Optimising the duration of Cooling in Mild Neonatal Encephalopathy

Sudhin Thayyil

The COMET trial Group
Back ground
Cooling in moderate and severe encephalopathy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>Risk ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Infants with severe encephalopathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CoolCap</td>
<td>28</td>
<td>40</td>
<td>32</td>
<td>35</td>
<td>28.6</td>
</tr>
<tr>
<td>NICHD</td>
<td>23</td>
<td>32</td>
<td>34</td>
<td>40</td>
<td>25.4</td>
</tr>
<tr>
<td>TOBY</td>
<td>53</td>
<td>98</td>
<td>54</td>
<td>95</td>
<td>46.0</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>170</td>
<td></td>
<td>170</td>
<td></td>
<td>100.00</td>
</tr>
<tr>
<td>Total events</td>
<td>104</td>
<td></td>
<td>120</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 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                  |            |                     |                     |

Cooling vs. Usual care
Long term outcomes after mild encephalopathy

Adverse outcome in > 1/4

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

Wang et al., Neuroscience 2017
Cooling in mild encephalopathy: a meta-analysis

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

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Cooling Events</th>
<th>Cooling Total</th>
<th>Usual care Events</th>
<th>Usual care Total</th>
<th>Peto Odds Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Battin 2001 (SHC)</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>6</td>
<td>0.54 [0.04, 6.89]</td>
<td>2001</td>
</tr>
<tr>
<td>Wyatt 2007 (SHC)</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>6</td>
<td>2.26 [0.19, 27.57]</td>
<td>2007</td>
</tr>
<tr>
<td>Zhou 2010 (SHC)</td>
<td>1</td>
<td>21</td>
<td>1</td>
<td>18</td>
<td>0.85 [0.05, 14.27]</td>
<td>2010</td>
</tr>
<tr>
<td>Jacobs 2011 (WBC)</td>
<td>4</td>
<td>16</td>
<td>8</td>
<td>24</td>
<td>0.68 [0.17, 2.65]</td>
<td>2011</td>
</tr>
<tr>
<td>Lally 2013 (WBC)</td>
<td>4</td>
<td>9</td>
<td>2</td>
<td>10</td>
<td>2.92 [0.44, 19.25]</td>
<td>2013</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>12</td>
<td>57</td>
<td>14</td>
<td>64</td>
<td>1.09 [0.45, 2.66]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 2.16, df = 4 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.19 (P = 0.85)

Kariholu et al., PAS 2018
Cooling in Mild Encephalopathy – National Survey

Do not offer cooling

25% of the cooling centers

Offer cooling

75% of the cooling centres

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

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

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)

- 72 h
- 0 h
- Mild HIE
- 24 h
- 48 h

B. Phase II trial

Thalamic [NAA]

- Duration of cooling

C. Phase III trial

(Confirmatory phase)

- 0 h
- Vs
- "X" h

N=32

N=200

N=1200
COMET Trial design

A. Feasibility
(Learning and exploratory phase)

B. Phase II trial

C. Phase III trial
(Confirmatory phase)

N=32
N=200
N=1200
COMET Trial design

A. Feasibility

B. Phase II trial

C. Phase III trial

(Learning and exploratory phase)

Duration of cooling

N=32

N=200

N=1200
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

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

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

- 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
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

<table>
<thead>
<tr>
<th>Gold standard examiner</th>
<th>Name:</th>
<th>Date of exam:</th>
<th>Time of exam:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinician desiring to be certified</td>
<td>Name:</td>
<td>Date of exam:</td>
<td>Time of exam:</td>
</tr>
</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>NORMAL</th>
<th>MILD HIE</th>
<th>MODERATE HIE</th>
<th>SEVERE HIE</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEVEL OF CONSCIOUSNESS</td>
<td>0 = Alert and responsive</td>
<td>1 = Hyperalert (jitter)</td>
<td>2 = Lethargic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SPONTANEOUS ACTIVITY</th>
<th>NORMAL or decreased</th>
<th>Decreased activity</th>
<th>No activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>POSTURE</td>
<td>Predominantly flexed</td>
<td>Mild flexion of distal joints</td>
<td>Distal flexion, complete extension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TONE</th>
<th>Normal or slightly increased flexor tone</th>
<th>Hypotonia (focal or general)</th>
<th>Flaccid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2b = Hypotonia</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PRIMITIVE REFLEXES</th>
<th>Suck</th>
<th>Moro</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 = Strong, easily elicited</td>
<td>0 = Complete</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AUTONOMIC SYSTEM</th>
<th>Pupils</th>
<th>Heart rate</th>
<th>Respiration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In dark: 2.5 to 4.5 mm in light: 1.8 to 2.5 mm</td>
<td>100 to 160 bpm</td>
<td>Regular respirations</td>
</tr>
</tbody>
</table>

### Signs of HIE in Each Category

- **Normal**
- **Mild HIE**
- **Moderate HIE**
- **Severe HIE**

### Your Determination:

#### Total # Categories should be NO MORE THAN 6 Total (Count Only the Highest Level in each sign)

- # Normal
- # Mild
- # Moderate
- # Severe

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

- MILD
- MODERATE
- SEVERE (circle one)
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

Total Recruitment: 32 babies

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

Term/Late preterm baby requiring resuscitation at birth and requiring admission to NICU

NICHD neurological examination between (1 to 6h after birth)

Mild Encephalopathy

aEEG

Normal voltage

Parental consent

Mod/Severe Encephalopathy and/or seizures

Exclude (Cool for 72h)

Mod/Severe voltage abnormality

(4 to 7 d)

3T MRI/MRS

Normal voltage

(24 h)

48 h

72 h
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
## Randomisation

### Randomisation

**Subject ID**
- Automatically generated

**Mother's initials**
- 2 or 3 letters only

**Baby's date of birth**

**Baby's time of birth**

### 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

### NICHQ Neurological Examination

<table>
<thead>
<tr>
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<th>MILD</th>
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<tbody>
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<tr>
<td>Posture</td>
<td>Predominantly flexed when quiet</td>
<td>Mild flexion of distal joints (fingers, wrist)</td>
<td>Strong distal flexion, complete extension</td>
<td>Intermittent desynchronization</td>
</tr>
<tr>
<td>Tone</td>
<td>Strong, normal tone in all extremities</td>
<td>Slightly increased peripheral tone</td>
<td>Hypotonia or Hyperreflexia</td>
<td>Fascicul or Rigid</td>
</tr>
<tr>
<td>Reflex</td>
<td>Normal</td>
<td>Weak, Poor</td>
<td>Weak or has bite</td>
<td>Absent</td>
</tr>
<tr>
<td>Motor</td>
<td>Normal</td>
<td>Strong, easy to elicit</td>
<td>Low threshold to elicit</td>
<td>Incomplete</td>
</tr>
<tr>
<td>Autonomic Nervous System</td>
<td>Normal</td>
<td>Mydriasis</td>
<td>Miosis</td>
<td>Deviation/Dilatation/Non-reactive</td>
</tr>
</tbody>
</table>

**Pupils**
- Normal size

**Heart rate**
- Normal heart rate

**Respirations**
- Normal
Study procedures

- NICHD Exam
- Randomise
- Rectal temp
- Start cooling
- Start aEEG
- Blood collection
- Attach Faros

- NICHD Exam
- Blood collection
- MRI/MRS
# Temperature data collection

<table>
<thead>
<tr>
<th>Group</th>
<th>Rectal temperature</th>
<th>Axilla temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normothermia</td>
<td>Nil</td>
<td>4 hourly from 0 hours until 80 h</td>
</tr>
<tr>
<td>24 hours cooling</td>
<td>2 hourly until 36 hours</td>
<td>4 hourly from 36 hours until 80 h</td>
</tr>
<tr>
<td>48 hours cooling</td>
<td>2 hourly until 50 hours</td>
<td>4 hourly from 50 hours until 80 h</td>
</tr>
<tr>
<td>72 hours cooling</td>
<td>2 hourly until 80 hours</td>
<td>Nil</td>
</tr>
</tbody>
</table>

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

Baby

Gene expression

Enter in blood sampling log

Keep in NICU fridge (4°C) immediately after collection

2000 rpm for 10 minutes

Transfer to -80°C freezer in the lab within 48 hours
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

USA
- Wayne State University