

## CLINICAL RESEARCH ARTICLE



# Differences in standardized neonatal encephalopathy exam criteria may impact therapeutic hypothermia eligibility

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**BACKGROUND:** Therapeutic hypothermia (TH) is routinely provided to those with moderate or severe neonatal encephalopathy (NE). Subtle differences exist in the standardized exams used to define NE severity. We aimed to assess if an infant's TH eligibility status differed if they were evaluated using either the NICHD/Neonatal Research Network's (NICHD-NRN) or TOBY/British Association of Perinatal Medicine's (TOBY-BAPM) neurological exam.

**METHODS:** Encephalopathic infants  $\geq 36$  weeks with evidence of perinatal asphyxia and complete documentation of the neurological exam  $< 6$  h of age were included. TH eligibility using the NICHD-NRN and TOBY-BAPM criteria was determined based upon the documented exams.

**RESULTS:** Ninety-one encephalopathic infants were included. Despite good agreement between the two exams ( $\kappa = 0.715$ ,  $p < 0.001$ ), TH eligibility differed between them ( $p < 0.001$ ). A total of 47 infants were deemed eligible by at least one method—46 using NICHD-NRN and 35 using TOBY-BAPM. Of the 12 infants eligible per NICHD-NRN, but ineligible per TOBY-BAPM, two developed electrographic seizures and seven demonstrated hypoxic–ischemic cerebral injury.

**CONCLUSIONS:** Both the NICHD-NRN and TOBY-BAPM exams are evidence-based. Despite this, there is a significant difference in the number of infants eligible for TH depending on which exam is used. The NICHD-NRN exam identifies a greater proportion as eligible.

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## IMPACT:

- There are subtle differences in the NICHD-NRN and TOBY-BAPM's encephalopathy exams used to determine eligibility for TH.
- This results in a significant difference in the proportion of infants determined to be eligible for TH depending on which encephalopathy exam is used.
- The NICHD-NRN encephalopathy exam identifies more infants as being eligible for TH than the TOBY-BAPM encephalopathy exam.
- This may result in different rates of cooling depending on which evidence-based neurological exam for evaluation of encephalopathy a center uses.

## INTRODUCTION

Current evidence supports the provision of therapeutic hypothermia (TH) to those with moderate or severe neonatal encephalopathy (NE).<sup>1</sup> However, determining the true grade of encephalopathy is challenging in the newborn infant in the first 6 h of life.<sup>2,3</sup> Therefore, each of the randomized controlled trials (RCTs) described modified encephalopathy exams for TH eligibility that aimed to identify those ultimately categorized as moderate or severe NE.<sup>4,5</sup> This led to minor variations in eligibility exams between the RCTs, and subsequently between the various jurisdictions that incorporated these evidence-based assessments into their practice.

In North America, TH eligibility is most commonly based on the clinical encephalopathy criteria described by the NICHD RCT (NICHD-Neonatal Research Network (NRN) system), with training available for researchers through the NRN (<https://neonatal.rti.org/>

[pdf/Neurocertification\\_HIE\\_Trials\\_SS\\_05212019.pdf](#)). In the United Kingdom, eligibility is often determined using the methodology described in the TOBY RCT, and recently reaffirmed by the British Association of Perinatal Medicine (TOBY-BAPM system).<sup>6</sup> Both of these systems require infants to demonstrate evidence of perinatal asphyxia, plus clinical findings consistent with moderate or severe encephalopathy using a standardized exam.<sup>4,5</sup> If both of these criteria are met, the infant is eligible for TH by the NICHD-NRN system, while TOBY-BAPM next requires the infant to demonstrate a moderate to severely abnormal amplitude-integrated electroencephalography (aEEG). If an aEEG is not available, BAPM guidelines advise that TH should proceed if the clinical exam criteria are met. Therefore, tremendous importance is placed upon the clinical neurological exam with its critical role in determining TH eligibility.

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The clinical neurological exams used in both systems differ with the potential for these differences to impact the level of encephalopathy defined for an infant, and therefore result in variation in TH eligibility between centers, and nations, for an individual infant depending on which system is being applied. The aim of this study was to determine if the differences in the NICHD-NRN's and TOBY-BAPM's clinical neurological exam impacted an infants' TH eligibility.

## METHODS

This is a secondary analysis of infants with NE who underwent TH between July 2014 and May 2019 in a large tertiary-level neonatal intensive unit. The need to initiate TH was determined by the clinician and based upon an adaptation of standard criteria (Table 1). These modified criteria include providing TH to those with milder encephalopathy, such that those with mild, moderate, and severe NE were included in this cohort.<sup>7</sup> All infants had a systematic neurological exam performed and documented by both an attending neonatologist and a pediatric neurologist within the first 6 h of life prior to the initiation of TH, if the grade of NE differed the worst grade was utilized.

For inclusion in this analysis, all infants had to be  $\geq 36$  weeks gestation, have signs of perinatal hypoxia-ischemia (defined using TOBY-BAPM A criteria—including one of; pH of  $< 7.00$  or base deficit of  $\geq 16$  mmol/L on cord blood or any gas within 60 min of birth; or continued need for resuscitation at 10 min after birth (intubation or IPPV); or 10 min Apgar score of  $\leq 5$ ),<sup>4</sup> and sufficient documentation of the neurological exam to allow determination of TH eligibility by both the NICHD-NRN and TOBY-BAPM neurological exam criteria. Institutional Review Board approval was obtained to conduct this analysis.

Demographic, clinical, and laboratory data were collected from the medical records. All infants included in this cohort underwent TH, had multichannel electroencephalography (EEG) during cooling, and had a magnetic resonance imaging (MRI) scan following re-warming. The continuous EEGs were placed as soon as possible after the decision to initiate TH and were maintained throughout TH and re-warming. For this analysis, the clinical neurophysiology report from the first 24 h of age was

used to define the EEG grade of encephalopathy. The presence of electrographic seizures at any point during the EEG monitoring was recorded.

## NICHD-NRN exam

The NICHD neurological exam (B criteria) indicates that infants with moderate or severe NE are eligible for TH. The NICHD-NRN neurological exam assesses six domains: level of consciousness, spontaneous activity, tone, posture, primitive reflexes (two sub-domains assessed independently, with the worst score providing the global grade for primitive reflexes—suck, and Moro reflex), and autonomic activity (three sub-domains assessed independently, with the worst score providing the global grade for autonomic activity—pupillary reaction, heart rate, and respirations) (Fig. 1).<sup>5</sup> If  $\geq 3$  domains are consistent with moderate or severe NE, then the infant is eligible for TH. They are defined as moderate NE if they have  $\geq 3$  domains consistent with moderate or severe NE, but more domains are moderate than severe, and they are graded as severe if they have  $\geq 3$  domains consistent with moderate or severe NE, but more domains are severe than moderate. In addition, if they are encephalopathic on exam, they do not have sufficient moderate or severe criteria to meet the TH threshold, but develop seizures in the first 6 h of life, and they are categorized as moderate NE.

## TOBY-BAPM exam

The TOBY neurological exam criteria also indicate that infants with moderate or severe NE are eligible for TH. The TOBY-BAPM neurological exam requires that a moderate or severely abnormal level of consciousness (lethargy, stupor, or coma) must be present plus one additional finding of either clinical seizure, weak or absent suck, hypotonia, or abnormal reflexes including oculomotor or pupillary reflexes (Fig. 1).<sup>4</sup> The TOBY trial defined infants as TH eligible or not eligible, but did not define the clinical grade of NE within those that were eligible for TH.<sup>1</sup>

## Magnetic resonance imaging

All infants had a cerebral MRI performed within the first week of life. All scans were performed on a 3-T Siemens scanner (Siemens, Erlangen,

**Table 1.** The Brigham and Women's Hospital Neonatal Encephalopathy Scale.

Stage	Normal (0 points each)	Mild/Stage 1 (1 point each)	Moderate/Stage 2 (2 points each)	Severe/Stage 3 (3 points each)
<b>1. Level of Consciousness</b>	Normal 0	Hyper-alert/Irritable 1	Lethargic/Obtunded 2	Stupor/Coma 3
<b>2. Spontaneous Activity</b>	Normal 0	Normal 0	Decreased 2	Absent 3
<b>3. Muscle Tone</b>	Normal 0	Normal 0	Mild Hypotonia 2	Flaccid 3
<b>4. Posture</b>	Normal 0	Mild Distal Flexion 1	Strong Distal Flexion 2	Decerebrate 3
<b>5. Primitive Reflexes</b>	Normal 0	Weak 1	Weak/Absent 2	Absent 3
Suck	0	1	2	3
Moro	Normal 0	Strong/Low Threshold 1	Weak/Incomplete/High Threshold 2	Absent 3
<b>6. Autonomic Function</b>	Normal 0	Mydriasis 1	Miosis 2	Unequal/Fixed/Dilated/Poor Reflex 3
Pupils	Normal 0	Tachycardia 1	Bradycardia 2	3
Heart Rate	0	1	2	Variable 3
Respirations	Normal 0	Normal 0	Periodic Breathing 2	Apnea 3
<b>Total Score</b>	–	–	–	–

The grade of NE is defined as follows: mild if they do not meet the criteria for moderate or severe NE; an infant is scored as moderate if they have three or more domains consistent with moderate or severe NE, but more domains are moderate than severe, and they are scored severe if they have three or more domains consistent with moderate or severe NE, but more domains are severe than moderate.

TH eligibility threshold itself is determined using the total score derived from this exam, rather than the defined grade. A total score of  $\geq 4$  is eligible for TH in the Brigham and Women's Hospital. This threshold identifies most mild infants, and all with moderate and severe NE as being eligible for TH (range of scores associated with each grade of NE—Mild 1–12, Moderate 6–20, and Severe 9–27). Seizures are not included in the exam; however, the presence of seizures and findings of NE automatically define the grade of NE as at least moderate and eligible for TH.

A more detailed version of the above exam, with additional information including definitions and graphics on how to assess the exam components, the checklists used for TH eligibility assessment, and full details of the Brigham and Women's Therapeutic hypothermia guidelines are available at <https://www.brighamandwomens.org/pediatric-newborn-medicine/for-medical-professionals/guidelines-for-clinical-care>.

NICHD exam criteria			TOBY exam criteria	
<b>Grade of encephalopathy</b>			<b>TH eligibility criteria</b>	
<b>Domains</b>	<b>Moderate NE</b>	<b>Severe NE</b>	<b>Domains</b>	<b>TH eligibility criteria</b>
<b>1.Level of consciousness</b>	Lethargic	Stupor/coma	<b>Level of consciousness</b>	Lethargy , stupor or coma
<b>2.Spontaneous Activity</b>	Decreased	No activity	<b>And any ONE of the following</b>	
<b>3.Muscle tone</b>	Hypotonia	Flaccid	<b>Muscle tone</b>	Hypotonia
<b>4.Posture</b>	Hypertonia Distal flexion Complete extension	Rigid Decerebrate	<b>Abnormal reflexes</b>	Including oculomotor or pupillary
<b>5.Primitive reflexes</b>				Absent or weak suck
Suck	Weak	Absent	<b>Seizure</b>	Clinical seizures
Moro	Incomplete	Absent		
<b>6.Autonomic function</b>				
Pupils	Constricted	Deviated, dilated, non-reactive		
Heart rate	Bradycardia	Variable		
Respiration	Periodic breathing	Apnea		
<b>Seizures-not a component of grade- but if present met TH eligibility</b>				
Exam eligible if ≥3 moderate/severe domains			Exam eligible if LOC meets criteria and ≥1 additional criteria	

**Fig. 1 Comparison of TH eligibility B criterion in NICHD and TOBY RCTs.** Panel A; NICHD Exam (B) criterion, and Panel B; TOBY Exam (B) criterion.

Germany). The standard clinical imaging protocol included T1, T2, and diffusion-weighted imaging. The images for this study were analyzed independently by a pediatric neuroradiologist and a neonatologist (E.Y., T. E.J.), who were blinded to the clinical grades of encephalopathy. The presence and type of any MRI abnormalities were detailed. Analysis of the pattern and severity of brain injury was classified according to the grading system developed by Barkovich et al.<sup>8</sup> A score of  $\geq 2$  in the deep nuclear gray matter, or a score of  $\geq 3$  in a watershed pattern, was considered consistent with moderate–severe MRI injury.

### Statistical analysis

Statistical analysis was performed using PASW statistics 18.0. Nonparametric data were reported as median values with interquartile range (IQR) and comparisons were performed using the Mann–Whitney *U* test or Kruskal–Wallis *H* test, as appropriate. The  $\chi^2$  test was used when comparing proportions. The TOBY trial defined infants as TH eligible or not eligible, but did not define the grade of NE within those that were eligible for TH.<sup>1,4</sup> Therefore, in comparing the eligibility methods, the primary assessment compared if the infant met the clinical neurological exam (B criteria) TH eligibility Yes/No using both exam methods. Agreement between assessment methods was described using  $\kappa$  values. Statistical significance was taken as  $p < 0.05$ .

## RESULTS

One hundred and one infants met our defined inclusion criteria between 2014 and 2019. Of these, ten were excluded, four as they were  $< 36$  weeks gestational age, and six due to insufficient exam documentation. Thus, the final study population consisted of 91 infants with NE: 45 mild, 43 moderate, and 3 severe NE per standardized exam (Table 1). The median age of the neurological exam used for analysis was 2 h (IQR 0.75–4 h). The clinical and demographic details by grade of NE are provided in Table 2.

### TH eligibility by NICHD-NRN and TOBY-BAPM neurological exam criteria

Forty-six (50.5%) infants were eligible for TH per the NICHD-NRN exam, while 35 (38%) infants were eligible for TH per the TOBY-BAPM exam (Table 3). This represents a good agreement between

the systems, with a  $\kappa$  value of 0.715,  $p < 0.001$ . However, the differences in TH eligibility between the systems were significant ( $p < 0.001$ ), with the NICHD system identifying more infants as eligible. The two neurological assessments differed in determining TH eligibility for 13 infants.

Figure 2 demonstrates the distribution of the exam components for those who did and did not meet both the (a) NICHD-NRN and (b) TOBY-BAPM exam criteria. From Fig. 2, it is clear that the disagreement between the systems was predominantly related to the categorization of the level of consciousness. Twelve (26%) of the 46 infants eligible per NICHD-NRN had a level of consciousness that did not meet TOBY-BAPM criteria and were therefore ineligible for TH per TOBY-BAPM. Table 4 provides further details of initial screening and short-term outcomes specifically for the 13 infants for whom the exams disagreed on their TH eligibility.

### Comparing screening criteria, seizure frequency, and MRI outcomes associated with TOBY-BAPM vs. NICHD-NRN TH eligibility exams

There was no difference in demographic, screening criteria, or short-term outcome measures between the 35 infants who were eligible per TOBY-BAPM compared to the 46 infants that were eligible per the NICHD-NRN exam (Table 5).

Similarly, there was no difference in demographics or screening criteria for the 56 infants who were not eligible per TOBY-BAPM compared to the 45 infants who were not eligible per the NICHD-NRN neurological exam. However, the clinical grade of NE did differ between those not eligible by the two different exams ( $p < 0.001$ ), reflecting the disagreement in the “Methods” discussed above. Electrographic seizures developed after 6 h of age in 3 (5%) infants who were not eligible per TOBY-BAPM exam and in 1 (2%) infant who was not eligible per NICHD-NRN exam. There was hypoxic–ischemic cerebral injury on MRI in 13 (23%) infants who were not eligible per TOBY-BAPM and 6 (13%) infants who were not eligible per NICHD-NRN. Neither of these differences was statistically significant (Table 5).

**Table 2.** Screening criteria and TH eligibility based on Brigham and Women's grade of NE.

Grade of NE <sup>a</sup>	Mild NE (45)	Moderate NE (43)	Severe NE (3)
Gestational age	38.9 (1.26)	38.8 (1.69)	40.7 (1.12)
Birth weight	3249 (2175–4733)	3085 (2090–4520)	3650 (3270–4050)
Sex (female)	21 (47)	22 (51)	1 (33)
Method of delivery			
SVD	11 (24)	13 (30)	0
Instrumental	3 (7)	7 (16)	2 (66)
Em-LSCS	28 (62)	21 (49)	1 (33)
EI-LSCS	3 (7)	2 (5)	
pH	6.97 (6.78–7.28)	6.97 (6.8–7.28)	6.94 (6.8–7.23)
BD	14.1 (2.3–26.2)	14 (5–22.4)	13.4 (7.9–18.8)
Ap 5	7 (2–9)	5 (0–8)	0 (0–2)
Ap 10	8 (6–10)	7 (0–10)	2 (1–3)
Invasive ventilation	11 (24)	20 (47)	3 (100)
Inotrope	2 (4)	7 (16)	3 (100)
Electrical or clinical seizure 1st 6 h	0	1 (2)	1 (33)
Electrical seizure	1 (2)	9 (21)	3 (100)
Phenobarbitone	0	8 <sup>c</sup> (18.6)	2 (66)
EEG background <sup>b</sup>			
Normal	7 (17)	7 (19)	0
Mild	32 (78)	20 (56)	0
Moderate	2 (5)	8 (22)	0
Severe	0	1 (3)	3 (100)
MRI injury (Barkovich)			
None	39 (87)	26 (61)	0
Mild	6 (13)	9 (21)	0
Moderate–severe	0	8 (19)	3 (100)
Length of stay	7 (6–11)	10 (6–19)	14 (9–33)
Died	0	0	2 (68)

<sup>a</sup>Grade of NE was defined using Brigham and Women's encephalopathy exam as detailed in Table 1.

<sup>b</sup>EEG on four mild NE and seven moderate NE not available.

<sup>c</sup>One infant received phenobarbitone prior to neurological assessment; all other infants received it after TH eligibility assessment.

**Table 3.** Agreement between TOBY-BAPM and NICHD-NRN TH eligibility exams.

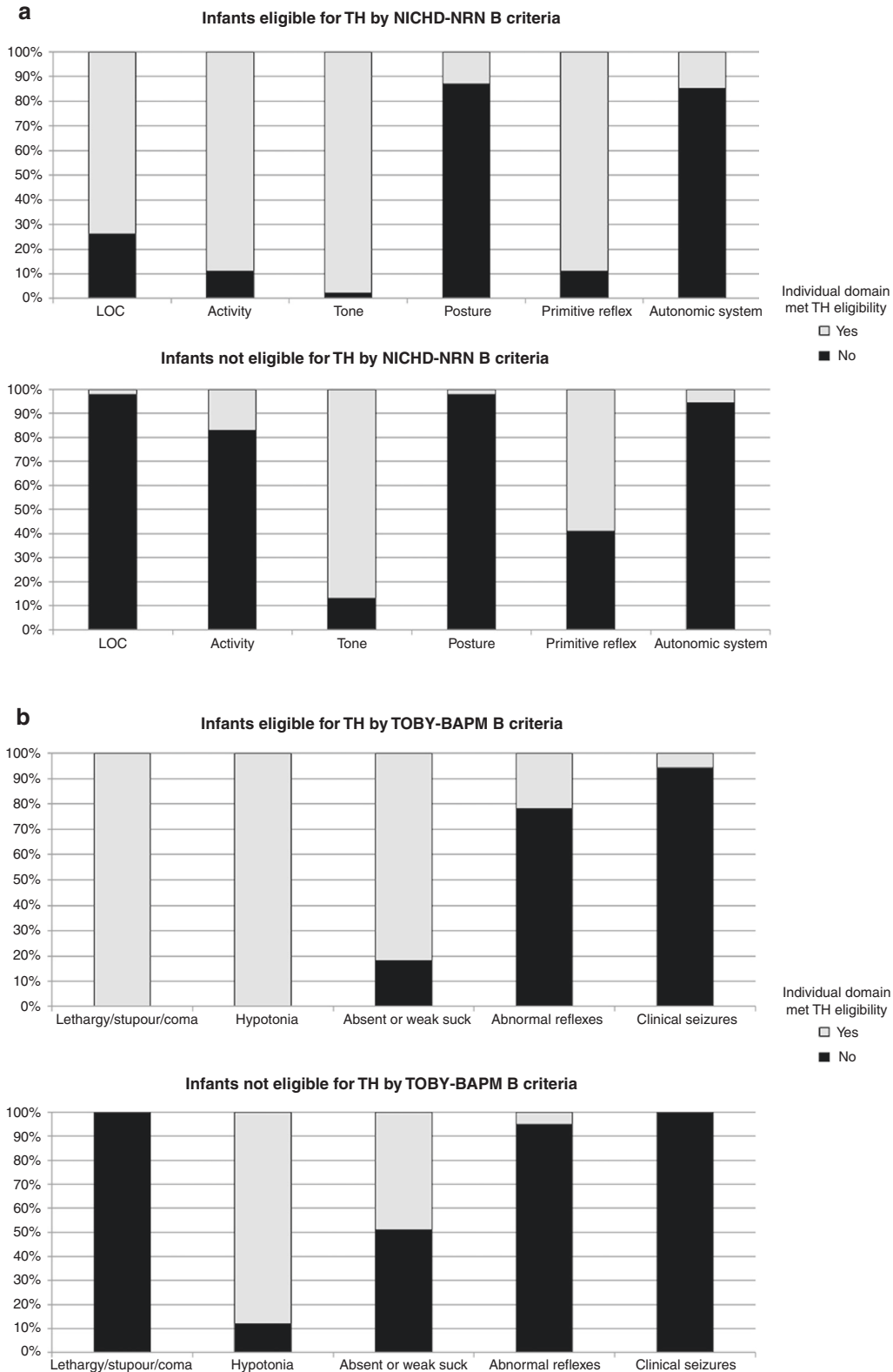
	TOBY-BAPM eligible	TOBY-BAPM not eligible
NICHD-NRN eligible	34	12
NICHD-NRN not eligible	1	44

## DISCUSSION

Our results demonstrate that there is a notable difference in TH eligibility depending on which standardized neurological exam is used for the evaluation of clinical encephalopathy. The TOBY-BAPM neurological exam defined 24% fewer infants as being eligible for TH compared to the NICHD-NRN exam. There were no differences in short-term outcomes between the methods of assessment, and neither method identified all infants who developed seizures or had cerebral MR injury. However, among the 12 infants who were determined eligible for TH by NICHD-NRN exam, but were ineligible per TOBY-BAPM exam, two infants developed electrographic seizures and seven infants demonstrated cerebral injury. Although not statistically significant, these differences are potentially clinically relevant.

The primary driver for the difference in TH eligibility was due to the evaluation and importance of the level of consciousness in the TOBY-BAPM criteria. In this cohort, a quarter of those who met NICHD-NRN TH eligibility had a level of consciousness that did not meet TOBY-BAPM criteria. Unlike the TOBY-BAPM exam, the NICHD-NRN does not weight the level of consciousness differently to other domains. This is consistent with the original work by Sarnat and Sarnat.<sup>3</sup> The Sarnats did not identify any one domain that was a prerequisite for defining severity, or that should be weighted over the other exam components. Furthermore, Robertson and Finer did not actually include the level of consciousness at all when describing moderate NE in their seminal work, rather defining it as consisting of "hypotonia and suppressed primitive reflexes."<sup>2</sup> Therefore, although the level of consciousness is one of the more overt signs of encephalopathy, the seminal work on defining grade of NE did not identify it as being superior to other components of the exam.

Both the TOBY-BAPM and NICHD-NRN neurological exams are evidence-based for the assessment of TH eligibility and are appropriate for use in clinical settings.<sup>4,5</sup> This paper cannot determine if either is superior to the other, and indeed showed no difference in short-term outcomes between the two, rather we report that there is a notable difference in TH eligibility depending on which of the two systems are applied.



**Fig. 2 TH Eligibility Exam Findings.** Distribution of exam sub-components among infants that were and were not eligible for TH based upon; **a** NICHDNRN B criteria and **b** TOBY-BAPM B criteria.

This has several implications. First, this has the potential to impact the care an infant receives dependent on the location in which they are born, with more infants eligible for TH in North America than in the United Kingdom. Second, TH rates are a frequent metric used by centers and health systems for

benchmarking, and in some instances, infer the rate of moderate–severe NE based upon these rates. However, this paper demonstrates that comparison of TH rates between health systems, or the inference of rates of moderate–severe NE based upon TH rates, may be fundamentally flawed if different eligibility



**Table 4.** Details of infants with a discrepancy in TH eligibility per NICHD-NRN and TOBY-BAPM neurological exams.

Case	NICHD-NRN eligible	TOBY-BAPM eligible	pH <sup>a</sup>	BD <sup>a</sup>	Apgar 5 min	Apgar 10 min	Intubated/IPPV at 10 min	NICHD Grade < 6 h	cEEG by 24 h	Seizure <sup>b</sup>	Severity of MRI injury (predominant pattern)
1	Y	N	6.99	12.5	5	6	Yes	Moderate	Moderate	N	None
2	Y	N	6.85	16.3	6	8	No	Moderate	Mild	N	None
3	Y	N	7.15	11.5	4	6	Yes	Moderate	Normal	N	None
4	Y	N	6.8	16.7	5	7	No	Moderate	Moderate	Y	None
5	Y	N	6.9	12	7	8	Yes	Moderate	Mild	N	None
6	Y	N	6.87	16.1	3	4	Yes	Moderate	Moderate	N	None
7	Y	N	7.24	7.0	1	7	Yes	Moderate	Mild	N	Mild (Watershed)
8	Y	N	6.83	18.3	6	7	No	Moderate	Mild	N	Mild (Watershed)
9	Y	N	7.15	16.3			No	Moderate	Normal	N	Mild (Watershed)
10	Y	N	7.16	10.3	4	7	Yes	Moderate	Normal	N	Moderate–severe (Watershed)
11	Y	N	6.98	8.3	8	8	No	Moderate	Mild	N	Moderate–severe (Watershed)
12	Y	N	6.95	14.1	8	9	Yes	Moderate	Moderate	Y	Moderate–severe (Watershed)
13	N	Y	6.93	14.9	7	7	No	Not eligible	Mild	N	None

<sup>a</sup>Cord blood or postnatal gas in the first hour of life.

<sup>b</sup>All seizures occurred after 6 h of age.

methods are used. The potential difference between the incidence of TH and moderate/severe HIE was recently highlighted by Shipley et al.<sup>9</sup> They demonstrated that while the rate of TH in the United Kingdom is 1.26/1000 live births, the rate of moderate/severe HIE in infants  $\geq 36$  weeks in the Shipley was 2.03/1000 live births for the same time period. Shipley reported that excluding those who died prior to initiation of TH, 37.9% of those  $\geq 36$  weeks with a discharge diagnosis of moderate or severe HIE in the UK did not receive TH. Therefore, the appropriate metric for benchmarking is to report the grade of NE defined by the cumulative data and derived at the time of discharge.

Our center's TH eligibility criteria (as detailed in Table 1) allow treatment to be provided to those with milder encephalopathy. This practice is becoming more common, with the use of TH in mild NE increasing internationally.<sup>10–13</sup> While there is currently no evidence of treatment benefit among this population, Oliveira et al. reported that this was being driven by concern that these infants are at risk of injury and that the early grade of NE was not sensitive enough to discern which infant will have an adverse outcome.<sup>10</sup> Supporting the first point, the evidence of injury among mild NE is now well established, with numerous groups demonstrating both significant risk of cerebral injury and adverse neurodevelopmental outcomes in this population.<sup>7,14–17</sup> Regarding the early neurological assessment, as discussed previously, the NICHD-NRN and TOBY-BAPM TH eligibility assessments were developed to identify infants at high risk of cerebral injury. Now as clinicians consider the question of managing those with milder encephalopathy, we must first acknowledge that these standard assessment methods do not identify these children nor do they even define mild NE.

For this reason, the PRIME study published a novel modified NICHD assessment defining mild NE.<sup>18</sup> Furthermore in an attempt to improve the sensitivity of the early assessment to detect the minimum threshold for injury, PRIME also proposed applying a scaled score (Total Sarnat Score [TSS]) to their modified NICHD exam.<sup>19</sup> Rather than defining an infant as mild, moderate, or severe, using the same exam sub-components the TSS scores them from 1 to 18. This approach was applied in recognition that

encephalopathy is a spectrum, with a range of severity existing both within individual grades and between them.

The PRIME study reported that a score of  $\geq 5$  in the first 6 h provided the optimum sensitivity for identifying those who would have cognitive deficits at 2 years. This equated to an infant with mild encephalopathy who did not meet the threshold for moderate NE. This approach was replicated by Morales et al. using the MARBLE study cohort.<sup>20</sup> They reported that they could identify all who developed cognitive deficits at 2 years using a TSS threshold score of  $\geq 4$ , again by capturing those at the more severe end of the mild NE spectrum. More recently, our own group has further validated this approach, reporting that both the TSS and a scaled score based upon the SIBEN exam each had a superior sensitivity to standard HIE grades for identifying infants at increased risk of cerebral injury.<sup>21</sup> Similar to the MARBLE cohort, we found that the optimum threshold was a TSS of  $\geq 4$ . In the current manuscript, we could not determine if either of the standard methods of TH eligibility assessment is superior, rather we demonstrated the discrepancies that exist between them. However, now that TH is the standard of care for encephalopathic infants at high risk of injury, we must look to further optimize our eligibility criteria. Potentially this will require a re-evaluation of the use of classical grades of NE to define risk thresholds, with the possibility that the greater granularity offered by numerical scoring systems may improve our risk stratification.

There are several limitations to our study. The first is that the synthesis of the neurological exam criteria was performed retrospectively. However, the exams themselves were performed and documented prospectively by experienced clinicians, which should limit potential bias. An additional limitation, as discussed above, is that our center provides TH to those with milder encephalopathy. As such all infants included in this study received TH. This would have no impact on the neurological exams performed, as in all cases the exams were performed prior to the initiation of TH. It could have impacted the frequency of seizures and MR injury in the population; however, given that all infants underwent TH, it should not have impacted on differences between assessment methods. Lastly, it is recognized that we did

**Table 5.** Comparing demographics, screening criteria, and short-term outcomes for Infants who were and were not eligible for TH depending on neurological exam criteria used (NICHD-NRN vs. TOBY-BAPM).

	Exam eligible for TH			Exam not eligible for TH		
	NICHD-NRN (46)	TOBY-BAPM (35)	<i>p</i> value	NICHD-NRN (45)	TOBY-BAPM (56)	<i>p</i> value
<i>Demographics</i>						
Gestational age	38.9 (±1.7)	38.8 (±1.8)	0.7	38.9 (±1.3)	39.0 (±1.3)	0.6
Birth weight	3147 (2755–3553)	3125 (2685–3650)	0.9	3249 (2890–3800)	3224 (2855–3696)	0.8
Sex (female)	23 (50)	18 (51)	0.9	21 (47)	26 (46)	0.9
<i>Screening criteria</i>						
pH	6.97 (6.90–7.11)	6.97 (6.91–7.03)	0.9	6.97 (6.92–7.00)	6.97 (6.90–7.01)	0.9
BD	14.0 (11.2–17.4)	14.2 (11.3–18.1)	0.8	14.1 (12.8–16.9)	14.0 (12.1–16.6)	0.7
Ap 5	5 (3–7)	5 (3–7)	0.9	7 (5–8)	7 (5–8)	0.5
Ap 10	7 (5–8)	6 (5–8)	0.6	8 (6–8)	7 (6–8)	0.7
<i>Grade of NE<sup>a</sup></i>						
Mild	0	1 (3)	0.5	45 (100)	44 (79)	<0.001
Moderate	43 (94)	31 (88)		0	12 (21)	
Severe	3 (6)	3 (9)		0	0	
<i>Seizures</i>						
1st clinical or electrical seizure <6 h	2 (4)	2 (6)	0.8	0	0	–
Electrical seizure (any age)	12 (26)	10 (29)	0.8	1 (2)	3 (4)	0.6
<i>EEG background<sup>a</sup></i>						
Normal	7 (18)	4 (14)	0.9	7 (17)	10 (19)	0.5
Mild	20 (51)	16 (48)		32 (78)	36 (69)	
Moderate	8 (21)	4 (14)		2 (5)	6 (12)	
Severe	4 (10)	4 (14)		0	0	
<i>MRI injury (Barkovich)</i>						
None	26 (56)	22 (63)	0.8	39 (87)	43 (77)	0.2
Mild	9 (20)	5 (14)		6 (13)	10 (18)	
Moderate–severe	11 (24)	8 (23)		0	3 (5)	
<i>Clinical outcome</i>						
Invasive ventilation	23 (50)	16 (46)	0.9	11 (25)	18 (32)	0.4
Inotrope	10 (22)	8 (23)	0.9	2 (4)	4 (7)	0.6
Length of stay	10 (6–18)	10 (6–18)	1.0	7 (6–11)	7 (6–13)	0.7
Died	2 (5)	2 (6)	0.8	0	0	–

Mean (±SD)—comparison *t* test, median (IQR)—comparison Mann–Whitney, *n* (%)—comparison  $\chi^2$ .

<sup>a</sup>Grade of NE was defined using Brigham and Women's encephalopathy exam as detailed in Table 1.

not include aEEG assessment in determining TH eligibility. However, while a component of TOBY-BAPM, this would not have increased the agreement, and would if anything have further decreased agreement, as only those who meet the neurological exam criteria by TOBY-BAPM are then assessed to see if they meet the aEEG criteria.

In conclusion, in our cohort, we have demonstrated that there was a notable difference in TH eligibility depending on which evidence-based clinical encephalopathy exam was applied. This has significant implications for the care of the individual infant, for benchmarking between health systems, and must be considered as we look to optimize future TH eligibility criteria.

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## AUTHOR CONTRIBUTIONS

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## COMPETING INTERESTS

The authors declare no competing interests.

## CONSENT STATEMENT

A waiver of consent was approved by the Partners Healthcare Human Research Committee.

## ADDITIONAL INFORMATION

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