Brigham and Women's Hospital
Founding Member, Mass General Brigham

Manual of Brigham Infant Brain Studies (BIBS)

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HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Table of Contents

- Meet the Team — 3
- Overview of Studies — 4-5
- Individual Study Summaries
  - Neuroimaging Studies
    - Preterm Serial Imaging Study — 6-8
    - Serial MRI for TH and Healthy Controls — 9-10
    - Tecotherm MRI in HIE Study — 11-12
  - Neuromonitoring Studies
    - Auditory Exposures (LENA) Study — 13-14
    - DCS Monitoring in Preterm Infants — 15-16
    - TCOM Monitoring in HIE — 17
    - Evaluating Inter-rater Variability of a Standard Clinical Neurological Exam for Neonatal Encephalopathy with Video-Taping — 18
    - Preemie Multimodal Monitor Study — 19
  - Registries and Retrospective Cohorts
    - CRICO Registry — 20
    - BWH NE Retrospective Cohort
      - Cooling Database — 21
      - Evaluated Non-Cooled Database — 22
    - BWH ELGA Retrospective Cohort — 23

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Founding Member, Mass General Brigham

Department of Pediatric Newborn Medicine: Manual of Neuroscience Studies

BRIGHAM INFANT BRAIN STUDIES BIBS

Meet the Team

Principal Investigators



Mohamed El-Dib
mel-dib@bwh.harvard.edu



Carmina Erdei
cerdei@bwh.harvard.edu



Terrie Inder
tinder@bwh.harvard.edu

Research Managers



Liz Singh
esingh@bwh.harvard.edu



Yvonne Sheldon
ysheldon@bwh.harvard.edu



Hoda El-Shibiny
helshibiny@bwh.harvard.edu

Research Nurses



Tina Steele
tdufresne@bwh.harvard.edu



Debbie Cuddyer
Dcuddyer@bwh.harvard.edu

Neonatal Neurology Research Fellows



Sriya Roychaudhuri
sroychaudhuri@bwh.harvard.edu



Seh-Hyun Kim
skim210@bwh.harvard.edu



Gabriel Cote Corriveau
gcotecorriveau@bwh.harvard.edu

Research Assistants



Katie Hannon
khannon3@bwh.harvard.edu



Danielle Sharon
dsharon1@bwh.harvard.edu



Yasemin Ersen
yersen@bwh.harvard.edu

Project Manager



Sylva Yeghiayan
syeghiayan@bwh.harvard.edu

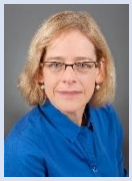
Collaborators



Mari Franceschini
MFRANCESCHINI@mgh.harvard.edu



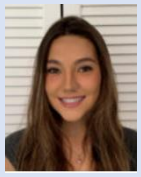
John Sunwoo
jsunwoo@mgh.harvard.edu



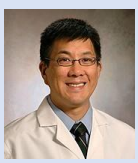
Ellen Grant
ellen.grant@childrens.harvard.edu



Emily Herzberg
eherzberg@mgh.harvard.edu



Alyssa Martin
Amartin46@mgh.harvard.edu



Edward Yang
edward.yang@childrens.harvard.edu

Overview of Studies

Preterm Serial Imaging Study

- PI: Carmina Erdei
- Study Contact: Danielle Sharon
- Aim: To identify and characterize any brain injury that occurs in the very preterm infant throughout their NICU course, as well as regular patterns of brain growth in this population.

Serial MRI for TH and Healthy Controls

- PI: Terrie Inder
- Study Contact: Yasemin Ersen
- Aim: To examine the effects of neonatal encephalopathy on infant brain and neurobehavioral development over the first year of life. The goal of this phase is to develop and pilot a neonatal MRI protocol to assess brain structure and connectivity

Tecotherm MRI in HIE

- PI: Mohamed El-Dib
- Study Contact: Yasemin Ersen, Sriya Roychaudhuri
- Aim: Serial MRI in infants during therapeutic hypothermia to better identify evolution of injury

Auditory Exposures (LENA) Study

- PI: Carmina Erdei
- Study Contacts: Yasemin Ersen
- Aim: To examine auditory environments in the NICU and to measure the various auditory exposures infants in the BWH NICU receive using sound recordings captured by the LENA device.

DCS Monitoring in Preterm Infants

- PIs: Mohamed El-Dib, Maria Franceschini, Terrie Inder
- Study Contacts: John Sunwoo, Alyssa Martin, Katie Hannon
- Aim: To assess cerebral blood flow monitoring and its correlation to IVH

TCOM Monitoring in HIE

- PI: Mohamed El-Dib
- Study Contact: Katie Hannon
- Aim: TCO2 monitoring in TH to evaluate hypo/ hypercapnia

Evaluating Inter-rater Variability of a Standard Clinical Neurological Exam for Neonatal Encephalopathy with Video-Taping

- PI: Mohamed El-Dib
- Study Contact: Katie Hannon, Sriya Roychaudhuri
- Aim: Assess the inter-observer agreement of the standard neurological assessment of NE among infants with various neurological states. Development of an educational tool for standard NE assessment

Preemie Multimodal Monitor Study

- PI: Mohamed El-Dib
- Study Contact: Katie Hannon, Seh-Hyun Kim
- Aim To evaluate if the physiological data collected clinically and continuously during the first week of life is predictive of brain injury in infants born < 29 weeks gestation

CRICO Registry

- PI: Mohamed El-Dib, Terrie Inder
- Study Contact: Hoda El-Shibiny
- Aim: The CRICO NE Registry collected data (detailed demographic and clinical) on neonates either evaluated for therapeutic hypothermia (TH) or those who received TH in 14 participating centers starting April 15, 2018. Upon data analysis, we have noted several areas of improvement in both implementation of therapy, safety of related care and avoidance of risks from TH

BWH NE Retrospective Cohort

- PI: Mohamed El-Dib
- Study Contact: Hoda El-Shibiny
  Aim: - To identify the outcomes of infants with mild encephalopathy who received hypothermia therapy and compare these to the outcomes of infants with moderate/severe encephalopathy who underwent the same therapy. To analyze outcomes of therapeutic hypothermia based upon gestational age. To analyze the outcomes of therapeutic hypothermia based upon cooling time and cooling method.

BWH ELGA Retrospective Cohort

- PI: Mohamed El-Dib
- Study Contact: Hoda El-Shibiny
- Aim: This study aims at defining prenatal, perinatal and clinical factors associated with brain injury on HUS and abnormality in brain development as well as injury on TE MRI in preterm infants born at < 32 weeks GA and/or less than 1500 grams BW and admitted to BWH NICU. Identifying these factors could provide more information on neuroprotective interventions which can be utilized in this population.

Preterm Serial Imaging Study


Dr. Erdei


Dr. El-Dib


Danielle Sharon

Principle Investigator: Carmina Erdei, MD
Co-Investigators: Mohamed El-Dib, MD
Research Nurse: Voalte Research RN covering for day
Tina Steele | tdufresne@bwh.harvard.edu
Debbie Cuddyer dcuddyer@bwh.harvard.edu
Study Contacts: Danielle Sharon dsharon1@bwh.harvard.edu

Study Aim: The goal of this study is to identify and characterize any brain injury that occurs in the very preterm infant throughout their NICU course, as well as regular patterns of brain growth in this population. In addition, we aim to utilize early MRI to risk-stratify preterm infants and tailor rehabilitative interventions according to risk in order to explore associations between risk stratified NICU rehabilitative intervention and short- and long-term outcomes.

Specific Aims:

1. Use serial MRI to define the timing and factors associated with the key forms of brain injury in the preterm infant during the NICU stay, including intraventricular hemorrhage, white matter abnormality, and cerebellar hemorrhage.
2. Define the pattern of brain growth during the NICU stay and the factors influencing the trajectory of total and regional brain growth.
3. Utilize early MRI to risk-stratify preterm infants into low-risk or high-risk groups, and tailor rehabilitative intervention for preterm infants according to their risk.
4. Explore preliminary associations between risk stratified NICU rehabilitative intervention and short- and long-term outcomes of preterm infants.

Inclusion Criteria:

1. Infants currently admitted to the BWH NICU
2. Infants born <33 weeks gestational age
3. Infants weighing 0.5-4.5 kg
4. Infants considered in stable condition per their clinical physician

Exclusion Criteria:

1. Infants with confirmed or suspected congenital anomaly or genetic syndrome
2. Infants with congenital infection

Study Design:

- Control Groups
    a. BWH standard of care developmental therapy – very preterms discharged from BWH NICU
- Low Risk Intervention Group (no neurological injury)
    a. Receiving developmental therapy throughout BWH NICU stay using SENSE framework
        i. Weekly intervention plan per the SENSE program, family education utilizing SENSE materials
- High Risk Intervention Group (neurological injury identified on serial imaging)
    a. Receiving more intensive developmental therapy in BWH NICU using SENSE-plus framework
        i. Enhanced rehabilitative support and targeted motor therapy at increased frequency
        ii. Enhanced reading with infant several times a week and video family education

Enrollment Procedure:

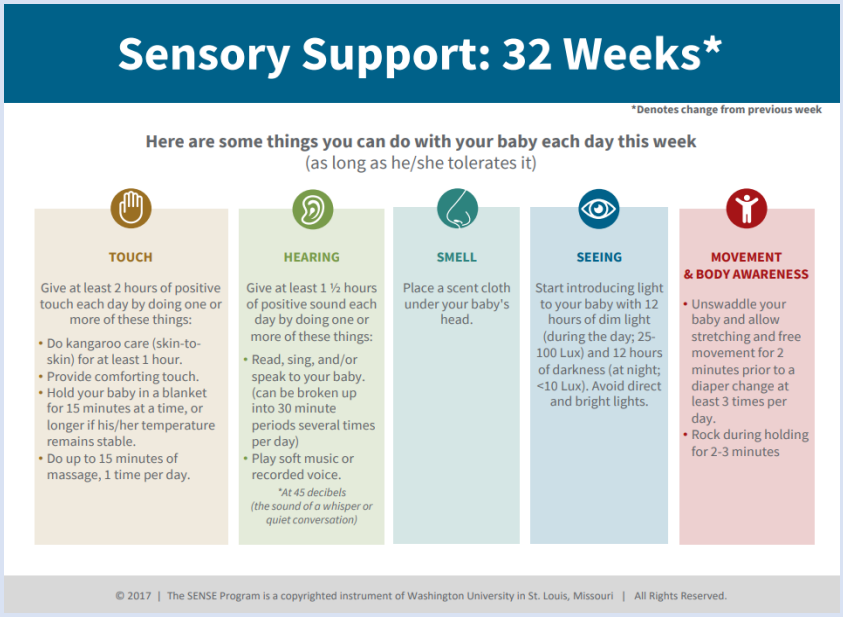
1. Plan to enroll up to 75 infants over 2 years: 50 "risk group" infants (25 "low-risk", 25 "high-risk" groups) and 25 control infants.
2. Parents or guardians of eligible infants will be approached and asked if they would be willing to participate and receive SENSE intervention and MRI in the BWH Aspect Embrace scanner a total of three times: 1st scan within first weeks of enrollment, 2nd scan at 34-36 wks. & 3rd/final scan at term equivalent age of 38-41 wks.
3. Babies who are approached to enroll, but do not consent, will be recruited as controls if receiving a clinically indicated term MRI. Alternatively, if babies are receiving a BTM term equivalent scan as part of another research study they may also be approached to be in control group. Babies not enrolled in the study will continue to receive our NICU developmental therapies as part of our standard of care.
4. Babies enrolled will be categorized into risk groups in which they receive weekly age-appropriate therapeutic exposures delivered by parents and the therapy team per SENSE or SENSE-plus protocols.

MRI procedure:

1. Early MRI or HUS risk stratifies babies into low risk" or "high risk"
2. All infants will be accompanied by an appropriately trained research nurse skilled in neonatal resuscitation and a respiratory therapist will accompany research team if infant is intubated or on CPAP.
3. The research nurse may need assistance from the bedside nurse in positioning the baby into the MRI bed and transporting to the Aspect suite.
4. Infants will be fed 30-60 minutes prior to the start of the scan unless NPO for clinical reasons.
5. The infants will be prepared for the MRI according to DPNM MRI guidelines.
6. Cardio-respiratory monitoring as well as continuous video monitoring will occur throughout the MRI scan.
7. Infants enrolled in this study will have their clinically indicated, term equivalent MRI at the BTM scanner and be accompanied by the research nurse.

SENSE Program: The Supporting and Enhancing NICU Sensory Experiences (SENSE) program was developed to engage and empower parents in consistently providing positive, developmentally appropriate sensory exposures to their infants in the NICU every day of hospitalization. The SENSE program scaffolds the amount of sensory intervention each baby should receive per week including specific doses and targeted timing (based on postmenstrual age) of evidence-based interventions of auditory, tactile, vestibular, kinesthetic, olfactory, and visual exposures to be conducted daily through hospitalization for preterm infants (see sample week plan below). The SENSE plus intervention is an enhanced version of the SENSE intervention in which feedback from the neurological examinations and/or MRIs will enhance the motor therapy provided for the infant. NICU therapy team will be providing education and support for parents and bedside logs will be used for families and staff to record sensory exposures. Parents will also have access to an App to record sensory inputs and access educational materials.
Risks: MRI is considered minimal risk. Infants will not be sedated but "Fed and Wrapped" for MRI, and the study will be stopped immediately if the infant shows any sign of stress or discomfort. Scans are read by a pediatric neuroradiologist and will go into the patient's medical record. Any incidental findings are discussed with the family and follow-up arranged.

Benefits: Because we are performing multiple MRIs, there is the possibility of discovering abnormal findings on one or more of the research studies. In the case that we do, the finding(s) may be caught earlier than if the infant had not received these research scans, leading to faster and possibly more effective interventions that can be tailored to help the child reach the best outcome. The overall potential benefit of this research is that the findings of this study have the potential to improve the detection and understanding of brain injury and brain growth so that we can better devise strategies to prevent injury and/or treat these preterm infants in the future.



Sensory Support: 32 Weeks*

*Denotes change from previous week

Here are some things you can do with your baby each day this week
(as long as he/she tolerates it)

TOUCH

Give at least 2 hours of positive touch each day by doing one or more of these things:

- Do kangaroo care (skin-to-skin) for at least 1 hour.
- Provide comforting touch.
- Hold your baby in a blanket for 15 minutes at a time, or longer if his/her temperature remains stable.
- Do up to 15 minutes of massage, 1 time per day.

HEARING

Give at least 1 ½ hours of positive sound each day by doing one or more of these things:

- Read, sing, and/or speak to your baby. (can be broken up into 30 minute periods several times per day)
- Play soft music or recorded voice.

*At 45 decibels (the sound of a whisper or quiet conversation)

SMELL

Place a scent cloth under your baby's head.

SEEING

Start introducing light to your baby with 12 hours of dim light (during the day; 25-100 Lux) and 12 hours of darkness (at night; <10 Lux). Avoid direct and bright lights.

MOVEMENT & BODY AWARENESS

- Unswaddle your baby and allow stretching and free movement for 2 minutes prior to a diaper change at least 3 times per day.
- Rock during holding for 2-3 minutes

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Serial MRI for TH and Healthy Controls


Dr. Inder


Yasemin Ersen

PI: Terrie Inder, MbChB, MD
Research Nurse(s): Tina Steele pager# 39895 tel: 617-525-7376
email: tdufresne@bwh.harvard.edu
Liz Singh email: esingh@bwh.harvard.edu
Study Contacts: Yasemin Ersen | Email: yersen@bwh.harvard.edu

Study Aim: The overall goal of this study is to examine the effects of neonatal encephalopathy on infant brain and neurobehavioral development over the first year of life. This goal is to assess brain structure and connectivity in the un-sedated infant using serial MRI within the setting of the 3T Prisma scanner in the Building of Transformative Medicine (BTM) building of Brigham and Women's Hospital.

Specific Aims:

1. To define the nature of the temporal evolution of a perinatal ischemic brain injury, including its secondary impact on brain development, in term-born infants with HIE receiving therapeutic hypothermia compared to typical control infants.
2. To define the relationships between perinatal ischemic brain injury, subsequent cerebral development and neurodevelopmental outcome at 12 months of age.

Enrollment Procedure: Plan to enroll 68 infants into 3 groups:
1) 24 infants undergoing 72 hrs of Therapeutic Hypothermia in BWH NICU (TH group)
2) 24 infants that are healthy controls located on BWH postpartum units (Control group 1)
3) 20 infants that are healthy plus controls located on BWH postpartum units (Control group 2)

Inclusion Criteria:

TH group

1. Infants undergoing 72 hrs therapeutic hypothermia in BWH NICU
2. Evidence of brain injury on initial clinical MRI (typically day 2-4)

Control Group 1

1. Infant born ≥ 38 weeks gestation and 2) delivered by uncomplicated non-instrumental birth by vaginal or cesarean section (excluding emergency delivery).
3. No sentinel event prior to delivery.

Control Group 2

1. Infant born ≥ 38 weeks gestation and 2) delivered by uncomplicated non-instrumental birth by cesarean section (excluding emergency delivery).
3. No sentinel event prior to delivery.

Exclusion Criteria: Infant's parents unable to complete the consent form in English or Spanish, maternal age <18 years

TH group

1. Infants with severe congenital anomalies, genetic or metabolic syndromes.
2. Infants with need for extracorporeal membrane oxygenation.

Control Group 1

1. Delivery by instrumental or emergency cesarean section.
2. Congenital anomaly, genetic or metabolic syndrome if known.
3. Significant resuscitation required at delivery (any PPV or CPR).
4. 5-minute Apgar score ≤7 or blood gas pH <7.15 and BE ≤- 5mEq/L.

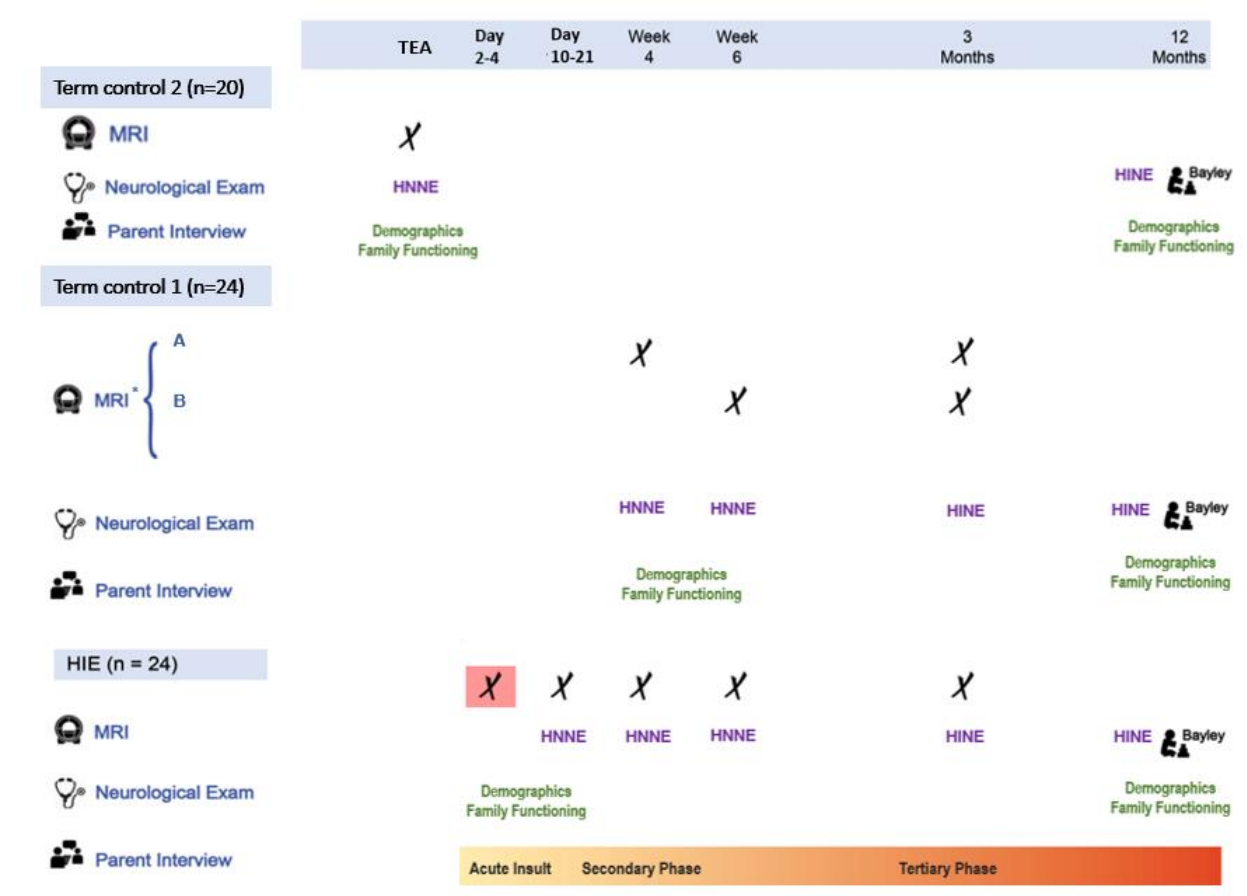
Control Group 2

1. Maternal illness or medications.
2. Any resuscitation required at delivery.
3. NICU hospitalization.
4. Delivery by vaginal delivery, instrumental or emergency cesarean section.
5. Congenital anomaly, genetic or metabolic syndrome if known.

Risks: MRI is considered minimal risk, infants will not be sedated but "Fed and Wrapped" for MRI and study will be stopped immediately if the infant shows any sign of stress or discomfort or if the parents request it. Scans are read by a pediatric neuroradiologist - any incidental findings discussed with family & follow-up arranged.

MRI procedure: (See diagram below for timetable)

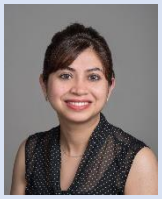
1) TH group infants will be scanned in the BTM building 3T Prisma scanner at up to 5 time points.
2) Control group 1 infants will be scanned at 2 time points that align with TH group and control group 2 infants will be scanned once at term equivalent age before discharge.
3) All infants will be accompanied by an appropriately trained investigator or research nurse skilled in neonatal resuscitation. They will be monitored with continuous cardio-respiratory monitoring through-out the time in the MRI scanner.
4) Along with each scan, infants will receive a neurodevelopmental evaluation. The Hammersmith Neonatal Neurological Examination (HNNE) will be used through the first 6 weeks, and the Hammersmith Infant Neurological Examination (HINE) will be used for the subsequent timepoints. At 12 months of age, the Bayley Scales of Infant Development will be administered.
5) Infants in the TH group will be recruited after confirmation of presence of brain injury on their first clinical MRI (day 2-4). These infants will have their second clinical MRI (day 10-14) at the BTM scanner and be accompanied by the research nurse.
6) Any TH group infant not clinically stable to transport to BTM will be scanned in Aspect.



Timetable of MRI scans in both Healthy Control and HIE Groups

Tecotherm MRI in HIE


Dr. El-Dib


Sriya Roychaudhuri


Yasemin Ersen

Research Nurse(s): Tina Steele tel: 617-525-7376
Email: tdufresne@bwh.harvard.edu
Debbie Cuddyer: dcuddyer@bwh.harvard.edu
Liz Singh: esingh@bwh.harvard.edu
Yvonne Sheldon: ysheldon@bwh.harvard.edu
Please Voalte the research nurse covering for the day with any immediate questions!
Study Contacts: Yasemin Ersen | Email: yersen@bwh.harvard.edu

Study Aim: The overall aim of this study is to assess the nature and timing of brain injury in the infant undergoing TH using early serial MRI within the setting of the 1T Aspect Embrace Neonatal MRI scanner in the NICU. The goal is to scan babies undergoing TH over 4 time points within the first 4 days of life. The first scan ideally will occur within the first 24 hours of life, the second scan on day of life 2, the third scan on day of life 3 and the fourth standard **clinically indicated** scan on day of life 4, after re-warming (this last DOL4 scan will be attended by NICU RN).

Specific Aims:

1. To understand the nature and timing of brain injury in infants who are undergoing therapeutic hypothermia.
2. To look at the evolution of brain injury while infants are actively undergoing therapeutic hypothermia.

Enrollment Procedure: Plan to enroll and scan up to 25 infants over the course of 2 years. Per department standard operating procedure, a research nurse or investigator will do an initial approach for research participation. Then, parent(s) will be approached by a research study team member responsible for recruitment of subjects. Due to the time sensitive nature of this study, families may be approached within the infant's first day of life.

Inclusion Criteria:

I. Infants with neonatal encephalopathy undergoing therapeutic hypothermia based on BWH clinical practice guidelines
II. Infants considered in stable condition per their clinical physician.

Exclusion Criteria:

I. Infants with two or more confirmed or suspected congenital anomaly or genetic syndrome.
II. Infants with congenital TORCH infections.
III. Mother < 18 years of age.

Risks: MRI is considered minimal risk; infants are not sedated for purpose of obtaining MRI but infants **are** on sedation per therapeutic hypothermia clinical guideline and therefore would be for 1st 3 daily research scans and would be "Fed and Wrapped" for the 4th clinically indicated MRI after rewarming. Any infant showing signs of stress or discomfort and unable to be consoled would have their scan stopped. Scans are read by a pediatric neuroradiologist - any incidental findings discussed with family & follow-up arranged. There is a potential risk associated with placing/removing rectal probes which is necessary to switch to MRI compatible probe for temperature monitoring. This is done in accordance with DPNM guideline and done by a trained research nurse. MRI compatible EEG leads (FDA approved for a 1.5T and 3T scanner but not for the 1T scanner) will remain on the baby's head for the research MRI but the EEG is unable to be monitored – therefore, seizure detection will be unavailable during scan. Infant will remain on CRM/pulse oximetry and face visible via camera in Aspect scanner.

Benefits: There is no expected direct benefit for infants taking part in this study. The overall potential benefit of this research will be increasing knowledge about the nature, timing, and evolution of brain injury among babies actively undergoing cooling protocol, something we don't know much about. This may also provide information to assist with new therapies alongside TH.



The Tecotherm Cooling Blanket is MRI safe, has an extended tubing that is long enough to use with Aspect yet has a small footprint, and will be set up by research team in the NICU MRI suite

MRI procedure: (See diagram below for timetable)

7) Infants will be scanned in the Aspect scanner daily up until day of life 4 (pending clinical stability) when they receive their standard clinical MRI after re-warming. The NICU RN caring for the infant will attend the clinically indicated 4th scan after rewarming. Not every infant may receive all 4 scans depending upon when born and consented.
8) Infants will remain under cooling protocol using the Tecotherm cooling blanket for the duration of the MRI scan.
    a. This is an FDA approved cooling blanket that is used by transport teams on outpatient born infants
9) All infants will be accompanied by an appropriately trained investigator or research nurse skilled in neonatal resuscitation. For the purposes of this study, a neonatologist or experienced neonatal fellow or nurse practitioner will always accompany infants to scanner as well as a member of research team and respiratory therapist, if needed for infants on respiratory support. Infants will be monitored with continuous cardio-respiratory monitoring through-out the time in the MRI scanner.

PRIOR TO MRI – After below steps-Infant will be transported to Aspect MRI suite in transport isolette that is off- will not be actively cooling for the very brief trip from bedside to scanner.

1) Ensure HC is <38cm (with cEEG leads on) and weight is <4.5kg. for Aspect scanner
2) Tecotherm blanket will be set up and cooled to target temperature of 33.5. and placed in Aspect MRI bed (@ set temp of 25°C- lowest temp to operate bed).
3) Any ferrous containing equipment will be removed prior to MRI this includes: skin temp probe and cover, aEEG leads (gel or needle), rectal probe for Criticool (not MRI compatible), NIRS, TCOM, CRM leads, and pulse oximeter (may remain on for transport).
4) cEEG leads may remain on but need to be disconnected from monitoring cable at connection (see picture) BCH team will be notified of pause in monitoring during MRI.



5) Per MRI CPG infants will have ear protection with ear plugs & Mini-muffs, MRI safe pulse oximeter and ECG leads then will be wrapped in the Tecotherm blanket to maintain cooling as this blanket is MRI compatible.
6) MRI compatible, lubricated rectal probe will be inserted 4-6cm and secured to thigh. This is to ensure that infant temperature can be monitored during scan time and Tecotherm blanket will adjust to maintain target of 33.5 degrees Celsius.
7) IV fluids can remain running for scan, pumps are safe outside scanner, arterial lines (if present) need to be run through MR safe transducer.

DURING MRI

1) Document heartrate, oxygen level, and rectal temperature every **10 minutes** in Epic
2) Adjust Tecotherm temperature as needed for any temperature fluctuation
3) Research nurse practitioner or fellow/attending must remain present for duration of scan

AFTER MRI

1) Remove Invivo rectal temperature probe
2) Remove earplugs/earmuffs, headband, pulse ox, and MRI compatible EKG leads
    a. Put fresh set of EKG leads and pulse ox on baby for transport
    b. Keep MRI supplies in bag with patient label for use on daily research scans
3) Remove infant from Tecotherm cooling blanket and place in transport isolette.
4) Transport baby back to NICU room- RT will be present if on respiratory support.
5) Bedside Nurse will be responsible for placing on Criticool and reapplying:
    a. NIRS, aEEG, re-inserting Criticool rectal probe,
    b. Switch Critcool back to servo mode from manual mode
6) Respiratory Therapist will replace TCOM if applicable and transition to bedside equipment as needed
7) Research RN will:
    a. Reconnect cEEG leads and notify BCH EEG team that monitoring is resuming
    b. Document rectal temp after transfer back to Criticool

	Enrollment	DOL 1	DOL 2	DOL 3	DOL 4	12-24 mon.
MRI		✗	✗	✗	✗	
Neurological Exam						HINE Bayley
Parent Interview	Demographics Family Functioning					Demographics Family Functioning

Auditory Exposures (LENA) Study


Dr. Erdei


Yasemin Ersen

Research Nurse(s): Tina Steele pager# 39895
tdufresne@bwh.harvard.edu
Office Tel: 617-525-7376 Please Voalte
Debbie Cuddyer dcuddyer@bwh.harvard.edu
office #: 617-525-4129
Study Contacts: Yasemin Ersen yersen@bwh.harvard.edu
Carmina Erdei cerdei@bwh.harvard.edu

Study Aim: This study seeks to examine auditory environments in the NICU and to measure the various auditory exposures infants in the BWH NICU receive using sound recordings captured by the LENA device.

Specific Aims:

1. To understand and quantify the current auditory levels for infants in the NICU in the context of COVID-19 pandemic.

Hypothesis:

1. Infants typically receive varying forms of auditory exposure throughout their NICU stay.
2. Infants in the BWH NICU will be exposed to similar distributions of negative auditory experiences (alarm noise, mechanical noise etc.), silence, and human voice as other published literature.

Inclusion Criteria:

1. Infants currently admitted to the BHW NICU
2. Infants born at <33 weeks GA and currently ≥30 weeks CGA

Exclusion Criteria:

1. Mother < 18 years of age
2. Planning on transfer and unable to complete approximately 6 weeks of measures

Enrollment Procedure:

1. We are planning to enroll 20 infants in this pilot study
2. Families of infants meeting the inclusion criteria will be approached to participate in the study for approximately 6 weeks- 1 auditory exposure (LENA) recording per week (up to 16hrs) with ideal goal of 6 interventions total

Study Procedure:

1. Study team will place Lena in the incubator or crib of enrolled infant
    a. Lena will be sanitized in between use and just before placing in bed
    b. Lena will be placed in a plastic bag and affixed to bed using tape
2. Lena records auditory exposures for 16 hrs- research team will retrieve it next day to download the auditory exposure info onto a specific software
3. Study team will vary the days of week and times slightly to capture variation over days of week
4. Data collected: basic clinical data including infant gestational age at birth, corrected gestational age at time of measurement, NICU outcomes, setting of recording (crib/isolette), and weight.

Risks: There are no specific risks or discomforts related to the use of the LENA device for research purposes in enrolled infants. As with any participation in a research study, there is a small, potential risk of breach of confidentiality. To minimize this risk, randomly assigned study codes will be given to each subject**.**

Benefits: There is no expected direct benefit for infants taking part in this study. The overall potential benefit of this research will be increasing knowledge about the auditory exposures infants receive during their NICU stay which can inform future auditory interventions.



- Lena will be placed in incubator/crib (sanitized and contained inside a new bag before each use) and secured with tape to side of bed by research team once weekly for 6 weeks and collected the next day for download
- The LENA device records information and then the software used to download it translates it into info about it (see below example.)

Example of auditory exposures data in our NICU:

Measures	Percent Range
Meaningful Language	4.03-7.07%
Distant Language	9.90-21.15%
Electronic Noise	11.49-23.23%
Background Noise	7.08-30.52%
Silence	35.04-59.39%

- Does recording infringe on privacy? **No**
  - Audio recordings are automatically deleted immediately after software processing into data (number of adult words, conversational turns, electronic sounds, silence, etc.).
  - The ***recorder has <u>no</u> playback*** capability and the system doesn't recognize the meanings of words so no one will know what was said during the auditory measurement.

DCS Monitoring in Preterm Infants






Dr. El-Dib Dr. Franceschini John Sunwoo Alyssa Martin

PI: Mohamed El-Dib, MD
Co-investigators: Maria Angela Franceschini, Ph.D. (MGH), Terrie Inder, MbChB, MD
Study Contacts: John Sunwoo // jsunwoo@mgh.harvard.edu
Alyssa Martin// amartin46@mgh.harvard.edu
Research Nurse(s): Tina Steele Tel: 617-525-7376 Email: tdufresne@bwh.harvard.edu
Debbie Cuddyer email: dcuddyer@bwh.harvard.edu Yvonne Sheldon email:ysheldon@bwh.harvard.edu

Study Aim: We wish to establish a new NIRS device, diffuse correlation spectroscopy (DCS), as a safe, noninvasive and informative bedside tool for assessing and monitoring brain health in ELGA (<29 weeks gestational age) infants during the first few days of life.

1. To test the feasibility of DCS (Diffuse Correlation Spectroscopy) to monitor cerebral activity, perfusion and oxygen consumption in extremely premature infants during the first week of life.
2. To assess if these baseline values are impacted by intermittent hypoxic episodes.
3. To assess if cerebral blood flow disturbances correlate with incidence of intraventricular hemorrhage.
4. Correlate the DCS findings with clinical outcome at hospital discharge.

Inclusion Criteria:
Older infant's group, 30-35 weeks GA preemies (n=12)
Stable premature infants born 30-35 weeks GA and are <48 hrs of age.
ELGA group, ≤ 29 weeks GA preemies (n=100)
Premature infants born at ≤ 29 weeks GA and are <48 hrs of age.
Exclusion Criteria:
If there are contraindications to NIRS optical sensor placement on the scalp, major congenital anomalies, or complex cyanotic congenital cardiac disease in either inclusion group.

Risks: There is no more than minimal risk to infants from the monitoring device- it is non-invasive and attached with hydrogel. The site is repositioned and skin integrity checked with cares to ensure no irritation occurs.
Benefits: There will be no direct benefit to infants participating in this study. However, we hope that, in the future, the DCS monitoring will allow us to gain insight into the relationship between cerebral blood flow and the cause of IVH in the premature brain.

Additional Labs/Procedures: DCS continuous measurement for up to 72 hours. When available, we will also monitor enrolled infants with aEEG and FDNIRS. The aEEG leads are currently used in NICU for clinical care and the FDNIRS handheld probe is currently used in research. Depending on availability of the FDNIRS device and access to the infant, every 4 to 12 hrs., we will perform FDNIRS measurements by using a hand–held optical sensor. **Bedside nurse will need to reposition DCS probe and 2nd pulse oximeter every 3-4 hrs for skin care. DCS probe is applied with hydrogel and can be secured with headband or CPAP hat. (See reverse side for positioning and securing tips)

Information for Nurses Caring for babies enrolled in DCS study

- DCS probe should be repositioned every 3-4 hrs with care times



DSC monitor

- Extra study pulse oximeter is needed to record data to study laptop and can also be repositioned with cares
- If the baby is not visible to the research assistant, they will use a baby monitor camera to stream (not record) video only, no voice (it is inactivated) to ensure the probe is positioned appropriately



Positioning Tips: Cavilon may also help with securing the probe and while still being safe for baby's skin whether intubated or on CPAP

If infant is intubated: Probe can to be positioned with the hydrogel and secured with a piece of Mepitel™ tape- it can be positioned with the NIRS probe with each probe moved a bit to the side of the head. Depending upon the GA of baby and how much they are moving- the Mepitel™ may not be needed. A headband made with a baby hat can also help secure both devices as is often done with our clinical NIRS monitoring.



DCS sensor on Preemie Annie doll- headband can be used to secure



Side view of probe under CPAP hat, wires should be secure to hat using silk tape

If infant is on CPAP: The probe can be positioned under the CPAP hat but should not be under the sponge in middle of forehead to prevent pressure from being applied. The wires can be secured to the hat to prevent them from moving and prevent the baby from grabbing them.

DCS probe under CPAP hat and secured with additional Mepitel™ Tape, secure the wires to CPAP hat using silk tape





TCOM Monitoring in HIE


Dr. El-Dib


Katie Hannon


Dr. Szakmar

PI: Mohamed El-Dib, MD,
Co-investigators:
Seh Hyun Kim, MD, Terrie Inder, MbChB, MD // Helen Christou, MD //Maria Angela Franceschini, Ph.D. (MGH) // Eniko Szakmar, MD // John Sunwoo, PhD// Jill Robinson, RRT
Study Contact: Mohamed El-Dib mel-dib@bwh.harvard.edu , Katie Hannon khannon3@bwh.harvard.edu
Research Nurse(s): Voalte- available when in hospital
Tina Steele pager# 39895 email: tdufresne@bwh.harvard.edu Tel: 617-525-7376
Debbie Cuddyer// dcuddyer@bwh.harvard.edu // Tel: 617-525-4129
Yvonne Sheldon// ysheldon@bwh.harvard.edu // Tel: 617-732-7954

Background: Low pCO2 has been associated with worse neurodevelopmental outcome in those receiving therapeutic hypothermia for neonatal encephalopathy. This consistent finding suggests that the close monitoring of carbon dioxide is highly important in this vulnerable patient population.

Study Aim:

1) To evaluate the feasibility of applying transcutaneous CO2 monitoring (TCOM) in neonates receiving therapeutic hypothermia and to quantify the agreement between tcPCO2 and PCO2 in this population with or without respiratory support
2) To assess the correlation between cerebral oxygen saturation as a marker for cerebral perfusion and tcPCO2, as a marker of PCO2 in neonates receiving therapeutic hypothermia

Inclusion Criteria: All infants greater than or equal to 34 weeks gestation and eligible for therapeutic hypothermia per BWH criteria will be enrolled regardless of their respiratory support
Exclusion Criteria: Infants with major birth defect, genetic or metabolic syndrome
Neonates in extremis with possibility of redirection to palliative care

Risks: The TCOM application and monitoring will follow the standard NICU clinical procedures and guidelines including repositioning after no longer than 8 hours. Although there is a potential risk for skin irritation or thermal injury from the TCOM sensor, this device has been tested before on very preterm infants with more fragile skin and skin complications were minimal. Skin condition will be assessed and documented as per NICU policy.
Benefits: While there is no direct benefit to the infants enrolled in this study, the results from this observational trial could improve the supportive care of infants with NE and may have an impact on long term outcome.
Procedures:

- TCOM will be applied until baby is fully re-warmed and will be maintained by the covering RT
- A data collecting device will stay in the room during recording to collect data from all baby monitors.
- If a blood gas is not clinically indicated, a blood gas will be obtained with each routine blood draw (at 24 hours of life and every morning) up to 4 total blood gases (this is not charged to the patient unless clinically indicated), please ensure that TCOM is reading at time of blood gas draw.
- Dr El-Dib will place a nursing communication order smart phrase with study instructions.

Evaluating Inter-rater Variability of a Standard Clinical Neurological Exam for Neonatal Encephalopathy with Video-Taping


Dr. El-Dib


Dr. Roychaudhuri


Katie Hannon

PI: Dr. Mohamed El-Dib
Study Contact: Dr. Sriya Roychaudhuri sroychaudhuri@bwh.harvard.edu
Katie Hannon khannon3@bwh.harvard.edu
Research Nurses: Tina Steele Tel: 617-525-7376
email: tdufresne@bwh.harvard.edu
Debbie Cuddyer Tel: 617-525-4129 email: dcuddyer@bwh.harvard.edu

Study Aim:

Specific Aims

1. Assess the inter-observer agreement of the standard neurological assessment of NE among infants with various neurological states.
2. Development of an educational tool for standard NE assessment to aid trainees.

Inclusion Criteria: Infants ≥ 34 weeks' gestation, and in-patient (in neonatal intensive care, or well-baby nurseries)

Exclusion Criteria: Infants <34 weeks' gestation.

Enrollment Procedure:

For babies who are admitted in the nursery or have been admitted to the NICU for more than 24 hours, standard approach for parental consent will be completed in accordance with our departmental standard operating procedure for participant recruitment in the NICU with an initial visit with Research Nurse or PI and assent from family for research approach.

For the acutely sick babies who are evaluated in the NICU triage area or admitted to the NICU immediately after birth for concern for neonatal encephalopathy, examination and videotaping will occur immediately on admission and parents' consent to participate in the study will be obtained within 72 hours. If parents do not consent, or 72 hours have lapsed, the videotape will be immediately and permanently deleted.

Risks: Partaking in this study will result in an additional clinical examination being performed on the infant, exclusively for the purposes of this study. This represents no significant risk or discomfort, but is recognized to be an additional burden on the infant and family. However, the neurological assessment takes less than ten minutes, and will be scheduled in collaboration with nurses caring for the infant with the goal to minimize any disruption to the infant's routine care.

Confidentiality will be ensured by randomly assigned alphanumeric identifiers to each subject. The original consent forms will be stored in a secure locked cabinet at BWH. MRNs will be stored electronically, separate from PHI data that will be stored in a password protected redcap database, accessible only to the PI and study staff members. Video-taped exams will be located on a departmental shared drive accessible only to study staff.

Benefits: There is not expected to be any direct benefit to the participants of this study. However, the potential benefit to society in general is that this study will for the first time validate the inter-observer agreement for the standard assessments utilized in identifying and characterizing neonatal encephalopathy.

Additional Labs/Procedures: There are no additional procedures or labs.

Preemie Multimodal Monitor Study

PI: Mohamed El-Dib, MD,
Study Contact: Seh-Hyun Kim (Research Fellow) // skim210@bwh.harvard.edu
Research Nurse(s): Tel: 617-525-7376 Voalte- available when in hospital
Tina Steele pager# 39895 email: tdufresne@bwh.harvard.edu
Debbie Cuddyer// dcuddyer@bwh.harvard.edu // Tel: 617-525-4129
Yvonne Sheldon// ysheldon@bwh.harvard.edu // Tel: 617-732-7954



Dr. El-Dib



Dr. Kim

Background: Very preterm infants in the NICU receive close monitoring of their physiologic measures (i.e. heart rate, blood pressure, oxygen saturations, etc.) to help clinicians determine their clinical status. By collecting and storing this data, we hope to capture trends in the data that can be correlated to brain injury and neurological outcomes.

Study Aim: To evaluate if the physiological data collected clinically and continuously during the first week of life is predictive of brain injury in infants born < 29 weeks gestation. Goal is to enroll 150 infants over 2 years.

Inclusion Criteria: Infants born < 29 weeks and are <7 days old, inpatient in the BWH NICU.

Exclusion Criteria: Infants in extremis who have high likelihood not to survive.

Risks: This study is considered minimal risk as the data is already being obtained clinically. The only risk is to privacy which is minimized by each infant receiving a unique subject ID and all identifiable data collection being kept in a password protect database. There is no direct contact with the infant during data collection.
Benefits: There are no direct benefits expected to the infant, but the results of this study may help optimize neurodevelopmental outcomes of very preterm infants in the future.

Study Procedures:

- Infants <29 weeks GA will have their bedside monitoring equipment connected to the Moberg Monitor (ideally within the 1st DOL) bt the study team or a member of the NNCCN team.
  - This may include GE monitor, TCOM, NIRS, aEEG, and mechanical ventilator.
  - This study has ***IRB approval to collect this PRIOR to consent***
- The monitor will remain at the bedside for 7 days (+/- 2 days) to collect this data- study team will remove at the end of this period.
- This data is stored on a secure BWH database until the family can be approached for consent
- Families will be approached at a later time during infant's admission to obtain consent
  - If a family declines the data will be permanently destroyed/deleted
  - If a family is approached by Research Nurses for a general research approach and declines ALL research the recording will be stopped and deleted prior to approaching
- When families consent to the study the physiologic monitoring data will be stored and basic demographic, and NICU outcome data will be collected from EPIC.

CRICO Registry



Dr. El-Dib



Hoda El-Shibiny

1. **Title:** Optimization and Standardization of Care during Therapeutic Hypothermia in the Term Born Infant with Encephalopathy
2. **PI:** Mohamed El-Dib mel-dib@bwh.harvard.edu and Terrie Inder
3. **Data manager/contact:** Hoda El-Shibiny helshibiny@bwh.harvard.edu
4. **Centers Involved:** 14 medical centers include: Brigham and Women Hospital, Boston Children's Hospital, Massachusetts General Hospital, Beth Israel Deaconess Medical Center, Newton -Wellesley Hospital, South Shore Hospital, North Shore Medical Center, Beverly Hospital, Cambridge Health Alliance, Good Samaritans Medical Center, Holy Family Hospital, Saint Elizabeth's Medical Center, Mount Auburn Hospital, and MedFlight Boston.
5. **Short description of the Aims of the project:**
   - The CRICO NE Registry collected data on neonates either evaluated for therapeutic hypothermia (TH) or those who received TH in participating centers starting April 15, 2018.
   - Upon data analysis, we have noted several areas of improvement in both implementation of therapy, safety of related care and avoidanceof risks from
   - The aim of the study is the implementation of quality improvement projects aimed at decreasing variation inpractices and improved safety of current practice and establishing an analytic plan with statistical supportfor reporting.
6. **Short description of the data collected:**
   - Demographic- GA, BW, Delivery and Transport data.
   - Maternal History
   - Delivery History
   - Infant Delivery: Resection event, Cord and Blood gases, The scores of the four NE exam scores during 6 hours of evaluation
   - Neurology Exam BWH and BCH Score and Sarnat grade
   - Therapeutic Hypothermia details (Start and end of passive and active cooling, rewarming phase, and complete or early exit)
   - Neuromonitoring aEEG and cEEG details, score based on the 1st report.
   - Short Term Outcome – Discharge details, Feeding details, and MRI.
   - Side Effects of TH. Hematological data- Blood products received- SC fat necrosis- Pulmonary Hypertension and any other concern.

7. **Dates and Numbers of patients already collected:**
   - Start date: 4/18/2018- to-date
   - **Total Numbers of cooled and evaluated babies enrolled to Date : 1243**

BWH NE Retrospective Cohort- **Cooling Database**



Dr. El-Dib



Hoda El-Shibiny

1. **Title:** Quality Evaluation of Expanded Hypothermia Therapy Guidelines for At-Risk Neonates
2. **PI:** Mohamed El-Dib mel-dib@bwh.harvard.edu
3. **Data manager/contact:** Hoda El-Shibiny helshibiny@bwh.harvard.edu
4. **Center Involved**: BWH
5. **Short description of the Aims of the project:**
6. **Main aims of this study are**:

   - To identify the outcomes of infants with mild encephalopathy who received hypothermia therapy and compare these to the outcomes of infants with moderate/severe encephalopathy who underwent the same therapy.
   - To analyze outcomes of therapeutic hypothermia based upon gestational age.
   - To analyze the outcomes of therapeutic hypothermia based upon cooling time and cooling method.

7. **Short description of the data collected**: The database integrates different databases. The total number of the collected data points is 680 variables- The main variables are:
8. **The CRICO database:** Demographic- GA, BW, Delivery and Transport data.

   - Maternal History
   - Delivery History
   - Infant Delivery: Resection event, Cord and Blood gases, The scores of the four NE exam scores during 6 hours of evaluation.
   - Neurology Exam BWH and BCH Score and Sarnat grade.
   - Therapeutic Hypothermia details (Start and end of passive and active cooling, rewarming phase, and complete or early exit)
   - Neuromonitoring aEEG and cEEG details, score based on the 1st report.
   - Short Term Outcome – Discharge details, Feeding details, and MRI.
   - Side Effects of TH. Hematological data- Blood products received- SC fat necrosis- Pulmonary Hypertension and any other concern.

   - **BWH MRI Scoring database**: Injury location, pattern of injury, Barkovich Scoring system, Deep Grey Matter, White Matter/Cortex, Cerebellum, abnormality, injury location and sequences of injury, overall score, and Severity of Injury.

9. **Dates and Numbers of patients already collected**:

   - Data collected -Start date: 01/ 20/ 2014, and updated to December 31, 2021
   - Population: Babies enrolled on Therapeutic Hypothermia Protocol
   - **Total numbers of enrolled babies: 381**

BWH NE Retrospective Cohort- **Evaluated Non-Cooled Database**



Dr. El-Dib



Hoda El-Shibiny

1. **Title:** Quality Evaluation of Expanded Hypothermia Therapy Guidelines for At-Risk Neonates
2. **PI:** Mohamed El-Dib mel-dib@bwh.harvard.edu
3. **Data manager/contact:** Hoda El-Shibiny helshibiny@bwh.harvard.edu
4. **Center Involved**: BWH
5. **Main aims of this study are**:

   - To identify the outcomes of infants who evaluated for hypothermia therapy and did not receive treatment.
   - To analyze outcomes of evaluated not cooled based upon gestational age.

6. **Short description of the data collected**: The database is structured based on the CRICO database. The total number of the collected data points is 425 variables- please find the below summary:

7. **The CRICO database:** Demographic- GA, BW, Delivery and Transport data.

   - Maternal History
   - Delivery History
   - Infant Delivery: Resection event, Cord and Blood gases, The scores of the four NE exam scores during 6 hours of evaluation.
   - Neurology Exam BWH and BCH Score and Sarnat grade.
   - Therapeutic Hypothermia details (Start and end of passive and active cooling, rewarming phase, and complete or early exit)
   - Neuromonitoring aEEG and cEEG details, score based on the 1st report.
   - Short Term Outcome – Discharge details, Feeding details, Anesthesia details and MRI.

8. **Dates and Numbers of patients already collected**:

   - Data collected -Start date: 04/ 20/ 2018, and updated to December 31, 2021
   - Population: Babies evaluated for therapeutic hypothermia and not treated.
   - Total numbers of enrolled babies:381

BWH ELGA Retrospective Cohort



Dr. El-Dib



Hoda El-Shibiny

1. **Title:** Assessment of Risk Factors Associated with Adverse Outcome in Preterm Infants
2. **PI:** Mohamed El-Dib mel-dib@bwh.harvard.edu
3. **Data manger/contact:** Hoda El-Shibiny helshibiny@bwh.harvard.edu
4. **Center Involved**: BWH
5. **Short description of the Aims of the project:**
   This study aims at defining prenatal, perinatal and clinical factors associated with brain injury on HUS and abnormality in brain development as well as injury on TE MRI in preterm infants born at < 32 weeks GA and/or less than 1500 grams BW and admitted to BWH NICU. Identifying these factors could provide more information on neuroprotective interventions which can be utilized in this population.
6. **Short description of the data collected :**
   - All VON variables
   - Kidokoro Scores from TE MRIs
   - NIRS data
   - Ultrasound data
   - Discharge summaries
   - Lab data (blood gases, mode of ventilation, hematocrit)
7. **Dates and Numbers of patients already collected:**
   - 760 babies in database, all with VON data
   - Currently have babies with DOB between January 2015 to December 2020
   - We are approved to have access to babies born from January 2010 to August 2025
   - Inclusion criteria:
     - Preterm infants born at or less than 32 weeks gestational age (GA) or with birth eight less than 1500 grams admitted to Brigham and Women's Hospital NICU.