for late preterm delivery from 24-36 completed weeks of gestation.[25] In 1972 when the study was first published, 28 weeks gestation was considered the limit of viability. In fact, there were no survivors enrolled in the landmark trial at <26 weeks gestation. Therefore, this study was skewed towards moderate and late preterm pregnancies, including those at risk from 34-36 weeks. The study has rigorous long term outcome data, including 30-year neurodevelopmental follow-up.[10] The investigators found no difference in intelligence using the Weschler scales, memory and attention, psychiatric illness, or quality of life by steroid exposure. The median gestational age at delivery for follow-up participants initially in the betamethasone group was 35 weeks, 0 days (IQR 33 weeks, 4 days to 38 weeks 0 days), similar to participants in the ALPS trial.

The long-term neurocognitive benefits of a single course of antenatal corticosteroids were most recently described in a meta-analysis by Sotiriadis et al, which included randomized and non-randomized prospective studies of women delivering. While most studies included steroid exposure at up to 34 weeks, this analysis[24] included the initial Auckland cohort from Liggins and Howie[25] with steroid exposure up to 36 6/7 wks. The authors concluded that antenatal corticosteroids decreased the risk of severe disability and increased intact survival.[24] Clinical studies of multiple course steroids have generally found worse neurodevelopmental outcomes compared with those who had a single course and

delivered at term, but multiple courses of steroids are not recommended in the United States and have fallen out of favor in most of the world.[9,26,27]

Despite reassuring clinical data, there is older evidence for potential harm derived from animal data. Huang and colleagues showed a decrease in cerebral length and depth, but not in whole-brain weight in sheep delivered after a single course of antenatal corticosteroids.[28] Other investigators showed that a single dose of dexamethasone administered to pregnant rats can disrupt brain cell differentiation.[29] Some experts however raise caution when evaluating the effect of antenatally administered steroid in animal models since the timing of peak growth in the fetal brain varies by the choice of model.[30] While animal models have suggested a relationship between antenatal corticosteroids and adverse neurodevelopment, this relationship has never been noted from human randomized clinical trials evaluating a single course of steroids.

Clinical data on neurodevelopment after late preterm steroids is currently limited to the initial Auckland cohort.[10,25] However, there are more recent data from a randomized trial of exposure to open-label betamethasone compared with usual care in women undergoing term scheduled cesarean, the Antenatal Steroid for Term Elective Cesarean Trial (ASTECS).[31] The trial's follow-up study (ASTECS-2) was not pre-planned and used questionnaires completed by parents as well as school assessment data.[32] At the time of assessment, the children were ages 8-15 years; data were available for 407 children (41% of the offspring from the trial). No differences were observed between the offspring of mothers randomized to antenatal betamethasone compared with the offspring of mothers randomized to usual care in the total difficulties score of the strengths and difficulties questionnaire (SDQ) (mean of 8.03±6.83 compared with mean of 7.85±6.49, respectively) or in any of the subscales. No significant differences were observed between the betamethasone and usual care groups for standard assessment tests, with level 4 achievement observed in 86% and 88% for mathematics, 91% and 94% for science, and 87% and 93% for English, respectively. The only difference in outcomes between groups was in the school assessment of quartile by ability, a subjective measure, which showed a higher precent of children in the lower quartile of academic ability in the betamethasone group (18%, compared with 9% in the usual care group; p=.03). The authors of the study concluded *"no adverse effect was seen on health, behaviour and academic achievement of children born following a single course of antenatal betamethasone at term."* Despite the lack of difference in multiple cognitive measures and the risk of a Type 1 error with multiple comparisons, this isolated finding has been used to suggest a signal for harm after steroid exposure at term.

2.3 Hypoglycemia and Neurodevelopment

While a link between hypoglycemia and brain injury exists, there is no agreement on a value that defines pathologic hypoglycemia, nor is there a value below which the brain is absolutely affected.[33] Low neonatal glucose concentrations can lead to brain injury via the glucose transporters, namely GLUT-1 and GLUT-3.[34] In cases where there is deficiency of these transporters, the brain switches to alternate pathways to create fuel, which can lead to brain injury.[35] These controversies were addressed in a NICHD Workshop held in 2008. The group acknowledged that many previously defined thresholds for hypoglycemia do not necessarily reflect "dangerous" levels. Participants also recognized that as many as 5% to 15% of normal newborn infants will have a low plasma glucose, usually noted as <40 to 45 mg/dL, and called for more research to define pathologic hypoglycemia and establish normograms.[33]

The ALPS trial found a higher frequency of hypoglycemia (defined as <40 mg/dl) in infants of women who were randomized to receive betamethasone compared with placebo, 24.0% versus 15.0% (RR 1.60, 95% CI 1.37-1.87).[1] Exposure to betamethasone was also associated with shorter special care nursery stays. Unpublished data also show that infants with hypoglycemia had short randomization to delivery times compared with those without hypoglycemia: 29.7 hours (IQR 16.8-48.8) versus 34.6 hours (IQR 14.5-141.3). The data collected were only binary; information on actual glucose levels was not captured.

2.4 Rationale for the Follow-Up Study

It is unknown whether late preterm antenatal betamethasone treatment is associated with long-term neurocognitive functioning. Some animal models suggest potential for harm since the brain is rapidly developing during this period. However, both limitations in animal models and reassuring clinical data suggest that the potential for adverse outcomes related to betamethasone treatment are unlikely. The ALPS cohort provides a unique opportunity to assess the potential long-term risk or benefit of antenatal corticosteroids in the late preterm period on neurocognitive functioning and whether there are any long-term consequences of what is believed to be transient neonatal hypoglycemia.

3 Study Design

3.1 Primary Research Question

This study will address the following primary research question: In women at risk for late preterm delivery, does administration of antenatal betamethasone treatment in the late preterm period of 34 to 36 weeks gestation have an effect on the cognitive function of their children aged 6 years? Cognitive function will be measured by the DAS-II core components of the general conceptual ability (GCA) that includes verbal ability, non-verbal reasoning ability, and spatial ability.

3.2 Secondary Research Questions

This study will address the following secondary research questions.

- Does antenatal betamethasone at 34 to 36 weeks gestation compared with placebo have an effect on any sub component of the DAS-II (verbal ability, non-verbal reasoning ability, and spatial ability)?
- Does antenatal betamethasone at 34 to 36 weeks gestation have an effect on the frequency of screening positive on the SRS for autism spectrum conditions at age 6?
- Does antenatal betamethasone at 34 to 36 weeks gestation have an effect on childhood behavioral and emotional problems as measured by the child behavior checklist at age 6?
- Is neonatal hypoglycemia, and its duration and severity, associated with cognitive function in 6 year old children?
- Does neonatal hypoglycemia mediate a treatment effect of antenatal betamethasone on cognitive function?
- Is earlier gestational age at delivery within the late preterm to term period associated with cognitive function in 6 year old children? And, if such an association is present, does treatment with antenatal betamethasone modify the association?

3.3 Design Summary

This study is a follow-up cohort study of the ALPS trial. Assuming 82%-83% follow-up, approximately 2000 children whose mothers were enrolled in ALPS will undergo one two-hour study visit in which the DAS-II will be administered. Information about the child's health will be obtained, and the Social Responsiveness Scale and Child Behavior Checklist will be administered.

3.4 Eligibility Criteria

3.4.1 Inclusion Criteria

1. Mother enrolled in ALPS
2. Mother enrolled at one of the thirteen centers that participated in the MFMU Network for the 5-year cycle 2011-2016 and agreed to take part in the follow-up study.
3. At least six years of age; the intention is to enroll all children at age six; however, if a child is found at a later age he/she will still be eligible

3.4.2 Exclusion Criteria

1. Death of the child
2. Refusal of the family or inability of the child to take part in a study visit at the clinical center or at home

3.5 Informed Consent Criteria

Written informed consent must be obtained from the parent or guardian as well as the child's assent to participate, as required by the local IRB. Study staff will explain in concrete, age-appropriate terms the purpose of the project, what the child will be asked to do, and what procedures they will undergo. The child will be allowed to ask questions about the process. If the child provides assent to participation, the research staff will ask the child to write his/her name on a separate form.

Each center will develop its own consent forms according to the requirements of its own institutional review board using the model consent forms in Appendix B. Each center will also develop its own patient research authorization documents, as required by the HIPAA Privacy Rule, following the guidelines of its own institution. A copy of the signed consent form(s) will be provided to the parent or guardian and a copy of the assent form to the child.

If feasible, families who are not fluent in English will be enrolled by a person fluent in their language. Both verbal and written informed consent and authorization will be obtained in that language; if this is not possible, the child will be excluded.

The parents/guardians will also be asked if they are willing to be contacted at a later date for a potential longer-term follow-up study of their children. A check box will be provided on the consent form that will need to be checked separately for permission to contact study participants at a later date.

4 Study Procedures

4.1 Locating and Contacting Participants

Locating and contacting participants will be conducted through the parallel ALPS FS Pulmonary study. Each center will be provided with a list of children (identified by their unique Network code) whose mothers were in the ALPS trial, agreed in the informed consent for the primary trial to future contact and who would satisfy the inclusion criteria once they reach six years of age. Mothers who declined future contact during the ALPS trial may also be contacted according to the regulations of the center's IRB. Study staff will start with and give priority to the oldest children first using contact information available from the original study, including identifiers such as social security number from the medical records. Other sources will include services the family may be using, as well as hospital admissions and county agencies. Public search software can also be used. An attempt will be made to locate as many women as possible within the first year of the study, even if their children are not yet old enough to participate.

4.2 Screening for Eligibility and Consent

Once a potentially eligible child is located, research study staff will confirm the identity of the child, explain the purpose of the pulmonary follow-up study to the parent(s) or guardian and invite the family to participate. Any questions will be answered. Interested families will be asked to attend a single follow-up visit with their index child at the original ALPS clinical center. A more convenient center may be chosen if the family has relocated since the delivery of the index child. If the family plans on participating in the pulmonary follow-up, the neurocognitive follow-up can also be explained to the parent or guardian, and they can be invited to participate in the neurocognitive follow-up.

- Initial verbal consent to participate is requested using a standardized script.
- The visit will be scheduled during the year that the child is six.
- The neurocognitive follow-up should take place following the pulmonary assessment but after a sufficient rest and food, so that the cognitive testing is not adversely affected by the prior spirometry testing. It is also permitted to conduct the neurocognitve assessment before the pulmonary assessment depending on the availability of the examiner. Alternately, the child can return for a second visit to complete the neurocognitive follow-up.
- If a family has moved and is unwilling to travel, a home visit may be arranged.

4.3 Baseline Procedures

As an extension to the ALPS trial, additional details related to neonatal hypoglycemia was abstracted from the neonatal medical records. Glucose values and the duration, severity, and treatments for hypoglycemia that were obtained will be included in this dataset. Height and weight are measured as part of the parallel ALPS FS Pulmonary study.

4.4 Study Visit Procedures

The neurocognitive follow-up visit is expected to take approximately two hours. The following events and procedures will be conducted specifically for this during the single study visit:

- Written informed consent (and assent if appropriate) obtained.

- A break that can include a meal (if the neurocognitive assessment is conducted on the same day as the pulmonary follow-up).
- Administration of the DAS-II by a study certified psychologist
- The Gross Motor Function Classification System

While the DAS-II is being administered to the child, the parent or guardian will complete the following questionnaires.

- Questions about the index child's health
- Social Responsiveness Scale (SRS) for autism screening. Any child screening positive will be referred for more formal clinical evaluation.
- Child Behavior Checklist (CBCL).

4.5 Patient Management and Follow-Up

Approximately two to four weeks following the visit, the parents/guardians will be sent a letter reporting the DAS-II score and the range in scores that are within age expectation for learning/cognitive abilities.

The letter will inform the parent/guardian that the assessments were for the purposes of research, and do not provide a complete assessment of the child's learning and emotional strengths and weaknesses and recommend that if the parent/guardian has any concerns that they can share the results with their child's school, psychologist, or physician for planning an evaluation that fits their child's individual needs.

4.6 Adverse Event Reporting

Detailed information concerning adverse events assessed to be definitely, probably or possibly related to study procedures will be collected and evaluated throughout the conduct of the study. Death or any life threatening event will be reported regardless of relatedness to study procedures. The NICHD Project Scientist and the BCC will be informed within 24 hours of being notified of any death or life-threatening event of an enrolled child by secure e-mail/phone/fax. Adverse events will be reported to the Data and Safety Monitoring Committee.

4.7 Study Outcome Measures and Ascertainment

4.7.1 Primary Outcome

The primary outcome is defined as general conceptual ability score (GCA) < 85 (one standard deviation below the mean) evaluated on the DAS-II core components that include verbal ability, non-verbal reasoning ability, and spatial ability. The DAS II GCA correlates well with full scale IQ as measured by the WPPSI (0.89).

4.7.2 Child Secondary Outcomes

1. Sub components of the DAS-II (verbal ability, non-verbal reasoning ability, and spatial ability)
2. Screening positive on the SRS for autism spectrum conditions
3. Score on GMFCS
4. Child Behavior Checklist subscales

5 Statistical Considerations

5.1 Data Relevant to the Primary Outcome

Talge et al published an analysis of 168 former late preterm (34-36 weeks of estation at birth) children matched on birth weight z-score with 168 term children.[18] The children were followed up with neurocognitive testing at age 6 using the Wechsler Intelligence Scale for Children Revised. Twenty-one percent of the children who were born in the late preterm period had an IQ less than 85 compared with 12% in the term group. About 84% of the infants in the ALPS trial were born late preterm. Therefore it is reasonable to assume that the proportion of children in the placebo group with IQ < 85 is about 20%.

5.2 Sample Size and Power

The ALPS clinical trial included 2831 mother-infant pairs. After excluding those who did not consent to future contact, deaths, and sites no longer participating in the MFMU Network, and assuming an enrollment rate of 82-83%, the available sample size for this study is 2000. These mothers already consented to future contact, and a previous unplanned follow-up study (Progesterone Follow-up) achieved a similar rate.[36]

With a sample size of approximately 1000 per group and a two-sided type I error of 5%, there is 83% power to detect a 25% reduction in the proportion of children with DAS GCA < 85 in the betamethasone group (from 20% in the placebo group to 15% in the betamethasone group) There is 76% power to detect a 25% increase in the proportion of children with DAS GCA < 85 in the betamethasone group (from 20% in the placebo group to 25% in the betamethasone group).

5.3 Analysis Plan

The primary analysis and secondary analyses involving dichotomous outcomes will consist of a comparison of binomial proportions. The relative risk and confidence interval will be reported. All analyses that examine whether prenatal treatment with betamethasone (vs. placebo) confers long-term benefit will follow the intention-to-treat approach. Betamethasone treatment was randomly assigned and was successful in producing well-balanced groups with regards to baseline patient characteristics. However, a comprehensive comparison of the baseline attributes of the patient treatment groups will serve as a basis for understanding whether any baseline variables should be examined as potential confounders in multivariable models. Socioeconomic status influences child cognitive function, therefore the analysis will be adjusted for maternal education or medical insurance status. An evaluation of treatment by center will be included and analyses will account for center, either by adjusting for center in a multivariable model or by using mixed models.

For logistic regression models, the Hosmer-Lemeshow test will assess goodness of fit and over-dispersion using the tolerance limits on the ratio of the Pearson Chi-square to its degrees of freedom. If the model assumptions are violated, the robust estimate of the covariance matrix of the estimates will serve as the basis for confidence intervals and tests of significance. Partial Wald or score tests will be used to test covariate effects and Madalla's R^2 used to describe the strength of effect for each covariate.

General linear models including analysis of variance will be used to test for differences in continuous outcomes. Model assumptions such as normally distributed residuals will be tested.

5.3.1 Non-participation and loss to follow-up

There are several levels of missing outcome defined: 1) inability to contact the family 2) refusal of consent to participate and 3) loss to follow-up. Baseline characteristics will be compared between participants and non-participants. Loss to follow-up will be defined for those children where consent for

the study has been obtained but it was not possible to administer the DAS-II. A sensitivity analysis including participants lost to follow-up will be applied with different assumptions regarding their outcome, to determine whether the results are robust.

6 Data Collection

6.1 Data Collection Forms

Data will be collected on standardized forms on which nearly all responses have been pre-coded. Each form is briefly described below:

- AF06 Study Visit Form includes information regarding informed consent and the child's health and motor function.
- AF07 DAS-II Form includes all scores for each component of all three core components of the general conceptual ability (GCA) that includes verbal ability, non-verbal reasoning ability, and spatial ability.
- AF08 Social Responsiveness Scale
- AF09 Child Behavior Checklist
- AF12 Adverse Event Form

The following forms will be used to collect data regarding neonatal hypoglycemia:

- LP17 Hypoglycemia Form includes information regarding duration, severity, and treatments for neonatal hypoglycemia
- LP18 Glucose Log includes neonatal glucose measurements

6.2 Web Data Entry System

For this protocol, web-based data entry screens corresponding to the study forms listed above will be developed and maintained by the staff of the BCC. Clinical center staff will enter data into the MySQL database located at the BCC through a web-based data management system (MIDAS). A Users' Manual documenting this system is provided to the centers by the BCC.

6.3 Centralized Data Management System

Daily data conversions from the MySQL database create up-to-date SAS datasets. Data are reviewed weekly using edit routines similar to those implemented on-line during data entry, as well as additional checks for data consistency within or across forms. A database of resulting potential data problems is generated in MIDAS for initial review by BCC staff, who will then evaluate the comments keyed in association with edits on missing or unusual values. Valid edits will be flagged in MIDAS for resolution at the clinical centers.

At regular intervals, specialized data reviews comparing data availability and consistency across forms are run by the BCC staff on the entire database or on a specific subset of data. These reports are also submitted to the centers for correction or clarification.

An audit trail, consisting of all prior versions of each data form as entered in the computer for each participant, is maintained so that the succession of corrections can be monitored.

6.4 Performance Monitoring

The BCC will present regular reports to the ALPS Neurocognitive Follow-Up Study Subcommittee and the Steering Committee. These include:

- Monthly Enrollment Reports- reports of the number of children enrolled by month and clinical center are provided monthly to the ALPS FS Neurocognitive Subcommittee and all other members of the Steering Committee. Weekly or bi-weekly reports are provided electronically if needed.
- Quarterly Steering Committee Reports- reports detailing enrollment, data quality, incidence of missing data and adherence to study protocol by clinical center, are provided quarterly to the ALPS FS Neurocognitive Subcommittee and all other members of the Steering Committee.

7 Study Administration

7.1 Organization and Funding

The study is funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). The study is conducted by the NICHD Maternal-Fetal Medicine Units (MFMU) Network, consisting of fourteen clinical centers, the Biostatistical Coordinating Center (BCC) and the NICHD, and is administered under cooperative agreements between each of the centers and the NICHD. Each of the funded institutions is represented by a Principal Investigator. A complete description of the organization of the MFMU Network is provided in the MFMU Network Policy Manual.

For this study, 13 of the 14 centers that were part of the Network from 2011 to 2016 will participate, which includes three centers that are not currently in the MFMU Network.

7.1.1 MFMU Clinical Centers

Each of the funded institutions is represented by a Principal Investigator. A complete description of the organization of the MFMU Network is provided in the MFMU Network Policy Manual. The participating Principal Investigators of the MFMU Network clinical centers have agreed to abide by the study protocol, to have comparable staff, facilities and equipment and to ensure the proper conduct of the study at each of their centers including: recruitment and study procedures as specified in the protocol, accurate data collection and the transmission of information to the Steering Committee.

7.1.2 Biostatistical Coordinating Center

The BCC is responsible for all aspects of biostatistical design, data management, interim and final statistical analyses, and preparation of publications based on the study results. The Principal Investigator of the BCC reports to the Steering Committee.

7.1.3 NICHD

In addition to its role as funding agency, the NICHD participates in the activities of the Network, including the development of protocols, administration and conduct of the studies, and preparation of publications.

7.1.4 Network Advisory Board

Appointed by the NICHD, the members of the Network Advisory Board consist of a group of experts who are not affiliated with research conducted by the Network and represent the disciplines of maternal-fetal medicine, neonatology and biostatistics/epidemiology. The role of the board includes the review and prioritization of proposed studies, in addition to the identification of scientifically and clinically important questions and ideas that might be conducted by the Network. The NICHD Program Scientist convenes and attends the meetings.

7.2 Committees

7.2.1 Steering Committee

This committee consists of fifteen members. The Principal Investigator from twelve clinical centers, the Principal Investigator from the BCC, and the NICHD MFMU Network Project Scientist are all voting members. The Chair of the Steering Committee may vote to break a tie. The Chair, a person independent of the participating institutions, is appointed by NICHD. The Steering Committee has the responsibility for identifying topics for Network studies, designing and conducting study protocols and monitoring study implementation, recruitment, and protocol adherence. The committee receives recommendations from the Data and Safety Monitoring Committee and the Network Advisory Board.

7.2.2 Protocol Subcommittee

The subcommittee will consist of the Chair of the ALPS Subcommittee, the other MFMU Network investigators on the ALPS subcommittee, the BCC PI, nurse coordinators, designated external consultants, and the NICHD MFMU Network Project Scientist. The Protocol Subcommittee is responsible for the preparation and conduct of the study, and reporting the progress of the study to the Steering Committee.

7.2.3 Publications Committee

The Publications Committee is a standing committee of the Steering Committee. The functions of this committee are to develop publication policies and to review all manuscripts and abstracts prior to submission. The goals of this committee are fair and appropriate authorship credit and high quality publications.

Data and Safety Monitoring Committee

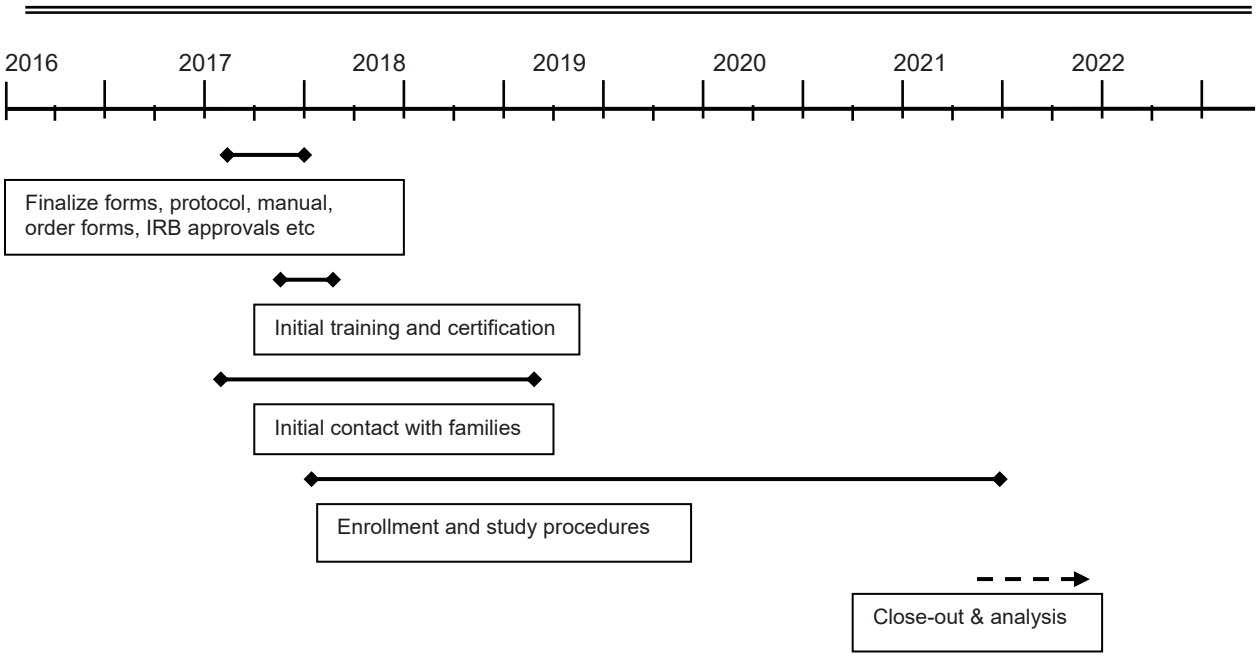
The Data and Safety Monitoring Committee (DSMC), a group of individuals not affiliated with any of the participating institutions, was established by the NICHD to monitor MFMU Network studies. For this study, the committee is charged with monitoring safety only. Recommendations are made to the NICHD and disseminated to the Steering Committee.

8 Study Timetable

8.1 Timetable

The study timetable is depicted below.

Figure 2. Timetable



The oldest child reached 6 at the end of October 2016 and study visits will start in June 2017. For some sites (centers that joined the Network in 2011 and sub-sites that started later) the oldest child will not turn 6 until later in 2017. The youngest child will reach 6 in March 2021.

The staff at each participating center must be trained, certified and have IRB approval to conduct the study before recruitment at that center can begin. The forms, protocol, and manual of operations will be finalized and IRB approval obtained at the centers before enrollment begins. Training on study procedures and conduct of the DAS-II took place in April and May 2017. Certification of a clinical center will include IRB approval, an approved consent form, HIPAA authorization, and institutional approval for the ultimate release of the dataset in addition to an acceptable video of a DAS-II exam on a test subject.

Initial contact with the families will begin as soon as IRB approval is received for the ALPS pulmonary follow-up and it is planned that the main effort of searching and locating families will be concluded after about a year.

Enrollment will continue through March 2021 at least. After completion of the follow-up visit, a two-month period will be dedicated to complete data entry and close-out. Approximately 6 months will be required to complete the final report to the Steering Committee and to submit the study's report on follow-up for publication.

Appendix A Design Summary

Childhood Cognitive Function in a Birth Cohort after a Randomized Trial of Antenatal Corticosteroids: the ALPS Neurocognitive Follow-Up Study

OBJECTIVE: To examine whether children of mothers who were at risk of a late preterm delivery and treated with corticosteroids have better cognitive function compared with children whose mothers did not receive corticosteroids.

ORGANIZATION

Clinical Centers: UAB, Ohio State, Utah, Brown, Columbia, UTMB, Case Western, UT-Houston, UNC, Northwestern, Stanford, U Colorado, Duke

Subcommittee: Dr. Cynthia Gyamfi-Bannerman (Chair)

DESIGN

Major Eligibility Criteria:
- Mother enrolled in ALPS
- Child is 6 years of age or older

Sample Size:
- 2000 ALPS children

Assumptions:
- Outcome event = GCA < 85
- Placebo group event rate = 20%
- Betamethasone group event rate = 15%
- Type 1 error = 5% 2-sided
- Power =83%

SCHEDULED EVALUATIONS/DATA COLLECTION

- Neonatal glucose values
- Duration and type of treatment for hypoglycemia
- Height and weight (
- DAS-II
- General health of the child
- Gross Motor Function Classification System (GMFCS)
- Social Responsiveness Scale (SRS)
- Child Behavior Checklist (CBCL)
-

OUTCOME MEASURES

Primary:
- General Conceptual Ability (GCA)

Secondary
- Verbal ability, non-verbal reasoning ability, and spatial ability component scales of the DAS II
- Screen positive on the SRS for autism spectrum disorder
- Child Behavior Checklist subscales

TIMETABLE

- April 2017 - June 2017: Training/Certification
- June 2017 - May 2021: Enrollment
- May 2017 - July 2021: Data processing
- July 2021 - Dec 2021: Final analysis

Appendix B Sample Informed Consent Form

B.1. Sample Informed Consent Form – without Common Rule 2018 changes

Research Study Title: The ALPS Neurocognitive Follow-Up Study

Sponsor*:* The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health

Principal Investigator: _____Phone (____) ___ - ____

Introduction

You and your child are invited to take part in a research study. This consent form provides the information about the risks and benefits of the study. A member of the research team is available to answer your questions and to provide further explanations. You are free to choose whether or not you and your child will take part in the study. If you agree to take part in the research, you will be asked to sign this consent form. This process is known as informed consent.

You are being approached to participate in this study because you participated in the Antenatal Late Preterm Steroids (ALPS): A Randomized Placebo-Controlled Trial to determine if giving steroids to women who are at risk for late preterm delivery will decrease the likelihood that the baby will need respiratory (breathing) support like a ventilator or oxygen soon after birth. The current study is a follow-up study to determine the effect of giving steroids to women who participated in this original study and whether this treatment leads to benefit in terms of cognitive function in your child at 6 years of age.

Thirteen medical centers across the country are participating in this follow-up research study. In all, 2000 children will be enrolled in this follow-up research study.

Length of the Follow-up Research Study

Your participation in this follow-up research study will occur just today and will last approximately two hours.

Information on Research Procedures

If your child participates in this follow-up research study, information from the original ALPS study will be used in this research study as well as height and weight measurements.

You and the child will be asked to allow the following measurement and assessment to be obtained from the child. This will take around one hour:

- Assessment of your child's cognition and learning abilities, measured by the Differential Ability Scales-II (DAS-II)

You will be asked questions about your child. These questions will take around 30 minutes to complete:

- Your child's health and motor function
- Your child's social abilities, using the Social Responsiveness Scale (SRS)
- Your child's social and behavioral abilities , using the Child Behavior Checklist (CBCL)

Even if you consent to participate in this follow-up research study, you may refuse any part of the follow-up research study or not answer any questions that make you feel uncomfortable.

Possible Risks

A risk of taking part in this study is the possibility of a loss of confidentiality. Loss of confidentiality includes having your personal information shared with someone who is not on the study team and was not supposed to see or know about your information. The study team plans to protect your confidentiality. The plans for keeping your information private are described in the 'confidentiality' section of this consent form.

The cognitive assessment should be fun for your child, but s/he may get tired of sitting or being asked questions.

Benefits

If you decide to take part in this follow-up research study, you and your child may not directly benefit from participation. However, you and your child may benefit from receiving the results of the neurocognitive assessments. The results of the assessments will be shared with you and a letter will be sent to you that you can share with your physician or your child's pediatrician. These assessments will be provided free of charge.

Alternative Procedures

The alternative to this follow-up research study is not to participate.

Costs

There will be no cost to you for the study visit.

Compensation

(THIS SECTION WILL BE CENTER SPECIFIC.) You will be paid $XX to compensate you for the time and travel associated with the research study.

Payment for Injury or Harm

(THIS SECTION WILL BE CENTER SPECIFIC.) This hospital is not able to offer financial compensation or absorb the costs of medical treatment in the event of injury resulting from the research. In the event of such injury, treatment will be provided but it is not provided free of charge. Since this is a research study, payment for any injury resulting from your participation in this research study may not be covered by some health insurance plans.

Right to Withdraw From the Research Study

This study is voluntary and it is up to you to decide whether or not you want to participate. You are free to withdraw your consent and stop taking part in this research study at any time without giving a reason. Refusal to take part or the decision to withdraw from the study will involve no penalty or loss of benefits to which you are otherwise entitled. Your refusal will not affect your legal rights or quality of health care that you will receive at this hospital.

Any significant new information which becomes available during your participation in this research, and which may affect your health, safety, or willingness to continue in this research study, will be given to you.

Right of the Investigator to Withdraw

The researchers of this institution or the National Institutes of Health can withdraw you from this study without your approval. A possible reason for withdrawal could be the early termination of the study by the National Institutes of Health.

Confidentiality

You have the right to privacy. All information obtained from this research that can be identified with you will remain confidential within the limits of the law.

If we lose track of you, study staff may collect information from the internet including social network sites in order to find your contact information.

The information collected for this research study will be held at the data coordinating center (George Washington University Biostatistics Center in Rockville, Maryland) in a database consisting of information from all of the participants in this study. Your information in the database will **only** be used for statistical analysis and may appear in scientific publications but will not identify you. The information at the data coordinating center will include your current and previous zip codes but does **not** include names, addresses, social security numbers, hospital numbers, or other personal identifiers.

Instead the data coordinating center will use a unique code for each participant consisting of a number and the first letter of your first name. The key to the code linking it to you will be kept here in a locked file. Only the research study staff employed for this study at this hospital will have access to the key to the code.

The following individuals and/or agencies will be able to look at and copy your research records:

The investigator (study doctor), study staff and other medical professionals who may be evaluating the study. Authorities from this institution, including the Institutional Review Board (IRB)

The Office of Human Research Protections (OHRP)

The National Institute of Child Health and Human Development (NICHD) which sponsors this study, including persons or organizations working with the sponsors, such as the data coordinating center, George Washington University Biostatistics Center in Rockville, Maryland.

The results of this research study will be provided to the sponsor, NICHD (and/or their representatives). In addition, data from this study will be put in a public data set that will be available to other research investigators. This public data set will not contain any identifying patient data and will not be used for commercial purposes.

A description of the ALPS clinical trial and this follow-up study is available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

This permission does not end unless you cancel it, even if you leave the study. You can cancel this permission any time except where a healthcare provider has already used or released your child's health information or relied on your permission to do something. Even if you cancel this authorization, the researchers may still use and disclose protected health information (PHI) they already have obtained about you as necessary to maintain the integrity or reliability of the research. However, no new protected health information or new biological specimens will be collected from you after you revoke your authorization.

To cancel your authorization, you will need to send a letter to < > stating that you are canceling your authorization. This letter must be signed and dated and sent to this address: < >. A copy of this revocation will be provided to the study doctor and his or her research team. Not signing this form or later canceling your permission will not affect your health care treatment outside the study, payment for health care from a health plan, or ability to get health plan benefits.

Your protected health information will be treated confidentially to the extent permitted by applicable laws and regulations. Federal law may allow someone who gets your health information from this study to use

or release it in some way not discussed in this section and no longer be protected by the HIPAA Privacy Rule.

By signing this form you authorize the study doctor and members of the research team to use and share with others (disclose) your PHI for the purpose of this study. If you do not wish to authorize the use or disclosure of your PHI, you cannot participate in this study because your PHI is necessary to conduct this study.

Certificate of Confidentiality

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by National Institute of Child Health and Human Development which is funding this project. You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

Questions

The researchers are available to answer your questions about this research. A representative of the Institutional Review Board is also available to answer questions about your child's rights as participants in research or to answer your questions about an injury or other complication resulting from your or your child's participation in this research study.

If you have questions or if your child is hurt while taking part in this research study, you should contact _____ at (___) ___-____.

If you have any questions about the informed consent process or any other rights as a research subject, please contact _____, at (____) ___-____. _____ .

Signatures

By signing below, you indicate that you have read this consent form, the study has been explained to you, your questions have been answered, and you agree to take part in this study. You do not give up any of your legal rights by signing this form. A copy of this consent form will be given to you

Study Participant

Print Name_____Signature_____Date _____

Person Obtaining Consent

Print Name_____Signature_____Date _____

The investigator or study team may wish to contact you in the future to request permission for additional research. Please initial the appropriate statement to indicate whether or not you give permission for future contact.

(Initial) YES_____ NO_____ I give permission to be contacted in the future for research purposes.

Investigator Statement

I certify that the research study has been explained to the above individual by me or my research staff including the purpose, the procedures, the possible risks and the potential benefits associated with participation in this research study. Any questions have been answered to the individual's satisfaction.

_____	_____	_____
Investigator Name *(Print Name)*	Signature	Date

B.2 Sample Informed Consent Form – with Common Rule 2018 changes

Research Study Title: The ALPS Neurocognitive Follow-Up Study

Sponsor*:* The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health

Principal Investigator: _____Phone (____) ___ - ____

Key Information

This research is being done to find out whether children who were born to women who received antenatal steroids have higher IQ and learning skills at 6 years of age. Women who took part in the Antenatal Late Preterm Steroids (ALPS) trial are eligible.

If you consent, you will be in the study for one day for your study visit. At the study visit, your child will participate in an assessment including IQ and learning skills. The research staff will collect information about your child's medical history including height, weight, moving (gross motor skills), and social and behavioral skills.

There are risks to the study that are described in this consent. The IQ and learning skills assessment should be fun for your child, but s/he may get tired of sitting or being asked questions.

You and your child may not directly benefit from participation. However, you and your child may benefit from receiving the results of the IQ and learning assessments, which you can share with your physician or your child's pediatrician. Participation in this research study is voluntary and if you do not take part, you will receive the routine care usually provided.

Introduction

You and your child are invited to take part in a research study. This consent form provides the information about the risks and benefits of the study. A member of the research team is available to answer your questions and to provide further explanations. You are free to choose whether or not you and your child will take part in the study. If you agree to take part in the research, you will be asked to sign this consent form. This process is known as informed consent.

You are being approached to participate in this study because you participated in the Antenatal Late Preterm Steroids (ALPS): A Randomized Placebo-Controlled Trial to determine if giving steroids to women who are at risk for late preterm delivery will decrease the likelihood that the baby will need respiratory (breathing) support like a ventilator or oxygen soon after birth. The current study is a follow-up study to determine the effect of giving steroids to women who participated in this original study and whether this treatment leads to benefit in terms of cognitive function in your child at 6 years of age.

Thirteen medical centers across the country are participating in this follow-up research study. In all, 2000 children will be enrolled in this follow-up research study.

Length of the Follow-up Research Study

Your participation in this follow-up research study will occur just today and will last approximately two hours.

Information on Research Procedures

If your child participates in this follow-up research study, information from the original ALPS study will be used in this research study as well as height and weight measurements.

You and the child will be asked to allow the following measurement and assessment to be obtained from the child. This will take around one hour:

- Assessment of your child's cognition and learning abilities, measured by the Differential Ability Scales-II (DAS-II)

You will be asked questions about your child. These questions will take around 30 minutes to complete:

- Your child's health and motor function
- Your child's social abilities, using the Social Responsiveness Scale (SRS)
- Your child's social and behavioral abilities , using the Child Behavior Checklist (CBCL)

Even if you consent to participate in this follow-up research study, you may refuse any part of the follow-up research study or not answer any questions that make you feel uncomfortable.

Possible Risks

A risk of taking part in this study is the possibility of a loss of confidentiality. Loss of confidentiality includes having your personal information shared with someone who is not on the study team and was not supposed to see or know about your information. The study team plans to protect your confidentiality. The plans for keeping your information private are described in the 'confidentiality' section of this consent form.

The cognitive assessment should be fun for your child, but s/he may get tired of sitting or being asked questions.

Benefits

If you decide to take part in this follow-up research study, you and your child may not directly benefit from participation. However, you and your child may benefit from receiving the results of the neurocognitive assessments. The results of the assessments will be shared with you and a letter will be sent to you that you can share with your physician or your child's pediatrician. These assessments will be provided free of charge.

Alternative Procedures

The alternative to this follow-up research study is not to participate.

Costs

There will be no cost to you for the study visit.

Compensation

By signing this consent form, you acknowledge and agree that in the event that this research project results in the development of any marketable product, you will have no ownership interest in the product and no right to share in any profits from its sale or commercialization.

(THIS SECTION WILL BE CENTER SPECIFIC.) You will be paid $XX to compensate you for the time and travel associated with the research study.

Payment for Injury or Harm

(THIS SECTION WILL BE CENTER SPECIFIC.) This hospital is not able to offer financial compensation or absorb the costs of medical treatment in the event of injury resulting from the research.

In the event of such injury, treatment will be provided but it is not provided free of charge. Since this is a research study, payment for any injury resulting from your participation in this research study may not be covered by some health insurance plans.

Right to Withdraw From the Research Study

This study is voluntary and it is up to you to decide whether or not you want to participate. You are free to withdraw your consent and stop taking part in this research study at any time without giving a reason. Refusal to take part or the decision to withdraw from the study will involve no penalty or loss of benefits to which you are otherwise entitled. Your refusal will not affect your legal rights or quality of health care that you will receive at this hospital.

Any significant new information which becomes available during your participation in this research, and which may affect your health, safety, or willingness to continue in this research study, will be given to you.

Right of the Investigator to Withdraw

The researchers of this institution or the National Institutes of Health can withdraw you from this study without your approval. A possible reason for withdrawal could be the early termination of the study by the National Institutes of Health.

Confidentiality

You have the right to privacy. All information obtained from this research that can be identified with you will remain confidential within the limits of the law.

If we lose track of you, study staff may collect information from the internet including social network sites in order to find your contact information.

The information collected for this research study will be held at the data coordinating center (George Washington University Biostatistics Center in Rockville, Maryland) in a database consisting of information from all of the participants in this study. Your information in the database will **only** be used for statistical analysis and may appear in scientific publications but will not identify you. The information at the data coordinating center will include your current and previous zip codes but does **not** include names, addresses, social security numbers, hospital numbers, or other personal identifiers.

Instead the data coordinating center will use a unique code for each participant consisting of a number and the first letter of your first name. The key to the code linking it to you will be kept here in a locked file. Only the research study staff employed for this study at this hospital will have access to the key to the code.

The following individuals and/or agencies will be able to look at and copy your research records:

The investigator (study doctor), study staff and other medical professionals who may be evaluating the study. Authorities from this institution, including the Institutional Review Board (IRB)

The Office of Human Research Protections (OHRP)

The National Institute of Child Health and Human Development (NICHD) which sponsors this study, including persons or organizations working with the sponsors, such as the data coordinating center, George Washington University Biostatistics Center in Rockville, Maryland.

The results of this research study will be provided to the sponsor, NICHD (and/or their representatives). In addition, data from this study will be put in a public data set that will be available to other research investigators. This public data set will not contain any identifying patient data and will not be used for commercial purposes. When the data set is shared, it will be done without obtaining additional permission from you.

A description of the ALPS clinical trial and this follow-up study is available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

This permission does not end unless you cancel it, even if you leave the study. You can cancel this permission any time except where a healthcare provider has already used or released your child's health information or relied on your permission to do something. Even if you cancel this authorization, the researchers may still use and disclose protected health information (PHI) they already have obtained about you as necessary to maintain the integrity or reliability of the research. However, no new protected health information or new biological specimens will be collected from you after you revoke your authorization.

To cancel your authorization, you will need to send a letter to < > stating that you are canceling your authorization. This letter must be signed and dated and sent to this address: < >. A copy of this revocation will be provided to the study doctor and his or her research team. Not signing this form or later canceling your permission will not affect your health care treatment outside the study, payment for health care from a health plan, or ability to get health plan benefits.

Your protected health information will be treated confidentially to the extent permitted by applicable laws and regulations. Federal law may allow someone who gets your health information from this study to use or release it in some way not discussed in this section and no longer be protected by the HIPAA Privacy Rule.

By signing this form you authorize the study doctor and members of the research team to use and share with others (disclose) your PHI for the purpose of this study. If you do not wish to authorize the use or disclosure of your PHI, you cannot participate in this study because your PHI is necessary to conduct this study.

Certificate of Confidentiality

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by National Institute of Child Health and Human Development which is funding this project. You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

Questions

The researchers are available to answer your questions about this research. A representative of the Institutional Review Board is also available to answer questions about your child's rights as participants

in research or to answer your questions about an injury or other complication resulting from your or your child's participation in this research study.

If you have questions or if your child is hurt while taking part in this research study, you should contact _____ at (___) ___-____.

If you have any questions about the informed consent process or any other rights as a research subject, please contact _____, at (____) ___-____. _____ .

Signatures

By signing below, you indicate that you have read this consent form, the study has been explained to you, your questions have been answered, and you agree to take part in this study. You do not give up any of your legal rights by signing this form. A copy of this consent form will be given to you

Study Participant

Print Name_____Signature_____Date _____

Person Obtaining Consent

Print Name_____Signature_____Date _____

The investigator or study team may wish to contact you in the future to request permission for additional research. Please initial the appropriate statement to indicate whether or not you give permission for future contact.

(Initial) YES_____ NO_____ I give permission to be contacted in the future for research purposes.

Investigator Statement

I certify that the research study has been explained to the above individual by me or my research staff including the purpose, the procedures, the possible risks and the potential benefits associated with participation in this research study. Any questions have been answered to the individual's satisfaction.

_____	_____	_____
Investigator Name *(Print Name)*	Signature	Date

B.3 Sample Assent Form

Research Purpose

We are asking you to be in a research study. This paper will tell you all about the study and help you decide whether or not to be in the study. Read this paper carefully and ask any questions you have.

You might have questions about

* what you will be asked to do,
* how long it will take,
* if the study is scary or dangerous, or
* if anyone will find out what you did.

When we have answered all of your questions, you can decide whether or not to be in the study. You can talk to your family about it before deciding.

Information on Research

What is a research study?

A research study is when doctors and nurses collect a lot of information to learn more about something. We are doing a study to learn more about the health of children. After we tell you about it, we will ask if you'd like to be in this research study or not.

Why are you being asked to be part of this research study?

When you were a baby, you were part of a research study. This is the second part of that study. We want to find out about your health now. So we are getting information from boys and girls like you who were in the first part of the study.

About 2,000 children will be in this study.

Why is the study being done?

The study may help to find out how a mom's and baby's health is related to the child's health a few years later.

What will happen to you if you are in this study?

Only if you agree, two things will happen:

1.) A nurse will ask your mom or dad questions.

2.) You will be asked to look at pictures, answer questions, work with cards and blocks and draw with a pencil.

Risks

Will any part of the study hurt or cause problems?

The study should be fun for you, but you may get tired of sitting or being asked questions.

Benefits

Will the study help you or others?

This study won't make you feel any different. But the doctors might find out something that will help other children like you stay healthy. By being part of this study, your family can get your results and better understand how healthy you are.

Alternative Procedures

What happens if you say no to this study?

*Nothing will happen. **You** will just go back home with your family.*

Confidentiality

Who will see the information collected about you?

The information collected about you during this study will be kept safely locked up. Nobody will know it except the people doing the research.

Compensation

What do you get for being in the study?

< >

Voluntary Participation

Do you have to be in the study?

You do not have to be in the study. No one will be upset if you don't want to do this study. If you don't want to be in this study, you just have to tell us. It's up to you.

Additional Information

Do your parents know about this study?

This study was explained to your parents and they said that we could ask you if you want to be in it. You can talk this over with them before you decide.

Do you have any questions?

You can ask questions any time. You can ask now. You can ask later. You can call any of the people whose names and phone numbers are listed on the first page. You can take more time to think about being in the study and talk some more with your parents about being in the study.

Other information about the study.

You can change your mind and stop being part of it at any time. All you have to do is tell one of the people in charge of the study.

You will be given a copy of this paper to keep.

If you decide to be in the study, please write your name below.

Signature

Child

Print Name_____Signature_____Date _____

Person Obtaining Assent

Print Name_____Signature_____Date _____

Check which applies (to be completed by the person conducting assent discussion).

☐ The subject is capable of reading and understanding the assent form and has signed above as documentation of assent to take part in this study.

☐ The subject is not capable of reading the assent form, however, the information was explained verbally to the subject who signed above to acknowledge the verbal explanation and his/her assent to take part in this study.

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Childhood Cognitive Function in a Birth Cohort after a Randomized Trial of Antenatal Corticosteroids: the ALPS Neurocognitive Follow-Up Study

Summary of Protocol Changes

Updated 11 Sep 2017

Affected Section(s)	Summary of Revisions Made	Rationale
Section 2.1 Background: Introduction	• Old text: "Long-term effects of late preterm steroid exposure are poorly understood because administration in this period is newly recommended, and clinical data are scant on the effect of late preterm steroid exposure on the developing brain. However, emerging evidence suggests that late preterm birth has an a priori risk of neurocognitive delay." • New text: "Long-term effects of late preterm steroid exposure are poorly understood because administration in this period is newly recommended, and clinical data are scant on the effect of late preterm steroid exposure on the developing brain*, though the available data are reassuring*. However, emerging evidence suggests that late preterm birth has an a priori risk of neurocognitive delay *compared with birth at term*."	Minor change in text for clarity
Section 2.2 Background: Steroids and Neurodevelopment	• Old text: "These findings were most recently described in a meta-analysis by Sotiriadis et al, which included randomized and non-randomized prospective studies of women delivering preterm who received a single course of antenatal corticosteroids." • New text: "*The long-term neurocognitive benefits of a single course of antenatal corticosteroids* were most recently described in a meta-analysis by Sotiriadis et al, which included randomized and non-randomized prospective studies of women delivering." • Old text: "Clinical studies of multiple course steroids have generally found worse neurodevelopmental outcomes compared with those who had a single course and delivered at term, but multiple	Minor change in text for clarity

	course steroids have fallen out of favor in most of the world." • New text: "Clinical studies of multiple course steroids have generally found worse neurodevelopmental outcomes compared with those who had a single course and delivered at term, but multiple course*s of* steroids *are not recommended in the United States and* have fallen out of favor in most of the world."	
Section 3.2 Study Design: Secondary Research Questions	Removed the following secondary outcomes: 4. Does antenatal betamethasone treatment at 34 to 36 weeks gestation compared with placebo have an effect on child height, weight, and BMI at age 6? 8. Is small birthweight for gestational age or large birthweight for gestational age associated with cognitive function in 6 year old children (among those from the placebo group)?	

Updated 25 Sep 2017

Affected Section(s)	Summary of Revisions Made	Rationale
Section 4.3 Study Procedures: Baseline Procedures	• Old text: "As an extension to the ALPS trial, additional details related to neonatal hypoglycemia will be abstracted from the neonatal medical records. Glucose values and the duration, severity, and treatments for hypoglycemia will be obtained." • New text: "As an extension to the ALPS trial, additional details related to neonatal hypoglycemia *was* abstracted from the neonatal medical records. Glucose values and the duration, severity, and treatments for hypoglycemia *that were* obtained *will be included in this dataset.*"	Clarified that the additional data on neonatal hypoglycemia was already collected.
Appendix B Sample Informed Consent Form Section B.1 Information on Research Procedures	• Old text: "If your child participates in this follow-up research study, you and the child will be asked to allow the following measurement and assessment to be obtained from the child." • New text: "If your child participates in this follow-up research study, *information from the original ALPS study will be used in this research study as well as height and weight measurements. Y*ou and the child will be asked to allow the following measurement and assessment to be obtained from the child."	Minor change in text for clarity

Updated 19 Oct 2017

Affected Section(s)	Summary of Revisions Made	Rationale
Section 4.5 Patient Management and Follow-up	• Old text: "Approximately two to four weeks following the visit, the parents/guardians will be sent a letter with pertinent neurodevelopment data as follows: DAS-II score and the range in scores that are within age expectation for learning/cognitive abilities, SRS score and the range in scores that are within age expectation for social abilities, CBCL score and the range in scores that are within age expectation for social and behavioral abilities" • New text: "Approximately two to four weeks following the visit, the parents/guardians will be sent a letter *reporting the* DAS-II score and the range in scores that are within age expectation for learning/cognitive abilities."	Minor change in text for clarity
Appendix B: Sample Informed Consent Form	Added certificate of confidentiality section to the informed consent forms: *"This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.*	

	The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by National Instutute of Child Health and Human Development which is funding this project. You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it."	

Updated 1 Apr 2019

Affected Section(s)	**Summary of Revisions Made**	**Rationale**
Appendix B.1 Sample Informed Consent Form – without Common Rule 2018 changes	• Added *"– without Common Rule 2018 changes"* to title • Corrected typo in Certificate of Confidentiality section *"Institute"*	Clarified that this is the consent without the optional changes to comply with 2018 Common Rule and fixed typo
Appendix B.2 Sample Informed Consent Form – with Common Rule 2018 changes	Added consent form with Common Rule 2018 changes: • Added key information • Added to compensation *"By signing this consent form, you acknowledge and agree that in the event that this research project results in the development of any marketable product, you will have no ownership interest in the product and no right to share in any profits from its sale or commercialization."* • Added to confidentiality *"When the data set is shared, it will be done without obtaining additional permission from you."*	Optional changes to comply with the 2018 Common Rule (if implementation required by a site IRB)

Title: Childhood Cognitive Function in a Birth Cohort after a Randomized Trial of Antenatal Corticosteroids: the ALPS Neurocognitive Follow-Up Study

Objectives:

Primary Objective

1. To examine whether children of mothers who were at risk of a late preterm delivery and treated with corticosteroids have an effect on cognitive function compared with children whose mothers did not receive corticosteroids.

Secondary Objectives

1. Does antenatal betamethasone at 34 to 36 weeks gestation compared with placebo have an effect on any sub component of the DAS-II (verbal ability, non-verbal reasoning ability, and spatial ability)?
2. Does antenatal betamethasone at 34 to 36 weeks gestation have an effect on the frequency of screening positive on the Social Responsiveness Scale (SRS) for autism spectrum conditions at age 6?
3. Does antenatal betamethasone at 34 to 36 weeks gestation have an effect on childhood behavioral and emotional problems as measured by the child behavior checklist at age 6?

Study population:

- ALPS children enrolled in follow-up

Exposures:

- Antenatal betamethasone vs. placebo

Outcomes:

- Primary Outcome: Dichotomous general conceptual ability score (GCA) from DAS-II (<85 vs. ≥85)

- Secondary Outcomes

Outcome	Age	Form	Question on form
GCA (continuous)			DAS-II
Verbal ability	<7 yrs old	AF07A and AF07C	Sum of T-scores calculated from raw scores on Verbal Comprehension and Naming Vocabulary
	≥7 yrs old	AF07H and AF07I	Sum of T-scores calculated from raw scores on Word Definitions and Verbal Similarities
Non-verbal reasoning	<7 yrs old	AF07B and AF07E	Sum of T-scores calculated from raw scores on Picture Similarities and Matrices
	≥7 yrs old	AF07E and AF07J	Sum of T-scores calculated from raw scores on Matrices and Sequential and Quantitative Reasoning

Spatial ability	<7 yrs old	AF07D and AF07F	Sum of T-scores calculated from raw scores on Pattern Construction and Copying
	≥7 yrs old	AF07D and AF07G	Sum of T-scores calculated from raw scores on Pattern Construction and Recall of Designs
SRS total score ≥ 60		AF09	T-scores
GMFCS level		AF06	Q.9 Gross Motor Function Classification System (GMFCS)
CBCL scores		AF08	
Total problems		AF08	T-scores & percent for normal, borderline, clinical
Internalizing behavior		AF08	T-scores & percent for normal, borderline, clinical
Externalizing behavior		AF08	T-scores & percent for normal, borderline, clinical
Dysregulation profile		AF08	Raw scores & percent for normal, borderline, clinical
Anxious/depressed		AF08	Raw scores & percent for normal, borderline, clinical
Attention problems		AF08	Raw scores & percent for normal, borderline, clinical
Aggressive behavior		AF08	Raw scores & percent for normal, borderline, clinical

Statistical analyses:

- Baseline characteristics will be compared between participants and non-participants.
- All analyses that examine whether prenatal treatment with betamethasone (vs. placebo) confers long-term benefit will follow the intention-to-treat approach.
- Child characteristics: Chi-square will be used for categorical variables and the Wilcoxon signed-rank test will be used for continuous variables
- Covariates: maternal age, GA at delivery (weeks), child's age, gender, and maternal education (college degree or higher)
- An evaluation of treatment by center will be included and analyses will account for center, either by adjusting for center in a multivariable model or by using mixed models.
- Primary outcome analysis: Log-binomial regression will be performed to compare binomial proportions and the relative risk and confidence interval will be reported
- Sensitivity analyses:
    - A sensitivity analysis including participants lost to follow-up will be applied with different assumptions regarding their outcome, to determine whether the results are robust (assume all have the primary outcome and then all do not have the primary outcome).
        - Loss to follow-up will be defined for those children where consent for the study has been obtained but it was not possible to administer the DAS-II (participants

with invalid scores due to examiner error and participants who refused to complete the DAS-II).

- A sensitivity analysis including participants who refused to participate or were excluded due to severe autism, developmental delay or maternal or child deaths will also be conducted. In the sensitivity analysis, these children will be assigned a GCA < 85.

- Secondary outcome analyses:
  - Dichotomous outcomes: Log-binomial regression will be performed to compare binomial proportions and the relative risk and confidence interval will be reported
  - Continuous outcomes: General linear models including analysis of variance will be used to test for differences.

Tables:

- Table 1. Maternal and Child Characteristics by Treatment Group
- Table 2. Primary and Secondary Outcomes

Table 1. Maternal and Child Characteristics by Treatment Group

Characteristic	Betamethasone (N=)	Placebo (N=)
Original Trial, Maternal		
Race/ethnicity		
Black/African American	N (%)	N (%)
White	N (%)	N (%)
Asian	N (%)	N (%)
Hispanic	N (%)	N (%)
Other/unknown	N (%)	N (%)
Age, y	Mean (SD)	Mean (SD)
Gestational age at delivery, weeks	Mean (SD)	Mean (SD)
Small for gestational age (< 10^{th} percentile)	N (%)	N (%)
Follow-up Study, Child		
Age, y	Mean (SD)	Mean (SD)
Gender		
Female	N (%)	N (%)
Male	N (%)	N (%)
Private insurance	N (%)	N (%)
Race/ethnicity		
Black/African American	N (%)	N (%)
White	N (%)	N (%)
Hispanic	N (%)	N (%)
Other/unknown	N (%)	N (%)
College degree or higher (maternal)	N (%)	N (%)

Table 2. Primary and Secondary Outcomes

Outcome	Betamethasone (N=)	Placebo (N=)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
GCA	Mean (SD)	Mean (SD)	Mean Difference (95% CI)	Mean Difference (95% CI)
GCA < 85	N (%)	N (%)	RR (95% CI)	RR (95% CI)
Verbal ability	Mean (SD)	Mean (SD)	Mean Difference (95% CI)	Mean Difference (95% CI)
Non-verbal reasoning	Mean (SD)	Mean (SD)	Mean Difference (95% CI)	Mean Difference (95% CI)
Spatial ability	Mean (SD)	Mean (SD)	Mean Difference (95% CI)	Mean Difference (95% CI)
SRS t-score ≥60	N (%)	N (%)	RR (95% CI)	RR (95% CI)
GMFCS level				
Level I	N (%)	N (%)	Referent	Referent
Level II	N (%)	N (%)	RR (95% CI)	RR (95% CI)
Level III	N (%)	N (%)	RR (95% CI)	RR (95% CI)
Level IV	N (%)	N (%)	RR (95% CI)	RR (95% CI)
Level V	N (%)	N (%)	RR (95% CI)	RR (95% CI)
CBCL				
Total problems t-score	Mean (SD)	Mean (SD)	Mean Difference (95% CI)	Mean Difference (95% CI)
Normal	N (%)	N (%)		
Borderline	N (%)	N (%)		
Clinical	N (%)	N (%)		
Internalizing behavior t-score	Mean (SD)	Mean (SD)	Mean Difference (95% CI)	Mean Difference (95% CI)
Normal	N (%)	N (%)		
Borderline	N (%)	N (%)		
Clinical	N (%)	N (%)		
Externalizing behavior t-score	Mean (SD)	Mean (SD)	Mean Difference (95% CI)	Mean Difference (95% CI)
Normal	N (%)	N (%)		
Borderline	N (%)	N (%)		
Clinical	N (%)	N (%)		
Dysregulation profile	Mean (SD)	Mean (SD)	Mean Difference (95% CI)	Mean Difference (95% CI)
Anxious/depressed	Mean (SD)	Mean (SD)	Mean Difference (95% CI)	Mean Difference (95% CI)
Normal	N (%)	N (%)		
Borderline	N (%)	N (%)		
Clinical	N (%)	N (%)		

Attention problems	Mean (SD)	Mean (SD)	Mean Difference (95% CI)	Mean Difference (95% CI)
Normal	N (%)	N (%)		
Borderline	N (%)	N (%)		
Clinical	N (%)	N (%)		
Aggressive behavior	Mean (SD)	Mean (SD)	Mean Difference (95% CI)	Mean Difference (95% CI)
Normal	N (%)	N (%)		
Borderline	N (%)	N (%)		
Clinical	N (%)	N (%)		

Dr. Cynthia Gyamfi-Bannerman

10/24/22

Title: Childhood Cognitive Function in a Birth Cohort after a Randomized Trial of Antenatal Corticosteroids: the ALPS Neurocognitive Follow-Up Study

Objectives:

Primary Objective

1. To examine whether children of mothers who were at risk of a late preterm delivery and treated with corticosteroids have an effect on cognitive function compared with children whose mothers did not receive corticosteroids.

Secondary Objectives

1. Does antenatal betamethasone at 34 to 36 weeks gestation compared with placebo have an effect on any sub component of the DAS-II (verbal ability, non-verbal reasoning ability, and spatial ability)?
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3. Does antenatal betamethasone at 34 to 36 weeks gestation have an effect on childhood behavioral and emotional problems as measured by the child behavior checklist at age 6?

Study population:

- ALPS children enrolled in follow-up

Exposures:

- Antenatal betamethasone vs. placebo

Outcomes:

- Primary Outcome: Dichotomous general conceptual ability score (GCA) from DAS-II (<85 vs. ≥85)

- Secondary Outcomes

Outcome	Age	Form	Question on form
GCA (continuous)			DAS-II
Verbal ability	<7 yrs old	AF07A and AF07C	Sum of T-scores calculated from raw scores on Verbal Comprehension and Naming Vocabulary
	≥7 yrs old	AF07H and AF07I	Sum of T-scores calculated from raw scores on Word Definitions and Verbal Similarities
Non-verbal reasoning	<7 yrs old	AF07B and AF07E	Sum of T-scores calculated from raw scores on Picture Similarities and Matrices
	≥7 yrs old	AF07E and AF07J	Sum of T-scores calculated from raw scores on Matrices and Sequential and Quantitative Reasoning

Spatial ability	<7 yrs old	AF07D and AF07F	Sum of T-scores calculated from raw scores on Pattern Construction and Copying
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SRS total score > 65		AF09	T-scores
GMFCS level		AF06	Q.9 Gross Motor Function Classification System (GMFCS)
CBCL scores		AF08	
Total problems		AF08	T-scores & percent for normal, borderline, clinical
Internalizing behavior		AF08	T-scores & percent for normal, borderline, clinical
Externalizing behavior		AF08	T-scores & percent for normal, borderline, clinical
Dysregulation profile		AF08	T-scores & percent for normal, borderline, clinical
Anxious/depressed		AF08	T-scores & percent for normal, borderline, clinical
Attention problems		AF08	T-scores & percent for normal, borderline, clinical
Aggressive behavior		AF08	T-scores & percent for normal, borderline, clinical

Statistical analyses:

- Baseline characteristics will be compared between participants and non-participants.
- All analyses that examine whether prenatal treatment with betamethasone (vs. placebo) confers long-term benefit will follow the intention-to-treat approach.
- Child characteristics: Chi-square will be used for categorical variables and the Wilcoxon signed-rank test will be used for continuous variables
- Covariates: maternal age, GA at delivery (weeks), child's age, gender, and maternal education (college degree or higher)
- An evaluation of treatment by center will be included and analyses will account for center, either by adjusting for center in a multivariable model or by using mixed models.
- Primary outcome analysis: Log-binomial regression will be performed to compare binomial proportions and the relative risk and confidence interval will be reported
- Sensitivity analyses:
    - A sensitivity analysis including participants lost to follow-up will be applied with different assumptions regarding their outcome, to determine whether the results are robust (assume all have the primary outcome and then all do not have the primary outcome).
        - Loss to follow-up will be defined for those children where consent for the study has been obtained but it was not possible to administer the DAS-II (participants

with invalid scores due to examiner error and participants who refused to complete the DAS-II).

- A sensitivity analysis including participants who refused to participate or were excluded due to severe autism, developmental delay, custody issues, or maternal or child deaths will also be conducted. In the sensitivity analysis, children documented as having a neuromotor/neurological condition, cognitive condition, or behavioral condition on the AF01A Exclusion Form will be included and assigned a GCA < 85.

- Secondary outcome analyses:
  - Dichotomous outcomes: Log-binomial regression will be performed to compare binomial proportions and the relative risk and confidence interval will be reported
  - Continuous outcomes: General linear models including analysis of variance will be used to test for differences.

Tables:

- Table 1. Maternal and Child Characteristics by Treatment Group
- Table 2. Primary and Secondary Outcomes

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Follow-up Study, Child		
Age, y	Mean (SD)	Mean (SD)
Gender		
Female	N (%)	N (%)
Male	N (%)	N (%)
Private insurance	N (%)	N (%)
Race/ethnicity		
Black/African American	N (%)	N (%)
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Hispanic	N (%)	N (%)
Other/unknown	N (%)	N (%)
College degree or higher (maternal)	N (%)	N (%)

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Outcome	Betamethasone (N=)	Placebo (N=)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
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Non-verbal reasoning	Mean (SD)	Mean (SD)	Mean Difference (95% CI)	Mean Difference (95% CI)
Spatial ability	Mean (SD)	Mean (SD)	Mean Difference (95% CI)	Mean Difference (95% CI)
SRS t-score >65	N (%)	N (%)	RR (95% CI)	RR (95% CI)
GMFCS level				
Level I	N (%)	N (%)	Referent	Referent
Level II	N (%)	N (%)	RR (95% CI)	RR (95% CI)
Level III	N (%)	N (%)	RR (95% CI)	RR (95% CI)
Level IV	N (%)	N (%)	RR (95% CI)	RR (95% CI)
Level V	N (%)	N (%)	RR (95% CI)	RR (95% CI)
CBCL				
Total problems t-score	Mean (SD)	Mean (SD)	Mean Difference (95% CI)	Mean Difference (95% CI)
Normal	N (%)	N (%)		
Borderline	N (%)	N (%)		
Clinical	N (%)	N (%)		
Internalizing behavior t-score	Mean (SD)	Mean (SD)	Mean Difference (95% CI)	Mean Difference (95% CI)
Normal	N (%)	N (%)		
Borderline	N (%)	N (%)		
Clinical	N (%)	N (%)		
Externalizing behavior t-score	Mean (SD)	Mean (SD)	Mean Difference (95% CI)	Mean Difference (95% CI)
Normal	N (%)	N (%)		
Borderline	N (%)	N (%)		
Clinical	N (%)	N (%)		
Dysregulation profile	Mean (SD)	Mean (SD)	Mean Difference (95% CI)	Mean Difference (95% CI)
Anxious/depressed	Mean (SD)	Mean (SD)	Mean Difference (95% CI)	Mean Difference (95% CI)
Normal	N (%)	N (%)		
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Clinical	N (%)	N (%)		

Attention problems	Mean (SD)	Mean (SD)	Mean Difference (95% CI)	Mean Difference (95% CI)
Normal	N (%)	N (%)		
Borderline	N (%)	N (%)		
Clinical	N (%)	N (%)		
Aggressive behavior	Mean (SD)	Mean (SD)	Mean Difference (95% CI)	Mean Difference (95% CI)
Normal	N (%)	N (%)		
Borderline	N (%)	N (%)		
Clinical	N (%)	N (%)		

Childhood Cognitive Function in a Birth Cohort after a Randomized Trial of Antenatal Corticosteroids: the ALPS Neurocognitive Follow-Up Study

Summary of Statistical Analysis Plan Changes

Updated 2 Nov 2022

Affected Section(s)	**Summary of Revisions Made**	**Rationale**
Outcomes	Changed cutoff for screening positive on the Social Responsiveness Scale to t-scores >65 instead of ≥60	Modified so that the outcome reflects moderate to severe impairment in reciprocal social behavior
Outcomes	Changed "raw scores" to "t-scores" for dysregulation profile, anxious/depressed, attention problems, and aggressive behavior	Clarified that these outcomes for the Childhood Behavior Checklist would be reported as t-scores
Sensitivity Analyses	• Old text: "A sensitivity analysis including participants who refused to participate or were excluded due to severe autism, developmental delay or maternal or child deaths will also be conducted. In the sensitivity analysis, these children will be assigned a GCA < 85." • New text: "A sensitivity analysis including participants who refused to participate or were excluded due to severe autism, developmental delay, *custody issues,* or maternal or child deaths will also be conducted. In the sensitivity analysis, *children documented as having a neuromotor/neurological condition, cognitive condition, or behavioral condition on the AF01A Exclusion Form will be included and* assigned a GCA < 85.	Clarified that the second sensitivity analysis would include children with custody issues and that in the sensitivity analysis children documented as having a neuromotor/neurological condition, cognitive condition, or behavioral condition would be considered to have the primary outcome.