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Corresponding author Rosemary D. Higgins, MD, Associate Dean for Research, Interim Chair, Rehabilitation Sciences, Professor, Department of Global and Community Health, College of Health and Human Services, George Mason University, 4400 University Drive 2G7, Peterson Family Health Science Hall, Room 5415, Fairfax, Virginia 22030, 703-993-1952, rhiggin@gmu.edu.

Author Contributors

• This manuscript represents a Phase III study of myo-Inositol for treatment of retinopathy of prematurity conducted within the NICHD Neonatal Research Network (NRN). The Inositol Subcommittee members had monthly conference calls during protocol development and early implementation, and regular teleconferences during implementation, data analysis, and manuscript drafting. The following authors have made significant contributions as determined by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals:

• Ira Adams-Chapman, MD MPH, was the NRN Follow-up Principal Investigator (FU PI) at the Emory University, and oversaw participant follow-up in the study, which saw 13 infants for follow-up. She drafted the manuscript and received input from the coauthors below as part of manuscript revision.

• Kristi L. Watterberg, MD, was the NRN PI at the University of New Mexico and the Vice Chair of the Inositol Protocol Subcommittee. As the subcommittee vice chair, she helped develop the protocol and monitor implementation. As the PI, she oversees recruitment at the site, which enrolled 10 infants into this study. She also provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.

• Tracy L. Nolen, DrPH, served as a statistician for this study and completed the statistical analyses for the paper. She developed the tables for the paper and provided critical revision to the manuscript and approved the final version of the manuscript.

• Shawn Hirsch, MPH, served as a statistician for this study and completed the statistical analyses for the paper. He provided critical revision to the manuscript and approved the final version of the manuscript.

• Carol A. Cole, RPh, was a member of the Inositol Protocol Subcommittee, and a research pharmacist at the University of Rochester. As a site research pharmacist, she helped implement the study at the site, which enrolled 63 infants. She contributed critical revisions of the manuscript and approved the final manuscript for submission

• C. Michael Cotten, MD, MHS, was the NRN Co-PI at Duke University and a member of the Inositol Protocol Subcommittee. As the site investigator, he oversaw recruitment at the site, which enrolled 75 infants into this study. He contributed critical revisions of the manuscript and approved the final manuscript for submission.

• William Oh, MD, was a member of the Inositol Protocol Subcommittee, and a site investigator at Brown University. As the site investigator, he helped with recruitment at the site, which enrolled 37 infants into this study. He contributed critical revisions of the manuscript and approved the final manuscript for submission.

• Brenda B. Poindexter, MD MS, was the NRN PI at Indiana University, co-PI for enrollment at Cincinnati Children's Hospital Medical Center, and a member of the Inositol Protocol Subcommittee. As the PI, she oversaw recruitment at Indiana University, which enrolled 39 infants into this study. As the co-PI, she oversaw recruitment at Cincinnati Children's, assisted with participant recruitment and protocol implementation, which enrolled 50 infants into the study. She contributed critical revisions of the manuscript and approved the final manuscript for submission.

• Kristin M. Zaterka-Baxter, RN BSN, served a critical role as the main coordinator at the Data Coordinating Center. She helped develop and train the NRN PIs and coordinators for the study, and provided day-to-day assistance with protocol and procedural questions as well as data form entry. She also maintained administrative documents for certification, and organized face-to-face subcommittee meetings and monthly teleconferences with investigators. She provided critical revision of the manuscript as well as approval of the final manuscript.

• Abhik Das, PhD, was the PI for NRN Data Coordinating Center at RTI International. He provided overall statistical and analytical guidance for the trial and served on the Inositol Subcommittee. He contributed to conception and design of the project, designed data collection instruments, supervised data collection for the NRN, performed data analysis and interpretation of data, revised the manuscript for intellectual content. He provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.

• Conra Backstrom Lacy, RN, was the NRN Coordinator for the University of New Mexico. She served on the Inositol Subcommittee, helping to develop the protocol, and monitor implementation. She contributed to the conception and design of the project, designed data collection instruments, and served as the resource for data collection related activity for the other NRN sites. As the research coordinator, she assisted with recruitment at the site, which enrolled 10 infants into this study. She provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.

• Ann Marie Scorsone, MS, was the NRN Coordinator for the University of Rochester. She served on the Inositol Subcommittee, helping to develop the protocol, and monitor implementation. She contributed to the conception and design of the project, designed data collection instruments, and served as the resource for data collection related activity for the other NRN sites. As the research coordinator, she assisted with recruitment at the site, which enrolled 63 infants into this study. She provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.

• Andrea F. Duncan, MD MSClinRes, was the NRN FU PI at the McGovern Medical School at The University of Texas Health Science Center at Houston and oversaw participant follow-up in the study, which saw 64 infants for follow-up in the study. She provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.

• Sara B. DeMauro, MD MSCE, was the NRN site investigator and FU PI at the University of Pennsylvania, and oversaw participant follow-up in the study, which saw 25 infants for follow-up in the study. She provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.

• Ricki F. Goldstein, MD, was the NRN FU PI at Duke University, and oversaw participant follow-up in the study, which saw 60 infants for follow-up in the study. She provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.

• Tarah T. Colaizy, MD MPH, was the NRN FU PI at the University of Iowa, and oversaw participant follow-up in the study, which saw 43 infants for follow-up in the study. She provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.

Neurodevelopmental outcome of preterm infants enrolled in

• Deanne E. Wilson-Costello, MD, was the NRN FU PI at Case Western Reserve University, and oversaw participant follow-up in the study, which saw 31 infants for follow-up in the study. She provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Isabell B. Purdy, PhD CPNP, was the NRN FU PI at the University of California – Los Angeles, and oversaw participant follow-up in the study, which saw 18 infants for follow-up in the study. She provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Susan R. Hintz, MD MS Epi, was the NRN FU PI at Stanford University, and oversaw participant follow-up in the study, which saw 17 infants for follow-up in the study. She provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Roy J. Heyne, MD, was the NRN FU PI at the University of Texas Southwestern, and oversaw participant follow-up in the study, which saw 11 infants for follow-up in the study. He provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Gary J. Myers, MD, was the FU PI at the University of Rochester, and oversaw participant follow-up in the study, which saw 50 infants for follow-up in the study. He provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Janell Fuller, MD, was the NRN FU PI at the University of New Mexico, and oversaw participant follow-up in the study, which saw 7 infants for follow-up in the study. She provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Stephanie Merhar, MD MS, was the NRN FU PI at Cincinnati Children's Hospital Medical Center, and oversaw participant follow-up in the study, which saw 33 infants for follow-up. She provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Heidi M. Harmon, MD MS, was the NRN FU PI at Indiana University, and oversaw participant follow-up in the study, which saw 29 infants for follow-up. She provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Myriam Peralta-Carcelen, MD MPH, was the NRN Follow-up Principal Investigator (FU PI) at the University of Alabama at Birmingham, and oversaw participant follow-up in the study, which saw 16 infants for follow-up. She provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Howard W. Kilbride, MD, was the NRN FU PI at Children's Mercy Hospital, and oversaw participant follow-up in the study, which saw 20 infants for follow-up. He provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Nathalie L. Maitre, MD, PhD, was the FU PI at the Nationwide Children's Hospital, and oversaw participant follow-up in the study, which saw 21 infants for follow-up. She provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Betty R. Vohr, MD, was the NRN FU PI at Brown University, and oversaw participant follow-up in the study, which saw 27 infants for follow-up. She provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Girija Natarajan, MD, was the NRN FU PI at Wayne State University and oversaw participant follow-up in the study, which saw 8 infants for follow-up. She provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Helen Mintz-Hittner, MD, was a research ophthalmologist at the McGovern Medical School at The University of Texas Health Science Center at Houston and conducted primary outcome examinations for study participants recruited at this center, which enrolled 71 infants into the study. She provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Graham E. Quinn, MD MSCE, was the research ophthalmologist at University of Pennsylvania and conducted primary outcome examinations for study participants recruited at this center, which enrolled 28 infants into the study. He provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• David K. Wallace, MD MPH, was the research ophthalmologist at Duke University and conducted primary outcome examinations for study participants recruited at this center, which enrolled 75 infants into the study. He provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Richard J. Olson, MD, was the research ophthalmologist at the University of Iowa and conducted primary outcome examinations for study participants recruited at this center, which enrolled 48 infants into the study. He provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Faruk Orge, MD, was the research ophthalmologist at Case Western Reserve University and conducted primary outcome examinations for study participants recruited at this center, which enrolled 41 infants into the study. He provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Irena Tsui, MD, was the research ophthalmologist at University of California – Los Angeles and conducted primary outcome examinations for study participants recruited at this center, which enrolled 17 infants into the study. She provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Michael Gaynon, MD, was the research ophthalmologist at Stanford University and conducted primary outcome examinations for study participants recruited at this center, which enrolled 19 infants into the study. He provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Amy K. Hutchinson, MD, was the research ophthalmologist at Emory University and conducted primary outcome examinations for study participants recruited at this center, which enrolled 18 infants into the study. She provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Yu-Guang He, MD, was the research ophthalmologist at University of Texas Southwestern and conducted primary outcome examinations for study participants recruited at this center, which enrolled 15 infants into the study. He provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.

myo-inositol randomized controlled trial

Ira Adams-Chapman, MD MPH[1], **Kristi L. Watterberg, MD**[2], **Tracy L. Nolen, DrPH**[3], **Shawn Hirsch, MPH**[3], **Carol A. Cole, RPh**[4], **C. Michael Cotten, MD, MHS**[5], **William Oh, MD**[6], **Brenda B. Poindexter, MD MS**[7,8], **Kristin M. Zaterka-Baxter, RN BSN**[3], **Abhik Das, PhD**[9], **Conra Backstrom Lacy, RN**[2], **Ann Marie Scorsone, MS**[4], **Andrea F. Duncan, MD MS ClinRes**[10], **Sara B. DeMauro, MD MSCE**[11], **Ricki F. Goldstein, MD**[5], **Tarah T. Colaizy, MD MPH**[12], **Deanne E. Wilson-Costello, MD**[13], **Isabell B. Purdy, PhD CPNP**[14], **Susan R. Hintz, MD MS, Epi**[15], **Roy J. Heyne, MD**[16], **Gary J. Myers, MD**[4], **Fuller Janell, MD**[2], **Stephanie Merhar, MD MS**[7], **Heidi M. Harmon, MD MS**[17,12], **Myriam Peralta-Carcelen, MD MPH**[18], **Howard W. Kilbride, MD**[19], **Nathalie L. Maitre, MD, PhDD**[20], **Betty R. Girija Vohr, MD**[6], **Girija Natarajan, MD**[21], **Helen Mintz-Hittner, MD**[22], **Graham E. Quinn, MD MSCE**[23], **David K. Wallace, MD MPH**[24], **Richard J. Olson, MD**[25], **Faruk H. Orge, MD**[26], **Irena Tsui, MD**[27], **Michael Gaynon, MD**[28], **Amy K. Hutchinson, MD**[29], **Yu-Guang He, MD**[30], **Timothy W. Winter, DO**[31], **Michael B.**

• Mina Chung, MD, was the research ophthalmologist at the University of Rochester and conducted primary outcome examinations for study participants recruited at this center, which enrolled 63 infants into the study. She provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Timothy W. Winter, DO, was the research ophthalmologist at University of New Mexico and conducted primary outcome examinations for study participants recruited at this center, which enrolled 10 infants into the study. He provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Michael Yang, MD, was the research ophthalmologist at Cincinnati Children's Hospital Medical Center and conducted primary outcome examinations for study participants recruited at this center, which enrolled 50 infants into the study. He provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Kathryn M. Haider, MD, was the research ophthalmologist at Indiana University and conducted primary outcome examinations for study participants recruited at this center, which enrolled 39 infants into the study. She provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Martin S. Cogen, MD, was the research ophthalmologist at University of Alabama at Birmingham and conducted primary outcome examinations for study participants recruited at this center, which enrolled 40 infants into the study. He provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Denise Hug, MD, was the research ophthalmologist at Children's Mercy Hospital and conducted primary outcome examinations for study participants recruited at this center, which enrolled 25 infants into the study. She provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Don L. Bremer, MD, was the research ophthalmologist at Nationwide Children's Hospital and conducted primary outcome examinations for study participants recruited at this center, which enrolled 30 infants into the study. He provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• John P. Donahue, MD PhD, the research ophthalmologist at Brown University and conducted primary outcome examinations for study participants recruited at this center, which enrolled 37 infants into the study. He provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• William R. Lucas, Jr., MD, was the research ophthalmologist at Wayne State University and conducted primary outcome examinations for study participants recruited at this center, which enrolled 12 infants into the study. He provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Dale L. Phelps, MD, was the Lead Principal Investigator for the Inositol Study for the NRN and the Chair of the protocol subcommittee. She designed the Inositol trial with the Inositol Subcommittee and was involved in all stages of its development, implementation, and analysis, including training the NRN PIs and coordinators. She provided critical revision to this study's concept and to the draft manuscript, and approved the final version of the manuscript.
• Rosemary D. Higgins, MD, served as the Program Scientist for the NICHD NRN and a member of the Inositol Protocol Subcommittee. She helped developed the protocol, oversaw recruitment and follow up compliance, and assisted with data edits from the sites. She also provided critical revision to the manuscript and approved and submitted the final version of the manuscript.

Data Sharing

Data reported in this paper may be requested through a data use agreement. Further details are available at https://neonatal.rti.org/index.cfm?fuseaction=DataRequest.Home

Conflicts of Interest and Disclosures

None of the authors report any commercial, proprietary, or financial interest in any of the products described in this article. NICHD is the sponsor of the study and holds the investigational new drug (IND) application.

Abbott Nutrition Division, Abbott Laboratories, Columbus, OH, provided the inositol product. They had no role in the: design of the trial; the analyses, interpretation, or writing of the manuscript; or the decision to submit the manuscript for publication. They provided on-site monitoring to assist in quality assurance of the data collection.

Yang, MD[32], **Kathryn M. Haider, MD**[33], **Martin S. Cogen, MD**[34], **Denise Hug, MD**[35], **Don L. Bremer, MD**[36], **John P. Donahue, MD PhD**[37], **William R. Lucas, MD**[38] **[Jr.]**, **Dale L. Phelps, MD**[4], **Rosemary D. Higgins, MD**[39,40], **Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network**

[1]Department of Pediatrics, Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, GA

[2]University of New Mexico Health Sciences Center, Albuquerque, NM

[3]Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC

[4]University of Rochester School of Medicine and Dentistry, Rochester, NY

[5]Department of Pediatrics, Duke University, Durham, NC

[6]Department of Pediatrics, Women & Infants' Hospital, Brown University, Providence, RI

[7]Department of Pediatrics, Cincinnati Children's Hospital Medical Center and University of Cincinnati College of Medicine, Cincinnati, OH

[8]Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN

[9]Social, Statistical and Environmental Sciences Unit, RTI International, Rockville, MD

[10]Department of Pediatrics, McGovern Medical School at The University of Texas Health Science Center at Houston, Houston, TX

[11]Department of Pediatrics, The Children's Hospital of Philadelphia and The University of Pennsylvania, Philadelphia, PA

[12]Department of Pediatrics, University of Iowa, Iowa City, IA

[13]Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH

[14]Department of Pediatrics, University of California, Los Angeles, CA

[15]Department of Pediatrics, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto, CA

[16]Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX

[17]Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN

[18]Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL

[19]Department of Pediatrics, Children's Mercy Hospital and University of Missouri Kansas City School of Medicine, Kansas City, MO

[20]Department of Pediatrics, Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, OH

[21]Department of Pediatrics, Wayne State University, Detroit, MI

[22]Department of Ophthalmology and Visual Science, McGovern Medical School at The University of Texas Health Science Center at Houston, Houston, TX

[23]Department of Ophthalmology, The Children's Hospital of Philadelphia and The University of Pennsylvania, Philadelphia, PA

[24]Department of Ophthalmology, Duke University, Durham, NC; Currently Department of Ophthalmology, Indiana University School of Medicine, Indianapolis, IN

[25]Department of Ophthalmology and Visual Sciences, University of Iowa, Iowa City, IA

[26]Department of Ophthalmology, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH

[27]Department of Ophthalmology, University of California, Los Angeles, CA

[28]Department of Ophthalmology, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto, CA

[29]Department of Ophthalmology, Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, GA

[30]Department of Ophthalmology, University of Texas Southwestern Medical Center, Dallas, TX

[31]Division of Ophthalmology/Department of Surgery, University of New Mexico Health Sciences Center, Albuquerque, NM

[32]Department of Ophthalmology, Cincinnati Children's Hospital Medical Center and University of Cincinnati College of Medicine, Cincinnati, OH

[33]Department of Ophthalmology, Indiana University School of Medicine, Indianapolis, IN

[34]Department of Ophthalmology, University of Alabama at Birmingham, Birmingham, AL

[35]Department of Ophthalmology, Children's Mercy Hospital and University of Missouri Kansas City School of Medicine, Kansas City, MO

[36]Department of Ophthalmology, Nationwide Children's Hospital, Columbus, OH

[37]Alpert Medical School of Brown University and Consulting Staff, Women & Infants Hospital of Rhode Island, Providence, RI

[38]Department of Ophthalmology, Wayne State University, Detroit, MI

[39]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

[40]College of Health and Human Services, George Mason University, Fairfax, VA

Abstract

Objective: This study evaluates the 24 month follow up for the NICHD Neonatal Research Network (NRN) Inositol for Retinopathy Trial.

Study Design: Bayley Scales of Infants Development-III and a standardized neurosensory examination were performed in infants enrolled in the main trial. Moderate/severe NDI was defined as BSID-III Cognitive or Motor composite score <85, moderate or severe cerebral palsy, blindness, or hearing loss that prevents communication despite amplification were assessed.

Results: Primary outcome was determined for 605/638 (95%). The mean gestational age was 25.8 ±1.3 weeks and mean birthweight was 805 ± 192 grams. Treatment group did not affect the risk for the composite outcome of death or survival with moderate/severe NDI (60% vs 56%, p=0.40).

Conclusions: Treatment group did not affect the risk of death or survival with moderate/severe NDI. Despite early termination, this study represents the largest RCT of extremely preterm infants treated with *myo*-inositol with neurodevelopmental outcome data.

ClinicalTrials.gov ID—INS-3: NCT01954082

Introduction

Randomized clinical trials (RCTs) are crucial to determine the effect of promising neonatal interventions on the improving but still high rate of death or impairment among extremely preterm infants. One such intervention is administration of *myo*-inositol, an important component of membrane phospholipids with an important role in signal transduction and surfactant synthesis.[1] *Myo*-inositol was reported in small clinical trials during the 1990s to decrease the risk for death, respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD).[2,3] In a Cochrane meta-analysis of the 4 previously published RCTs of *myo*-inositol treatment in preterm infants, inositol supplementation was associated with a decreased risk of death, retinopathy of prematurity (ROP), and intraventricular hemorrhage (IVH) Grade 3 and 4, with no difference in BPD.[4] Only one of those studies evaluated neurodevelopmental outcome, and the assessment was limited in scope and not standardized.[2] In that study, Hallman and colleagues clinically evaluated outcomes at one year and found no statistically significant difference in major neurologic findings between the groups (9% in inositol-treated children compared to 18% in the placebo group), though the study was underpowered for that outcome. Given that previous studies were small and included limited or no long-term follow-up data, a larger RCT was indicated to examine these findings in a trial adequately powered to evaluate long term neurologic outcome.

To address this gap in knowledge, the Neonatal Research Network (NRN) of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) performed an RCT to evaluate the safety and efficacy of *myo*-inositol to reduce the risk of type I ROP in infants born < 28 weeks gestation. Study enrollment was terminated early due to increased mortality risk in the *myo*-inositol exposed infants.[5] The succeeding Cochrane review that included these findings identified no overall benefit of inositol supplementation at hospital discharge but emphasized the importance of follow-up assessments to identify any effects on long-term outcomes in early childhood.[6] This analysis evaluates the risk of death or survival with moderate/severe NDI at 24 months corrected age in enrolled infants.

Methods

Study Design:

This study was a double-blind placebo controlled RCT conducted under an Investigational New Drug application (IND) from the Food and Drug Administration and registered on clinicaltrials.gov (#NCT01954082). The study protocol was approved by the NRN Data

Safety Monitoring Committee (DSMB) and the Institutional Review Board for each clinical site. Informed consent was obtained from the parent/legal guardian at enrollment which included consent to participate in the pre-specified 24-month corrected age follow-up visit. Detailed study methods were previously published[5]. There were no changes in the protocol except for the early termination of enrollment in the trial and no further treatment of enrolled patients based on the recommendation of the DSMB. The analyses completed for the manuscript also are consistent with the approaches detailed in the protocol and statistical analysis plan with the exception of the added ad-hoc analysis of outcomes by study drug lot given the manufacturing issues identified. Standardized protocols for the neurodevelopmental follow-up assessment and annual certification of examiners were utilized throughout the study period.[7] Sample size estimates were outlined in the primary outcome publication.[5]

Patient population:

Infants born between April 17, 2014 and September 4, 2015 who were less than 28 and 0/7 weeks gestation and survived for at least 12 hours at one of the participating NRN centers were eligible for inclusion in the primary study. Infants with major congenital anomalies, any eye anomaly or those with a moribund condition were excluded.

Study Participants:

Participants were stratified by center and gestational age (GA) (<26 0/7 vs 26 0/7 to 27 6/7 weeks) and randomized in a 1:1 ratio to receive either placebo or 40 mg/kg/dose every 12 hours of *myo*-inositol parenterally or enterally for up to 10 weeks. Enrollment was discontinued due to an unexpected higher mortality rate in the *myo*-inositol treated group.

Outcomes:

Mortality or moderate/severe NDI at 24 months corrected age was a pre-specified primary outcome for this study. Secondary outcomes at 24 months included death, any ROP, the composite of any ROP or death, ophthalmologic outcomes (including nystagmus, strabismus and need for surgery); as well as the individual components of NDI.

Study definitions:

Neonatal morbidities were classified based on definitions outlined in the NRN Generic Database Protocol.[8] At the 24 months follow-up visit a standardized neurosensory examination was performed and the Bayley Scales of Infant and Toddler Development, 3rd Edition (BSID III) was administered by certified examiners who completed annual training to ensure inter-rater reliability.[7,9] Predefined criteria were specified for each of the following neurosensory examination categories: normal, suspect, neurologically abnormal/non-Cerebral Palsy (CP), and CP. According to the Pearson Corporation that developed the Bayley Scales, the mean value of the scaled scores is 100 and the standard deviation is 15.[9] Children who were untestable were assigned a cognitive score of 54, a composite language score of 46, and a composite motor score of 46. The Gross Motor Function Classification System (GMFCS) was used to distinguish severity of CP such that mild CP was defined as GMFCS Level 1, moderate CP as GMFCS Level 2–3, and severe CP as GMFCS Level 4–

5.[10] Neurodevelopmental impairment was defined as a BSID III Cognitive or Motor composite <85, or moderate or severe CP, or blindness (unilateral or bilateral), or hearing loss that does not permit the child to communicate despite amplification.

ROP status was diagnosed by a primary ophthalmologist at each center trained and certified on the 2006 International Classification of ROP.[11] Eye exams were performed up to 55 weeks postmenstrual age (PMA) until either eye met criteria for type 1 ROP, both eyes were fully vascularized, or two consecutive exams showed vessels to be in zone III.[12] ROP, for this neurodevelopmental follow-up study, was defined as having any ROP diagnosis in either eye by an ophthalmologist during the initial study, or having any ROP diagnosis or surgical/treatment intervention in either eye during the 2-year evaluation.

Statistical Analysis

Baseline characteristics and early neonatal morbidities were analyzed controlling for center where possible using the appropriate Cochran-Mantel-Haenszel tests for categorical and ordinal data and multivariable linear regression for continuous data. Comparisons were made between the inositol vs. placebo groups completing study follow-up, as well as between the total follow-up completers vs. those that died prior to follow-up vs. those that were lost-to-follow-up.

Analyses of the outcomes were performed on the intention-to-treat population with missing data treated as missing completely at random and excluded from the analysis. Robust Poisson regression estimated adjusted relative risks (RRs). A generalized linear model with a binomial distribution and identity link estimated the adjusted absolute risk difference (and associated 95% CIs) for *myo*-inositol vs. placebo for the main outcome and for the binary secondary outcomes. Growth at follow-up variables (height, weight, and head circumference) were analyzed with an analysis of covariance model. The analyses were controlled for the randomization factors of center and gestational age strata as fixed effects for the main outcome of moderate/severe NDI or death and its components as well as for all secondary outcomes where possible. A Kaplan-Meier curve and log-rank test were used to compare difference in survival probability between the inositol and placebo group. Individuals surviving through their last follow-up assessment were right censored. Because of manufacturing issues reported for the parent trial, a supplemental analysis of the outcomes was also performed by comparing the inositol lot 1 vs. inositol lot 2 groups.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.). As this follow-up analysis was a secondary objective of the clinical trial, all analyses are exploratory and not intended to be formal test of hypotheses; therefore, no adjustments were made for multiplicity.

Results

Population characteristics

Analyses of the primary outcome (death or type I ROP) and of mortality have been previously published.[5,13] These data represent a pre-planned analysis of mortality and NDI outcome at 24 months corrected age for children enrolled in this RCT prior to termination of the study. As previously reported,[5] treatment groups were similar at randomization. Of the 638 infants randomized in the phase III RCT, 539 survived to follow-up, of whom 506 (94%) were evaluated. (Figure 1) Demographic characteristics of the treatment and placebo groups of randomized infants subsequently completing 24 month follow--up were similar (Table 1). The mean GA±SD was 25.8 ±1.3 weeks in both treatment groups (p=0.50) with a similar distribution above or below 26 weeks. The 33 children lost to follow-up had a similar demographic and morbidity profile as those evaluated. Those who died prior to follow-up were of lower birthweight and gestational age and were more likely to have neonatal morbidities, including late onset sepsis, BPD, necrotizing enterocolitis, severe IVH, and periventricular leukomalacia (PVL) (Table 1 and Table 2). Early onset sepsis occurred infrequently and rates were similar in all groups.

Neonatal morbidities

Early neonatal morbidities were similar among those seen and those lost to follow-up. Neonatal morbidities were similar between the *myo*-inositol and placebo groups (Table 2). Any ROP was common and was diagnosed in 70% of enrolled patients by the 24 month follow-up visit. However, a much smaller percentage received either ophthalmologic treatment (Inositol 22% vs 17% placebo, p=0.20) or surgery (Inositol 8% v 6%, p=0.45). (Tables 3 and 4). Type 1 ROP through early follow-up was present in 13% of patients and risk did not differ by treatment group[5] (Table 2). BPD was common in both groups and present in 57% of all those who completed follow-up. Growth parameters were similar between the two groups at 24 month follow-up (Table 4).

24 Month Outcome of Death or Neurodevelopmental Impairment:

There was no difference in the risk of the composite outcome of death or survival with moderate/severe NDI for infants in this clinical trial [60% in myo-inositol treated vs 56% in placebo; ARR 1.06 (95% CI=0.93–1.21; p=0.40)]. Neurodevelopmental outcomes were similar among survivors in the two treatment groups. The increased mortality rate in the *myo*-inositol treated infants noted prior to hospital discharge remained stable through 24 month follow-up (Figure 2). Two different lots of study drug were used during the study period. No differences were seen for the composite neurodevelopmental outcome between those receiving *myo*-inositol or placebo by lot number (Table 5).

At a median age of 24 months corrected age, 49% of children in both groups met criteria for moderate or severe NDI at follow-up (Table 4). Among those with NDI, moderate impairment was more common than severe impairment in both treatment groups. BSID III Motor score < 85 (*myo*-inositol treated 41% v placebo 42%) and BSID III Cognitive score < 85 (*myo*-inositol treated 34% v placebo 32%) were the most frequent abnormal findings on psychometric testing but scores did not differ between the treatment groups (Table 4). Rates of severe motor and cognitive impairment, defined as having BSID III Cognitive and Motor scores <70 respectively, were also similar between the treatment groups (Table 4). The rate of any CP or moderate/severe CP was similar between groups. At follow-up, 95.2% were sitting without support, 89.6% were walking independently and 2.6% were walking but required a device or hands held.

Secondary outcomes:

Although ROP was present in 70% of patients in both groups, the majority did not receive ophthalmologic or surgical treatment. Treatment with *myo*-inositol did not change the risk of developing type 1 ROP. Among those seen for follow-up, children in the treatment and placebo group had similar rates of developing ROP or receiving medical or surgical treatment for ROP prior to the follow-up visit. Strabismus was noted at follow-up in 15% of children in both groups. Nystagmus was present in a smaller percentage (*myo*-inositol 5% v placebo 3%, p=0.36). Ocular outcomes were similar within and between the two lots of study drug (Table 6).

Discussion

In this study, *myo*-inositol treatment in the neonatal period in infants born < 28 weeks gestation was not associated with a statistically significant difference in the combined risk of death or survival with moderate/severe neurodevelopmental impairment at 24 months corrected age. The increased rate of death seen in the original trial persisted until 2 year follow up. Although small clinical trials performed during the pre-surfactant era reported a decreased risk of early adverse morbidities including BPD, sepsis, and severe IVH, it was necessary to determine if treatment with *myo*-inositol demonstrated the same benefits in a contemporary group of preterm neonates cared for during the surfactant era. Furthermore, previous clinical trials reported very limited or no neurodevelopmental outcome data for study subjects. This study represents the largest clinical trial evaluating the neurodevelopmental outcome of children born extremely preterm treated with *myo*-inositol, including its impact on survival, neonatal morbidities, and neurologic sequelae.

Differences in the patient populations and the risk for associated morbidities may explain the differences in our results compared to previous studies published in the 1990s. Over 50% of patients in both treatment groups were <26 weeks GA. The mean GA for infants enrolled in the previous studies by Hallman was 29 weeks GA.[2,3] Shifts in neonatal practice patterns, including increased antenatal steroid use, routine administration of surfactant, and lung protective strategies, may also explain some of the differences in our outcomes.

The findings of this trial were sufficiently compelling to prompt the recent Cochrane meta-analysis to conclude that inositol supplementation should not be a part of the routine nutritional management of preterm children and that further inositol trials are unwarranted based on the lack of reduction in mortality or early neonatal morbidities, including ROP, sepsis, BPD or severe Grade 3 or 4 IVH.[6] Furthermore, they stressed the importance of completing longer term follow-up on the children enrolled in previous clinical trials.

Neurodevelopmental outcome is strongly correlated with the presence of various neonatal morbidities, including IVH, PVL, late onset sepsis, and BPD.[14–17] The morbidity profile was similar for children in both treatment groups in our study. The rate of moderate/severe NDI was high (49%) but similar between the two treatment groups. (Tables 3 and 4) Based on concern that the BSID III may underestimate NDI, we analyzed our data using a cutoff of <85 to define moderate NDI and <70 to define severe NDI for the cognitive and motor scales of this instrument.[18] Treatment group did not affect the risk for moderate or severe NDI.

Hallman reported the neurodevelopmental outcome of 169 preterm infants at one year of age (73 in placebo group and 96 inositol treated),[2] and found no statistically significant difference in the rate of major handicap (18% vs 9%; p=ns) or CP (10% v 7%; p=ns) in the placebo compared to inositol treated infants. Information regarding severity of CP was not included in the analysis. In our RCT, rates of all severity levels of CP were similar between the two treatment groups. The slightly higher rate of any CP in our study is likely related to the lower GA of our patient population. Previous studies reported that inositol treated patients were less likely to have Grade 3 or 4 IVH. In our overall study population, there was no difference between groups, with 16% of patients in each group developing Grade 3 or 4 IVH. [5] Similarly, among those who completed follow-up, 13% of infants had a Grade 3 or 4 IVH and rates were similar between treatment groups.

The need to halt enrollment early reduced the sample size and thereby increased the possibility of either false positive or false negative findings. It was also not possible to adjust for center or gestational age stratum in all analyses. However, this study is the largest randomized trial of *myo*-inositol for premature infants and has multiple strengths to enhance its validity, including pharmacokinetic studies to determine the appropriate dose,[13] a high follow-up rate, and standardized neurodevelopmental assessments by certified masked examiners.

Conclusion

We found no difference between groups in the risk for death or survival with moderate or severe neurodevelopmental impairment at 24 months corrected age. Further studies of *myo-inositol* in this population are not warranted.

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Ira-Adams Chapman died following writing the manuscript. The study team appreciates her efforts in leading the follow up study, data analysis and completion of the manuscript. She is a very special person and will be missed by all of the team. Mina Chung, MD, was the research ophthalmologist at the University of Rochester and conducted primary outcome examinations for study participants recruited at this center. Dr. Chung provided important contributions to the study concept and design and she performed ophthalmologic evaluations on the 63 infants enrolled at this site. Dr. Chung died prior to preparation of the final manuscript. The study team which like to extend a special acknowledgement of her efforts on this project.

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Participating NRN sites collected data and transmitted it to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, RTI International had full access to all of the data in the study, and with the NRN Center Principal Investigators, takes responsibility for the integrity of the data and accuracy of the data analysis.

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NRN Steering Committee Chair: Richard A. Polin, MD, Division of Neonatology, College of Physicians and Surgeons, Columbia University, (2011-present).

Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island (UG1 HD27904) – Abbot R. Laptook, MD; Martin Keszler, MD; Elisabeth C. McGowan, MD; Angelita M. Hensman, PhD RNC-NIC; Barbara Alksninis, PNP; Mary Lenore Keszler, MD; Andrea M. Knoll; Theresa M. Leach, MEd Emilee Little, RN BSN; Elisabeth C. McGowan, MD; Michael R. Muller, PharmD; Elisa Vieira, RN BSN; Victoria E. Watson, MS CAS.

Case Western Reserve University, Rainbow Babies & Children's Hospital (UG1 HD21364) – Michele C. Walsh, MD MS; Anna Maria Hibbs, MD MSCE; Nancy S. Newman, BA RN; Michael Banchy, RPH; Monika Bhola, MD; Jeffrey L. Blumer, MD; Allison H. Payne, MD MS; Bonnie S. Siner, RN; Elizabeth Ross, MS; Eileen K. Stork, MD; H. Gerry Taylor, PhD; Gulgun Yalcinkaya, MD; Arlene Zadell, RN.

Children's Mercy Hospital, University of Missouri Kansas City School of Medicine (UG1 HD68284) – William E. Truog, MD; Eugenia K. Pallotto, MD MSCE; Prabhu S. Parimi, MD; Cheri Gauldin, RN BSN CCRC; Lisa Gaetano, MSN RN; Anne M. Holmes, RN MSN MBA-HCM CCRC; Kathy Johnson RN, CCRC; Allison Knutson, BSN RNC-NIC.

Cincinnati Children's Hospital Medical Center, University of Cincinnati Medical Center, and Good Samaritan Hospital (UG1 HD27853, UL1 TR77) – Kurt Schibler, MD; Cathy Grisby, BSN CCRC; Patricia Cobb, MS; Teresa L. Gratton, PA; Kristin Kirker, CRC; Stacey Tepe, BS; Sandra Wuertz, RN-BSN CCRP CLC; Kimberly Yolton, PhD.

Duke University School of Medicine, University Hospital, University of North Carolina, Duke Regional Hospital, and WakeMed Health and Hospitals (UG1 HD40492, UL1 TR1117) – Ronald N. Goldberg, MD; Joanne Finkle, RN JD; Kimberley A. Fisher, PhD FNP-BC IBCLC; William F. Malcolm, MD; Patricia L. Ashley, MD PHD; Deesha Mago-Shah, MD; Chi Dang-Hornik, PharmD BCPS; Sharon F. Freedman, MD; Kathryn E. Gustafson, PhD; Mary Miller-Bell, PharmD RPh; Sasapin Grace Prakalapakorn, MD MPH; Matthew M. Laughon, MD MPH; Carl L. Bose, MD; Janice Bernhardt, MS RN; Cindy Clark, RN; Diane D. Warner, MD MPH; Michael T. O'Shea, MD MPH; Janice Wereszczak CPNP-AC/PC; Jennifer Talbert, MS RN; Stephen D. Kicklighter, MD; Sofia Aliaga, MD, MPH; Jeffery Board, MD; Kevin Gertsch, MD; Jerry Magolan, MD; Linda Manor, RPh; Jan Niklas Ulrich, MD; Ginger Rhodes-Ryan, ARNP MSN NNP-BC; Donna White, BSN, RN-BC BSN; Alexandra Bentley, MD; Laura Edwards, MD.

Emory University, Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory University Hospital Midtown (UG1 HD27851, UL1 TR454) – David P. Carlton, MD; Barbara J. Stoll, MD; Ellen C. Hale, RN BS CCRC; Yvonne Loggins, RN; Diane I. Bottcher, RN MSN; Sheena L. Carter, PhD; Colleen Mackie, BS RT; Maureen Mulligan LaRossa, RN; Lynn C. Comerford, NNP; Gloria Smike, PNP MSN; Salathiel Kendrick-Allwood, MD; Angela Leon-Hernandez, MD.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Stephanie Wilson Archer, MA.

Indiana University, Riley Hospital for Children and Methodist Hospital at Indiana University Health (UG1 HD27856) – Gregory M. Sokol, MD; Susan Gunn, NNP CCRC; Dianne E. Herron, RN CCRC; Abbey C. Hines, PsyD; Elizabeth Hynes, RNC-NIC; Lu-Ann Papile, MD; Lucy Smiley CCRC.

McGovern Medical School at The University of Texas Health Science Center at Houston and Children's Memorial Hermann Hospital (UG1 HD87229) – Jon E. Tyson, MD MPH; Kathleen A. Kennedy, MD MPH; Amir M. Khan, MD; Andi Duncan, MD, Ricardo Mosquera, MD, MS, Elizabeth Allain, MS; Julie Arldt-McAlister, MSN APRN; Shanti Brown, RCPhT; Allison G. Dempsey, PhD; Elizabeth Eason, MD; Farida El-Ali, RPH; Carmen Garcia, RN BSN; Kartik Kumar, MD; Janice John, CPNP; Patrick M. Jones, MD MA; M. Layne Lillie, RN BSN; Karen Martin, RN; Sara C. Martin, RN; Georgia E. McDavid, RN; Shannon McKee EdS; Hatice Ozsoy, PhD RPh; Shawna Rodgers, RN; Daniel Sperry, RN; Emily K. Stephens, RN BSN; Vu Ta, PharmD; Christine Wong, PharmD; Sharon L. Wright, MT (ASCP).

Nationwide Children's Hospital and The Ohio State University Wexner Medical Center (UG1 HD68278) – Pablo J. Sánchez, MD; Leif D. Nelin, MD; Sudarshan R. Jadcherla, MD; Amanda E. Graf, MD; Patricia Luzader, RN; Christine A. Fortney, PhD RN; Gail E. Besner; Nehal A. Parikh, MD; David L. Rogers, MD; Richard P. Golden, MD; Catherine Olson Jordan, MD.

RTI International (U10 HD36790) – Dennis Wallace, PhD; Marie G. Gantz, PhD; Carla M. Bann, PhD; Jeanette O'Donnell Auman, BS; Margaret M. Crawford, BS CCRP; Jenna Gabrio, MPH CCRP; Carolyn M. Petrie Huitema, MS CCRP; James W. Pickett II, BS; Annie M. VonLehmden, BS.

Stanford University and Lucile Packard Children's Hospital (UG1 HD27880, UL1 TR93) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS CCRC; Steven Chinn, PharmD; Melinda S. Proud, RCP;

Barbara Bentley, PsychD MSEd; Maria Elena DeAnda, PhD; Anne M. DeBattista, RN PNP PhD; Beth Earhart, PhD; Lynne C. Huffman, MD; Casey E. Krueger, PhD; Ryan Lucash, PhD; Hali E. Weiss, MD.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (UG1 HD34216) – Waldemar A. Carlo, MD; Namasivayam Ambalavanan, MD; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN; Rebecca J. Quinn, PharmD; Brenda Reed Denson, PharmD; Ann Marie Arciniegas-Bernal, MD; Fred J. Biasini, PhD; Kristen C. Johnston, MSN CRNP; Cryshelle S. Patterson, PhD; Vivien A. Phillips, RN BSN; Sally Whitley, MA OTR-L FAOTA.

University of California - Los Angeles, Mattel Children's Hospital, Santa Monica Hospital, Los Robles Hospital and Medical Center, and Olive View Medical Center (UG1 HD68270) – Uday Devaskar, MD; Meena Garg, MD; Teresa Chanlaw, MPH; Rachel Geller, RN BSN.

University of Iowa (UG1 HD53109, UL1 TR442) – Edward F. Bell, MD; Jane E. Brumbaugh, MD; Karen J. Johnson, RN BSN; Jacky R. Walker, RN; Claire A. Goeke, RN; Kristine M. Johnson, BSPharm RPh; Angela Merriss, BA CPhT; Joanna L. Nohr, PharmD BCPS; Susannah Q. Longmuir, MD; Arlene V. Drack, MD; Diane L. Eastman, RN CPNP MA; Scott A. Larson, MD; Kevin R. Gertsch, MD; Vikki P. Bell.

University of New Mexico Health Sciences Center (UG1 HD53089, UL1TR41) – Robin K. Ohls, MD; Sandra Sundquist Beauman, MSN RNC; Tara Dupont, MD; Mary Ruffaner Hanson, RN BSN; Carol H, Hartenberger, MPH RN; Elizabeth Kuan, RN BSN; Susan J. Kunkel, PharmD; Jean Lowe, PhD; Nancy A. Morgan, RPh MBA.

University of Oulu, and Oulu University Hospital, Oulu, Finland – Mikko K. Hallman, MD.

University of Pennsylvania, Hospital of the University of Pennsylvania, Pennsylvania Hospital, and Children's Hospital of Philadelphia (UG1 HD68244) – Barbara Schmidt, MD MSc; Haresh Kirpalani, MB MSc; Soraya Abbasi, MD; Aasma S. Chaudhary, BS RRT; Toni Mancini, RN BSN CCRC; William V. Anninger, MD; Judy C. Bernbaum, MD; Gil Binenbaum, MD MSCE; Noah Cook, MD; Stefanie L. Davidson, MD; Marsha Gerdes, PhD; Hallam Hurt, MD; Monte D. Mills, MD; Mina Ricciardelli, PharmD; Kenneth Rockwell, Jr., PharmD MS; Jonathan Snyder, RN BSN; Sze Man Yau, RPh.

University of Rochester Medical Center, Golisano Children's Hospital, and the University of Buffalo Women's and Children's Hospital of Buffalo (UG1 HD68263, UL1 TR42) – Carl D'Angio, MD; Satyan Lakshminrusimha, MD; Anne Marie Reynolds, MD MPH; Stephen A. Bean, PharmD; Melissa F. Carmen, MD; Patricia R. Chess, MD; Rosemary Jensen; Rajeev S. Ramchandran, MD; Ann Marie Turner, PharmD; Ashley Williams, MS Ed; Michael G. Sacilowski, MAT; Holly Wadkins, MA; Julianne Hunn; Aimee Horan, LPN; Melissa Bowman, RN NP; Michele Hartley-McAndrew, MD; William Zorn, PhD; Osman Farooq, MD; Kelley Yost, PhD; Joan Merzbach, LMSW; Cait Fallone, MA; Kyle Binion, BS; Constance Orme; Premini Sabaratnam, MPH.

University of Texas Southwestern Medical Center, Parkland Health & Hospital System, and Children's Medical Center Dallas (UG1 HD40689) – Myra H. Wyckoff, MD; Luc P. Brion, MD; Diana M. Vasil, RNC-NIC; Sally S. Adams, MS RN CPNP; Christine Cha, PharmD; Juana Cisneros, RN; Maria M. De Leon, BSN RN; Frances Eubanks, BSN RN; Lynda Godowic, PharmD RPh; Laura Grau, RN; Alicia Guzman; Elizabeth Heyne, PsyD PA-C; Lizette E. Lee, RN; Helen C. Lira, PharmD; Azadeh Mozaffari, PharmD RPh; Lara Pavageau, MD; Catherine Twell Boatman, MS CIMI; Reshma Wright, RPh.

Wayne State University, Hutzel Women's Hospital and Children's Hospital of Michigan (UG1 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; Rebecca Bara, RN BSN; Prashant Agarwal, MD; Monika Bajaj, MD; Sanjay Chawla, MD; Kirsten Childs, RN BSN; Melissa February, MD; Laura A. Goldston, MA; Mary E. Johnson, RN BSN; Mirjana Lulic-Botica, RPh; Bogdan Panaitescu, MD; Eunice Woldt, RN MSN.

Data and Safety Monitoring Committee – Christine A. Gleason, MD, chair, University of Washington; Marilee C. Allen, MD, Johns Hopkins University School of Medicine; Robert J. Boyle, MD, University of Virginia Health System; Traci Clemons, PhD, The EMMES Corporation; Mary E. D'Alton, MD, Columbia Ob/Gyn Midtown; Abhik Das (ex officio), PhD, RTI International; Donald Everett, MA (non-voting member), National Eye Institute; Ralph E. Kauffman, MD, University of Missouri-Kansas City, Medical Research Department at Children's Mercy Hospital; Menachem Miodovnik, MD, Washington Hospital Center; T. Michael O'Shea, MD MPH, Wake Forest University School of Medicine; Lois Smith, MD, Harvard University Children's Hospital; Steven J. Weiner, MS, The George Washington University; Marian Willinger (ex officio), PhD, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development.

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Abbreviations

BSID-III	Bayley Scales of Infants Development-III
BPD	Bronchopulmonary Dysplasia
CP	Cerebral Palsy
DSMB	Data Safety Monitoring Board
FU PI	Follow-up Principal Investigator
GA	Gestational Age
GMFCS	Gross Motor Functional Classification System
IVH	Intraventricular Hemorrhage
IND	Investigational New Drug
NDI	Neurodevelopmental Impairment
NICHD	National Institute of Child Health and Human Development
NRN	Neonatal Research Network
PVL	Periventricular Leukomalacia
RCT	Randomized Controlled Trial
RDS	Respiratory Distress Syndrome
ROP	Retinopathy of Prematurity

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Article Summary

There was no difference in the risk for moderate/severe neurodevelopmental impairment in preterm infants enrolled in this RCT of treatment with myo-inositol.

What is known on this subject

There are limited data regarding the neurodevelopmental outcome of preterm infants treated with myo-inositol

What this study adds

In the largest randomized clinical trial of treatment with *myo*-inositol in preterm infants, treatment did not affect the risk for death or survival with moderate/severe neurodevelopmental impairment in early childhood

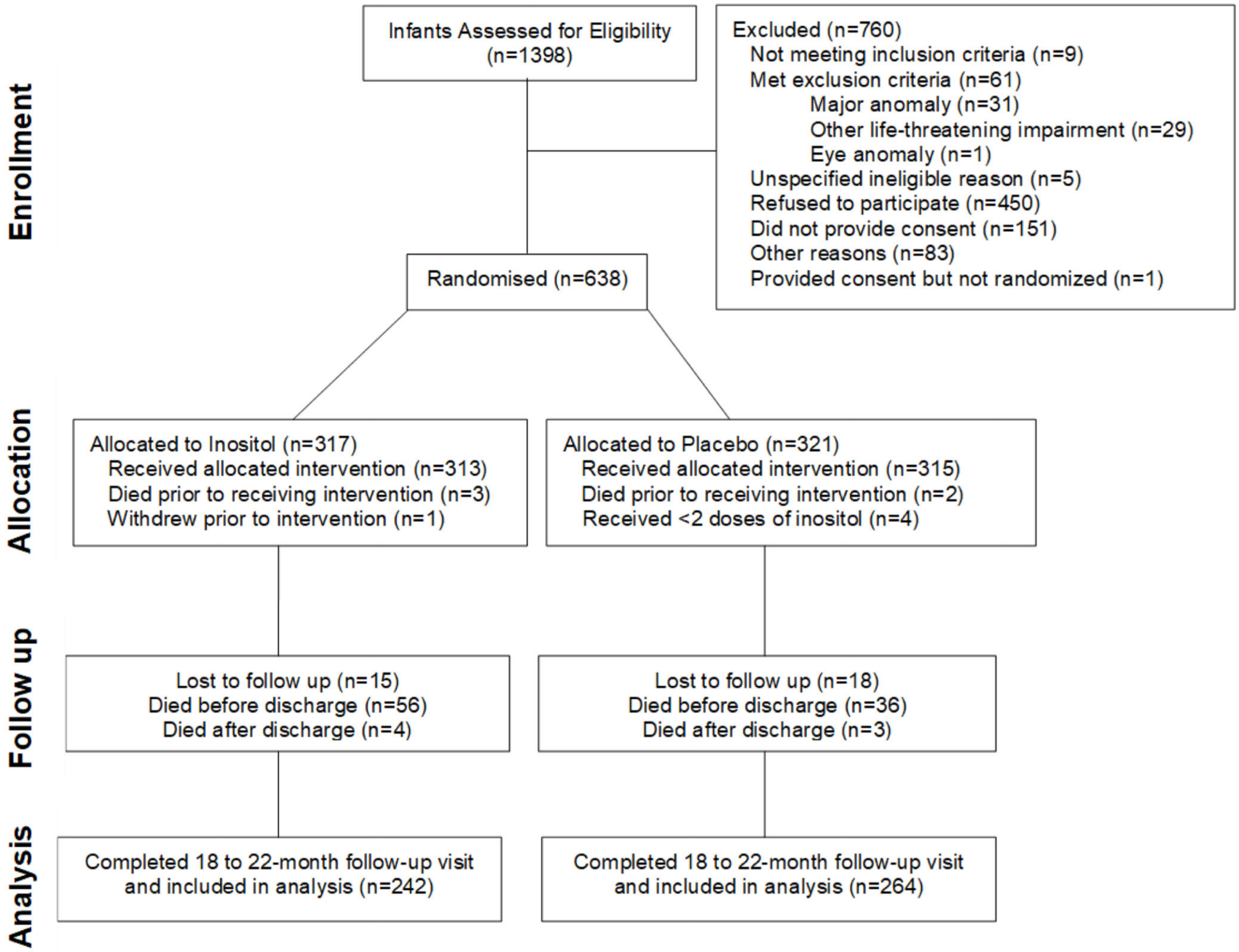

Figure 1:
Consort Diagram

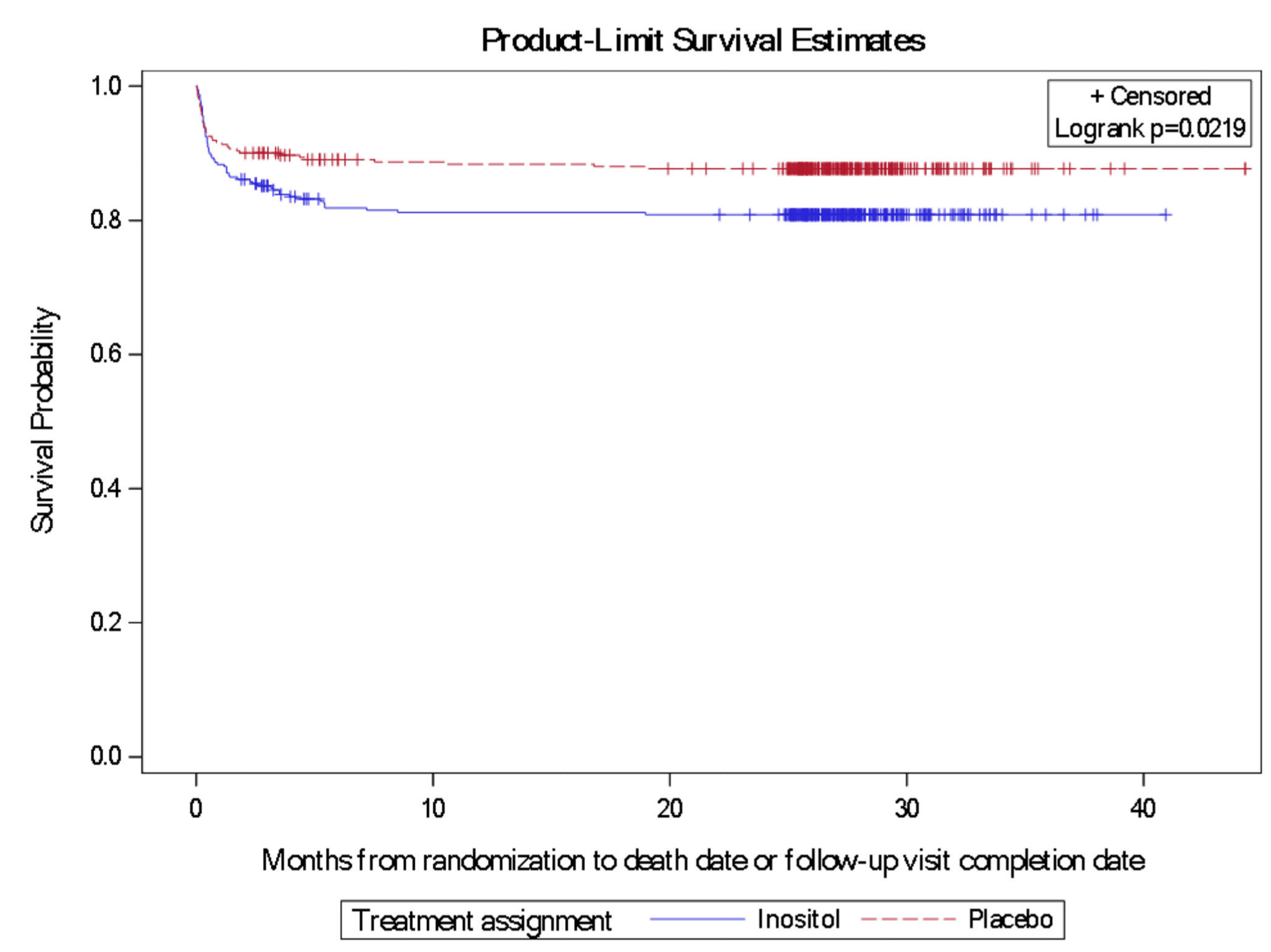

Figure 2:
Kaplan Meier Curve through 24 month follow-up

Table 1:

Baseline Characteristics and Demographics

Characteristic	Inositol Follow-up Completers (N=242)	Placebo Follow-up Completers (N=264)	P[1]	Total Follow-up Completers (N=506)	Death Prior to Follow-up (N=99)	LTF Prior to Follow-up (N=33)	P: Total vs. Death[1]	P: Total vs. LTF[1]	P: Death vs. LTF[1]
	Study Group								
Gestational Age (wks)									
Mean (SD)	25.8 (1.3)	25.8 (1.3)	0.50	25.8 (1.3)	24.8 (1.5)	26.1 (1.5)	<.001	0.18	<.001
<26 0/7 wk									
<26	119 (49.2%)	131 (49.6%)	0.88	250 (49.4%)	74 (74.7%)	15 (45.5%)	<.001	0.48	0.002
>= 26	123 (50.8%)	133 (50.4%)		256 (50.6%)	25 (25.3%)	18 (54.5%)			
Birthweight (gms)									
Mean (SD)	801.2 (193.9)	808.0 (190.9)	0.67	804.8 (192.1)	639.9 (155.9)	777.8 (196.3)	<.001	0.64	<.001
Sex									
Male	119 (49.2%)	127 (48.1%)	0.72	246 (48.6%)	59 (59.6%)	16 (48.5%)	0.10	0.79	0.26
Female	123 (50.8%)	137 (51.9%)		260 (51.4%)	40 (40.4%)	17 (51.5%)			
Race									
Non-Hispanic White	100 (43.7%)	107 (43.9%)	0.58	207 (43.8%)	41 (43.6%)	17 (56.7%)	0.52	0.79	0.36
Non-Hispanic Black	91 (39.7%)	91 (37.3%)		182 (38.5%)	40 (42.6%)	10 (33.3%)			
Asian	8 (3.5%)	6 (2.5%)		14 (3.0%)	3 (3.2%)				
Hispanic or Latino	30 (13.1%)	40 (16.4%)		70 (14.8%)	10 (10.6%)	3 (10.0%)			
Antenatal Steroids									
Yes	218 (90.1%)	238 (90.2%)	0.98	456 (90.1%)	81 (81.8%)	27 (84.4%)	0.02	0.30	0.74
No	24 (9.9%)	26 (9.8%)		50 (9.9%)	18 (18.2%)	5 (15.6%)			
Cesarean Delivery									
Yes	165 (68.5%)	186 (70.7%)	0.53	351 (69.6%)	48 (48.5%)	24 (72.7%)	<0.001	0.17	0.02
No	76 (31.5%)	77 (29.3%)		153 (30.4%)	51 (51.5%)	9 (27.3%)			
Apgar - 1 minute									
Median (IQR)	4.0 (2.0, 6.0)	3.0 (1.0, 5.0)	0.02	4.0 (2.0, 6.0)	2.0 (1.0, 5.0)	4.0 (2.0, 5.0)	0.02	0.89	0.02
Apgar - 5 minute									
Median (IQR)	7.0 (5.0, 8.0)	6.0 (5.0, 8.0)	0.06	7.0 (5.0, 8.0)	6.0 (3.0, 7.0)	6.0 (5.0, 8.0)	0.02	0.65	0.04

	Study Group								
Characteristic	**Inositol Follow-up Completers (N=242)**	**Placebo Follow-up Completers (N=264)**	**P[1]**	**Total Follow-up Completers (N=506)**	**Death Prior to Follow-up (N=99)**	**LTF Prior to Follow-up (N=33)**	**P: Total vs. Death[1]**	**P: Total vs. LTF[1]**	**P: Death vs. LTF[1]**
Chorioamnionitis									
Yes	37 (15.4%)	37 (14.1%)	0.60	74 (14.7%)	13 (13.3%)	2 (6.1%)	0.75	0.21	0.35
No	204 (84.6%)	226 (85.9%)		430 (85.3%)	85 (86.7%)	31 (93.9%)			
Early Onset Sepsis									
Yes	6 (2.5%)	8 (3.0%)	0.71	14 (2.8%)	2 (2.0%)	0 (0.0%)	>.99	>.99	>.99
No	236 (97.5%)	256 (97.0%)		492 (97.2%)	97 (98.0%)	33 (100.0%)			

LTF, Lost to Follow-up; P, P-value

[1]Analyses adjusted for center were possible.

Table 2:

Early Neonatal Morbidities

	Study Group								
Characteristic	**Inositol Follow-up Completers (N=242)**	**Placebo Follow-up Completers (N=264)**	**P[1]**	**Total Follow-up Completers (N=506)**	**Death Prior to Follow-up (N=99)**	**LTF Prior to Follow-up (N=33)**	**P: Total vs. Death[1]**	**P: Total vs. LTF[1]**	**P: Death vs. LTF[1]**
Bronchopulmonary Dysplasia (BPD) [2]	140/242 (58%)	149/263 (57%)	0.90	289/505 (57%)	19/ 22 (86%)	16/ 33 (48%)	0.008	0.61	0.004
Postnatal Steroid for BPD/CLD[2] (oxygen at 36 weeks)[3]	53/225 (24%)	56/241 (23%)	0.91	109/466 (23%)	20/ 96 (21%)	6/ 30 (20%)	0.52	0.80	0.92
Patent Ductus Arteriosus, Receiving Surgery	37/242 (15%)	39/264 (15%)	0.63	76/506 (15%)	5/ 98 (5%)	2/ 33 (6%)	0.004	0.25	0.66
Late Onset Sepsis	53/242 (22%)	47/264 (18%)	0.16	100/506 (20%)	39/ 92 (42%)	8/ 33 (24%)	<.001	0.31	0.06
NEC - Suspected or Proven	18/242 (7%)	21/264 (8%)	0.83	39/506 (8%)	16/ 99 (16%)	4/ 33 (12%)	0.008	0.32	0.78
NEC, Receiving Surgery	7/242 (3%)	4/264 (2%)	0.17	11/506 (2%)	11/ 99 (11%)	1/ 33 (3%)	0.005	>.99	0.26
Spontaneous Intestinal Perforation without Necrotizing Enterocolitis	13/242 (5%)	13/264 (5%)	0.82	26/506 (5%)	13/ 99 (13%)	2/ 33 (6%)	0.02	0.69	0.35
Any Intraventricular Hemorrhage	73/241 (30%)	67/263 (25%)	0.23	140/504 (28%)	45/ 91 (49%)	7/ 33 (21%)	<.001	0.31	<.001
Intraventricular Hemorrhage, Grade 3 or 4	35/241 (15%)	32/263 (12%)	0.38	67/504 (13%)	32/ 91 (35%)	2/ 33 (6%)	<.001	0.22	0.001
Periventricular Leukomalacia	14/242 (6%)	12/263 (5%)	0.53	26/505 (5%)	5/ 91 (5%)	1/ 33 (3%)	0.80	>.99	>.99
Type 1 ROP w/adjunction	35/238 (15%)	28/264 (11%)	0.16	63/502 (13%)	5/ 16 (31%)	6/ 32 (19%)	0.04	0.26	0.33

ROP, retinopathy of prematurity; BPD, Bronchopulmonary dysplasia; VPS, VP Shunt; VAD, Ventricular access device; NEC, Necrotizing enterocolitis; CLD, Chronic lung disease; P, P-value

[1] Analyses adjusted for center were possible.

[2] Bronchopulmonary dysplasia (BPD) is a form of chronic lung disease (CLD) most commonly seen in premature infants who require mechanical ventilation and oxygen therapy for acute respiratory distress. For the study, it is defined as supplemental oxygen required to maintain an oxygenation saturation of >90% at 36 weeks postmenstrual age (PMA) (NICHD physiologic definition)

[3] 46 participants were removed from analysis as they received a trial treatment that could have either been an active treatment or placebo.

Table 3:

Composite Outcome Of Death Or Survival With Moderate/Severe Neurodevelopmental Impairment Among Randomized Infants[1]

	Study Group				
Outcome	Inositol (N=302)	Placebo (N=303)	Adjusted Risk Diff (95% CI)	Adjusted RR (95% CI)	P-value
Corrected age at follow-up; Median (IQR)	24 (23,26)	24 (22,26)	N/A	N/A	
NDI or Death Prior to Follow-up	172/287 (60%)	161/289 (56%)	2 (−5 to 10)	1.06 (0.93 to 1.21)	0.40
Any ROP or Death Prior to Follow-up	231/302 (76%)	224/303 (74%)	1 (−6 to 7)	1.03 (0.94 to 1.12)	0.53
Death Prior to Follow-up	60/302 (20%)	39/303 (13%)	4 (−2 to 11)	1.53 (1.08 to 2.18)	0.02
Moderate or Severe NDI	112/227 (49%)	122/250 (49%)	−1 (−9 to 8)	1.01 (0.85 to 1.21)	0.88
Moderate NDI[2]	66/227 (29%)	79/250 (32%)			
Severe NDI[3]	46/224 (21%)	43/246 (17%)			
Any ROP[4]	181/260 (70%)	191/271 (70%)	−2 (−10 to 5)	0.99 (0.90 to 1.10)	0.92

NDI, neurodevelopmental impairment; ROP, retinopathy of prematurity

All analyses adjusted for center and gestational age strata

[1] Excludes lost to follow-up participants

[2] Occurrence of any of the following: GMFCS level II or III, Bayley III cognitive composite score between and including 70 and 84, Bayley III motor composite score between and including 70 and 84, unilateral blind or bilateral blind, permanent hearing loss that does not permit child to understand directions of the examiner and communicate despite amplification with cochlear implant or hearing aid

[3] Occurrence of any of the following: GMFCS level IV or V, Bayley III cognitive composite score < 70, Bayley III motor composite score < 70, unilateral blind or bilateral blind, permanent hearing loss that does not permit child to understand directions of the examiner and communicate despite amplification with cochlear implant or hearing aid

[4] Includes any report of ROP in the GDB NG-03 form, Follow-up NF-04 form, INS 3–14 Follow-up form (ophthalmologist diagnosed or treated ROP), or a documented finding of ROP on any ophthalmologic exam during the initial INS follow-up

Table 4:

Neurodevelopment Outcomes Among Follow-up Completers

	Study Group				
Outcome	**Inositol Follow-up Completers (N=242)**	**Placebo Follow-up Completers (N=264)**	**Adjusted Risk Diff (95% CI)**	**Adjusted RR (95% CI)**	**P-value**
Growth at Follow-up					
Weight - kg, mean (std)[1]	11.8 (2.2)	11.7 (1.7)	0.01 (−.32 to 0.34)		0.94
Head Circumference - cm, mean (std)[1]	47.5 (2.3)	47.6 (2.4)	−.12 (−.49 to 0.24)		0.50
Height - cm, mean (std)[1]	85.3 (4.1)	85.6 (4.3)	−.41 (−1.1 to 0.31)		0.26
Components of NDI					
Cerebral Palsy, Any[2]	39/240 (16%)	39/259 (15%)	1 (−5 to 7)	1.08 (0.72 to 1.62)	0.71
Cerebral Palsy, moderate or severe[2]	22/239 (9%)	16/258 (6%)	2 (−2 to 7)	1.49 (0.80 to 2.76)	0.21
GMFCS >=2[2]	25/238 (11%)	24/258 (9%)	1 (−4 to 6)	1.12 (0.66 to 1.90)	0.67
BSID III Cognitive <70[2]	31/231 (13%)	38/258 (15%)	−1 (−7 to 5)	0.91 (0.59 to 1.41)	0.66
BSID III Cognitive <85[1]	78/231 (34%)	83/258 (32%)	2 (−6 to 10)	1.05 (0.82 to 1.34)	0.72
BSID III Motor <70[2]	37/227 (16%)	34/253 (13%)	3 (−3 to 9)	1.20 (0.78 to 1.85)	0.40
BSID III Motor <85[1]	94/227 (41%)	107/253 (42%)	−1 (−10 to 7)	0.99 (0.81 to 1.22)	0.94
Bilateral Blindness[3]	3/240 (1%)	4/259 (2%)	0 (−2 to 2)	0.81 (0.18 to 3.58)	0.78
Unilateral Blindness[3,4]	4/240 (2%)	5/259 (2%)	0 (−3 to 2)	0.86 (0.23 to 3.18)	0.83
Bilateral Hearing Loss[2]	11/238 (5%)	6/252 (2%)	3 (−3 to 9)	1.93 (0.73 to 5.10)	0.19
Ophthalmologic Outcomes					
Any ROP through follow-up[2,5]	171/242 (71%)	185/264 (70%)	0 (−7 to 8)	1.02 (0.92 to 1.13)	0.75
Any Ophthalmologic treatment[1,6]	42/195 (22%)	37/221 (17%)	4 (−3 to 12)	1.30 (0.87 to 1.92)	0.20
Any Ophthalmologic surgery[1,7]	15/195 (8%)	13/221 (6%)	0 (−5 to 5)	1.32 (0.64 to 2.70)	0.45

	Study Group				
Outcome	Inositol Follow-up Completers (N=242)	Placebo Follow-up Completers (N=264)	Adjusted Risk Diff (95% CI)	Adjusted RR (95% CI)	P-value
Strabismus[1,8]	35/239 (15%)	39/263 (15%)	−1 (−7 to 5)	0.98 (0.66 to 1.47)	0.93
Nystagmus[2,9]	11/239 (5%)	8/263 (3%)	1 (−2 to 5)	1.51 (0.62 to 3.70)	0.36

NDI, neurodevelopmental impairment; GMFCS, gross motor function classification system; BSID III, Bayley Scales of Infant Development-III; ROP, retinopathy of prematurity

[1]Analyses adjusted for center and gestational age strata

[2]Analyses adjusted for gestational age strata

[3]Analyses not adjusted due to low cell count

[4]Includes bilateral blindness

[5]Includes any report of ROP in the GDB NG-03 form, Follow-up NF-04 form, INS 3–14 Follow-up form (ophthalmologist diagnosed or treated ROP), or a documented finding of ROP on any ophthalmologic exam during the initial INS follow-up

[6]Includes any reported eye surgery or medical treatment (in either eye) on the INS 3–14 Follow-up form

[7]Includes any reported eye surgery (in either eye) on the INS 3–14 Follow-up form

[8]Includes any report of Strabismus in the Follow-up NF-04 or NF-05 forms

[9]Includes any report of Nystagmus in the Follow-up NF-04 or NF-05 forms

Table 5:

Composite Outcome Of Death Or Survival With Major Morbidity For LOT 1 Only Vs LOT 2 Only[1]

	Lot 1 Use Only				Lot 2 Use Only				Inositol Lot	
Outcome	**Inositol (N=124)**	**Placebo (N=119)**	**RR (95% CI)**	**P**	**Inositol (N=137)**	**Placebo (N=148)**	**RR (95% CI)**	**P**	**RR (95% CI)**	**P**
NDI or Death Prior to Follow-up	75/116 (65%)	59/115 (51%)	1.29 (1.05 to 1.60)	0.02	72/132 (55%)	80/140 (57%)	0.93 (0.76 to 1.14)	0.49	0.85 (0.69 to 1.04)	0.11
Any ROP or Death Prior to Follow-up	99/124 (80%)	84/119 (71%)	1.14 (1.00 to 1.29)	0.05	103/137 (75%)	110/148 (74%)	1.01 (0.88 to 1.15)	0.91	0.88 (0.76 to 1.02)	0.09
Death Prior to Follow-up	31/124 (25%)	19/119 (16%)	1.50 (0.91 to 2.46)	0.11	27/137 (20%)	20/148 (14%)	1.45 (0.86 to 2.45)	0.17	0.80 (0.52 to 1.25)	0.34
Moderate or Severe NDI [2]	44/ 85 (52%)	40/ 96 (42%)	1.23 (0.90 to 1.69)	0.19	45/105 (43%)	60/120 (50%)	0.86 (0.65 to 1.14)	0.29	0.83 (0.61 to 1.11)	0.21
Any ROP [3]	74/101 (73%)	67/102 (66%)	1.10 (0.92 to 1.31)	0.31	79/119 (66%)	94/133 (71%)	0.95 (0.80 to 1.12)	0.52	0.91 (0.77 to 1.08)	0.27

NDI, neurodevelopmental impairment; ROP, retinopathy of prematurity; P, P-value

Robust Poisson regression adjusting for center where possible and GA strata were used to obtain p-values and estimated adjusted relative risks and 95% confidence intervals. Lot 1 was used as the reference group for the Inositol lot comparison.

[1] Excludes lost to follow-up participants

[2] Occurrence of any of the following: GMFCS level II or higher, Bayley III cognitive composite score < 85, Bayley III motor composite score < 85, unilateral blind or bilateral blind, permanent hearing loss that does not permit child to understand directions of the examiner and communicate despite amplification with cochlear implant or hearing aid

[3] Includes any report of ROP in the GDB NG-03 form, Follow-up NF-04 form, INS 3–14 Follow-up form (ophthalmologist diagnosed or treated ROP), or a documented finding of ROP on any ophthalmologic exam during the initial INS follow-up

Table 6:

Neurodevelopment Outcome For LOT 1 Only Vs LOT 2 Only Among Follow-up Completers[1]

	Lot 1 Use Only			Lot 2 Use Only			Inositol Lot Comparison
Outcome	**Inositol Follow-up Completers (N=93)**	**Placebo Follow-up Completers (N=100)**	**P**	**Inositol Follow-up Completers (N=110)**	**Placebo Follow-up Completers (N=128)**	**P**	**P**
Growth at Follow-up							
Weight - kg, mean (std)	11.9 (2.1)	11.9 (1.7)	0.83	11.8 (2.4)	11.5 (1.6)	0.22	0.62
Head Circumference - cm, mean (std)	47.5 (2.2)	47.7 (2.1)	0.33	47.7 (2.3)	47.5 (2.5)	0.69	0.45
Height - cm, mean (std)	85.2 (4.0)	85.7 (4.1)	0.35	85.3 (4.2)	85.7 (4.5)	0.43	0.48
Components of NDI							
Cerebral Palsy, Any	12/ 92 (13%)	12/ 99 (12%)	0.88	17/109 (16%)	24/124 (19%)	0.46	0.61
Cerebral Palsy, moderate or severe	9/ 92 (10%)	4/ 99 (4%)	0.14	9/109 (8%)	10/124 (8%)	0.94	0.69
GMFCS >=2	9/ 92 (10%)	7/ 99 (7%)	0.54	11/107 (10%)	13/123 (11%)	0.94	0.93
BSID III Cognitive <70	12/ 87 (14%)	9/ 99 (9%)	0.33	13/106 (12%)	22/123 (18%)	0.24	0.74
BSID III Cognitive <85	28/ 87 (32%)	23/ 99 (23%)	0.18	35/106 (33%)	44/123 (36%)	0.67	0.92
BSID III Motor <70	14/ 85 (16%)	7/ 96 (7%)	0.07	14/105 (13%)	20/121 (17%)	0.50	0.54
BSID III Motor <85	39/ 85 (46%)	36/ 96 (38%)	0.26	33/105 (31%)	52/121 (43%)	0.08	0.04
Bilateral Blindness	0/ 92 (0%)	1/ 99 (1%)		1/109 (1%)	3/124 (2%)	0.40	
Unilateral Blindness[1]	0/ 92 (0%)	2/ 99 (2%)		2/109 (2%)	3/124 (2%)	0.76	
Bilateral Hearing Loss	4/ 92 (4%)	1/ 98 (1%)	0.20	5/108 (5%)	5/119 (4%)	0.88	0.93
Ophthalmologic Outcomes							
Any ROP through follow-up[2]	68/ 93 (73%)	65/100 (65%)	0.26	76/110 (69%)	90/128 (70%)	0.91	0.52
Any Ophthalmologic treatment[3]	15/ 72 (21%)	14/ 82 (17%)	0.54	19/ 91 (21%)	16/108 (15%)	0.24	0.90
Any Ophthalmologic surgery[4]	5/ 72 (7%)	4/ 82 (5%)	0.58	9/ 91 (10%)	6/108 (6%)	0.24	0.60
Strabismus[5]	12/ 92 (13%)	12/ 99 (12%)	0.87	17/108 (16%)	22/128 (17%)	0.80	0.61
Nystagmus[6]	3/ 92 (3%)	4/ 99 (4%)	0.76	6/108 (6%)	3/128 (2%)	0.21	0.45

NDI, neurodevelopmental impairment; GMFCS, gross motor function classification system; BSID III, Bayley Scales of Infant Development-III; ROP, retinopathy of prematurity; P, P-value

Robust Poisson regression adjusting for center where possible and GA strata were used to obtain p-values and estimated adjusted relative risks and 95% confidence intervals.

[1] Includes bilateral blindness

[2] Includes any report of ROP in the GDB NG-03 form, Follow-up NF-04 form, INS 3–14 Follow-up form (ophthalmologist diagnosed or treated ROP), or a documented finding of ROP on any ophthalmologic exam during the initial INS follow-up

[3] Includes any reported eye surgery or medical treatment (in either eye) on the INS 3–14 Follow-up form

[4] Includes any reported eye surgery (in either eye) on the INS 3–14 Follow-up form

[5] Includes any report of Strabismus in the Follow-up NF-04 or NF-05 forms

[6] Includes any report of Nystagmus in the Follow-up NF-04 or NF-05 forms