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CORRESPONDENCE

Stakeholder engagement in neonatal clinical trials: an opportunity for mild neonatal encephalopathy research

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Neonatal selection of study design and clinical follow-up outcomes are usually defined by the scientific community, without any parental input. This investigation aimed to inquire on parental perspectives prior to implementation of new trials of mild hypoxic ischemic encephalopathy (HIE).

Neonatal neuroprotection strategies are still in development and few therapies have withstood the long transition from preclinical to Phase III trials. Therapeutic hypothermia (TH) has transformed the landscape of treatment of HIE and remains the only proven intervention to mitigate poor neurodevelopmental outcomes in infants with moderate and severe encephalopathy. However, for infants with mild HIE who were not included in the trials, the fundamental question of how to manage remains problematic.[1] While this topic persisted in yearly panels, commentaries, and opinions, no new randomized clinical trial (RCT) data have emerged to support or refute treatment. An increasing therapeutic drift is rendering a multicenter neonatal RCT for mild HIE challenging to perform, and the loss of equipoise may be difficult to accept.[2] Some scientists believe that only RCTs can provide efficacy evidence as they have the advantage of strong internal validity, while others justify effectiveness of more pragmatic approaches as applicable for a real-world setting, seeing external validity and feasibility as justifiable trade-offs.

At the core of the problem are two challenges[3,4]: (1) precisely defining mild encephalopathy, a condition that remains variably classified (especially within the 6 h after birth during which treatment is most effective), and (2) balancing risks and benefits of treatment during short- and long-term outcomes. The first challenge is easiest to address: if neonatologists can reach a consensus, they can also provide clear and clinically relevant definitions for care of mild HIE. The second challenge is more difficult and requires an uncomfortable discussion of ethical principles such as respect of person or, in this case, parental autonomy. In the prior clinical trials, the study design and outcome measures were solely determined by the investigators. When the risks of an intervention and its benefits are both real yet imprecise, and the outcome at stake is a child's development into adulthood, why would scientists not involve parents and adults living with the consequences of perinatal events as essential stakeholders in decision-making, from study design to outcome measures?[5] Arguments that parents cannot understand the complexities of the problem are specious and patronizing, as we discovered when we engaged two community stakeholder organizations (Hope for HIE and Cerebral Palsy Foundation).[6,7]

To investigate community stakeholder perspectives surrounding the science and treatment of mild HIE, we asked organizations to review and modify a survey that they would distribute to their stakeholders through social media channels. Hope for HIE (represented by executive director Betsy Pilon) and the CP Foundation (represented by executive director Rachel Byrne) are connected to large networks of families affected by HIE, have invested in improving outcomes, and have robust infrastructures for communication and outreach.

First, a pilot parental focus survey ($n = 42$) recruited interested parents of children with mild HIE via Hope for HIE. Results primarily allowed the revision of survey questions: increased diversity of the sample was necessary, especially with regard to educational level and employment, having only multiple choice questions was limiting, and stakeholders recommended neutral, accessible word choices to improve comprehension in the community. In particular, foundation partners requested we use "stories" to speak to parents about clinical scenarios and concrete examples of outcomes. Responses were recorded using a "slider" function to allow relative scaling and free text responses were encouraged to obtain qualitative impressions.

In March 2021, a 10-question online survey was administered over 2 weeks via organizations' social media channels (Instagram and Facebook): https://www.surveymonkey.com/r/HIE.

Of the 402 respondents who selected to take the survey, 289 were parents of children with HIE and 113 were self-identified adult survivors of perinatal events with mild disabilities. Self-report of highest education level showed that 34% of respondents had advanced degrees, 37% college degrees, 8% technical degree, 18% high school diplomas, and 4% never graduated any school. Half of respondents were working full-time.

Stakeholders ranked how important potential side effects would be to them, on a scale of 0–100. The main risk themes (Fig. 1) identified as important (>70 on the scale slider) by parents included were, in order of importance, (1) severe bleeding and clotting (58%), (2) effects on quality of mother–infant relationship and bonding (52%), (3) perception of pain/shivering needing medications (32%), (4) not being able to feed (especially at the breast) and needing intravenous fluids (25%), and (5) early separation for 72 h (24%).

We asked all participants to scale (from 0 to 100) the percentage chance that would be acceptable to them of their infant having any of the side effects stated above to benefit from a possible improved outcome. Participants selected a mean threshold of anything below 27% chance as acceptable for any improvement at 2 years.

When queried about the most important outcomes (Fig. 1), the majority of responders (90%) selected any small improvement in school age attention, memory, behavioral health, or learning

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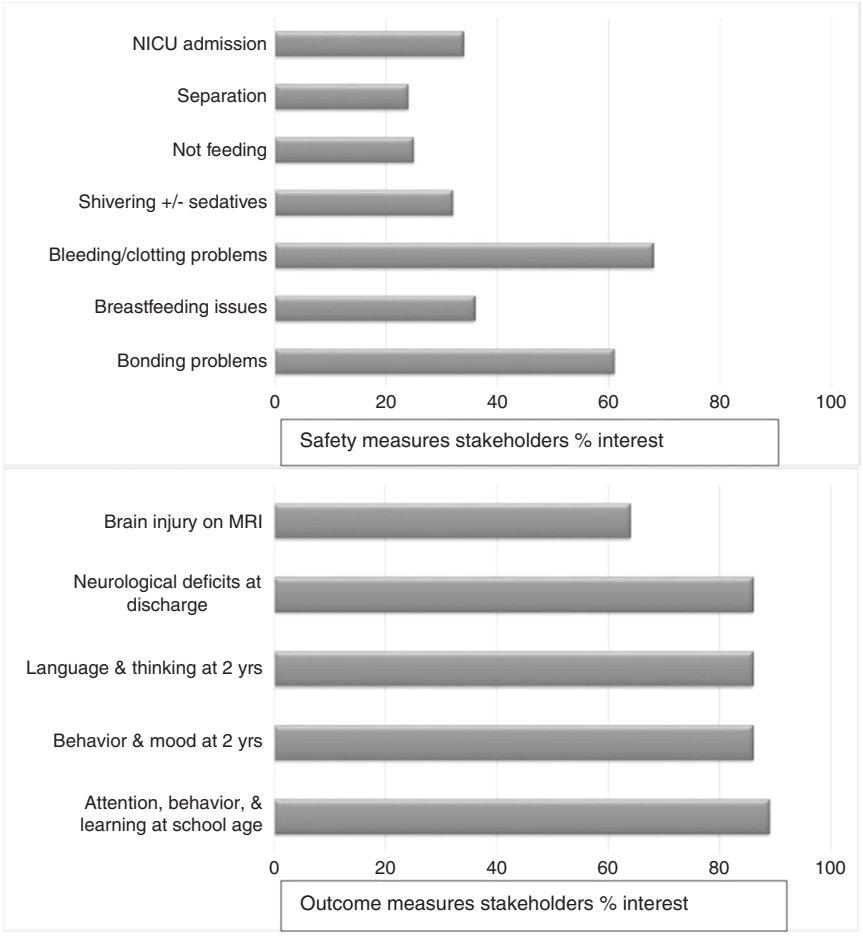


Fig. 1 Stakeholder selection of safety and clinical outcomes of interest. Data show percentage ($N = 403$ responders). Important priorities were presented by average responders who scored responses from 7 to 10 on the sliding scale.

performance as their most important outcome, followed closely by language and cognition outcomes at 2 years (86%). To tentatively evaluate what effect size of treatment would be meaningful to stakeholders, we asked them about cut-off that corresponded to any percentage of improvement of ≥1% compared to not having the treatment. All agreed that a 10% improvement would be meaningful and 70% stated that any treatment effect as small as ≤5% at 2 years would be impactful. With regards to clinical trials design (Fig. 2), and acknowledging the paucity and low quality of evidence, 70% preferred a design that would allow treatment to be guided by their local provider, with their regional experience of neonatal care. This design would be most consistent with a comparative effectiveness trial or at perhaps a pragmatic design trial that includes infants treated both through shared decision making with clinicians (existing practice) in addition to randomization.

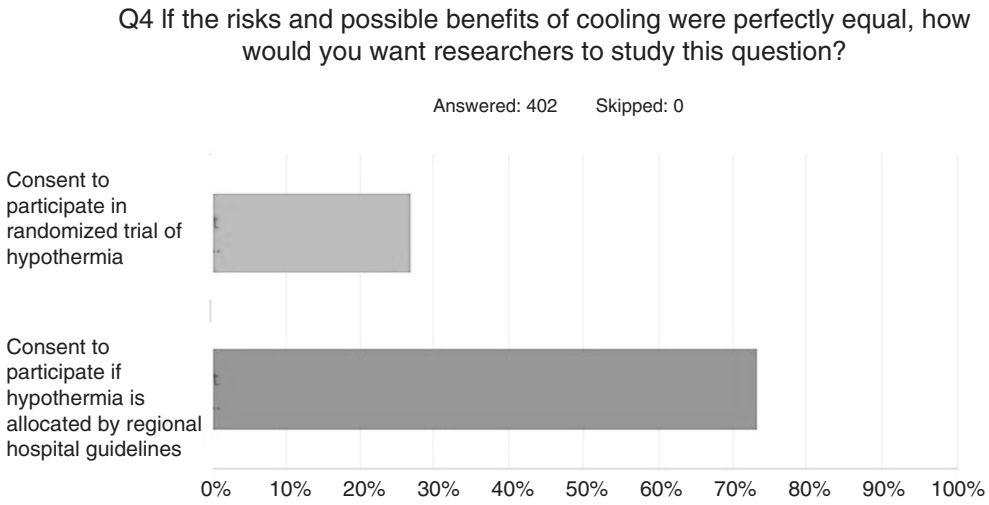
In neonatal RCTs, lack of equipoise for randomization of fragile newborns has resulted in non-participation, enrollment bias, and has threatened the external validity of findings, leading to higher budgets, early terminations, and resource waste.[8–10] Prior attempts to randomize in neonatal neuroprotection studies as for the Prophylactic Phenobarbital Neonatal Seizures (PROPHENO) trial have met equipoise issues that lead to termination after failure to enroll. A CER study[11] was subsequently completed to establish the safety of early discontinuation of anti-seizure medications prior to hospital discharge in neonates with acute symptomatic seizures.

Collectively, published and current data suggest that a classical RCT design to study TH for mild HIE is likely to face challenges resulting from increasing drift in practice, loss of equipoise, ethical concerns, physician bias, and rates of parental consent.[1–7]

Planning stages of neuroprotection trials for HIE presents unique opportunities to support and involve parents. In neonatal medicine, where so few new treatments are shown to be effective after trials testing their external validity, and value judgements used in adult patient trials are often inaccurate, it behooves scientists to treat parents as full partners.

We used this parental survey to guide the planning of a new adaptive trial of Comparative Effectiveness Study for Mild HIE (COOLPRIME)—ClinicalTrials.gov Identifier: NCT04621279—to start to systematically resolve the disjunction between the evolving clinical practice and the limited supporting scientific data by leveraging practice variation across multiple sites to provide a better estimate of treatment effects and associated risks.

Stakeholder engagement and shared decision making are not empty concepts: they are values espoused by our medical community and scientific institutions and should be our compass in designing the next generation of clinical trials for treatment of mild HIE.



ANSWER CHOICES	Responses	
I would want the treatment to be decided randomly (This is a randomized controlled trial, treatment is chosen as if by the flip of a coin).	26.87%	108
I would want the treatment to be decided by the guidelines of the regional hospitals. (This is a comparative effectiveness trial, where different hospitals results are compared to each other)	73.13%	294

Fig. 2 Stakeholder selection of study design. ($N = 403$ responders). Important priorities were presented by average responders who scored responses from 7 to 10 on the sliding scale.

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DATA AVAILABILITY

All datasets obtained in this survey are presented in the main manuscript. Data on which the conclusions of the paper rely is therefore available to readers.

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AUTHOR CONTRIBUTIONS

L.C. conceptualized and designed the study and drafted and finalized the manuscript. B.P. and R.B. designed the survey and disseminated the survey via their platforms. N. M. helped design and conceptualize the study and survey. All authors edited and approved the final submitted version.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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