Session 3: Key Considerations for Endpoint Selection for Neonatal Conditions

Moderator: Monica Lemmon, Duke University School of Medicine

Session 3: Objectives

Objectives:

- Discuss endpoint types and key aspects of selection for neonatal conditions, including the timing of outcome measurement and the interpretability, reliability, and validity of measured endpoints
- Consider how feasibility with respect to timing, costs, and other burdens may impact endpoint selection
- Consider the clinical importance of endpoints to various stakeholders, including patients and families

Session 3 Panelists

Keith Barrington
Sainte Justine University Health Center

Ashley Darcy-Mahoney
George Washington University School Nursing & Pediatrix

JaNeen Cross
Howard University School of Social Work

Deb Discenza
PreemieWorld

Daniel Fuentes
Chiesi USA, Inc.

Betsy Pilon
Hope for HIE

Naomi Knoble
U.S. Food & Drug Administration

Audience Q&A

Submit questions and comments via Slido

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Outcomes for Neonatal RCTs

Keith J Barrington

Outcomes should be

- Meaningful
  - For the individual
  - For parents
  - For society
- Measurable
  - Objective
  - Or with Low Inter-Rater Variation

Composite Outcomes should:

- Include components of equal importance
- Or
- Prioritize the components

- « Death or NDI »
- « Death or BPD »
- « Death or NEC or RoP or BPD or LOS »

- Do neither

Example

- Pulmonary outcomes
  - Lung damage is common and has long-term consequences in the preterm
  - Usually defined by respiratory support persisting near to term
  - Commonly O2 or respiratory support at 36 weeks PMA
  - « Bronchopulmonary Dysplasia »
    - Each time definition has been adjusted, it has been based on correlation with longer term respiratory morbidity

- We asked parents what outcomes mattered to them

Thivierge E, et al. Pulmonary important outcomes after extremely preterm birth: parental perspectives. Acta Paediatr. 2023.

- 285 parents of extremely preterm infants questioned
- 44% mentioned respiratory outcomes as being important to them

- None mentioned diagnosis of BPD or oxygen at 36 weeks
  - They either didn’t know or didn’t care!

Table 2: Themes invoked by parents when describing pulmonary important outcomes

NICU outcomes	Long-term outcomes (home)
Intubation	Home oxygen -Duration (more difficult with mobile child)
Duration of intubation	-More difficult when other children or pets -limitations in movement of child, parents/family
Spells on the tube	
Reintubations -fear of parents, ups and downs	Work of breathing, coughing, wheezing -difficulty breathing - Parental fear -Negative impact on child's sleep
Accidental extubations - fear of parents, ups and downs	-Negative impact on parent/family's sleep
Respiratory insufficiency -Fear of death -capacity to hold baby	Isolation of family -Avoiding contacts to decrease infections and adverse pulmonary outcomes
-Steroids to prevent death	-Recommendation to avoid daycare -parental impact, loss of work
Time on respiratory support - HFNC better than CPAP	Tracheostomy
Work of breathing	Hospital readmissions -Loss of work for parents
ENT problems: investigations, surgery, stridor	Hospital visits -Loss of work for parents
Nose/face/midface injuries from ventilation/intubation	Frequent infections - Loss of work for parents
Duration of oxygen past term	ENT problems, ENT surgery
Tracheostomy	Medication need -Difficulty giving it, follow-up, efficiency
	Feeding/nutritional impact of respiratory problems: oral aversion, gastrostomy
	Exercise limitation
	Limitation in school activities

Short-term pulmonary outcomes of importance to parents

- Outcomes reflecting lung injury:

- Duration of oxygen use past term
- Oxygen at discharge

Long-term outcomes of importance

- Duration of home oxygen
- Hospital readmissions
- Hospital visits or urgent doctor’s office visits
- Clinical respiratory distress
- Respiratory medications
- Feeding difficulties
- Exercise limitation

Barrington KJ, et al. Respiratory outcomes in preterm babies, is bronchopulmonary dysplasia important? Acta Paediatr. 2022.

- BPD is a poor predictor of outcomes important to parents

TABLE 2 Randomised trials reporting both BPD outcomes and long-term respiratory outcomes

Study	Interventions compared	Impacts on BPD of the active treatment	Impacts of the active treatment on long-term respiratory health
support	Prophylactic CPAP vs intubation for surfactant	No change	Prophylactic CPAP led to less asthma, reactive airway disease and BPD exacerbations, fewer respiratory hospitalisations and less negative respiratory consequences reported by parents
TOLSURF	Late surfactant vs placebo	No change	Fewer infants with pulmonary morbidity and fewer infants still receiving oxygen at follow-up
Roze et al	Late surfactant vs placebo	No change	Fewer rehospitalisations and fewer oxygen or steroid requirements after discharge
Rh-SOD	Intratracheal recombinant SOD vs placebo	More BPD	Less respiratory medication use, and fewer rehospitalisations or ER visits
Yeh et al	Early postnatal dexamethasone vs placebo	Less BPD	No difference in rehospitalisations or lower respiratory tract infections, and identical lung function tests in the long term
DART	Postnatal dexamethasone vs placebo	Less severe BPD	No difference in hospital readmission or duration of home oxygen therapy

Suggestion

- Primary outcome for respiratory interventions should be a measure of long term impacts,
- Constructed by parents and health professionals,
- Reflecting the clinical impacts of lung damage
- Could be at 2 years of age
- Very low cost

- Short term outcomes which should be collected,
- duration of oxygen use past 40 weeks,
- Proportion home on O2

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Session 3 Discussion Questions

- What does each stakeholder believe are the most important factors to consider for measuring efficacy?
- When designing a clinical trial, how can investigators/sponsors determine the degree of improvement that would be clinically meaningful ?
- How can study investigators/sponsors balance feasibility and meaningfulness when selecting outcome measures?

Session 3: Key Considerations for Endpoint Selection for Neonatal Conditions

Moderator: Monica Lemmon, Duke University School of Medicine

Session 4: Novel Approaches to Measure Clinical Benefit in Neonatal Clinical Trials

Moderator: Matthew Laughon, UNC Health

Session 4: Objectives

Objectives:

- Discuss new approaches to measuring clinical benefit in neonatal RCTs, such as defining a global rank score (GRS), EHR/technology-based clinical outcome assessment tools, and data-driven surrogate or intermediate endpoints
- Discuss considerations related to balancing efficacy with potential or known safety concerns and challenges with using new approaches to neonatal trial conduct

Session 4: Presenters & Panelists

Presentations:

- **Genny Taylor,** UNC Health
- **Kevin Hill,** Duke University Medical Center
- **Claudia Pedroza,** The University of Texas Health Science Center at Houston

Panelists:

- **Dionna Green,** U.S. Food & Drug Administration
- **Kanwaljit Singh,** Critical Path Institute
- **Susan McCune,** PPD Clinical Research Business, Thermo Fisher Scientific

Audience Q&A

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Genny Taylor

UNC Health

Neonatal Global Rank Score Development and Future Applications

Measuring Clinical Benefit in Neonatal Randomized Clinical Trials: Challenges and Opportunities

Genny Taylor, MD

Neonatology

UNC Health

Disclosures and Funding Support

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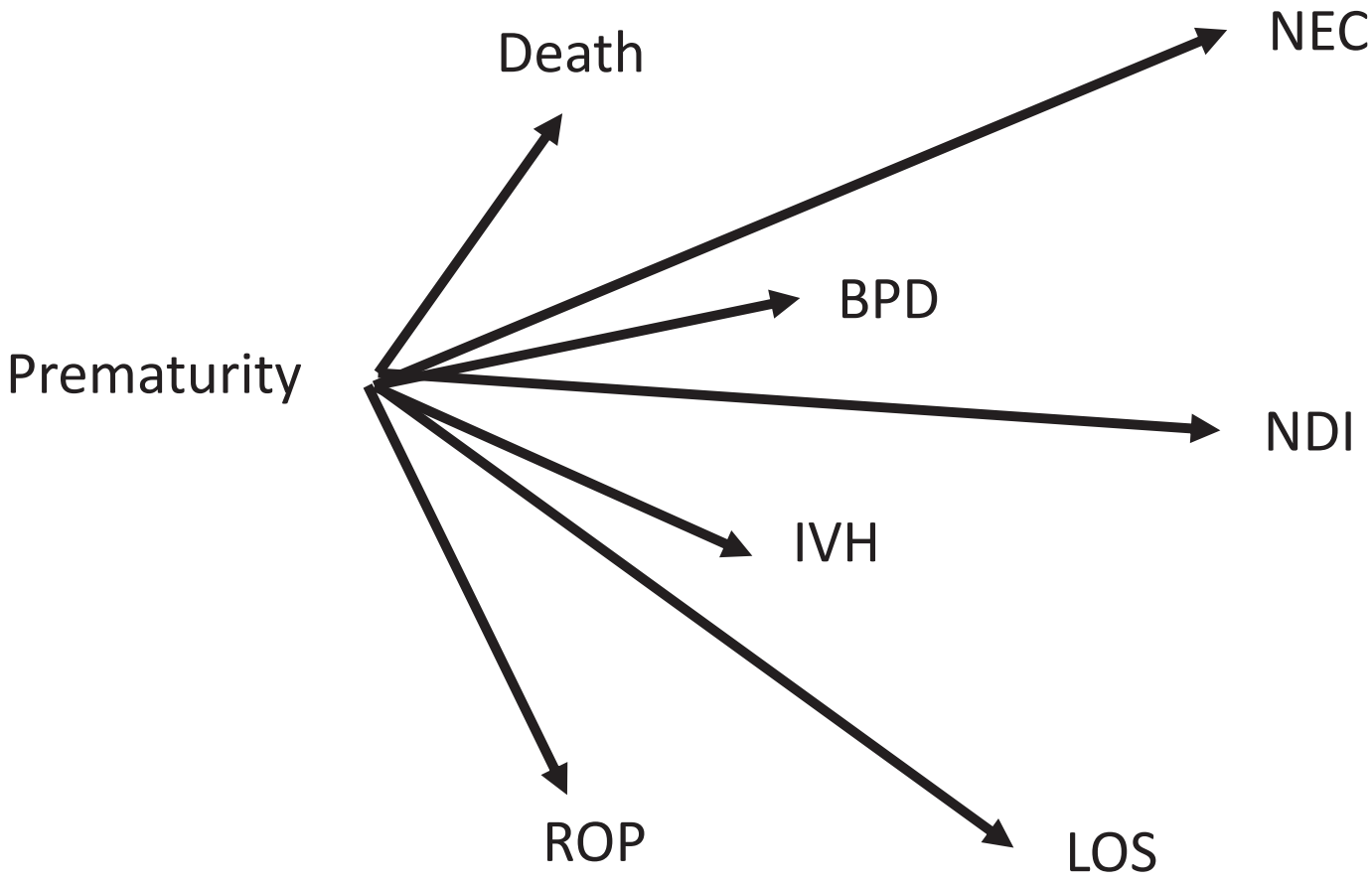
Environment, Epigenetics, Neurodevelopment & Health of Extremely Preterm Children, Environmental influences on Child Health Outcomes (ECHO) Consortium

U18FD006298 A03-3742; FDA/Food and Drug Administration; Co-investigator

Global Pediatric Clinical Trials Network Global Rank Score Subaward

#2021264 Doris Duke Charitable Foundation Caregivers at Carolina Program Award COVID-19 Supplement

Impact of Prematurity



Composite endpoints in neonatal trials

- 54% of trials used composite outcomes
- Most common:
  - Death or BPD
  - Death or disability
  - Disability
  - Death or NEC

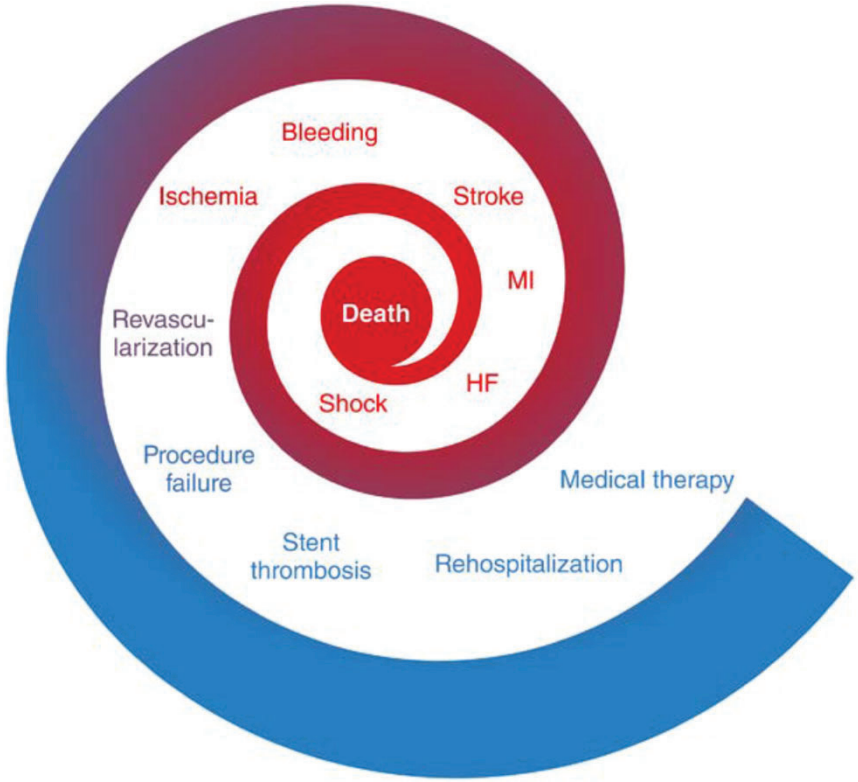
Webbe et al., Arch Dis Child Fetal Neonatal Ed 2020

Criticism of composite endpoints

- Assume uniform directionality of each component
- Relative clinical significance of each component treated as equal
- Inconsistently defined
- Inadequately reported

Endpoints in Cardiovascular Research

- Composite endpoints used frequently
- Most common components:
  - Death
  - Myocardial infarction
  - Stroke
  - Revascularization
- Critique of composite endpoints has led to statistical methods involving weighting or ranking



Armstrong et al.
Circulation. 2017.

Potential Benefits of Neonatal GRS

- Increase power
- Increase clinical relevance
- Evaluate both efficacy and safety endpoints

Table 3. Primary and Other Outcomes at 18 to 22 Months.*

Outcome	Aggressive Phototherapy	Conservative Phototherapy	Relative Risk (95% CI)†
	no./total no. (%)		
Death or neurodevelopmental impairment	465/902 (52)	493/902 (55)	0.94 (0.87–1.02)
Death‡	230/946 (24)	218/944 (23)	1.05 (0.90–1.22)
Neurodevelopmental impairment	235/902 (26)	275/902 (30)	0.86 (0.74–0.99)§

"Among infants whose birth weight was 650 g or less, 106 of 214 (50%) died in the aggressive-phototherapy group, as compared with 80 of 212 (38%) in the conservative-phototherapy group (P=0.03)."

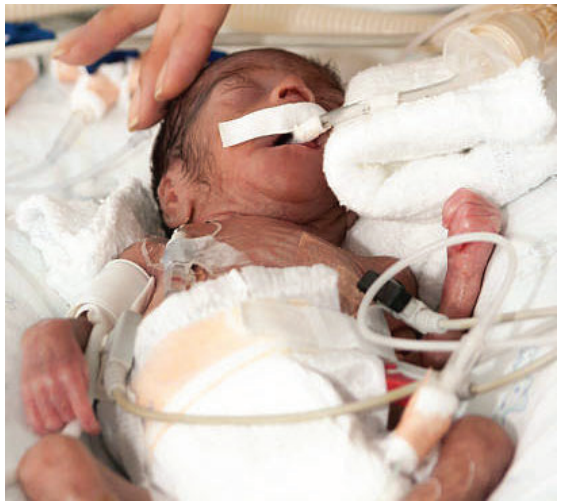
Morris et al. NEJM 2008.

Neonatal GRS Development

1. Content Selection by Steering Committee
2. Modified Delphi Consensus Process

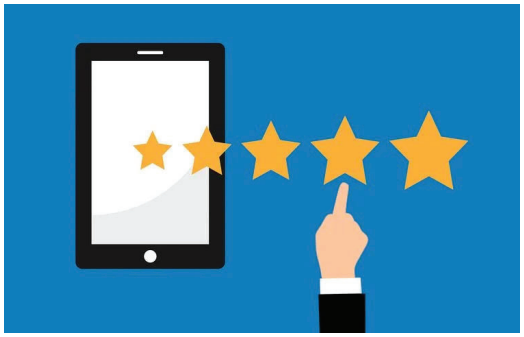
Content Selection

- Convened steering committee of neonatologists, clinical trialists & a parent
- Reviewed 216 outcomes
  - Systematic review of neonatal clinical trials[1]
  - Narrowed from birth to 2-years-old
- Consolidated to 31 outcomes



1. Webbe, et al. Arch Dis Child Fetal Neonatal Ed 2019
2. Webbe, et al. Arch Dis Child Fetal Neonatal Ed 2020

Modified Delphi Consensus Process



x3

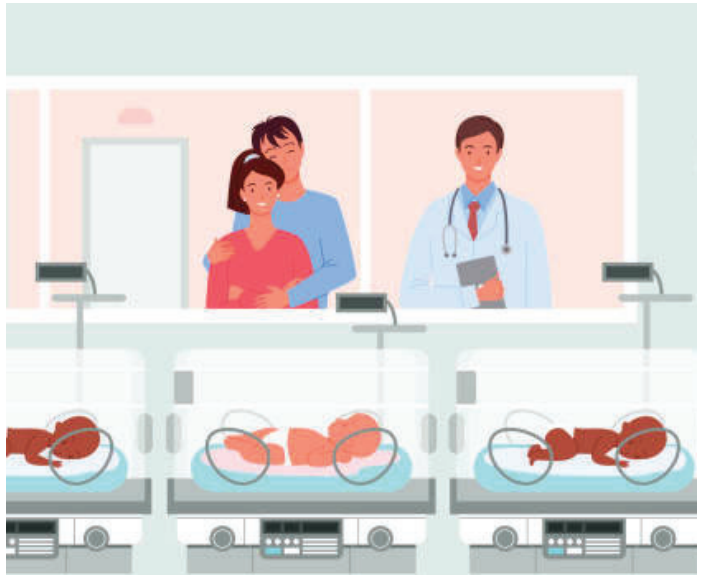
- Should [specific outcome] be included?
- *Would you use [outcome definition]?*
- Rank [specific outcomes] by severity.

- Review survey results.
- Finalize outcome selection.
- Finalize severity ranking.

Participants

Targeted equal power in process

1. Parents and other caregivers
   - Previously participated in research
2. Researchers and clinicians
   - Neonatal clinical trialists
   - Clinical neonatologists
   - NICU follow-up researchers
   - Pediatric subspecialists
   - Complex care pediatricians
   - Regulators



Participants by Round

	Round 1			Round 2		Round 3	
Stakeholder group	Started	In analysis	Completed*	Started	Completed	Started	Completed
Family Group	24	23	18	18	12	13	11
Medical Group	37	33	33	29	21	25	23
Total	61	56	51	47	33	38	34

*Reached end of survey after optional demographic section

Participant Expertise

- Family Group
  - All parents (83% mothers) except one grandmother
  - All caregivers to children born preterm, the majority born < 28 weeks GA
  - Children were age 3 years to 23 years old
  - Majority completed 4 years of college or greater
- Medical Group (N=26)
  - 81% neonatology
  - 8% pulmonology
  - 2% general pediatrics
  - 1% infectious disease

Preliminary Thematic Analysis

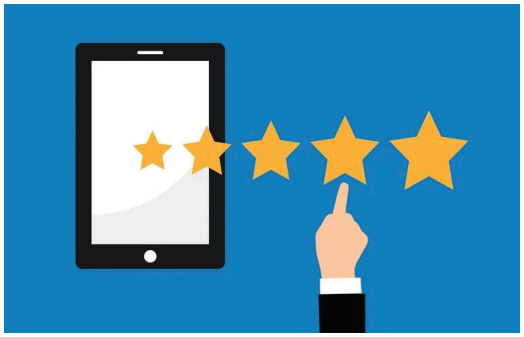
Family Group	Medical Group
Personal experience	Practice variation
Likelihood of long-term impact Marker of overall health Strain on family or society Feasibility Overlap with other outcomes Gratitude for being included in process	

Overview of Survey Results

- Consensus to include 19 outcomes
- Borderline consensus to include 4 additional outcomes
- Preliminary ranking

Percent in Each Quarter			
1st	2nd	3rd	4th
96.7%	0.0%	3.3%	0.0%
53.3%	30.0%	13.3%	3.3%
63.3%	23.3%	10.0%	3.3%
40.0%	53.3%	3.3%	3.3%
46.7%	53.3%	0.0%	0.0%
26.7%	56.7%	16.7%	0.0%
23.3%	50.0%	13.3%	13.3%
3.3%	63.3%	26.7%	6.7%
10.0%	53.3%	20.0%	16.7%
23.3%	16.7%	46.7%	13.3%
0.0%	16.7%	63.3%	20.0%
0.0%	20.0%	56.7%	23.3%
0.0%	13.3%	33.3%	53.3%
6.7%	20.0%	30.0%	43.3%
0.0%	6.7%	33.3%	60.0%
0.0%	10.0%	10.0%	80.0%
3.3%	3.3%	10.0%	83.3%
3.3%	10.0%	10.0%	76.7%

Next Steps



x3

- Should [specific outcome] be included?
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- Rank [specific outcomes] by severity.

- Review survey results.
- Finalize outcome selection.
- Finalize severity ranking.

Lessons in key stakeholder engagement

- Positives and negatives of multiple rounds in modified Delphi
- Use of mixed methodology could increase participation and quality
- Common themes emerged across stakeholder groups

Future Application of Neonatal GRS

- Statistical refinement and hypothesis generation using real world data
- Endpoint in prospective trials
- Foundation for other neonatal global rank scores

Neurodevelopmental GRS for NICU Grads

- Assessment at 2-years-old
- Standardized definitions
- Ranked components
- Include continuous and categorical variables
- Start with key stakeholder engagement using mixed methods

Summary

- Potential benefits of a neonatal global rank score
  - Increase statistical power
  - Increase clinical relevance by incorporating multiple morbidities
  - Increase clinical relevance though key stakeholder engagement
  - Provide framework to develop disease specific global rank scores

Kevin Hill

Duke University Medical Center

The Pragmatic Trial Within a Registry Concept

Case study: Studying Prophylactic Steroids and Congenital Heart Surgery - a Model for More Efficient Clinical Trials

Kevin Hill, MD MS
Duke University Medical Center
Duke Clinical Research Institute

DISCLOSURES

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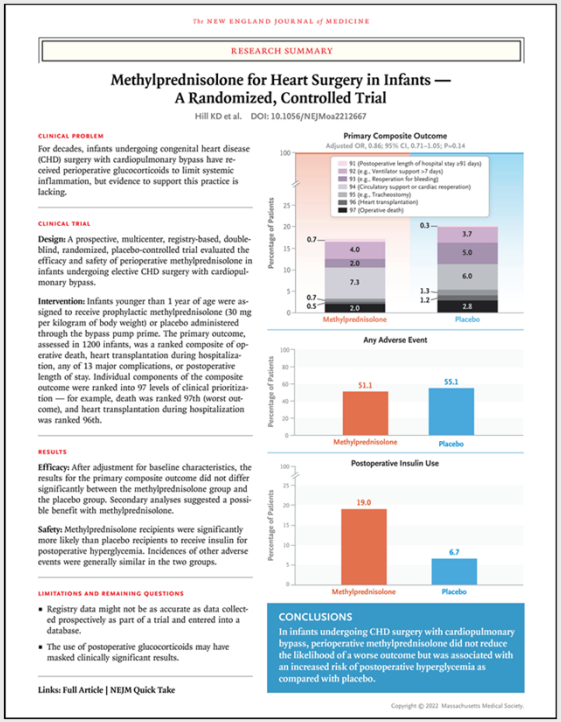
CAN WE MAKE TRIALS MORE EFFICIENT, COST EFFECTIVE AND INCLUSIVE?

Case Study

STeroids to **RE**duce **S**ystemic inflammation after Infant heart **S**urgery (STRESS Trial)

Multi-center pragmatic trial built into the STS registry using a global rank endpoint



The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Methylprednisolone for Heart Surgery in Infants — A Randomized, Controlled Trial

Hill KD et al. DOI: 10.1056/NEJMoa2212667

CLINICAL PROBLEM

For decades, infants undergoing congenital heart disease (CHD) surgery with cardiopulmonary bypass have received perioperative glucocorticoids to limit systemic inflammation, but evidence to support this practice is lacking.

CLINICAL TRIAL

Design: A prospective, multicenter, registry-based, double-blind, randomized, placebo-controlled trial evaluated the efficacy and safety of perioperative methylprednisolone in infants undergoing elective CHD surgery with cardiopulmonary bypass.

Intervention: Infants younger than 1 year of age were assigned to receive prophylactic methylprednisolone (30 mg per kilogram of body weight) or placebo administered through the bypass pump prime. The primary outcome, assessed in 1200 infants, was a ranked composite of operative death, heart transplantation during hospitalization, any of 13 major complications, or postoperative length of stay. Individual components of the composite outcome were ranked into 97 levels of clinical prioritization — for example, death was ranked 97th (worst outcome), and heart transplantation during hospitalization was ranked 96th.

RESULTS

Efficacy: After adjustment for baseline characteristics, the results for the primary composite outcome did not differ significantly between the methylprednisolone group and the placebo group. Secondary analyses suggested a possible benefit with methylprednisolone.

Safety: Methylprednisolone recipients were significantly more likely than placebo recipients to receive insulin for postoperative hyperglycemia. Incidences of other adverse events were generally similar in the two groups.

LIMITATIONS AND REMAINING QUESTIONS

- Registry data might not be as accurate as data collected prospectively as part of a trial and entered into a database.
- The use of postoperative glucocorticoids may have masked clinically significant results.

Links: Full Article | NEJM Quick Take

Primary Composite Outcome

Adjusted OR, 0.86; 95% CI, 0.71–1.05; P=0.14

91 (Postoperative length of hospital stay ≥91 days)
92 (e.g., Ventilator support >7 days)
93 (e.g., Reoperation for bleeding)
94 (Circulatory support or cardiac reoperation)
95 (e.g., Tracheostomy)
96 (Heart transplantation)
97 (Operative death)

Percentage of Patients

Methylprednisolone: 0.7, 4.0, 2.0, 7.3, 0.7, 0.5, 2.0
Placebo: 0.3, 3.7, 5.0, 6.0, 1.3, 1.2, 2.8

Any Adverse Event

Percentage of Patients

Methylprednisolone: 51.1
Placebo: 55.1

Postoperative Insulin Use

Percentage of Patients

Methylprednisolone: 19.0
Placebo: 6.7

CONCLUSIONS

In infants undergoing CHD surgery with cardiopulmonary bypass, perioperative methylprednisolone did not reduce the likelihood of a worse outcome but was associated with an increased risk of postoperative hyperglycemia as compared with placebo.

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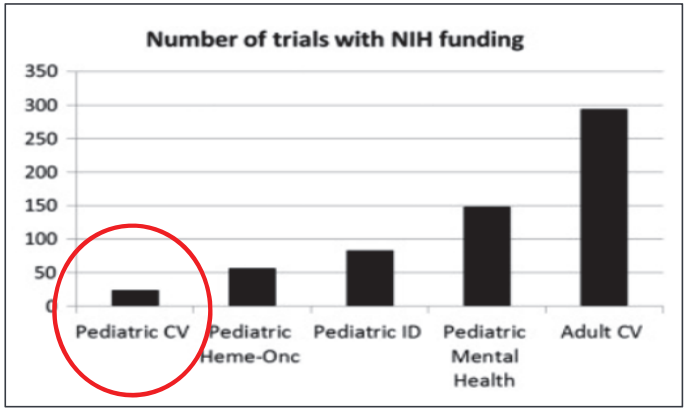
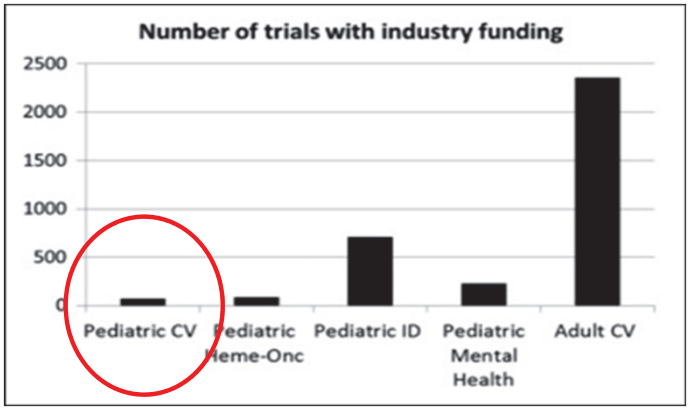
BACKGROUND: TRIAL CHALLENGES

Historically very few trials in children with heart disease[1]





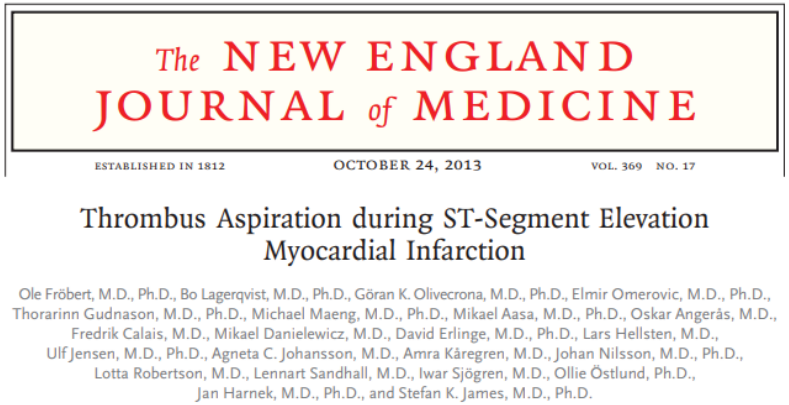
Why?

- Rare, heterogeneous patient cohort
- Difficult to consent and enroll
- High costs, limited funding

1. Hill et al. Am Heart J 2014 Jun;167(6):921-9

TRIAL WITHIN A REGISTRY

Leverage existing registry resources to minimize costs / maximize efficiency



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 24, 2013 VOL. 369 NO. 17

Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction

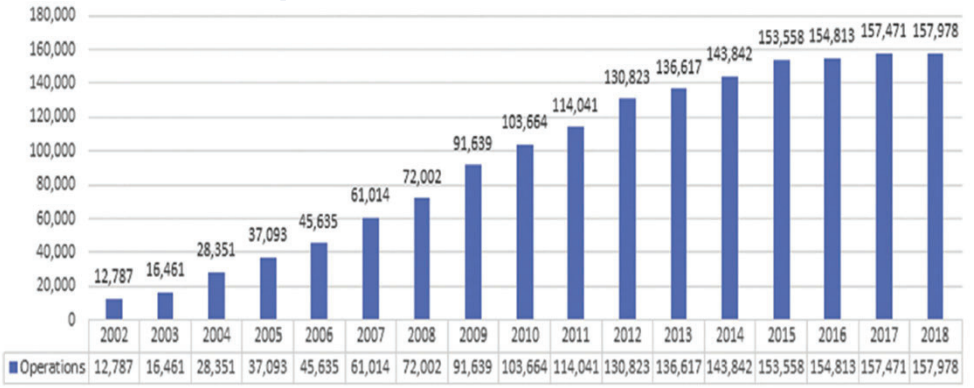
Ole Fröbert, M.D., Ph.D., Bo Lagerqvist, M.D., Ph.D., Göran K. Olivecrona, M.D., Ph.D., Elmir Omerovic, M.D., Ph.D., Thorarinn Gudnason, M.D., Ph.D., Michael Maeng, M.D., Ph.D., Mikael Aasa, M.D., Ph.D., Oskar Angerås, M.D., Fredrik Calais, M.D., Mikael Danielewicz, M.D., David Erlinge, M.D., Ph.D., Lars Hellsten, M.D., Ulf Jensen, M.D., Ph.D., Agneta C. Johansson, M.D., Amra Kåregren, M.D., Johan Nilsson, M.D., Ph.D., Lotta Robertson, M.D., Lennart Sandhall, M.D., Iwar Sjögren, M.D., Ollie Östlund, Ph.D., Jan Harnek, M.D., Ph.D., and Stefan K. James, M.D., Ph.D.

"The randomized registry trial represents a disruptive technology, a technology that transforms existing standards, procedures, and cost structures."

--Mike Lauer, Deputy Director Extramural Research, NIH

We (Peds Cards) have an abundance of registries!!!

Operations in the STS-CHSD



Includes >96% of all eligible congenital heart surgeries performed in the United States

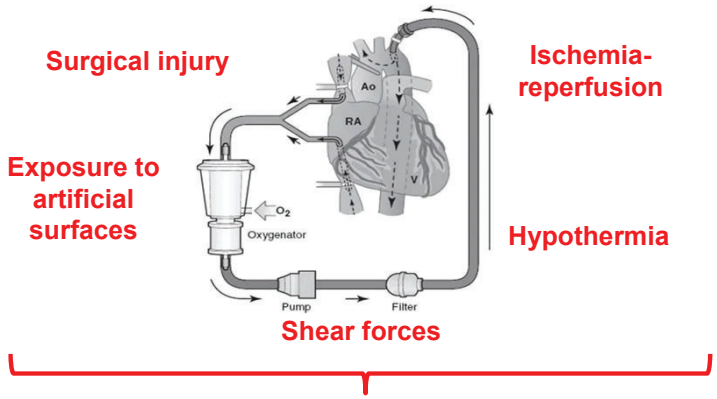
PCCC Pediatric Cardiac Critical Care Consortium

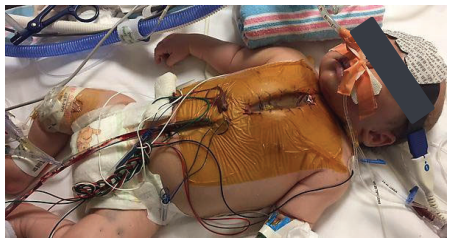
CCAS Congenital Cardiac Anesthesia Society

UNOS

BACKGROUND: PERIOPERATIVE CORTICOSTEROIDS

Used to treat CPB-related systemic inflammatory response

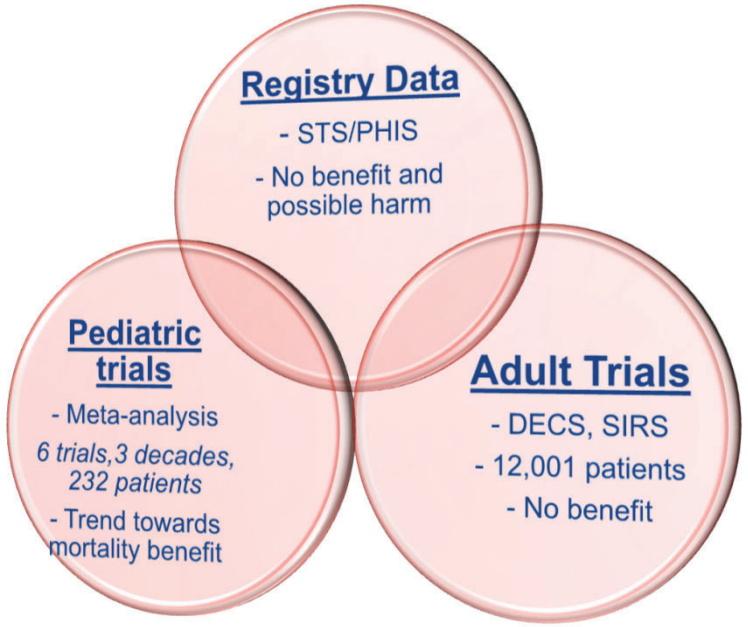




Safety and efficacy not established in children

Registry Data (2011-'16)

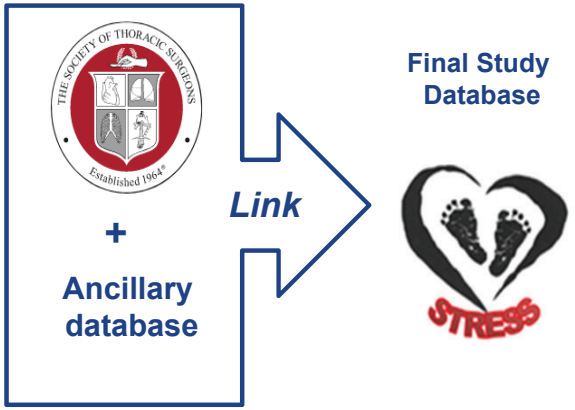
52% of neonatal surgeries used pre/perioperative steroids



TRIAL DESIGN

Pragmatic "trial within a registry"

- **Society of Thoracic Surgeons Congenital Heart Surgery Database (STS-CHSD)**
  - ❑ Mature registry in existence since 1998[1]
  - ❑ Demographic, surgical and outcomes data
    - ➢ *98% accuracy in prior audits*[2]
- **Randomized, placebo controlled trial**
  - ❑ Participants randomized 1:1 to methylprednisolone (30mg/kg) vs placebo at 24 STS-CHSD Centers



1. Kumar et al. Ann Thorac Surg 2021 Dec;112(6):1753-1762
2. Nathan et al. Ann Thorac Surg. 2017 Feb;103(2):629-636

Leverage registry to optimize trial design

Goal = pragmatic (simple) trial conducted in real world setting

ELSEVIER

American Heart Journal
Volume 226, August 2020, Pages 188-197

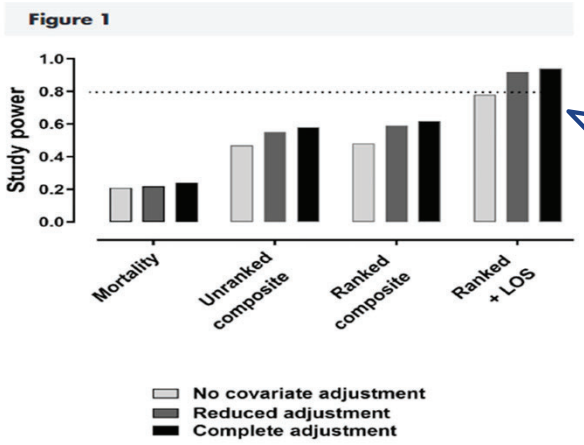
Clinical Investigation

Overcoming underpowering: Trial simulations and a global rank end point to optimize clinical trials in children with heart disease

- Enrollment timelines
- Adaptive designs
- Stopping rules
- Number of centers and cost
- Power gains
- Treatment vs placebo ratios
- Inclusion/exclusion criteria
- Outcome measures

ENDPOINTS

- **Primary endpoint: Ranked composite**
  - ❑ Participants assigned worst outcome experienced during hospitalization
  - ❑ Ranking commensurate with clinical impact
  - ❑ Covariate adjusted primary analysis
    - ➢ 1200 participants: > 90% power



Power increased with inclusion of LOS and planned covariate adjustment

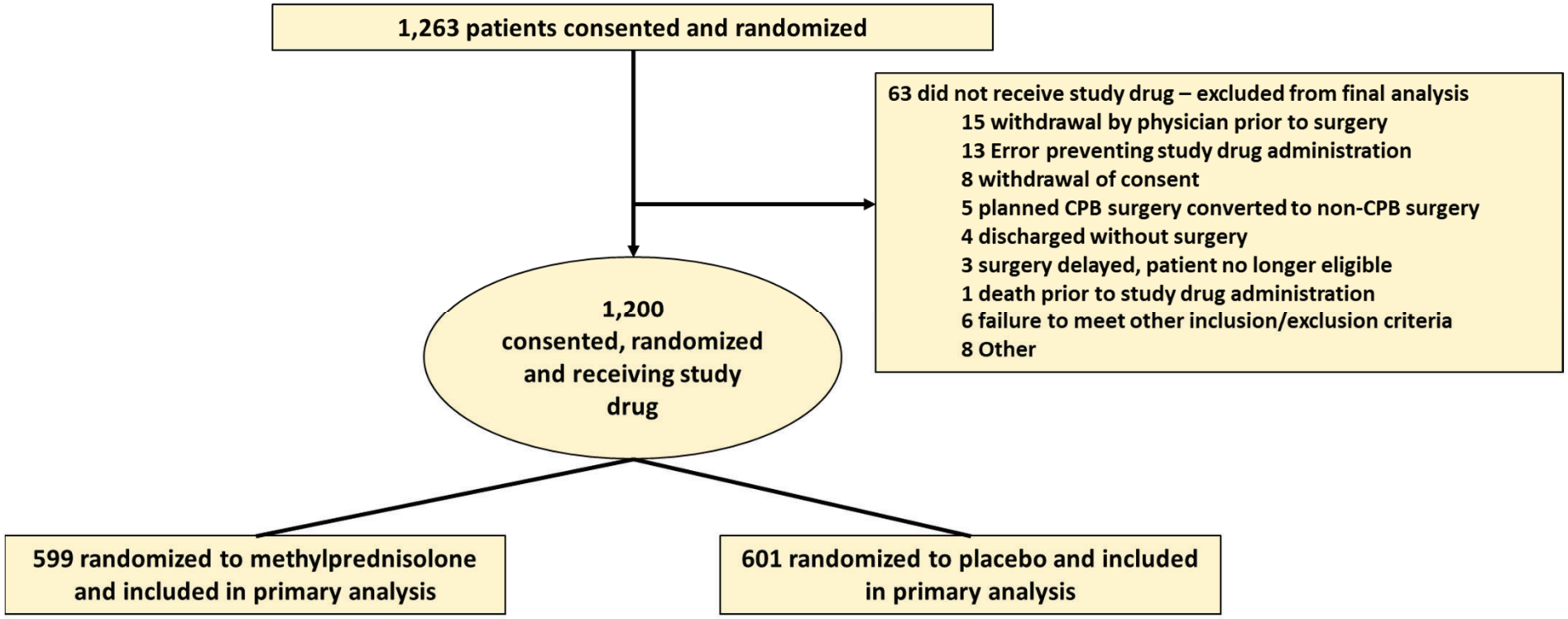
Rank	Description
97	Operative mortality
96	Heart transplant (during hospitalization)
95	Renal failure with permanent dialysis
	Neurologic deficit persistent at discharge
	Respiratory failure requiring tracheostomy
94	Post-operative mechanical circulatory support
	Unplanned cardiac reoperation
93	Reoperation for bleeding
	Unplanned delayed sternal closure
	Post-op unplanned interventional catheterization
92	Post-op cardiac arrest
	Multi-system organ failure
	Renal failure with temporary dialysis
	Prolonged ventilator support (> 7 days)
91	Post-operative length of stay > 90 days
1-90	Post-operative length of stay

ENDPOINTS

- **Primary endpoint: Ranked composite**
  - ❑ Participants assigned worst outcome experienced during hospitalization
  - ❑ Ranking commensurate with clinical impact
  - ❑ Covariate adjusted primary analysis
    - ➢ 1200 participants: > 90% power
- **Secondary endpoints**
  - ❑ Unadjusted analysis and “Win Ratio”
  - ❑ Composite mortality/major morbidity (>91)
  - ❑ Post-op LOS, Prolonged ventilation (> 7 days)
  - ❑ Post-op Low Cardiac Output Syndrome
  - ❑ Safety Endpoints
    - *Composite infection, Hyperglycemia, Insulin administration*

Rank	Description
97	Operative mortality
96	Heart transplant (during hospitalization)
95	Renal failure with permanent dialysis
	Neurologic deficit persistent at discharge
	Respiratory failure requiring tracheostomy
94	Post-operative mechanical circulatory support
	Unplanned cardiac reoperation
93	Reoperation for bleeding
	Unplanned delayed sternal closure
	Post-op unplanned interventional catheterization
92	Post-op cardiac arrest
	Multi-system organ failure
	Renal failure with temporary dialysis
	Prolonged ventilator support (> 7 days)
91	Post-operative length of stay > 90 days
1-90	Post-operative length of stay

RESULTS: TRIAL COHORT



CHALLENGES – CONTRACTING, ENROLLING, COVID, DATA ACCESS AND MORE

Grant funded
09/2016

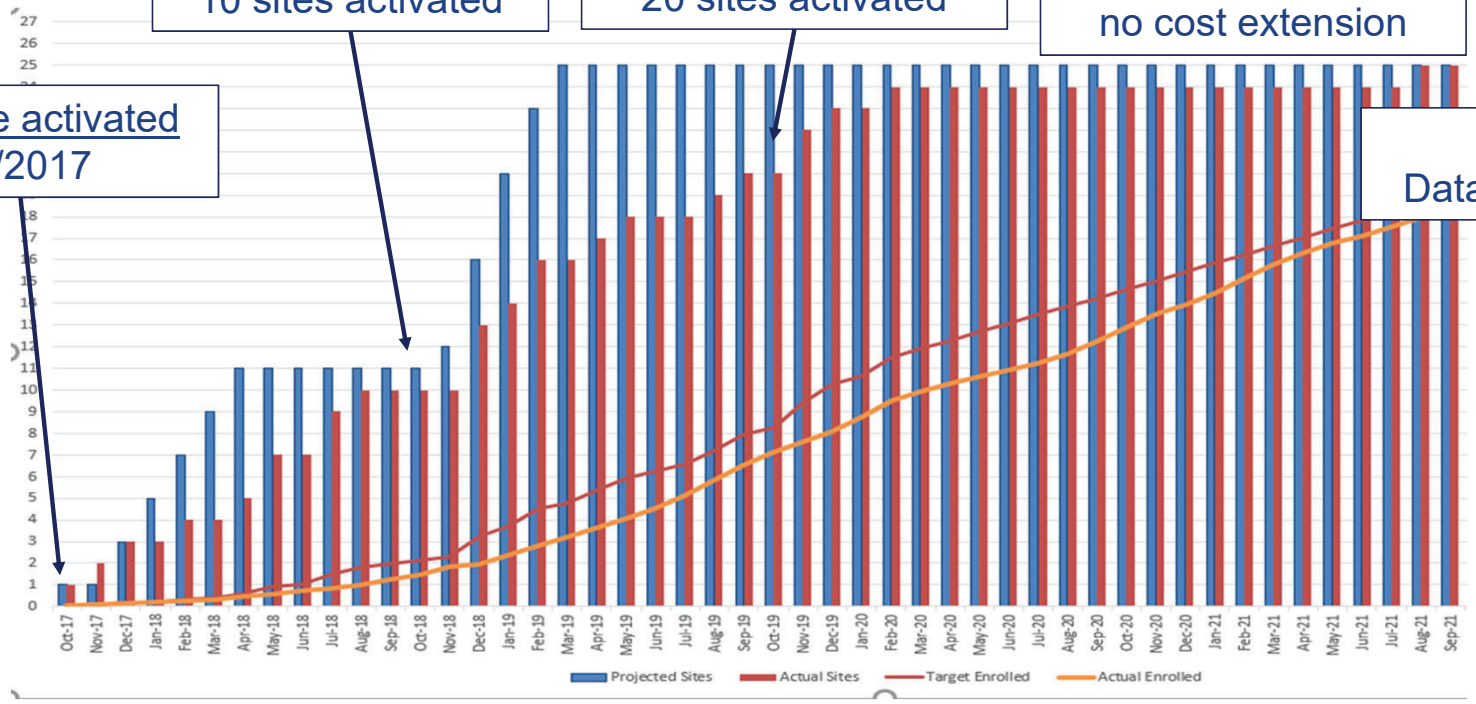
First site activated
10/2017

Year 2
99 pts enrolled
10 sites activated

Year 3
474 patients enrolled
20 sites activated

Year 4
COVID!!!
E-consent, more sites,
no cost extension

Year 5
Data access issues



RESULTS: BASELINE CHARACTERISTICS

Similar distribution of baseline characteristics

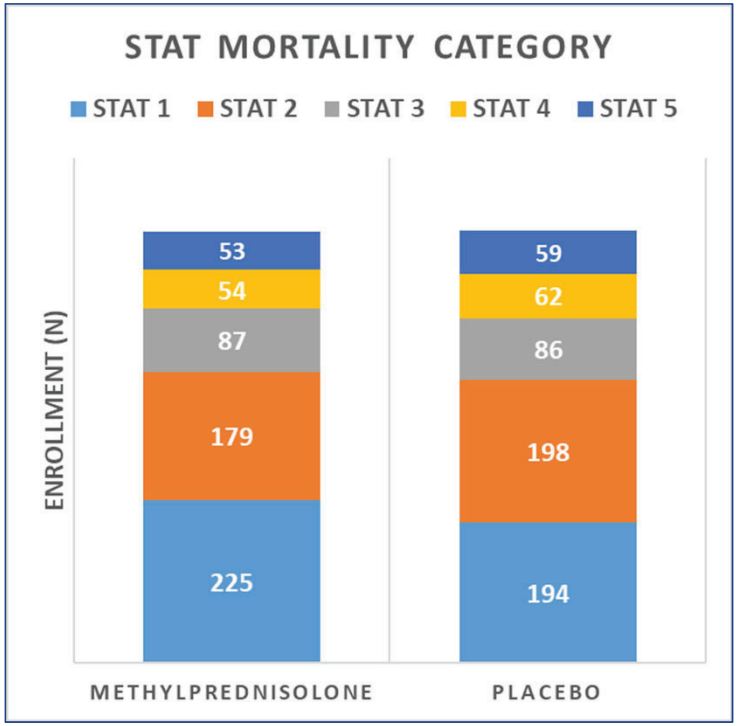
Characteristic	MP N=599	Placebo N=601
Median age at surgery, days (Q1, Q3)	126 (14, 191)	124 (14, 182)
Age Category		
≤30 days	177/599 (29.5%)	187/601 (31.1%)
Median wt at surgery, kg (Q1, Q3)	5.2 (3.7, 6.4)	5.0 (3.6, 6.3)
Male sex	320/599 (53.4%)	334/600 (55.7%)
Premature	100/598 (16.7%)	93/599 (15.5%)
Non-cardiac congenital anatomic abn.	26/599 (4.3%)	15/600 (2.5%)
Chromosomal abnormality or syndrome	200/599 (33.4%)	183/600 (30.5%)
Prior cardiothoracic operation	81/599 (13.5%)	110/600 (18.3%)
Any preoperative risk factor	223/594 (37.5%)	212/594 (35.7%)
Median CPB time, min (Q1, Q3)	122.0 (88, 161)	121.0 (90, 160)

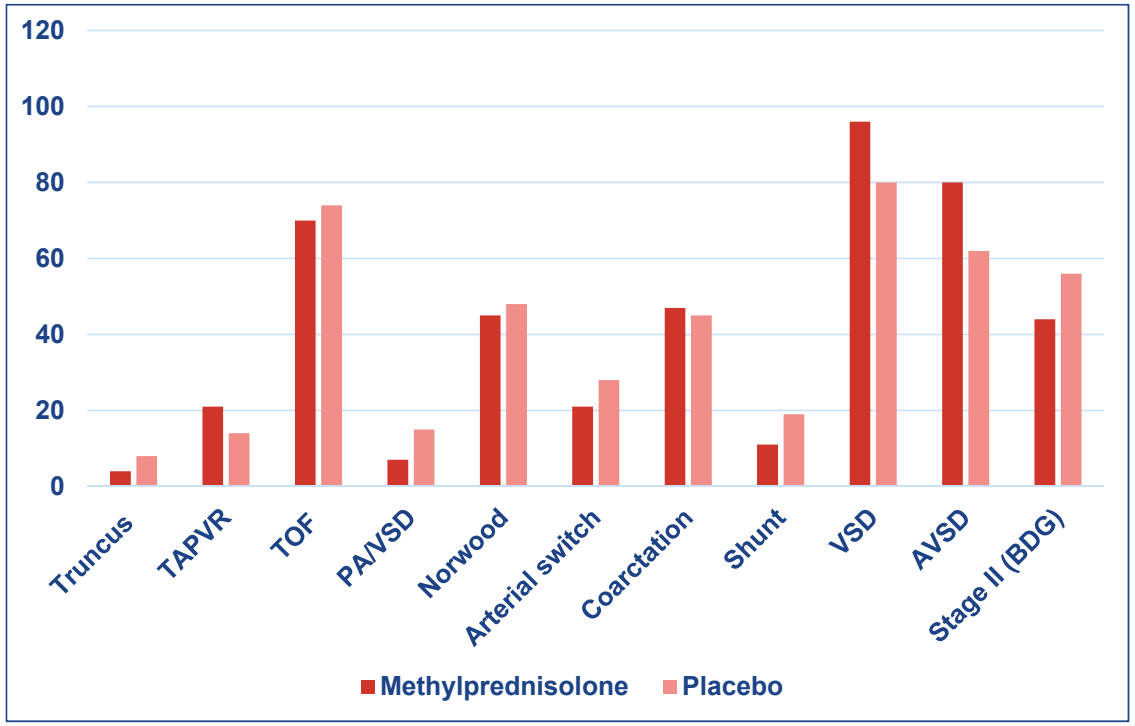
Diverse participant cohort

Characteristics	MP N=599	Placebo N=601
Ethnicity[2]		
Hispanic or Latino	80/580 (13.8%)	63/584 (10.8%)
Not Hispanic or Latino	500/580 (86.2%)	521/584 (89.2%)
Race[3]		
Caucasian	428/585 (73.2%)	425/583 (72.9%)
Black/African American	90/585 (15.4%)	102/583 (17.5%)
Asian	15/585 (2.6%)	12/583 (2.1%)
American Indian/Alaska Native	5/585 (0.9%)	4/583 (0.7%)
Native Hawaiian/Pacific Islander	4/585 (0.7%)	0
Multiracial	13/585 (2.2%)	15/583 (2.6%)
Other	30/585 (5.1%)	25/583 (4.3%)

RESULTS

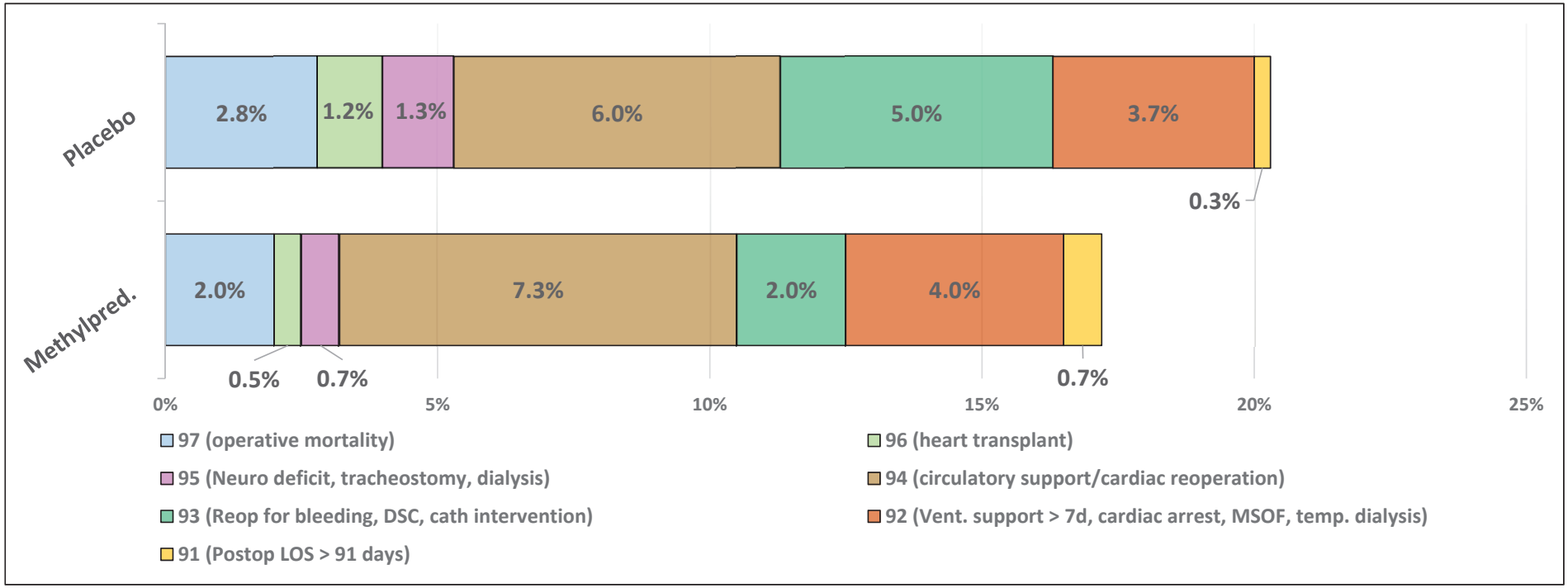
CASE COMPLEXITY AND PROCEDURAL DISTRIBUTION





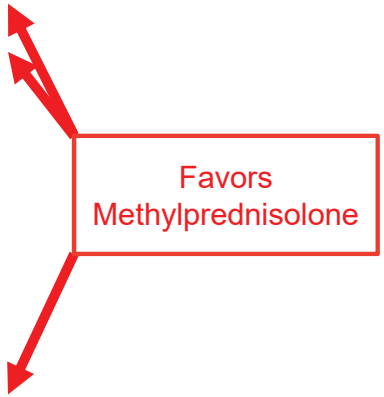
RESULTS: PRIMARY OUTCOME

Adjusted OR = 0.86, 95% CI 0.71 to 1.05; p=0.14



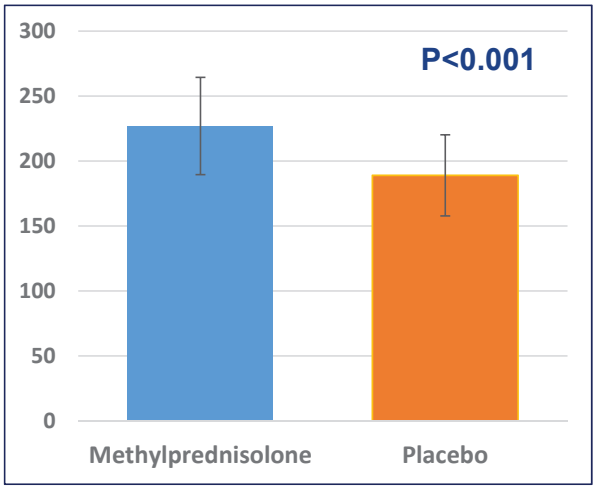
RESULTS: SECONDARY OUTCOMES

Component	Steroids N=599	Placebo N=601	OR	95% CI	P-value
Unadjusted analysis of primary outcome	**NA**	**NA**	**0.82**	**0.67, 1.00**	**0.047**
Win ratio analysis of primary outcome	**NA**	**NA**	**1.15**	**1.00, 1.32**	**0.046**
Operative mortality	12/599 (2.0%)	17/601 (2.8%)	0.74	0.34, 1.57	0.428
Composite morbidity/mortality (Rank > 91)	103/599 (17.2%)	122/601 (20.3%)	0.83	0.61, 1.13	0.228
Prolonged (> 7 days) post-operative mechanical ventilation	41/599 (6.8%)	51/601 (8.5%)	0.79	0.50, 1.25	0.309
Post-op low cardiac output syndrome	31/599 (5.2%)	37/601 (6.2%)	0.91	0.52, 1.57	0.723
Post-operative infectious complication	31/599 (5.2%)	24/601 (4.0%)	1.39	0.80, 2.42	0.242
Bleeding requiring reoperation	**7/599**	**21/601**	**0.34**	**0.14, 0.81**	**0.016**
Post-operative hospital LOS, median (IQR)	10 (6, 20)	11 (6, 23)	1.11	0.99, 1.25	0.066

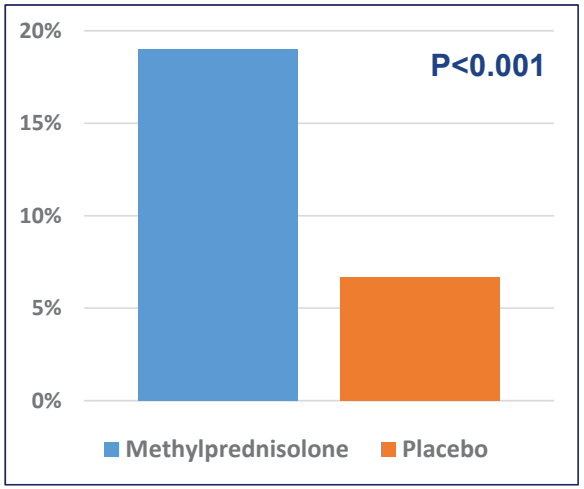


RESULTS: SAFETY AND OTHER OUTCOMES

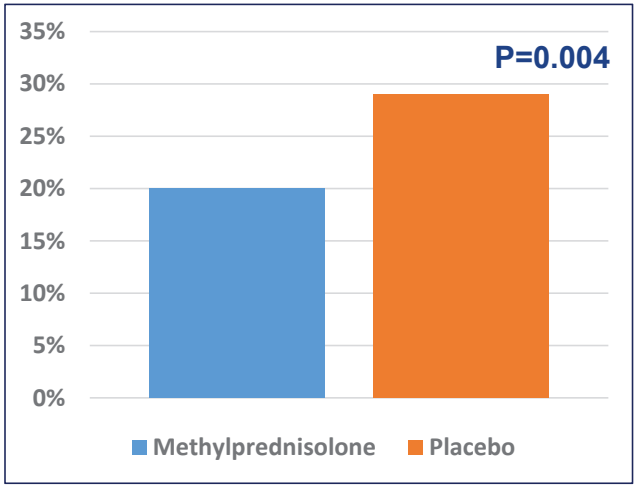
Methylprednisolone with higher post-operative blood glucose



Methylprednisolone more likely to receive post-op insulin



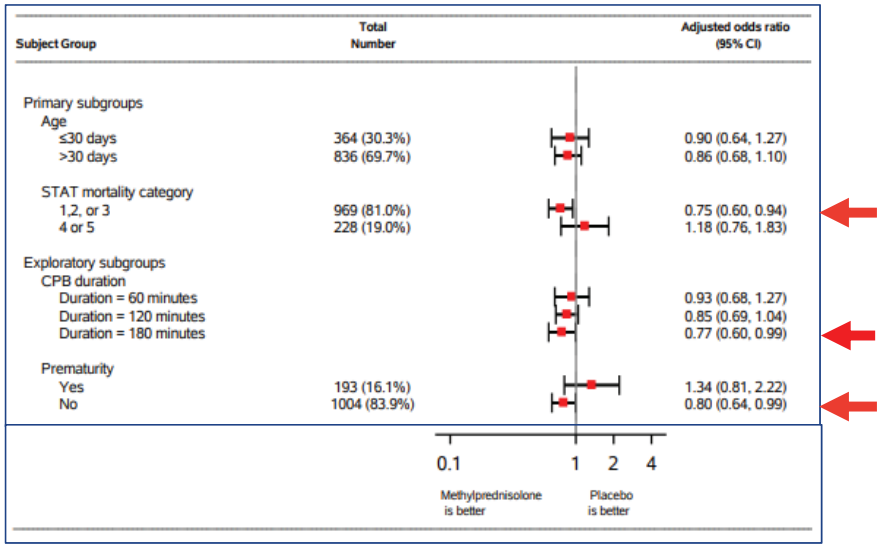
Methylprednisolone less likely to receive post-op hydrocortisone



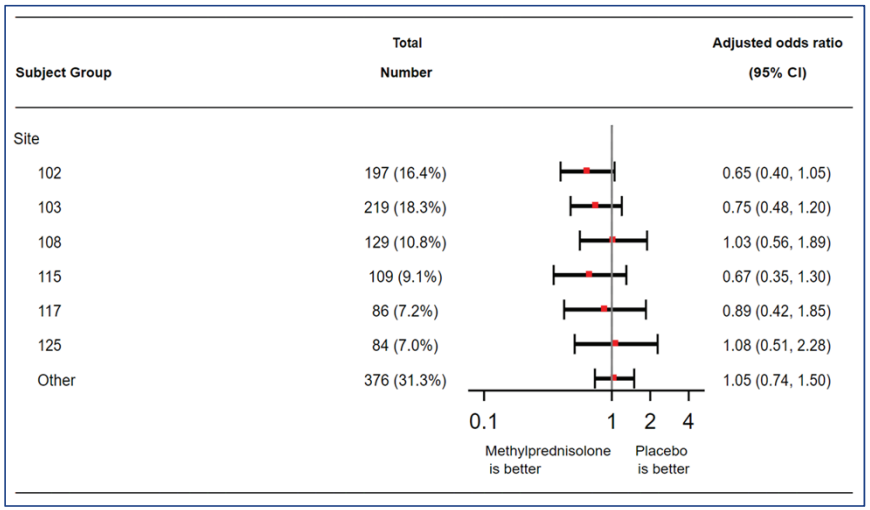
No differences in rates of any other complications

RESULTS: SUBGROUP ANALYSES

Potential benefit in STAT 1,2,3 cases, longer bypass duration and non-premature infants



No site-dependent treatment effect



No differences by race, ethnicity, gender, presence of other preop-risk factors, non-cardiac anatomic abnormalities or syndromes/chromosomal anomalies

TRIAL COSTS

Line item	STRESS	PRAGMATIC	TRADITIONAL
STS (Data Access etc)	$158,531	$0	$0
Site payments ($7,500 start up, $1,000 per patient)	$1,430,006	$2,104,706	$5,928,232
Leadership (faculty, DSMB, steering com, project management)	$530,819	$533,342	$942,986
Site management and monitoring	$426,905	$670,119	$1,024,864
Data management and stats	$400,961	$523,293	$1,343,372
Total budget	**$3,268,504**	**$4,164,862**	**$10,140,263**
Cost per patient enrolled	**$2,724**	**$3,470**	**$8,450**

CONCLUSIONS

- It is possible to conduct relatively large but cost-effective pragmatic trials in our patient population
  - Cost savings due to pragmatic design and use of registry infrastructure
- Novel trial endpoints like the global rank can help to circumvent some of the challenges we face with our unique patient population
  - Careful selection of variables is important
- Despite best efforts, interpreting trial results can be challenging

THANKS TO THE STRESS NETWORK

Leadership team

Jennifer Li
Scott Baldwin
Jeff Jacobs
Prince Kannankeril
Dave Bichel
Sean O'Brien

Steering committee

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David Overman (Children's Mn)

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James Jaggers (UC)
John Scott (Milwaukee)
Brett Anderson (NY Pres)
Michael Swartz (Rocherster)
Patrick McConnell (Nationwide)

Pirooz Eghtesady (WashU)
William Gibson (KUMC)
Sarah Tabutt (UCSF)
Jean Ballweg (Nebraska)
Joseph Turek (Duke)

Claudia Pedroza

The University of Texas Health Science Center at Houston

Bayesian neonatal trials: examples from the NICHD Neonatal Research Network

Claudia Pedroza, PhD
Martin Blakely, MD, MS
Jon Tyson, MD, MPH

Center for Clinical Research and Evidence-Based Medicine

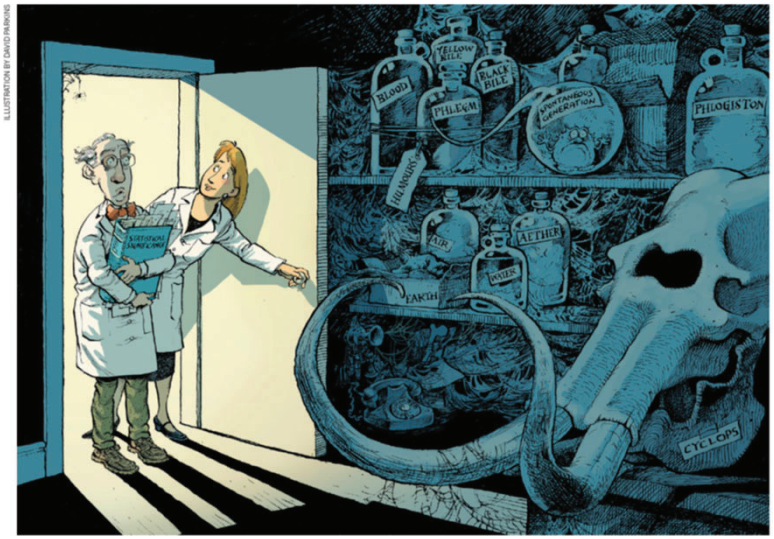
UTHealth
The University of Texas
Health Science Center at Houston
McGovern
Medical School

Frequentist methods' shortcomings

statistically non-significant result does not 'prove' the null hypothesis

Nor do statistically significant results 'prove' some other hypothesis.

Often misinterpreted and misused to erroneously dichotomize evidence into p<0.05 or not



Retire statistical significance

Valentin Amrhein, Sander Greenland, Blake McShane and more than 800 signatories call for an end to hyped claims and the dismissal of possibly crucial effects.

Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. Nature. 2019;567(7748):305-307.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest in Children

RESULTS

A total of 295 patients underwent randomization. Among the 260 patients with data that could be evaluated and who had a VABS-II score of at least 70 before cardiac arrest, there was no significant difference in the primary outcome between the hypothermia group and the normothermia group (20% vs. 12%; relative likelihood, 1.54; 95% confidence interval [CI], 0.86 to 2.76; P=0.14). Among all the patients with data that

CONCLUSIONS

In comatose children who survived out-of-hospital cardiac arrest, therapeutic hypothermia, as compared with therapeutic normothermia, did not confer a significant benefit in survival with a good functional outcome at 1 year. (Funded by the Na-

Moler et al. NEJM. 2015;372:1898-1908. DOI: 10.1056/NEJMoa1411480.

NEJM Evidence

Published December 14, 2022
NEJM Evid 2022; 2 (1)
DOI: 10.1056/EVIDoa2200196

ORIGINAL ARTICLE

A Bayesian Interpretation of a Pediatric Cardiac Arrest Trial (THAPCA-OH)

METHODS We performed a Bayesian analysis, interpreting the trial in probabilistic terms (i.e., the probability that therapeutic hypothermia had any benefit, and overall absolute improvements greater than 2%, 5%, and 10% for 1-year neurobehavioral outcome and

RESULTS In the primary analyses, the probability of any benefit from hypothermia was 94% for both the neurobehavioral outcome and survival at 1 year. For both outcomes, the

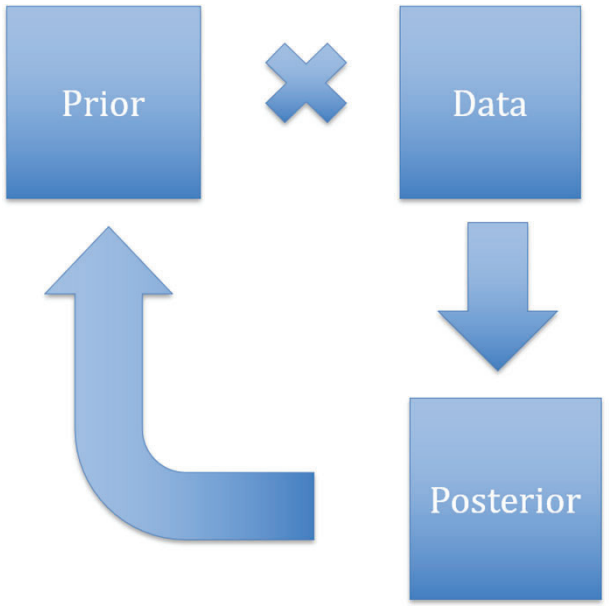
CONCLUSIONS There is a high probability that hypothermia provides a modest benefit in neurobehavioral outcome and survival at 1 year. (ClinicalTrials.gov number, NCT00878644.)

This probability **cannot be obtained** from a **frequentist analysis.**

Bayesian Statistics

- Uses probability to quantify likelihood of an outcome or event occurring
- A Bayesian approach is a formal statistical framework for updating probabilities as new evidence is collected
- After a new study is conducted, we update our probability

  How does this new study change the probability that treatment is beneficial/harmful?



Advantages of a Bayesian approach

- Formally incorporate
  - prior evidence *(e.g., previous RCT result(s) as prior for next RCT)*
  - skepticism about large effects (can mitigate large effects reported from small studies)
  - Evidence from adult studies in pediatric trials (e.g., lupus tx approved by FDA)
- Update current evidence as data accumulates
  - Flexibility for monitoring and adaptive designs
- Answers the clinically relevant question: given all the relevant evidence, what is the probability that this intervention improves clinical outcomes?
- Probability outputs are direct inputs for decision-making
  - Combine with different perspectives, e.g., patients with lived experience, caregivers, clinicians

NICHD NRN Studies with Bayesian Design/Analysis

- Morris BH, Oh W, Tyson JE, et al. Aggressive vs. conservative phototherapy for infants with extremely low birth weight. *N Engl J Med*. 2008 Oct 30;359(18):1885-96.
- Cycled Phototherapy: A Safer Effective Method to Control the Serum Bilirubin of Extremely Premature Infants? Tyson JE, Arnold C, et al. (ClinicalTrials.gov number: NCT03927833)
- Shankaran S, Laptook AR, Pappas A, et al. Effect of Depth and Duration of Cooling on Death or Disability at Age 18 Months Among Neonates With Hypoxic-Ischemic Encephalopathy: A Randomized Clinical Trial. *JAMA*. 2017 Jul 4;318(1):57-67.
- Laptook AR, Shankaran S, Tyson JE, et al. Effect of Therapeutic Hypothermia Initiated After 6 Hours of Age on Death or Disability Among Newborns With Hypoxic-Ischemic Encephalopathy: A Randomized Clinical Trial. *JAMA*. 2017 Oct 24;318(16):1550-1560.
- Preemie Hypothermia for Neonatal Encephalopathy. Faix RG, Laptook AR, et al. (ClinicalTrials.gov number: NCT01793129)
- Blakely ML, Tyson JE, Lally KP, et al. Initial Laparotomy Versus Peritoneal Drainage in Extremely Low Birthweight Infants with Surgical Necrotizing Enterocolitis or Isolated Intestinal Perforation: A Multicenter Randomized Clinical Trial. *Ann Surg*. 2021 Oct 1;274(4):e370-e380.

*Bayesian primary analysis

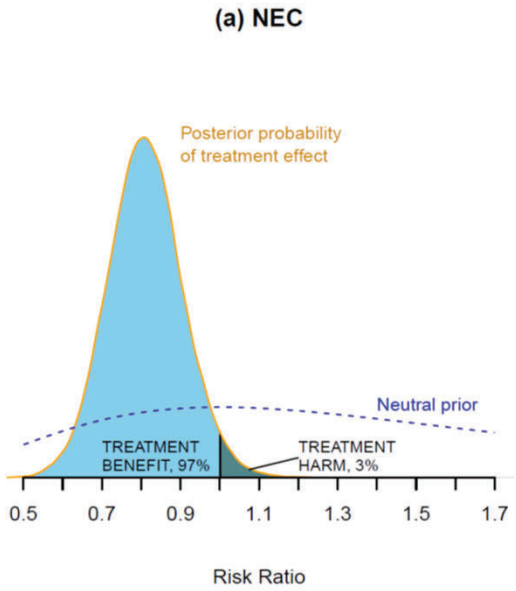
Initial Laparotomy Versus Peritoneal Drainage in Extremely Low Birthweight Infants With Surgical Necrotizing Enterocolitis or Isolated Intestinal Perforation

A Multicenter Randomized Clinical Trial

Blakely et al. Ann Surg. 2021;274(4):e370-e380

Primary outcome: death or NDI at 18 Months

Results: Treatment effect depends on pre-op diagnosis



Death/NDI	Lap	Drainage	Frequentist RR (95% CI)	Bayesian RR (95% CrI)	Pr(RD<0)
NEC	29/42 (69%)	44/52 (85%)	0.81 (0.64-1.04)	0.81 (0.63-1.00)	97%

Advantages of Bayesian Analyses

- Make more nuanced decisions than those based solely on whether p-values or CIs cross an arbitrary threshold
- Focus on point estimates and uncertainty around them
- Compute probabilities of benefit and harm, including probabilities of clinically important intervention effects
- Make decisions based on weighing benefits, harms, and costs for all stakeholders

Disadvantages

- Specification of prior distributions is challenging
- Unfamiliarity of clinicians/reviewers/editors
- Need greater buy-in from all stakeholders, particularly funding and regulatory agencies

Thank you

Dionna Green

U.S. Food & Drug Administration

Kanwaljit Singh

Critical Path Institute

International Neonatal Consortium

Kanwaljit Singh, MD MPH
Director INC, Critical Path Institute

International Neonatal Consortium

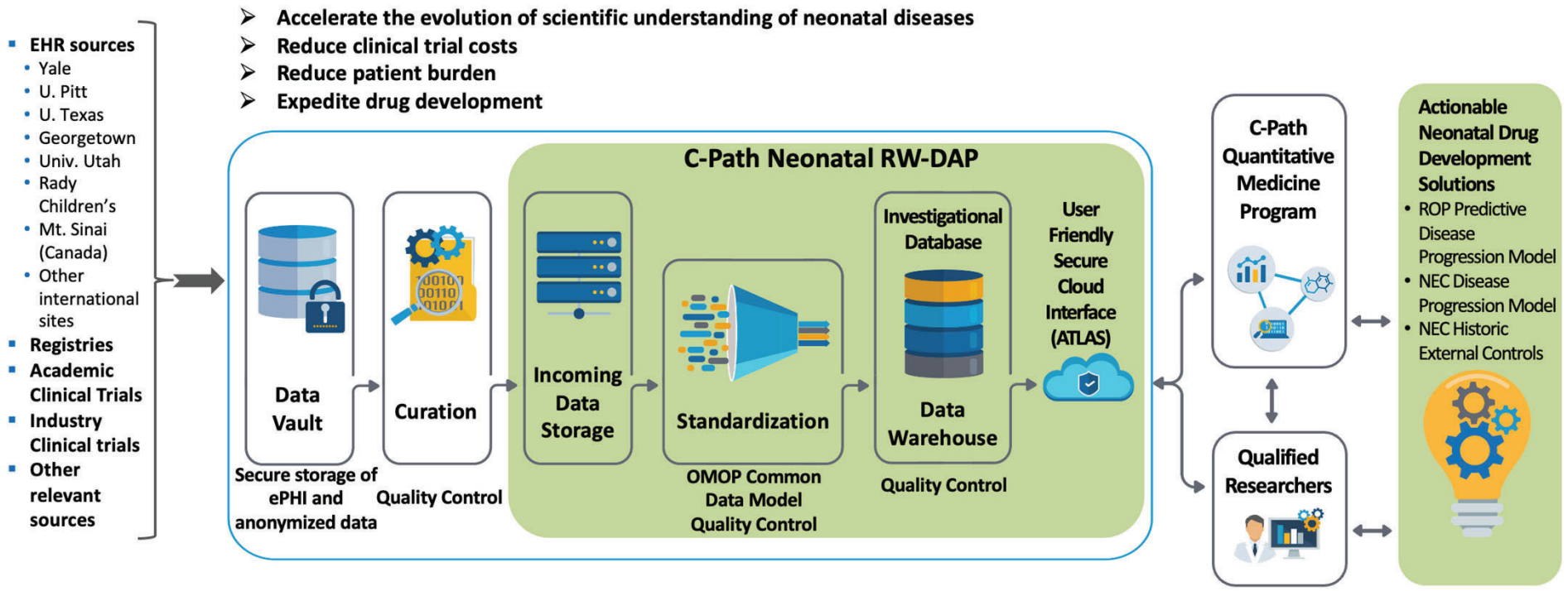
Critical Path Institute's
International Neonatal Consortium (INC)

- Public-private partnership of diverse stakeholders consisting of Industry members, academic researchers, nurses, families, and regulators
- Mission to accelerate drug development in neonates
- Operating as a pre-competitive collaboration to:
  1. Address the measurement and assessment of clinical outcomes in neonates, through teams that share data and expertise to advance regulatory science
  2. Improve the predictability of neonatal drug development

"By uniting stakeholders from research institutions, drug developers, regulatory agencies, patient advocacy and other organizations, INC can develop practical tools that can be incorporated into clinical trials for neonates, which will then lead to more successful, efficient trials and provide this population with better treatments." stated Dr. Janet Woodcock,, *efficient trials and provide this population with better treatments."*

~Dr. Janet Woodcock, CDER Director, May 2015

Neonatal Real World Data Analytics Platform



*ROP: Retinopathy of prematurity
*NEC: Necrotizing enterocolitis

Susan McCune

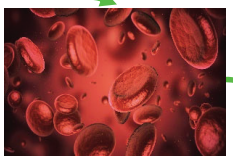
PPD Clinical Research Business, Thermo Fisher Scientific

Academia

- What is in the pipeline and how does that move to development
- Incentives – financial/academic

- Who tests this in models
- Do the models need to be developed
- How predictive are the models
- Development of biomarkers
- Incentives – financial/academic

- Development of assays
- Validation of assays
- Need for small volume sample technology
- Incentives – financial/academic



- Toxicology testing
- Juvenile animal testing
- GLP
- Incentives – financial/academic

Biotech Pharma

- Commercial product development
- Large batch scale up
- GLP
- Incentives – financial

PhRMA CRO

- Are first in human studies appropriate in healthy volunteers
- Phase 1 units
- Incentives – financial

- Phase 1b/2/3 trials
- Clinically meaningful endpoints/COAs
- Site engagement
- Recruitment/retention
- Costs
- Incentives – financial/academic

- Data standards
- Data analysis
- Submission to the regulatory agencies
- Incentives – financial

FDA U.S. FOOD & DRUG ADMINISTRATION

EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

pmda 独立行政法人 医薬品医療機器総合機構 Pharmaceuticals and Medical Devices Agency

Health Canada Government of Canada

Australian Government Department of Health and Aged Care Therapeutic Goods Administration

Slide designed by Susan McCune, MD, VP Pediatrics & Clinical Pharmacology, Rare Disease and Pediatrics Center of Excellence, PPD Clinical Research Business, Thermo Fisher Scientific

PPD

Session 4 Discussion Questions

- What new approaches are investigators considering for measuring clinical benefit in neonatal RCTs?
- What are the best approaches for validating an innovative measure of clinical benefit?
- How can innovative efficacy endpoints be efficiently incorporated into neonatal clinical trials?

Session 4: Novel Approaches to Measure Clinical Benefit in Neonatal Clinical Trials

Moderator: Matthew Laughon, UNC Health

Fireside Chat

Moderator: An Massaro, U.S. Food & Drug Administration

Moderators

Michele Walsh, NICH
Session 1

An Massaro, FDA
Session 2

Monica Lemmon, Duke University
Session 3

Matthew Laughon, UNC Health
Session 4

Fireside Chat

Moderator: An Massaro, U.S. Food & Drug Administration

Closing Remarks & Meeting Adjournment

Morgan Romine

Duke-Margolis Center for Health Policy

Thank You!

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