PROTOCOL FOR THE MULTISITE INVENTORY OF NEONATAL-PERINATAL INTERVENTIONS (MINI) STUDY

A) Background:

Although births at 22-23 weeks' gestation comprise 1 in 1000 live births in the U.S. (an incidence similar to fetal alcohol syndrome or Down syndrome), they account for nearly 1 in 7 deaths during the first year of life.[1] Rates of morbidity in these infants are several-fold higher than in infants born a few weeks later.[2] Only a few case reports exist of infants surviving birth at 21 weeks' gestation;[3] however, most infants born at 24 weeks' gestation in the developed world survive.[4] Therefore, infants born at 22-23 weeks comprise a "gray zone" for postnatal viability in most developed countries.[5] For these infants, substantial variations in medical care and outcomes exist between countries and between hospitals within the same country.[6]

Moreover, the landscape for care has changed rapidly for infants born at 22-23 weeks' gestation. From 2014 to 2019, the rate of active treatment for infants born alive at 22 weeks' gestation in the U.S. more than doubled, from 26% to 58%.[1] Despite high early mortality rates, in the U.S. alone, based on linked birth-death certificate records, greater than 1000 babies born at 22-23 weeks' gestation each year now survive the first year of life.[7] Similar trends have been seen elsewhere around the world.

Published evidence to guide clinical care for births at 22-23 weeks' gestation is lacking and there are limited data on the outcomes of these infants. While many studies group infants born at 22 and 26 weeks together as "extremely preterm" (<28 weeks) or "extremely low birth weight" (<1000 g)," these terms belie substantial heterogeneity in outcomes and physiology for infants born during this window of maturation. Challenges to the study and care of infants born at 22-23 weeks include that: their numbers are often small at any single hospital; their birth is often unplanned and urgent; and their inpatient care is often complex and prolonged with many factors influencing infants' eventual outcomes. An analysis by our group showed that, of 201 randomized controlled trials of extremely preterm infants from 2010-2019, fewer than 2% of enrolled infants (n=454/32442) were identified as being born at <24 weeks' gestation.[8] Because strategies for successful management of infants born at 22-23 weeks' gestation remain unclear, there are wide variations in practice within and between centers. Persistent challenges and controversies in care include: the optimal methods of delivery, support for postnatal transition, early respiratory and cardiovascular support, nutrition, and strategies to mitigate long-term morbidity.

B) Study goal:

The goal of the Tiny Baby Collaborative Multicenter Inventory of Neonatal-Perinatal Interventions (MINI) study is to serve as a registry detailing the outcomes and practices for all deliveries and infants admitted to intensive care at 22-23 weeks' gestation at participating hospitals.

The study will serve to detail the epidemiology of important perinatal interventions and outcomes for this inadequately studied group and suggest hypotheses about how to further improve care of the maternal-infant dyad. Data collected in this study will be used for real-time assessment of local perinatal care practices and may serve as the basis for local changes/quality improvement. Moreover, they will serve to identify "potentially better practices" that may be desirable for wider implementation.

C) Study design:
Prospective observational study

D) Subject population timeframe:
Inclusion criteria

1) All local births with gestational ages of 22 weeks 0 days - 23 weeks 6 days, regardless of pregnancy outcome or neonatal intensive care (NICU) admission; AND
2) All outborn NICU admissions with gestational age at birth of 22 weeks 0 days - 23 weeks 6 days

Timeframe
Centers will begin prospectively entering data upon study entry for all consecutive eligible births and NICU admissions. Where possible, retrospective data of up to 3 years has also been requested.

E) Methods and procedures:
Data will be collected from the hospital medical record by identified local personnel. Data for the study will be kept in a password-protected REDCap database securely housed and administered at Nationwide Children's Hospital. Only de-identified data will be shared and collated for this study. Each data entry will receive a unique ID number specific to the Tiny Baby Collaborative MINI Study. Each participating hospital will have access only to its own data from the de-identified REDCap database. The only protected health information (PHI) obtained for this study will be kept locally, per local hospital guidelines, and used to assure valid data collection on the correct subject. These guidelines will include, at a minimum, that any local PHI is kept on password protected computer files and/or in locked cabinets that only the local site PI and approved research personnel can access, and that PHI is destroyed after termination of the study. The database administrators at Nationwide Children's Hospital will have access to all participating hospitals' de-identified data. Data use agreements will be signed prior commencing local data collection. Database administrators will maintain the database on institutional servers at Nationwide Children's Hospital.

Data to be collected
The following forms comprise the minimum dataset for the MINI Study. See **Figure** for details on data collection.

- M00 - Screening
- M01 - Demographics
- M02 - Antenatal practices
- M03 - Delivery room practices
- M04 - Transport details
- M05 – NICU practices
- M06 - Neonatal outcome

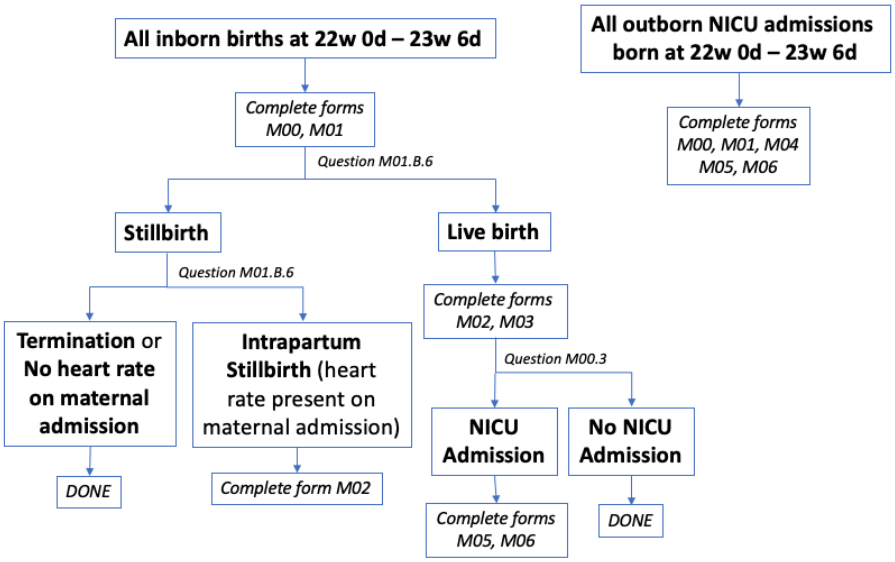

Figure. Data collection form flowchart

F) Responsibilities of participating hospitals:

- Each participating hospital must provide contact information for the person responsible for data submission.
- Each participating hospital must have IRB approval.
- Each participating hospital must complete the letter of agreement signed by both a representative neonatologist and obstetrician-gynecologist.
- Each participating hospital must agree to submit complete data for eligible infants.

F) Rights of participating hospitals:

- All participating hospitals own the data that they submit.
- Hospitals shall receive a report comparing their outcomes and practices to those of other participating hospitals in order to support local and collaborative-wide quality improvement activities
- Hospitals that submit at least 3 years of data may request to analyze data from the de-identified registry with Steering Committee approval

G) Study oversight:

The study Steering Committee is comprised of 9 individuals and has the following core functions:

- Approval of modifications to study policy, procedures, or data collection
- Approval of requests to use study data
- Approval of publications or abstracts resulting from the MINI Study

Decisions will be made by a simple majority of the Steering Committee. Additional details about the Steering Committee are found in the Bylaws of the Tiny Baby Collaborative.

G) Publications:

All publications of the MINI Study should have as final author the group author “Tiny Baby Collaborative.” All obstetrician/gyncologist and neonatologist representatives from participating sites will be included in group authorship.

H) Data security:

The data in the REDCap database file residing on protected servers at Nationwide Children's Hospital contains de-identified information. Research Information Services at Nationwide Children's Hospital have extensive experience hosting and maintaining RedCap databases and other clinical databases. Local identifiable data will be used to generate a unique study identification number and to insure valid data collection for the registry. The identifiable data is stored in a password-protected computer file and/or a locked cabinet at each site that only the study PI and research coordinators at that site can access.

I) Data analysis:

Proposals for using the data from the MINI Study for clinical research will be submitted to the Steering Committee of the Tiny Baby Collaborative for approval. Proposals with majority approval will proceed with de-identified data released to the investigators.

J) IRB approval and informed consent:

This protocol must be approved by the IRB at each participating center. Waiver of consent is requested on the basis that: there is no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside a research context; the research could not practicably be carried out without the requested waiver because patients will frequently be identified retrospectively from hospital records; and waiver will not adversely affect the rights and welfare of the subjects. No PHI will be requested for the MINI Study.

K) Risks and benefits:

There are no known direct health risks related to data collection for this observational registry. There is minimal potential risk of loss of confidentiality.

There are no direct benefits for study participation. Participation may help families, infants, and clinicians facing birth at 22-23 weeks' gestation in the future by providing better understanding of medical care and outcomes.

Based on the stated potential for benefit and the potential risks, the study is minimal risk and without the potential for direct benefit to subjects.

References

1. Rysavy MA, Mehler K, Oberthür A, Ågren J, Kusuda S, McNamara PJ, Giesinger RE, Kribs A, Normann E, Carlson SJ, Klein JM, Backes CH, Bell EF. An immature science: intensive care for infants born ≤23 weeks' gestation. *J Pediatr.* 2021; 233:16-25.
2. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, Laptook AR, Sanchez PJ, Van Meurs KP, Wyckoff M, Das A, Hale EC, Ball MB, Newman NS, Schibler K, Poindexter BB, Kennedy KA, Cotton 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;314:1039-1051.
3. Ahmad KA, Frey CS, Fierro MA, Kenton AB, Placencia FX. Two-year neurodevelopmental outcome of an infant born at 21 weeks' 4 days' gestation. *Pediatrics*. 2017;140:e20170103.
4. Patel RM, Rysavy MA, Bell EF, Tyson JE. Survival of infants born at periviable gestational ages. *Clin Perinatol*. 2017;44:287-303.

5. Guillén Ú, Weiss EM, Munson D, Maton P, Jeffries A, Norman M, Naulaers G, Mendes J, da Silva LJ, Zoban P, Hansen TWR, Hallman M, Delivoria-Papadopolous M, Hosono S, Albersheim SG, Williams C, Boyle E, Lui K, Darlow B, Kirpalani H. Guidelines for the management of extremely premature deliveries: a systematic review. *Pediatrics.* 2015;136:343–50.
6. Rysavy MA, Li L, Bell EF, 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;372:1801-1811.
7. United States Department of Health and Human Services (US DHHS), Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS), Linked Birth / Infant Death Records 2017 - 2018, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program, on CDC WONDER Online Database. Available at: http://wonder.cdc.gov/lbd-current-expanded.html Accessed September 27, 2020.
8. Pavlek LR, Rivera BK, Smith CV, Randle J, Hanlon C, Small K, Bell EF, Rysavy MA, Conroy S, Backes CH. Eligibility criteria and representativeness of randomized clinical trials that include infants born extremely premature: a systematic review. *J Pediatr*. 2021; 235:63-74.