

MFM Neo Clinical Trials Workshop Information
August 2016

At the NICHD Young Investigators Meeting, there is a Clinical Trials Workshop. In this activity, we will be discussing and designing a clinical trial. Prior to the workshop there will be a presentation on the topic to set the stage. In addition, the questions below will help you to prepare for the workshop – you will be expected to have reviewed this material and the suggested reading to actively participate in the workshop.

Questions to help you prepare for the Clinical Trial Design Workshop:
Use of Antenatal Steroids to Improve Outcomes in Periviable Preterm gestation

1. What is the quality of evidence for each of the following*
 - Antenatal corticosteroids (ACS) administered at 24-34 weeks gestation reduce the neonatal complications in infants
 - ACS administered at 20-23 weeks weeks gestation reduce the neonatal complications in infants
 - Is there clinical equipoise?
2. Before doing a RCT on the use of ACS in the perviable preterm period, is there a need for (a) descriptive epidemiology (b) observational study to determine if there are associated morbidities and assess the effectiveness and safety of treatment? Are these studies possible?
3. In an investigative design, what treatment regimens should/can be compared?
4. Masking: Should/can the treatment groups be masked or "blinded"? How could this be accomplished? Can the allocation, intervention, and assessments be masked?
5. Primary outcome:
 - a) Should this be efficacy or safety of the treatment? Which outcome(s) should be included as clinically significant measures? How do you specify the outcome measure(s)? Which should be the primary outcome? What should be the effect size?
 - b) Which perinatal outcome(s) are of secondary importance, but worthwhile collecting data on?
 - c) Are there any long-term effects that should be measured in the infants/mothers exposed in this protocol?
6. Are there possible adverse events or side effects that should be monitored?
7. "Study condition": This is the population with the "condition of interest". What would be the ideal study condition to test?
8. Study population:
 - a) What group of patients would you screen to obtain the study population?
 - b) What would your inclusion and exclusion criteria be?

*Quality of Evidence:

- I. One RCT
 - II. Controlled Trials / No randomization
 - cohort (case control studies)
 - multiple time series / dramatic effect
 - III. Opinion of experts / descriptive studies, expert committees
9. What proportion of women with the condition would be ineligible by the criteria? Are the inclusion and exclusion criteria likely to allow generalizability (external validity)?
 10. Are there any subgroups that should be focused on for stratification and/or analysis (age, race, ethnicity, parity, multiple gestation, etc)? What is the effect of subgroup analysis on study design? Should the trial be powered for subgroup analysis?
 11. To what extent would you "standardize" the clinical managements of the randomized patients? What method will be used to implement a random allocation sequence? Will the allocation be concealed until the intervention starts?

12. If a well-designed RCT showed no difference between groups, how would you explain these results?
13. **Sample Size** (will be discussed at the meeting)
 - a) Prevalence of primary outcome: How would you go about estimating the frequency of the primary outcome in this population?
 - b) Effect size: How much more effective should treatment be than non-treatment in terms of the primary outcome?
14. **Feasibility** (will be discussed at the meeting)
 - a) Study sample: What proportion of the eligible pool would reasonably consent to be randomized in a RCT?
 - b) How many pregnancies would be required to recruit the required sample?
15. Compliance with protocol and Protocol violations: how important is compliance with the protocol? What effect does protocol violations, withdrawals or loss to follow up have on the interpretation of the results? Would you exclude patients with protocol violations or who withdraw?
16. Statistical analysis. What statistical methods will be used to analyze the primary outcomes? What methods will be used to analyze the secondary outcomes?

Suggested Reading

American College of Obstetricians and Gynecologists. Antenatal Corticosteroid therapy for fetal maturation. Committee Opinion Number 273, May 2002.

American College of Obstetricians and Gynecologists Periviable birth: Interim update. *Am J Obstet Gynecol*. 2016 Apr 19. pii: S0002-9378(16)30058-8. doi: 10.1016/j.ajog.2016.04.017. [Epub ahead of print]

Ancel PY, Goffinet F; EPIPAGE-2 Writing Group, Kuhn P, Langer B, Matis J, Hernandorena X, Chabanier P, Joly-Pedespan L, Lecomte B, Vendittelli F, Dreyfus M, Guillois B, Burguet A, Sagot P, Sizun J, Beuchée A, Rouget F, Favreau A, Saliba E, Bednarek N, Morville P, Thiriez G, Marpeau L, Marret S, Kayem G, Durrmeyer X, Granier M, Baud O, Jarreau PH, Mitanchez D, Boileau P, Boulot P, Cambonie G, Daudé H, Bédu A, Mons F, Fresson J, Vieux R, Alberge C, Arnaud C, Vayssière C, Truffert P, Pierrat V, Subtil D, D'Ercole C, Gire C, Simeoni U, Bongain A, Sentilhes L, Rozé JC, Gondry J, Leke A, Deiber M, Claris O, Picaud JC, Ego A, Debillon T, Poulichet A, Coliné E, Favre A, Fléchelles O, Samperiz S, Ramful D, Branger B, Benhammou V, Foix-L'Hélias L, Marchand-Martin L, Kaminski M. Survival and morbidity of preterm children born at 22 through 34 weeks' gestation in France in 2011: results of the EPIPAGE-2 cohort study. *JAMA Pediatr*. 2015 Mar;169(3):230-8.

Boghossian NS, McDonald SA, Bell EF, Carlo WA, Brumbaugh JE, Stoll BJ, Laptook AR, Shankaran S, Walsh MC, Das A, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Association of Antenatal Corticosteroids With Mortality, Morbidity, and Neurodevelopmental Outcomes in Extremely Preterm Multiple Gestation Infants. *JAMA Pediatr*. 2016 Jun 1;170(6):593-601

Bonanno C, Wapner RJ. Antenatal corticosteroids in the management of preterm birth: are we back where we started? *Obstet Gynecol Clin North Am*. 2012 Mar;39(1):47-63.

Carlo WA, McDonald SA, Fanaroff AA, Vohr BR, Stoll BJ, Ehrenkranz RA, Andrews WW, Wallace D, Das A, Bell EF, Walsh MC, Laptook AR, Shankaran S, Poindexter BB, Hale EC, Newman NS, Davis AS, Schibler K, Kennedy KA, Sánchez PJ, Van Meurs KP, Goldberg RN, Watterberg KL, Faix RG, Frantz ID 3rd, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Association of antenatal corticosteroids with mortality and neurodevelopmental outcomes among infants born at 22 to 25 weeks' gestation. *JAMA*. 2011 Dec 7;306(21):2348-58.

Chauhan SP, Ananth CV. Periviable births: epidemiology and obstetrical antecedents. *Semin Perinatol*. 2013 Dec;37(6):382-8

Collaborative Group on Antenatal Steroid Therapy. Effect of antenatal steroid administration on the infant: Long-term follow-up. *J Pediatr* 104:259-267, 1984.

Costeloe KL, Hennessy EM, Haider S, Stacey F, Marlow N, Draper ES. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). *BMJ*. 2012 Dec 4;345:e7976

Crane JM, Magee LA, Lee T, Synnes A, von Dadelszen P, Dahlgren L, De Silva DA, Liston R; Canadian Perinatal Network (CPN) Collaborative Group. Maternal and perinatal outcomes of pregnancies delivered at 23 weeks' gestation. *J Obstet Gynaecol Can*. 2015 Mar;37(3):214-24.

Crowley P, Chalmers, I, Keirse MFNC. The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials. *Br J Obstet Gynaecol* 97:11-25, 1990.

Cummings J; COMMITTEE ON FETUS AND NEWBORN. Antenatal Counseling Regarding Resuscitation and Intensive Care Before 25 Weeks of Gestation. *Pediatrics*. 2015 Sep;136(3):588-95.

EXPRESS Group, Fellman V, Hellström-Westas L, Norman M, Westgren M, Källén K, Lagercrantz H, Marsál K, Serenius F, Wennergren M. One-year survival of extremely preterm infants after active perinatal care in Sweden. *JAMA*. 2009 Jun 3;301(21):2225-33.

Gilbert WM, Nesbitt TS, Danielson B. The cost of prematurity: quantification by gestational age. *Obstet Gynecol* 102:488-492, 2003.

Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics* 50:515-525, 1972.

Litmanovitz I, Reichman B, Arnon S, Boyko V, Lerner-Geva L, Bauer-Rusak S, Dolfin T; Israel Neonatal Network. Perinatal factors associated with active intensive treatment at the border of viability: a population-based study. *J Perinatol*. 2015 Sep;35(9):705-11.

Mercer BM, Raju TN. Periviable birth: management and counseling issues--volume 1. *Semin Perinatol*. 2013 Dec;37(6):381.

NIH Consensus Development Panel. Effect of corticosteroids for fetal maturation on perinatal outcomes. *JAMA* 1995;273:413-418.

Partridge JC, Robertson KR, Rogers EE, Landman GO, Allen AJ, Caughey AB. Resuscitation of neonates at 23 weeks' gestational age: a cost-effectiveness analysis. *J Matern Fetal Neonatal Med*. 2015 Jan;28(2):121-30.

Raju TN, Mercer BM, Burchfield DJ, Joseph GF Jr. Periviable birth: executive summary of a joint workshop by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, American Academy of Pediatrics, and American College of Obstetricians and Gynecologists. *Obstet Gynecol*. 2014 May;123(5):1083-96.

Rysavy MA, Li L, Bell EF, Das A, Hintz SR, Stoll BJ, Vohr BR, Carlo WA, Shankaran S, Walsh MC, Tyson JE, Cotten CM, Smith PB, Murray JC, Colaizy TT, Brumbaugh JE, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Between-hospital variation in treatment and outcomes in extremely preterm infants. *N Engl J Med*. 2015 May 7;372(19):1801-11.

Salihu HM, Salinas-Miranda AA, Hill L, Chandler K. Survival of pre-viable preterm infants in the United States: a systematic review and meta-analysis. *Semin Perinatol*. 2013 Dec;37(6):389-400.

Smith PB, Ambalavanan N, Li L, Cotten CM, Laughon M, Walsh MC, Das A, Bell EF, Carlo WA, Stoll BJ, Shankaran S, Lupton AR, Higgins RD, Goldberg RN; Generic Database Subcommittee; Eunice Kennedy Shriver National Institute of Child Health Human Development

Neonatal Research Network. Approach to infants born at 22 to 24 weeks' gestation: relationship to outcomes of more-mature infants. *Pediatrics*. 2012 Jun;129(6):e1508-16

Smolders-deHaas H, Neuvel J, Schmand B, et al. Physical development and medical history of children who were treated antenatally with corticosteroids to prevent respiratory distress syndrome: A 10-12 year follow-up. *Pediatrics* 86:65-70, 1990.

Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, Laptook AR, Sánchez PJ, Van Meurs KP, Wyckoff M, Das A, Hale EC, Ball MB, Newman NS, Schibler K, Poindexter BB, Kennedy KA, Cotten CM, Watterberg KL, D'Angio CT, DeMauro SB, Truog WE, Devaskar U, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012. *JAMA*. 2015 Sep 8;314(10):1039-51.

Tucker Edmonds B, McKenzie F, Panoch JE, Barnato AE, Frankel RM. Comparing obstetricians' and neonatologists' approaches to periviable counseling. *J Perinatol*. 2015 May;35(5):344-8

Wapner RJ. Antenatal corticosteroids for periviable birth. *Semin Perinatol*. 2013 Dec;37(6):410-413.

Wapner RJ. Antenatal corticosteroids for periviable birth. *Semin Perinatol*. 2013 Dec;37(6):410-3.