Centre for Perinatal Neuroscience

Imperial College London

Optimising the duration of Cooling in Mild Neonatal Encephalopathy

Sudhin Thayyil

The COMET trial Group

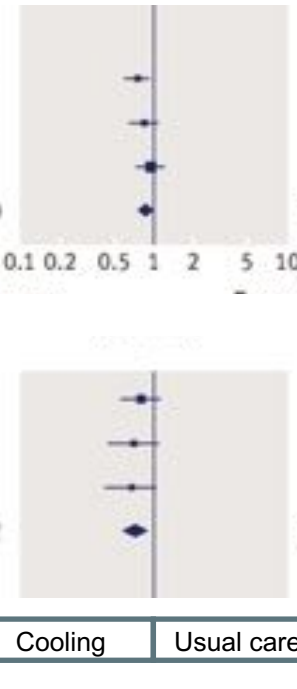
MRC Medical Research Council

NHS National Institute for Health Research

Back ground

Cooling in moderate and severe encephalopathy

Study or subgroup	Hypothermia Events	Hypothermia Total	Normothermia Events	Normothermia Total	Risk ratio (95% CI)	Weight (%)	Risk ratio (95% CI)
Infants with severe encephalopathy							
CoolCap	28	40	32	35		28.6	0.77 (0.61 to 0.96)
NICHD	23	32	34	40		25.4	0.85 (0.66 to 0.09)
TOBY	53	98	54	95		46.0	0.95 (0.74 to 1.23)
Subtotal (95% CI)		170		170		100.00	0.87 (0.75 to 1.01)
Total events	104		120				
Infants with moderate encephalopathy							
CoolCap	28	62	39	69		37.9	0.80 (0.57 to 1.13)
NICHD	22	69	30	66		31.5	0.70 (0.45 to 1.08)
TOBY	20	66	30	67		30.6	0.68 (0.43 to 1.06)
Subtotal (95% CI)		197		202		100.00	0.73 (0.58 to 0.92)
Total events	70		99				



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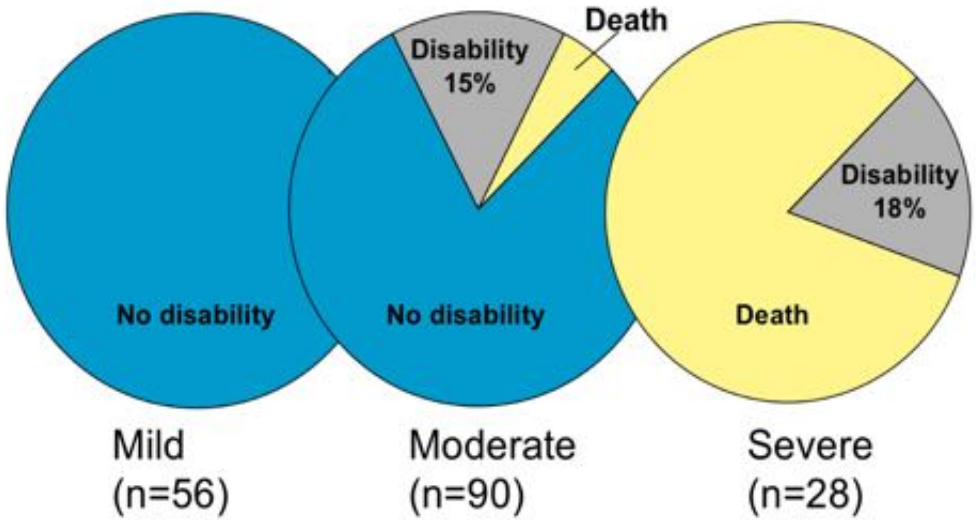
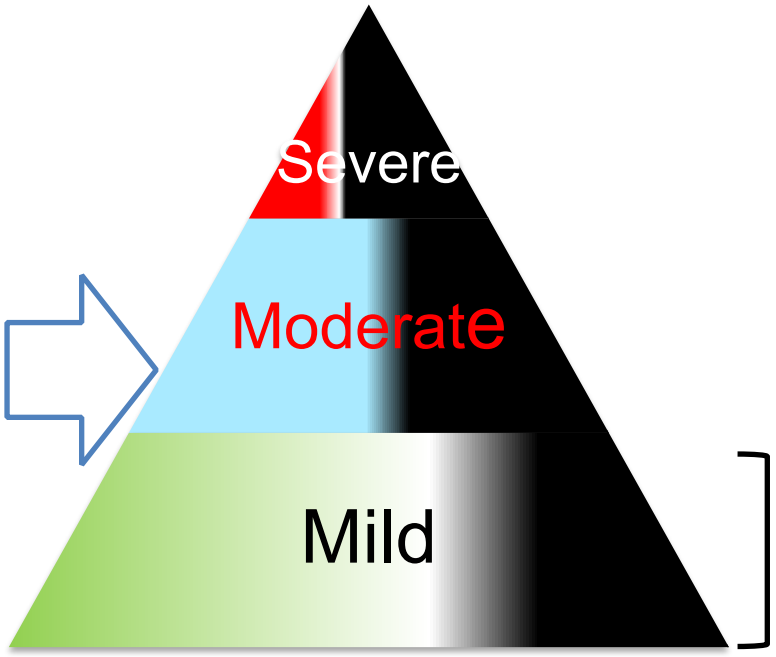
Long term outcomes after mild encephalopathy



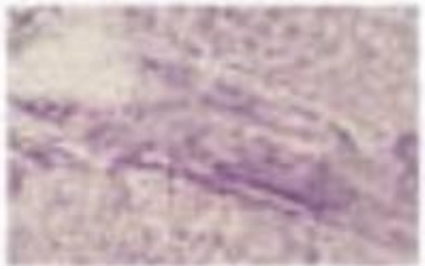


Adverse outcome in > ¼

Murray et al., Pediatrics 2016
Gagne-Loranger, Am J Perinatol, 2016 (MRI)
Walsh et al, J Pediatric, 2017 (MRI)
DuPont et al, J Peds, 2013
Chalak et al (PRIME study)

Preclinical data on cooling in mild encephalopathy

Hypoxic Injury + normothermia



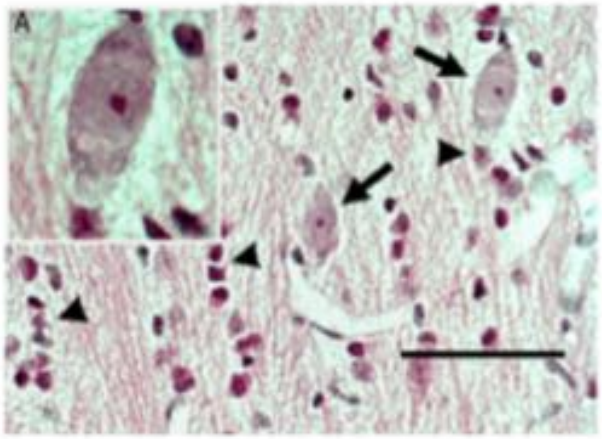
Hypoxic Injury + hypothermia (3.5h)

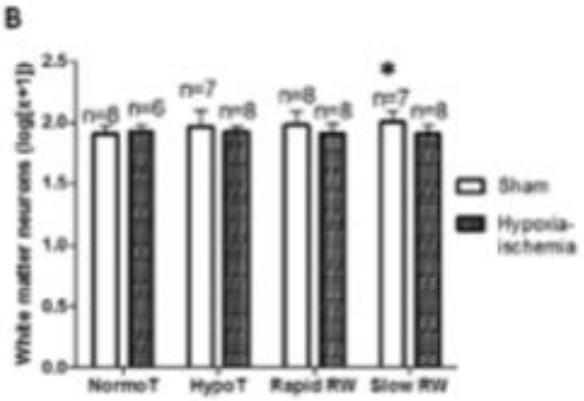
Sham control (normal hippocampus)

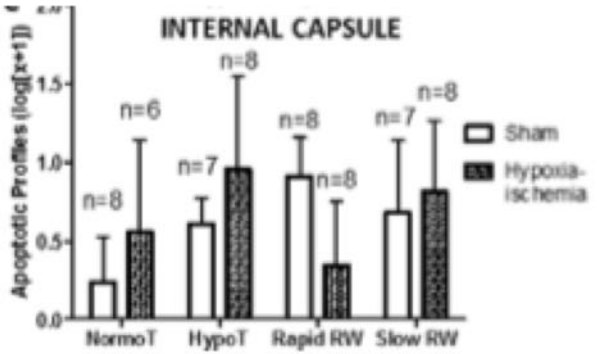
3.5 hours cooling prevents brain injury in mice model of mild encephalopathy

(Koo et al. Ped Res 2017)

Cooling healthy brain induce apoptosis







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Wang et al., Neuroscience 2017

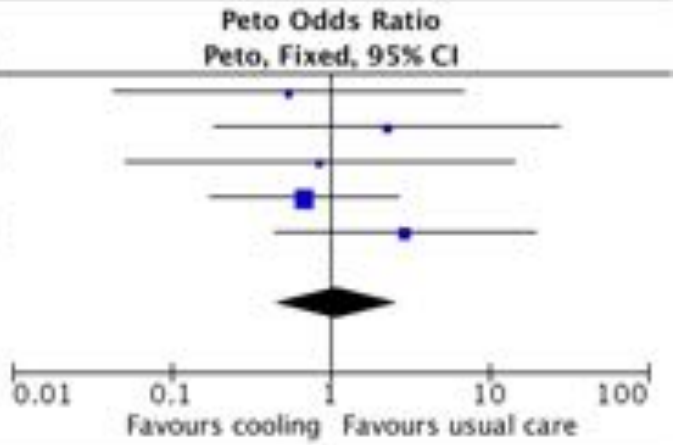
Cooling in mild encephalopathy: a meta-analysis

Effect of cooling on moderate or severe disability/death after mild encephalopathy

Study or Subgroup	Cooling Events	Cooling Total	Usual care Events	Usual care Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Battin 2001 (SHC)	1	5	2	6	12.3%	0.54 [0.04, 6.89]	2001
Wyatt 2007 (SHC)	2	6	1	6	12.7%	2.26 [0.19, 27.57]	2007
Zhou 2010 (SHC)	1	21	1	18	10.0%	0.85 [0.05, 14.27]	2010
Jacobs 2011 (WBC)	4	16	8	24	42.7%	0.68 [0.17, 2.65]	2011
Lally 2013 (WBC)	4	9	2	10	22.3%	2.92 [0.44, 19.25]	2013
Total (95% CI)		**57**		**64**	**100.0%**	**1.09 [0.45, 2.66]**	
Total events	12		14				

Heterogeneity: $Chi^2 = 2.16$, $df = 4$ ($P = 0.71$); $I^2 = 0\%$

Test for overall effect: $Z = 0.19$ ($P = 0.85$)



Kariholu et al., PAS 2018

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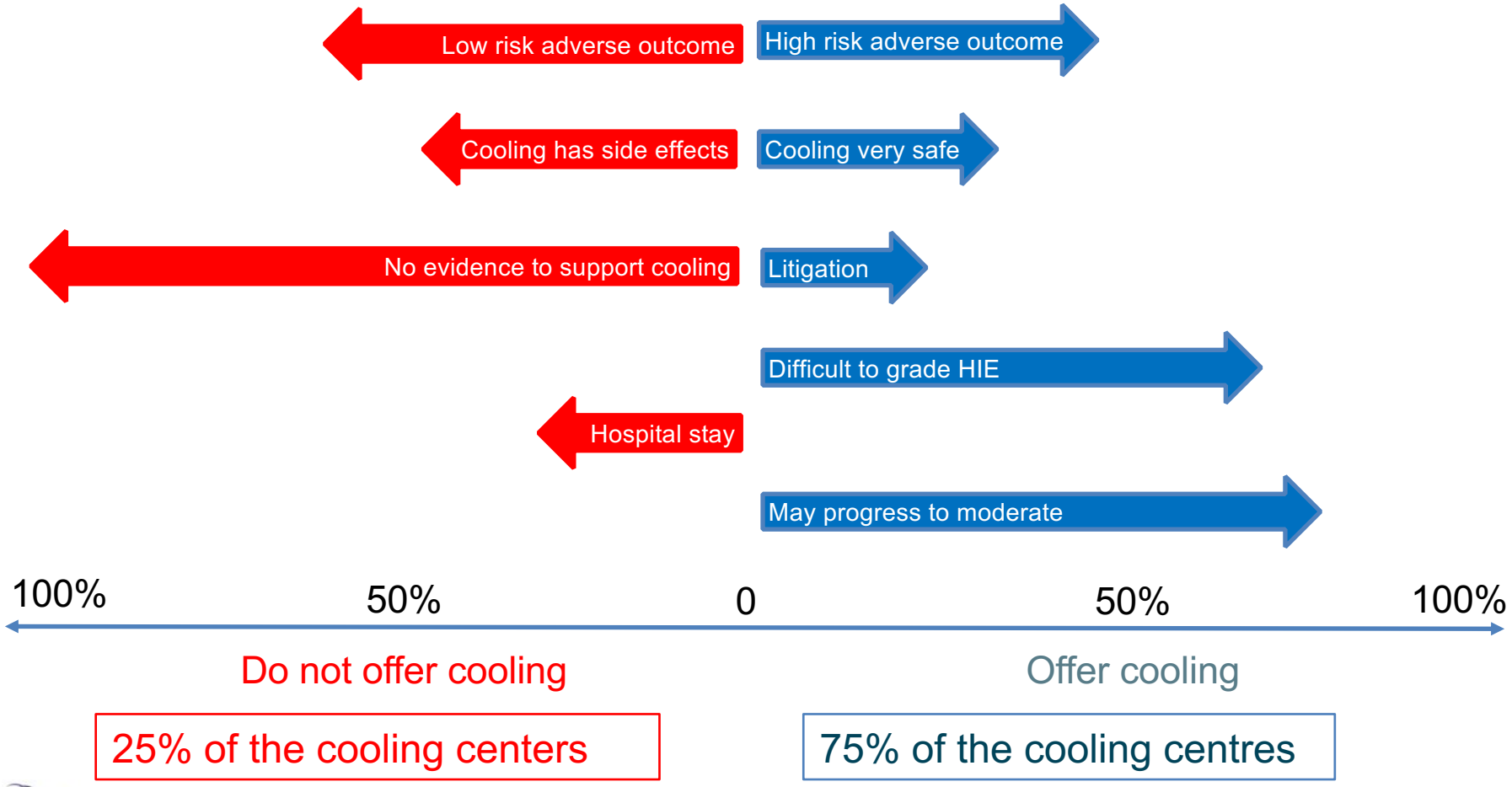
Cooling in Mild Encephalopathy – National Survey



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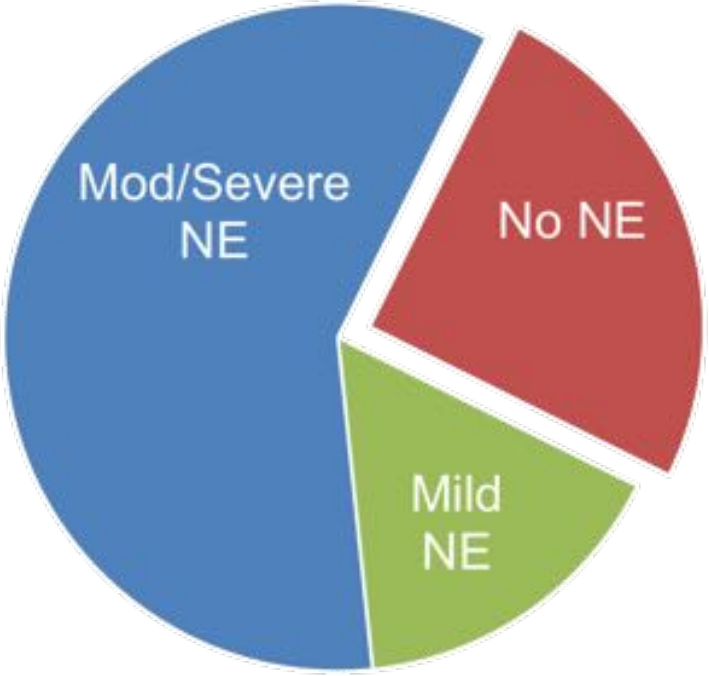
Oliveira et al., Arch Dis Childhood 2018

London neonatal transport for cooling

145 cooling transfers in London (2011-12)

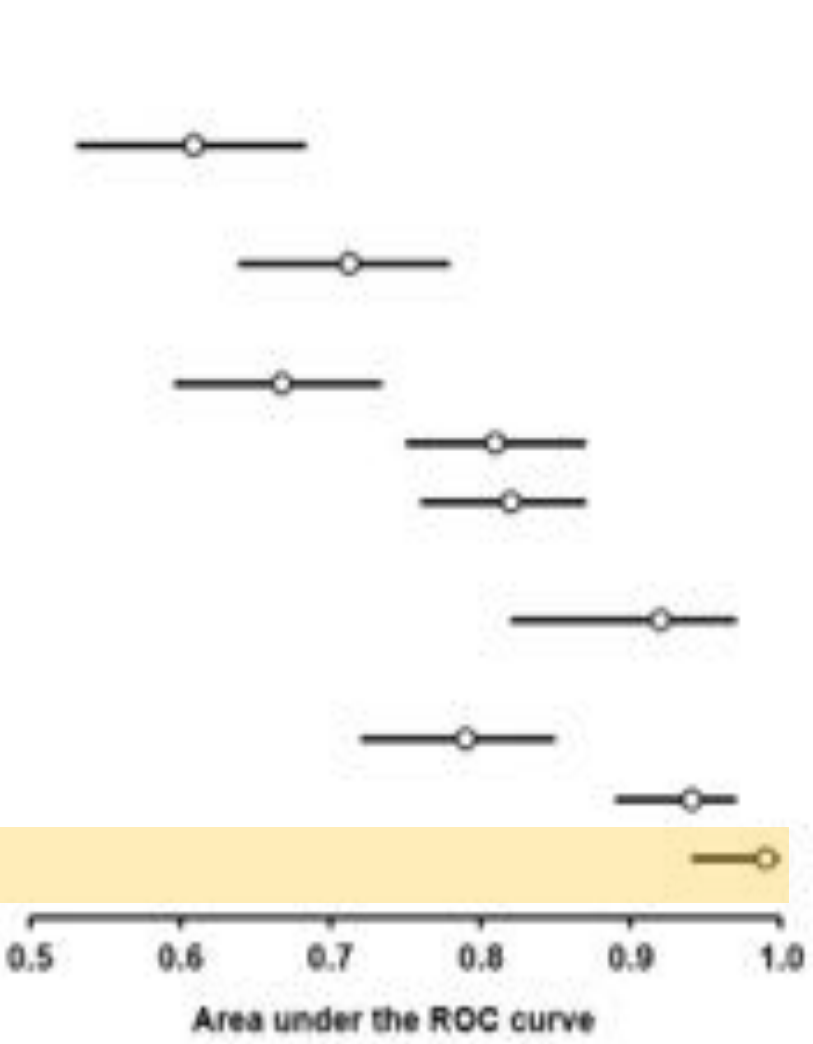
– a quarter of the babies cooled had “no encephalopathy”



Goel et al., ECPM 2015

Prognostic accuracy of MR biomarkers

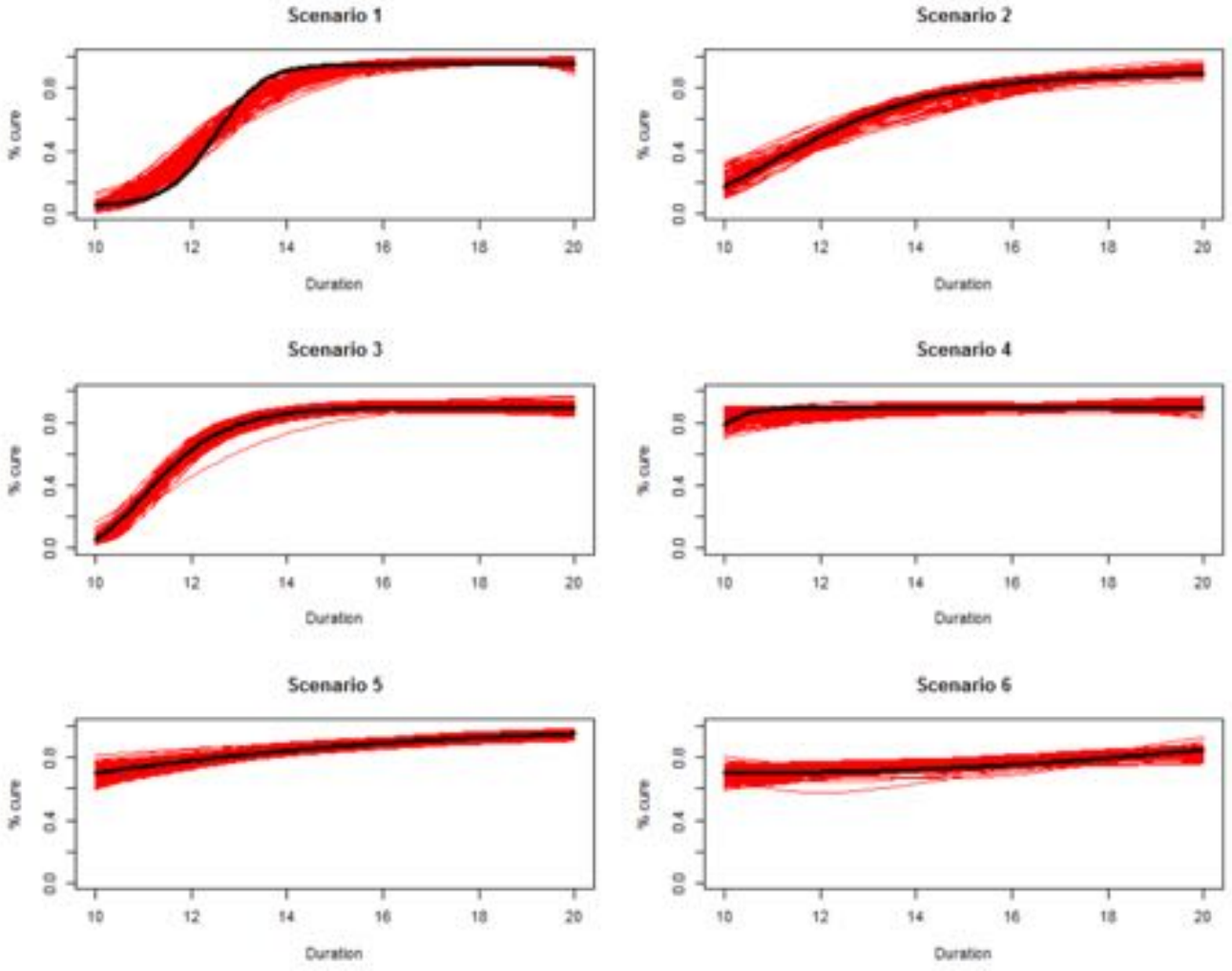
	Sensitivity	Specificity
Clinical assessment		
Discharge neuro. exam	26 (10, 48)	95 (90, 98)
Cerebral function monitor		
aEEG	45 (27, 64)	92 (86, 96)
MRI appearance		
Cortex	48 (30, 67)	81 (74, 87)
Basal ganglia/thalami	71 (52, 86)	88 (82, 93)
PLIC	71 (52, 86)	90 (84, 94)
Diffusion MRI		
Fractional anisotropy	75 (19, 99)	98 (91,100)
MR Spectroscopy		
NAA/Cr	65 (44, 83)	89 (82, 94)
Lac/NAA	89 (70, 98)	91 (85, 95)
[NAA]	100 (74,100)	97 (90,100)



Lally et al., Lancet Neurology (in press)

Optimising treatment durations

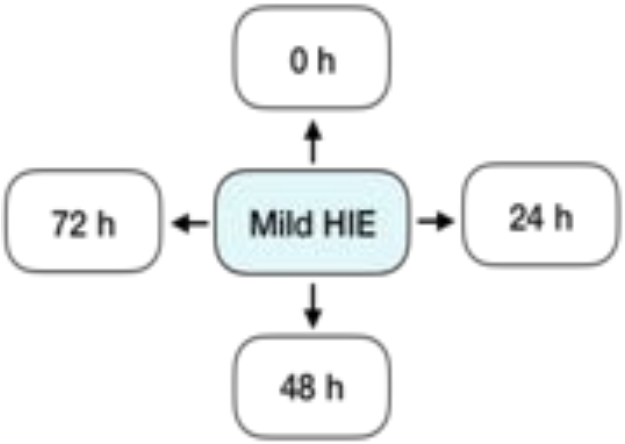
Quartagno et al., Clin Trials 2018



COMET Trial design

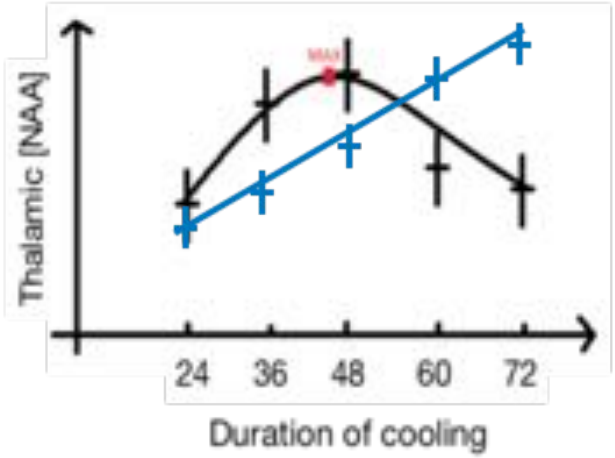
A. Feasibility

(Learning and exploratory phase)



N=32

B. Phase II trial



N=200

C. Phase III trial

(Confirmatory phase)

N=1200

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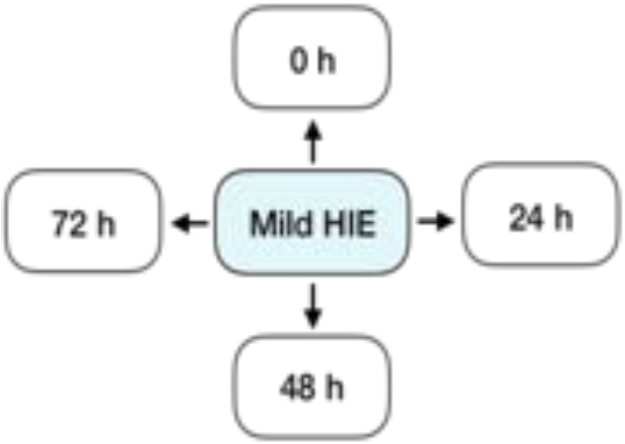
NHS National Institute for Health Research

COMET Trial design

A. Feasibility

(Learning and exploratory phase)



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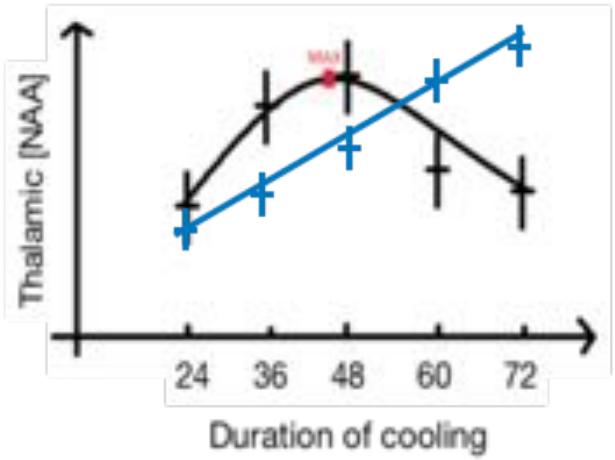

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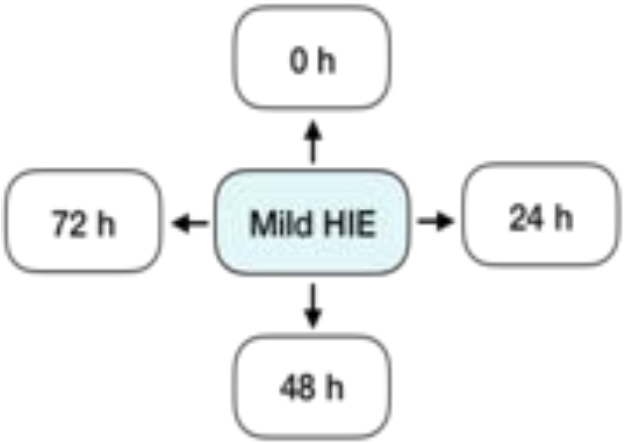

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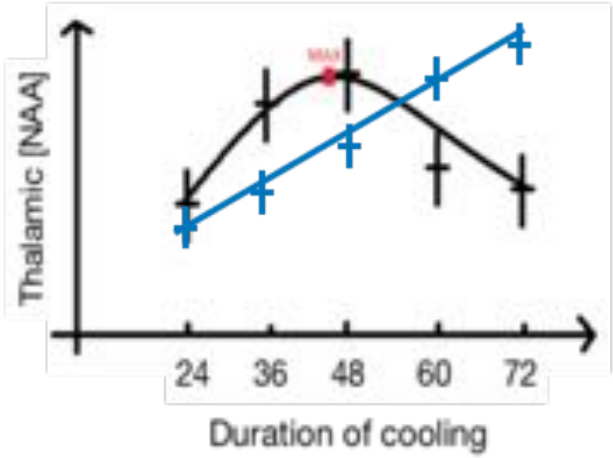

N=200

C. Phase III trial

(Confirmatory phase)

N=1200

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Protocol

Aims

- To examine the feasibility of recruiting and randomising babies with mild neonatal encephalopathy to multiple cooling durations.

- To examine the feasibility of obtaining adequate quality data on the primary outcome for the phase II trial (i.e. thalamic N-acetyl aspartate level) in the recruited babies

Inclusion criteria

- Age less than six hours.

AND

- Evidence of acute perinatal asphyxia (any one)
  - Metabolic acidosis (pH<7.0 and/or BE >-16) in cord and/or within 1h of birth
  - If blood gas not available or borderline (7.0 to 7.15, -10 to -16) in cord and/or blood gas within 1h of birth, at least one of the following criteria is required
    - Evidence of an acute obstetric event e.g. cord prolapse, abruption, shoulder dystocia
    - Need for continued resuscitation or ventilation at 10 minutes and/or a 10 min Apgar score <6

AND

- Evidence of mild NE (2 items) on an NICHD neurological examination performed between 1 and 6h of birth.

Defining mild encephalopathy

CATEGORIES	NORMAL		MILD		MODERATE		SEVERE	
1. Level of consciousness	Alert, responsive to external stimuli	☐	Hyper-alert, has a stare, jitteriness, high pitched cry, exaggerated response to minimal stimuli, inconsolable	☐	Lethargic	☐	Stupor, Coma	☐
2. Spontaneous activity	Normal	☐	Decreased, with or without periods of excessive activity	☐	Decreased	☐	No activity	☐
3. Posture	Predominantly flexed when quiet	☐	Mild flexion of distal joints (fingers, wrist)	☐	Strong distal flexion, complete extension	☐	Intermittent decerebration	☐
4. Tone	Strong flexor tone in all extremities	☐	Slightly increased peripheral tone	☐	Hypotonia or Hypertonia	☐	Flaccid or Rigid	☐
5. Reflex								
Suck	Strong, easy to elicit	☐	Weak, Poor	☐	Weak or has bite	☐	Absent	☐
Moro	Strong, easy to elicit	☐	Low threshold to elicit	☐	Incomplete	☐	Absent	☐
6. Autonomic Nervous System								
Pupils	Normal size	☐	Mydriasis	☐	Miosis	☐	Deviation/Dilated/ Non-reactive	☐
Heart rate	Normal heart rate	☐	Tachycardia (>160)	☐	Bradycardia (<100/minute)	☐	Variable heart rate	☐
Respirations	Normal	☐	Hyperventilation (>80/min)	☐	Periodic breathing	☐	Apnea or on ventilator ± spontaneous respirations	☐

- At least 2 categories in mild, moderate or severe
- Not more than 2 categories under moderate or severe

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Standardisation of neonatal neurological exam

- NICHD neurological examination extensively validated in several high profile clinical trials

  (Shankaran et al. NEJM 2005, NEJM 2012,JAMA 2014, JAMA 2016, Laptook et al JAMA 2017)

- TOBY trial did not standardise neurological examination and relied on aEEG instead

  (Azzopardi et al NEJM 2009)

- aEEG within six hours have very poor prognostic accuracy

  (Chandrasekheran et al., Am J Perinatology 2017)

Problems with the Thompson score

- Developed for use in low resource African settings
- Not validated in any cooling trials
- Intervals and cut-off are inaccurate
- No physiological basis, e.g. double counting of autonomic system disturbances
- Do not correlate with brain injury or major clinical outcomes

- Has crept into clinical practice in some UK neonatal units/Badger net

- Please do not use it !

Rationale for a certification process

- Ensure objective inclusion criteria
- Subjectivity of the examination can be minimized by certification
- Most neonatal trainees/consultants get very little training in neonatal neurological assessments
- Without specific training it is easy to under or over interpret neurological signs in encephalopathy.
- Lack of neurological examination skills and the fear of missing babies with moderate or severe encephalopathy, leads to cooling of all babies with perinatal asphyxia without allocating the Sarnat stage in many UK centres

NICHD Examination: Certification process

- PI and Co PI at each centre will be certified as gold standard examiner (GSE)

- 4 stage certification process
  a. Slides discussion/lecture with the GSE (approx. 30 minutes)
  b. Scoring on videos of HIE babies
  c. Simultaneous (independent) scoring with GSE on 2 babies
  d. Concordance check and final sign off by Prof Shankaran

NICHD Examination: Certification process

- Screen for appropriate infants ≥ 36 weeks GA admitted to NICU or in observation/transition area

- Type of infant for examination
  - Hypoxia-ischemia (fetal acidemia, low Apgars)
  - Abnormal neurological state from non-HI conditions
  - Post-operative infants

- Number of examinations: 2
  - Two infants with neurological abnormalities are preferable but not required
  - At least one examination should have abnormal findings in the categories to be scored

NICHD Examination: Certification process

- GS and MD independently examine the infant
  - Exams performed within 1 hour of each other
  - Each examiner completes a neurological exam form
    - Total the number of abnormalities
    - Determine level of encephalopathy

- GS examiner reviews exam with MD
  - Resolve any differences in exam, scoring and form completion
  - The neurological examination will be sent to Prof Shankaran who will review and inform site PI if MD is certified

NICHD Examination concordance scoring

COMET STUDY Neurologic Exam Certification Form

Gold standard examiner Name: date of exam: _ _/_ _/ 20 _ _ time of exam: _ _: _ _ Site.....
Clinician desiring to be certified: Name: date of exam: _ _/_ _/ 20 _ _ time of exam: _ _: _ _

Is infant sedated at the time of exam ? Y / N. Is the infant receiving cooling therapy at the time of exam ? Y / N. What is the age of the baby (hours)? .....

THE 6 CATEGORIES:	SIGNS OF HIE IN EACH CATEGORY				Your Determination:	
	NORMAL	MILD HIE	MODERATE HIE	SEVERE HIE		
1. LEVEL OF CONSCIOUSNESS	0 = Alert and responsive	1 = hyperalert/stare/jittery	2 = Lethargic	3 = Stupor/coma		= _____**
2. SPONTANEOUS ACTIVITY	0 = changes position when awake	1 = normal or decreased	2 = Decreased activity	3 = No activity		= _____
3. POSTURE	0 = predominantly flexed	1 = mild flexion of distal joints	2 = Distal flexion, complete extension	3 = Decerebrate		= _____
4. TONE	0 = strong flexor tone in all extremities + strong flexor hip tone	1=normal or slightly increased flexor tone	2a = Hypotonia (focal or general) 2b = Hypertonia	3a = Flaccid 3b = Rigid		= _____ _____ (Note a or b)
5. PRIMITIVE REFLEXES						Code highest level
Suck	0 = strong, easily elicited	1 = weak, poor	2 = Weak or has bite	3 = Absent	= _____	
Moro	0 = complete	1 = partial response, low threshold to elicit	2 = Incomplete	3 = Absent	= _____	_____
6. AUTONOMIC SYSTEM						Code highest level
Pupils	0 = In dark: 2.5 to 4.5 mm/In light: 1.5 to 2.5 mm	1 = Mydriasis	2 = Constricted	3 = Deviation/dilated/non-reactive to light	= _____	
Heart rate	0= 100 to 160 bpm	1 = Tachycardia (>160 bpm)	2 = Bradycardia	3 = Variable HR	= _____	_____ _____
Respiration	0 = regular respirations	1 = Hyperventilation (RR>60/m)	2 = Periodic breathing	3 = Apnea or requires ventilator 3a=on vent with spont breaths 3b=on vent without spont breaths	= _____	(If vent, code a or b)

1. Total # Categories should be NO MORE THAN 6 Total (Count Only the Highest Level in each sign)
#_____Normal # Mild #_____Moderate #_____Severe

2. Are there signs of HIE in at least 2 of the 6 categories above? Y N (circle one)

If yes, What is the Level of HIE? MILD MODERATE or SEVERE (circle one)

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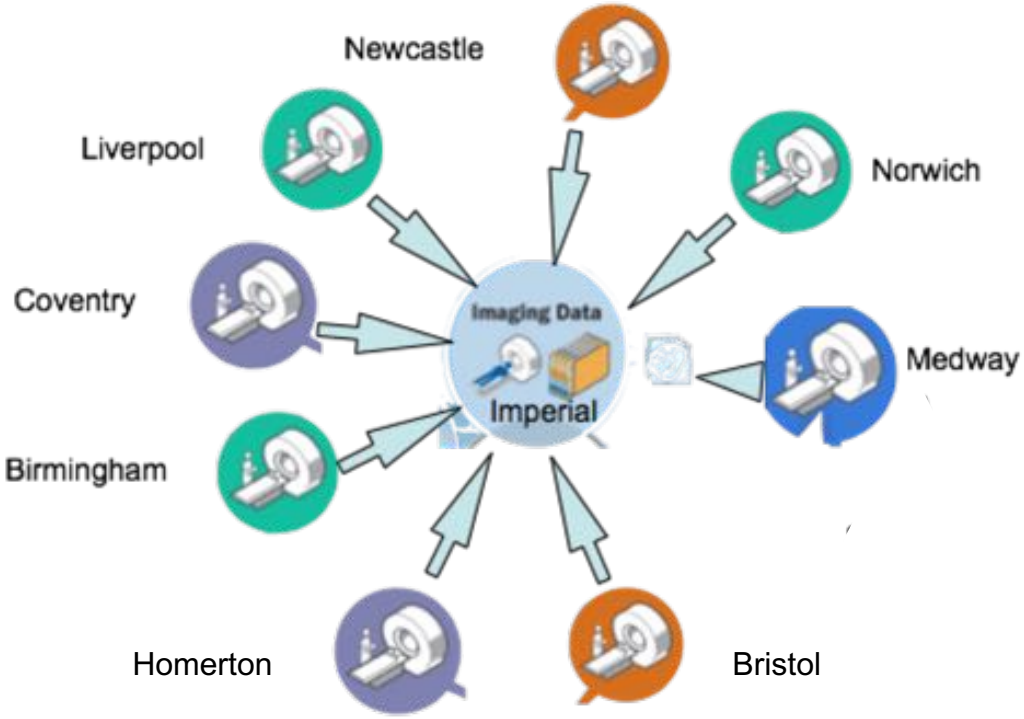
Exclusion criteria

- Babies without encephalopathy (i.e. less than 2 abnormal signs)
- Babies with moderate or severe encephalopathy who meet the current NICE/AAP guidelines for cooling therapy.
- Babies with seizures (clinical and/or aEEG/EEG)
- Babies with moderate or severe abnormalities on aEEG voltage criteria.
- Babies with life threatening congenital malformations

Seizures after enrollment

- Seizures aged < 6 h: Cooling for at-least 72 hours
- Analysis by intention to treat and per protocol
- Seizures after 6 h:
  - If in the cooled arm, give full 72 h cooling
  - If in the usual care, continue usual care (normothermia) or cool based on local policy

COMET feasibility study - centers



- Participating centers need to have 3T MRI and MR spectroscopy
- London Units can send babies to Imperial for 3T MRI and MRS

Total Recruitment: 32 babies

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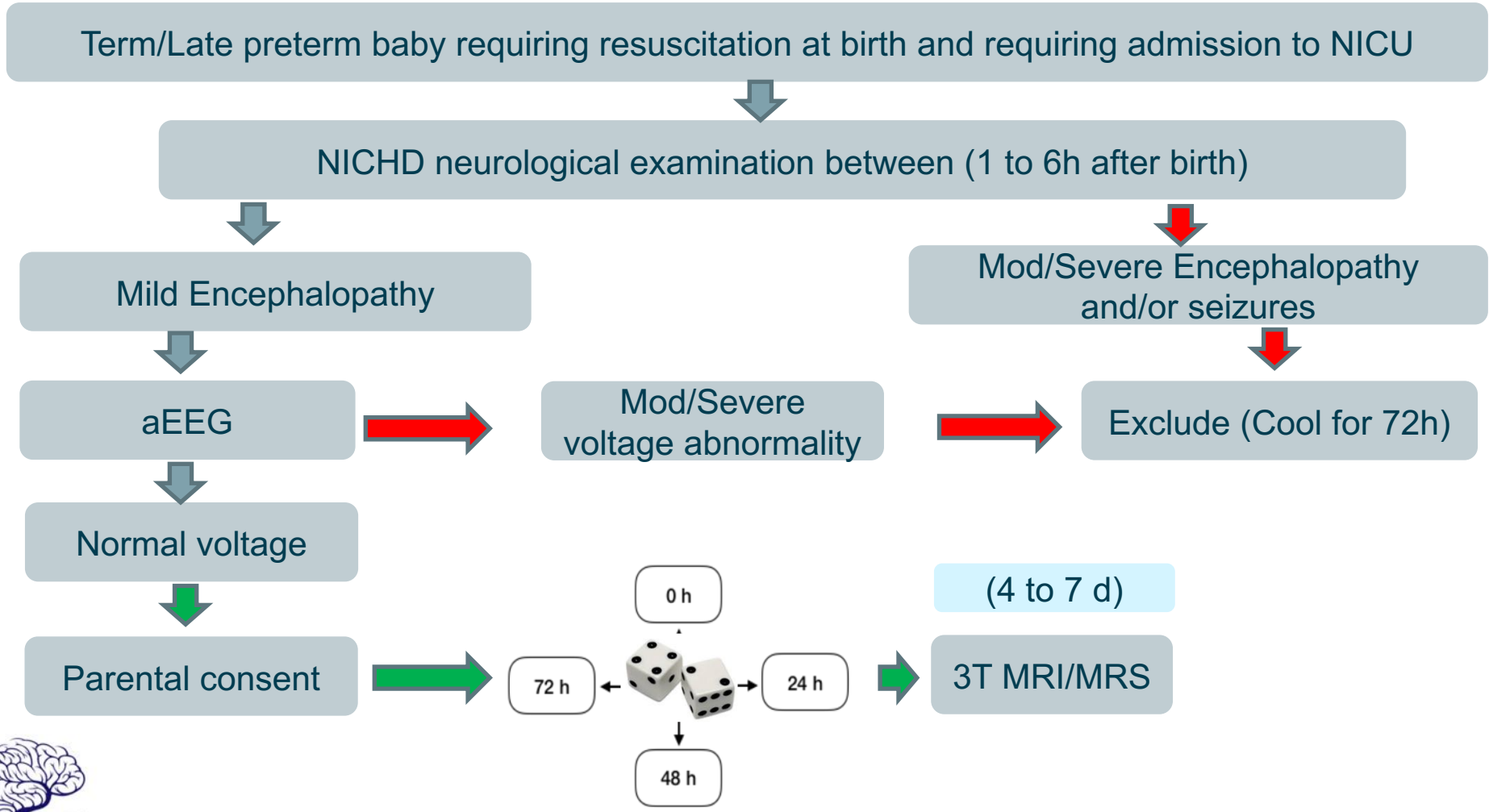
Study procedures



Study Website https://www.imperial.ac.uk/perinatal-neuroscience/current-research/

Cooling in Mild Neonatal Encephalopathy (COMET): (Funding NIHR)

Although cooling therapy is an established treatment for babies with moderate or severe neonatal encephalopathy, the risk benefits and optimal duration of this therapy for babies with encephalopathy is not known.

COMET trial uses a novel study design, with proton MR spectroscopy thalamic N-acetyl aspartate level, as the primary outcome measure. COMET is a sequential study that includes a *feasibility phase, phase II randomised controlled trial* to identify the 'optimal cooling duration', and then a *final confirmatory phase III clinical trial* to examine if cooling therapy at this optimal duration improves neurodevelopmental outcomes after mild encephalopathy.

Funding: National Institute of Health Research (UK), and Weston Garfield Foundation
Sponsor: Imperial College London

Cooling in Mild Encephalopathy (COMET) Trial: Protocol
Cooling in Mild Encephalopathy (COMET): Parent Information Sheet
Cooling in Mild Encephalopathy (COMET): REC Approval
Cooling in Mild Encephalopathy (COMET): HRA Approval

Cooling in Mild Encephalopathy (COMET) Trial: Case Report Form
Cooling in Mild Encephalopathy (COMET) Trial: Blood Collection SOP

Standard Operating Procedures 3T MRI

Click here to RANDOMISE

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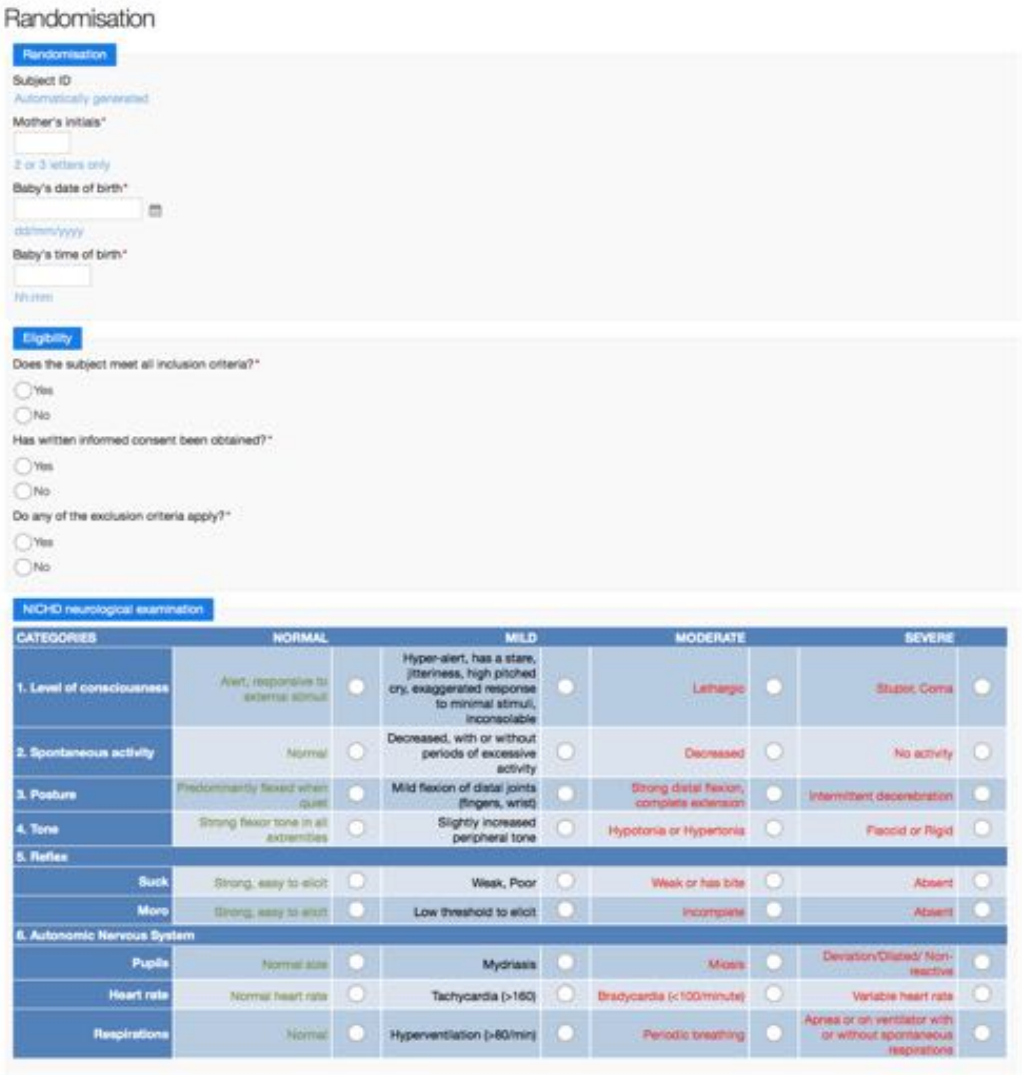
Randomisation



Randomisation

Randomisation

Subject ID
Automatically generated

Mother's initials*

2 or 3 letters only

Baby's date of birth*

dd/mm/yyyy

Baby's time of birth*

hh:mm

Eligibility

Does the subject meet all inclusion criteria?*
Yes
No

Has written informed consent been obtained?*
Yes
No

Do any of the exclusion criteria apply?*
Yes
No

NICHD neurological examination

CATEGORIES	NORMAL		MILD		MODERATE		SEVERE	
1. Level of consciousness	Alert, responsive to external stimuli		Hyper-alert, has a stare, jitteriness, high pitched cry, exaggerated response to minimal stimuli, inconsolable		Lethargic		Stupor, Coma	
2. Spontaneous activity	Normal		Decreased, with or without periods of excessive activity		Decreased		No activity	
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4. Tone	Strong flexor tone in all extremities		Slightly increased peripheral tone		Hypotonia or Hypertonia		Flaccid or Rigid	
5. Reflex								
Suck	Strong, easy to elicit		Weak, Poor		Weak or has bite		Absent	
Moro	Strong, easy to elicit		Low threshold to elicit		Incomplete		Absent	
6. Autonomic Nervous System								
Pupils	Normal size		Mydriasis		Miosis		Deviation/Dilated/ Non-reactive	
Heart rate	Normal heart rate		Tachycardia (>160)		Bradycardia (<100/minute)		Variable heart rate	
Respirations	Normal		Hyperventilation (>60/min)		Periodic breathing		Apnea or on ventilator with or without spontaneous respirations	

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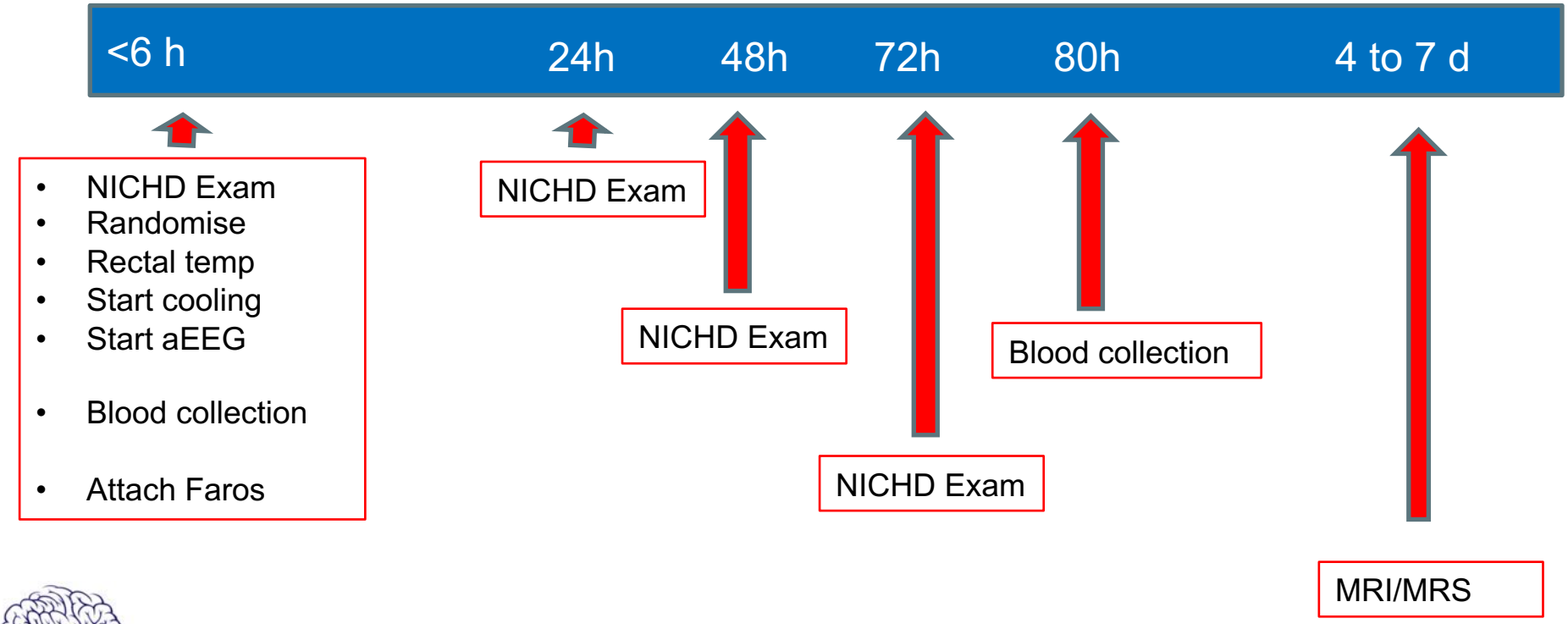
Study procedures



Temperature data collection

Group	Rectal temperature	Axilla temperature
Normothermia	Nil	4 hourly from 0 hours until 80 h
24 hours cooling	2 hourly until 36 hours	4 hourly from 36 hours until 80 h
48 hours cooling	2 hourly until 50 hours	4 hourly from 50 hours until 80 h
72 hours cooling	2 hourly until 80 hours	Nil

NB: In addition all cooling groups require temperatures at 0,1, and 2 hours, and usual care babies require axillary temperature at 0,1 and 2 hours

Other clinical data collection

Time since randomisation	Exact time (24h)	Rectal T (°C)	Axilla T (°C)	HR (bpm)	Shivering (Y/N)	NPAS score*	Morphine dose (mcg/kg/h)	Breathing support (V=Invasive ventilation; C=CPAP; O=Oxygen; N=None)
0 hour	Time of randomisation							
1 hour								
2 hours								
4 hours								
6 hours								
8 hours								
10 hours								

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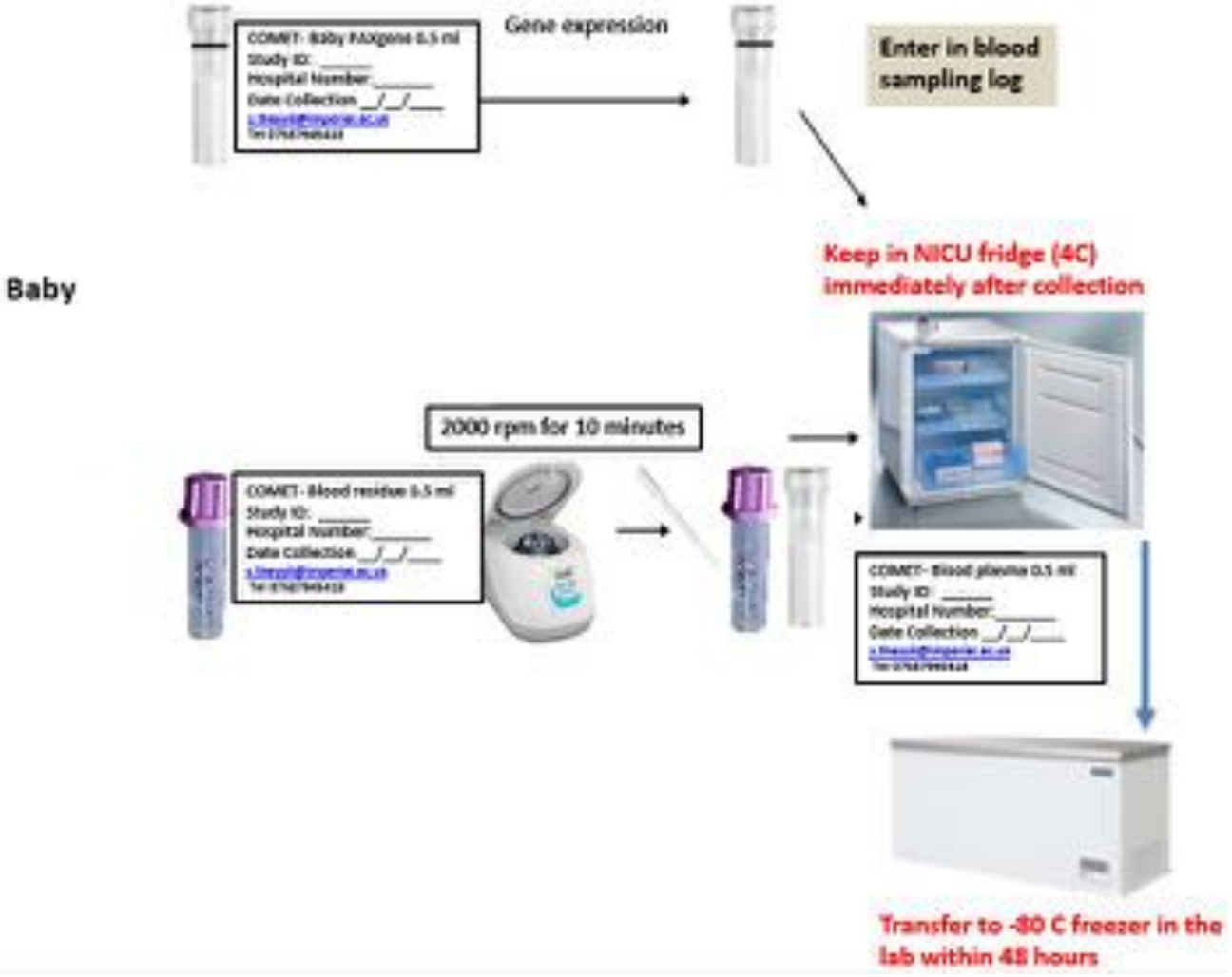
Blood collection



The COMET group

United Kingdom

- Imperial NHS Trust
- Medway NHS Hospital
- Birmingham Children's Hospital
- University Hospital of Coventry
- Norwich Hospital
- Liverpool Women's Hospital
- Newcastle Royal Infirmary
- St Michael's Bristol
- Homerton Hospital
- North Middlesex hospital
- Nottingham University Hospital
- University College London

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- Wayne State University