Neurodevelopmental Outcome after Cardiac Surgery Utilizing CPB in Children: A Prospective, Double Blinded and Randomized Study

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PROTOCOL TITLE:

Neurodevelopmental Outcome after Cardiac Surgery Utilizing CPB in Children: A Prospective, Double Blinded and Randomized Study.

PRINCIPAL INVESTIGATOR:

Name: Aymen Naguib, MD
Department/Center: Anesthesiology/Heart Center
Telephone Number: 614-722-5625
Email Address: Aymen.Naguib@nationwidechildrens.org

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	11/12/2019	Long Term Approach: replacing Stanford-Binet Intelligence Scales (5th ed.) at year 5 with Differential Ability Scales-II (DAS-II)	Yes
2	4/27/2020	Adding the ABAS-II and that it will be mailed out during COVID-19 pandemic to 6.3 Aim 1 Data Collection and Variables. Adding ABAS-II and the Child Behavior Checklist (CBL) to 6.6 Long Term Approach.	No
3	1/5/2022	Adding Sample Size to 1.0 Study Summary	No

1.0 Study Summary

Study Title	Neurodevelopmental Outcome after Cardiac Surgery Utilizing CPB in Children
Study Design	Prospective, Double Blinded and Randomized Study
Primary Objective	The overall goal of this project is to determine the role of anesthetic management in infants and children undergoing cardiac surgery utilizing CPB and deep hypothermic cardiac arrest.
Secondary Objective(s)	
Research Intervention(s)/ Investigational Agent(s)	Fentanyl Dexmedetomidine
IND/IDE #	101911
Study Population	Children < 1 yr. of age undergoing CPB
Sample Size	50
Study Duration for individual participants	5 years
Study Specific Abbreviations/ Definitions	CPB = cardiopulmonary bypass ASD = atrial septal defect VSD = ventricular septal defect AVSD = atrioventricular septal defect TOF = tetralogy of fallot

2.0 Objectives

2.1 The overall goal of this project is to determine the role of anesthetic management in infants and children undergoing cardiac surgery utilizing CPB and deep hypothermic cardiac arrest. An ideal anesthetic technique would ensure abolishing or diminishing stress response as would be evident by the stress markers levels and the level of two cerebral injury biomarkers (S 100 B and NSE) and may offer neuroprotection. This should translate to better immediate postoperative outcome and hopefully improve both the short and the long term neurodevelopmental outcome in these children.

2.2 **Specific Aim 1**: Evaluate the immediate neurodevelopmental outcomes prior to discharge from hospital, day of post-op Cardiology Clinic visit (usually 1-3 months), 6 months and one year postoperatively.

2.3 Hypothesis: The use of dexmedetomidine will lead to improved neuroprotection against the GABAA receptors agonists and possibly other insults such as brain ischemia. This will lead to improved neurodevelopmental outcome in the dexmedetomidine group.

2.4 **Specific Aim 2**: Identify the impact of dexmedetomidine on the stress response in children undergoing cardiac surgery utilizing cardiopulmonary bypass (CPB).

2.5 Hypothesis: The use of dexmedetomidine will significantly reduce the stress response. Also, blunting the stress response and the possible associated intraoperative hemodynamic stability will be associated with lowering the levels of different metabolic, hormonal and cytokine stress markers.

2.6 **Long term Aim**: Identify the impact of the use of dexmedetomidine on surgical stress and the neurodevelopmental outcome in children undergoing congenital cardiac surgery utilizing CPB less than one year of age.

2.7 Hypothesis: The use of dexmedetomidine will provide neuroprotection to children undergoing cardiac surgery utilizing CPB less than one year of age. This neuroprotection could be related to the mere use of dexmedetomidine as it was demonstrated by the in-vitro and in-vivo animal studies (10, 11) or due to better blunting of the stress response in these patients. This alteration in the stress response will lead to an improvement in the immediate perioperative outcome and ultimately to an improved long term neurodevelopmental outcome.

3.0 Background

3.1 Congenital heart defects are among the most common birth defects. It is estimated that more than 32,000 infants are born with congenital heart defects every year. This represents one of every 125 to 150 children born in the United States. Advances in the care of children undergoing congenital cardiac surgery allowed the improvement of the survival after these surgeries. In turn, the focus of outcome in children undergoing congenital heart surgery has shifted from cardiac survival to improvement in the neurodevelopmental outcome (1, 4, 14-16) and its substantial societal impact. Hence, improving these neurodevelopmental outcomes is of paramount importance and the goal of this investigation. Evaluation of children after undergoing surgical correction of CHD demonstrates a wide variety of neurodevelopmental delays including speech delay, cognitive impairment, visual-spatial and visual-motor skills, attention deficit disorder, motor delays and learning disabilities (17, 18).

3.2 Most of these children will require surgical palliation using CPB during the first year of life. Some of these children will have some form of brain insult even prior to surgery. This could be due to cyanosis, severe acidosis or abnormal pattern of cerebral blood flow as in patients with hypoplastic left heart syndrome (HLHS) where some studies have shown the presence of brain ischemia on magnetic resonance imaging, even prior to surgery(19, 20). While these are preoperative factors that will ultimately affect the neurodevelopmental outcome, there are

perioperative insults that can be modulated, abolished or avoided completely. For instance, surgical factors that increase stress response and the risk on end-organ perfusion, exposure to CPB and deep hypothermic cardiac arrest, are only few that are known to be directly responsible for these events. Exposure to anesthetic agents may add another component to the outcomes after pediatric cardiac surgery. The use of GABAA agonists such as propofol, barbiturates, and isoflurane, as well as medications that decrease excitatory transmission through NMDA glutamate receptors such as nitrous oxide and ketamine may trigger widespread neuronal apoptosis and eventually neurodegeneration during the vulnerable periods of brain development.

3.3 In addition, an increased plasma level of biomarkers such as, S100B and neuron specific enolase (NSE), have been linked to neurological injury and neurological outcomes after ischemic brain injury (21). Other studies have shown that increased S100B and NSE levels during and after cardiac surgery in adults was correlated with worsening of neurological outcome (22). The S-100ß is a calcium binding protein that is normally found in the intra- and extracellular brain tissue. Its presence in the plasma indicates disruption of the blood brain barrier and brain injury. The S-100ß is eliminated by the kidney and has a half life of 1-2 hours. On the other hand, NSE is an intracytoplasmic glycolytic enzyme that is found in the neurons and neuroendocrine cells. The detection of NSE in the plasma indicates high death rate of neurons and neuroendocrine cells.

3.4 Recent in-vitro and in-vivo animal studies have shown the possible neuroprotective effect of dexmedetomidine, a selective α2-agonist. A recent study by Degos et al (11) has shown that the use of dexmedetomidine in mouse models provided modulation of brain derived neurotrophic factor expression. This modulation resulted in significant neuroprotective effect in vivo and in vitro.

3.5 The stress response and associated inflammation have been shown to result in increased morbidity and mortality during the post-operative recovery period. However, due to their delicate metabolic balance, neonates and infants undergoing cardiac surgery are at even greater risk of experiencing complications and poor outcomes due to surgical stress and inflammation.

3.6 While the stress response plays a major role in initiating the catabolic state that follow surgery, the cytokine release contributes to the end-organ dysfunction (23, 24). The cytokines are produced mainly in the lungs and the myocardium and then spilled over into the circulation. There are proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6) and interleukin-8 (IL-8). Also, there are compensatory anti-inflammatory cytokines such as interleukin-10 (IL-10) and interleukin-1 receptor antagonist (IL-1ra). The proinflammatory cytokine response in children undergoing cardiac

surgery with CPB is characterized by large variation, compared to a generally well-defined response in adults. This is in contrast to the anti-inflammatory response that shows a more clear release pattern in children. It is the balance between the pro and anti-inflammatory cytokines that may predict the outcome for children undergoing cardiac surgery with CPB, rather than the change in a specific cytokine value.

3.7 Identifying a specific anesthetic regimen that will provide some neuroprotection while offering some blunting of the stress response may improve both immediate perioperative and long term neurodevelopmental outcome in children undergoing cardiac surgery with CPB under one year of age.

3.8 **Aim 1 Rationale**: The possible neuroprotection of dexmedetomidine has been studied in-vitro and in-vivo animal models (10, 11). There are no prospective randomized studies that show the effect of utilizing such approach on the physiological stress response and the long-term neurodevelopmental outcome in children undergoing cardiac surgery. In addition, this neuroprotection will be associated with lowering the levels two of the cerebral injury biomarkers [serum S-100ß (S100ß) and neuron-specific enolase (NSE)]. This should correlate with a better postoperative neurodevelopmental scores at 1 month, 3 months, 6 months and one year postoperatively.

3.9 In our pilot study (12), we came to the conclusion that the use of a dose of fentanyl that is higher than 10 µg/kg in addition to dexmedetomidine should be associated with a better blunting of the stress response. In addition, in our preliminary, follow-up study, patients who had more blunting of the stress response showed better neurodevelopmental outcome, although it did not reach statistical significance in some cases likely due to the small sample size.

3.10 **Aim 2 Rationale**: In our previous published study (12), we concluded that the use of a higher dose of fentanyl in addition to dexmedetomidine should provide better control of the stress response that will be superior to the use of fentanyl alone. In this study, we intend to prove the impact of dexmedetomidine on blunting these different stress markers even when compared to a higher dose of fentanyl alone.

4.0 Study Endpoints

4.1 Change in cytokine levels, hormone levels, and neurodevelopmental testing scores.

5.0 Study Intervention/Investigational Agent

5.1 Description: Fentanyl (15 µg/kg) and Dexmedetomidine (1 µg/kg bolus followed by 0.5 µg/kg/hr until end of CPB)

5.2 Drug/Device Handling: Research Pharmacy SOP for the Control of Investigational Drugs

5.3 Aymen Naguib, MD is the holder of the IND and will follow all FDA regulations.

6.0 Procedures Involved*

6.1 Describe and explain the study design.

6.2 **Aim 1 Approach**: Baseline neurodevelopmental status will be evaluated preoperatively using the standardized cognitive score from the Bayley Scales of Infant Development-III. The language and motor scores from the Bayley-III will be treated as secondary outcomes. Children will be retested prior to discharge from the hospital, at their post-op cardiology visit (usually 1-3 months post-op), six month and one year postoperatively to evaluate their neurodevelopment and its possible correlation to the S100ß and NSE values. We will, also, prospectively collect the postoperative clinical data as a measure of perioperative clinical outcome.

6.3 **Aim 1 Data Collection and Variables:** For the neurodevelopmental portion of the aim, children will have a baseline neurodevelopmental Bayley score during the preoperative period by our child Biobehavioral outcomes core team. These children will be retested at prior to discharge from the hospital, at their post-op cardiology visit (usually 1-3 months post-op), six month and one year postoperatively to evaluate neurodevelopment progress. Also, at each visit parents will complete the ABAS-II, a behavior rating scale. This assessment will be mailed home for completion during the COVID-19 pandemic restrictions. The neurodevelopmental scores will be correlated to the levels of the biomarkers S100ß and NSE.

Postoperative cardiothoracic intensive care unit (CTICU) data collection will include: length of positive pressure ventilation support, total chest tube output during the first 24 hours post-operatively, postoperative platelets count, postoperative absolute neutrophil count and postoperative coagulation profile including; prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR) and fibrinogen level. Data also included inotropic score upon arrival and at 24 hours post-operatively.

The inotropic score will be calculated as follow: dopamine (µg/kg/min) times 1 + milrinone (µg/kg/min) times 10 + epinephrine (µg/kg/min) times 100 (25).

Other data that will be collected include; total urine output during the first 24 hours post-op, blood urea nitrogen and creatinine upon arrival and at 24 hours post-op and the use of nurse-controlled analgesia (NCA) including starting opioid, the need to change the medication used and the total dose of opioids for the first 24 hours. Other variables include: cardiac arrest requiring resuscitation, ventricular or atrial arrhythmia causing hemodynamic disturbances which require treatment, nosocomial

infection during the hospitalization, disseminated intravascular coagulation (DIC), clinical evidence of seizures, the need for re-intubation, length of ICU stay, the need for transfusing blood or blood products and total volume given, length of hospital stay and post-operative mortality.

6.4 **Aim 2 Approach**: We will perform a prospective, randomized and blinded study comparing fentanyl plus dexmedetomidine to fentanyl alone. Stress markers' levels will be checked at five different points; at baseline, after sternotomy, after start of CPB, at the end of surgery and at 24 hours post operatively. These markers include; epinephrine, norepinephrine, ACTH, cortisol, glucose, lactate, TNF-α, IL-6, Il-8 and IL-10. The S100ß and NSE levels will be tested at baseline, end of surgery and 24 hours after surgery.

6.5 **Aim 2 Study Protocol and Data Collection**: Patients will be randomly assigned to one of two groups: Group 1 (25 patients) will receive dexmedetomidine in addition to 15 µg/kg of fentanyl whereas Group 2 (25 patients) will receive normal saline as a placebo in addition to 15 µg/kg of fentanyl.

Half of the fentanyl dose will be administered at the time of induction and after obtaining an intravenous access and the second half will be administered prior to skin incision.

For the dexmedetomidine group, a bolus of the drug will be administered at 1 µg/kg over 10 min followed by an infusion at 0.5 µg/kg/hr until the conclusion of cardiopulmonary bypass.

For placebo, normal saline will be administered at 1 µg/kg over 10 min and then given as an infusion at 0.5 µg/kg/hr until the conclusion of cardiopulmonary bypass

Per Standard of Care in our institution, mean arterial pressure and heart rate will be continuously monitored and recorded throughout the study period

Blood samples will be drawn from an existing arterial line post-induction, post-sternotomy, after beginning cardiopulmonary bypass, at the conclusion of surgery, and 24 hours postoperatively.

Blood samples will be analyzed for relative amounts of cortisol, epinephrine, norepinephrine, ACTH, nitrated albumin, and cytokines such as Tumor Necrosis Factor-α, Interleukin 8, Interleukin 6, and Interleukin 10.

Zero balance Ultrafiltrate (ZBUF) and Modified Ultrafiltrate fluid (MUF) will be collected at the conclusion of surgery and analyzed for cytokines such as Tumor Necrosis Factor-α, Interleukin 8, Interleukin 6, and Interleukin 10.

S100ß and NSE levels will be tested at baseline, end of surgery and 24 hours after surgery.

Arterial blood gases, glucose and lactate levels will be recorded at each of the blood draw time points

Per Standard of Care at our institution, cross clamp time and bypass time will be recorded.

At the start of the case, the attending anesthesiologist will receive two syringes for the study drugs. The first syringe will be labeled "study drug - fentanyl". Half of the drug volume will be administered at induction of anesthesia and the second half of the volume will be administered prior to skin incision. The second syringe will be labeled "study drug - dexmedetomidine/placebo at a concentration of 4µg/ml". The dexmedetomidine/placebo will be administered after obtaining the intravenous access as a loading dose of 1 mcg/kg over 10 minutes followed by an infusion at a rate of 0.5µg/kg/hr. The dexmedetomidine/placebo infusion will be discontinued after separation from CPB.

Blood collection and storage: 3 ml of blood will be collected at five time points including: after induction of anesthesia (baseline), after sternotomy, after initiation of CPB, at the conclusion of surgery (separation from CPB and administration of protamine and prior to skin closure) and at 24 hours post-operatively. The S100ß and NSE levels will be tested at baseline, end of surgery and 24 hours after surgery. In addition, a sample of zero balance Ultrafiltrate (ZBUF) and modified ultrafiltrate (MUF) fluid will be collected after separation from CPB and the conclusion of MUF. Blood samples will be collected in tubes with EDTA preservative and centrifuged at 1,500 x g, at 4oC degrees, for 10 minutes. The plasma will be aliquoted and stored at -80oC degrees until analysis. Plasma will be thawed on ice and centrifuged at 14,000 x g for 1 min prior to analysis. Arterial blood gases, glucose and lactate levels will be recorded at each of the blood drawing time points.

Hormone assays: ACTH and cortisol will be assayed by ELISA (Cal Biotech, Spring Valley, CA). Epinephrine and norepinephrine will be also assayed by ELISA (2-CAT; Rocky Mountain Scientific, Centennial, CO). All assays will be performed according to the manufacturer's instructions.

Cytokine assays: Cytokine levels in plasma and MUF samples will be measured at The Research Institute at Nationwide Children's Hospital using the MesoScale cytokine multiplex ELISA format (MesoScale Discovery, Rockville, MD). Measured cytokines include IFN-γ, IL-1β, IL-10, IL-12 p70, IL-6, IL-8 and TNF-α. Manufacturer-provided standards and controls will be included in each run to generate calibration curves.

S100B: Plasma S100ß levels will be measured by colorimetric ELISA analysis using a commercially available kit (BioVendor R&D, Inc., Candler, NC) with included calibration controls.

Neuron-specific enolase (NSE): Plasma enolase-2 (neuron-specific enolase) will be measured using a Quantikine ELISA kit (R&D Systems, Inc., Minneapolis, MN) with included calibration controls.

Tracheal Extubation Criteria: Assuming there are no preoperative contraindications for early tracheal extubation, the trachea will be extubated at the conclusion of the surgical procedure according to set criteria in our institution. After separation from CPB, hemodynamic stability without the need for vasopressor administration and absence of arrhythmias must be observed to ensure tracheal extubation. After reversal of heparin with protamine and achievement of hemostasis, the chest will be closed. If the patient continues to maintain stable hemodynamics after chest closure, a trial of spontaneous ventilation will be allowed after reversal of the neuromuscular relaxants. If the patient continues to maintain stable hemodynamics with acceptable respiratory rate, tidal volume and expected arterial oxygen saturation at the conclusion of the procedure, the trachea will be extubated.

Intraoperative data collection included: Age, weight, gender, diagnosis, induction time (from the start of the induction of anesthesia to first blood gas), bispectral index (BIS) value, cerebral saturation data, baseline hemoglobin, baseline platelets count, acute normovolemic hemodilution (ANH) volume prior to CPB, CPB circuit prime constituents, red blood cell (RBC) administration, additional blood products (platelet, cryoprecipitate and plasma) and total volume of each product given, UF and MUF volume, cardiopulmonary bypass time, aortic cross clamp time, and the time of tracheal extubation if applicable.

6.6 **Long Term Approach**: Baseline neurodevelopmental status will be evaluated preoperatively using the Bayley-III. Enrolled subjects will be re-evaluated at 5 years of age by administering the Differential Ability Scales-II (DAS-II). Parents will also complete the ABAS-II and the Child Behavior Checklist (CBL).

7.0 Data and Specimen Banking*

7.1 Data and specimens will not be banked for future use.

8.0 Sharing of Results with Subjects*

8.1 Subjects will receive results of the neurodevelopmental testing in the form of a post-visit letter from the Biobehavioral Outcomes Core.

9.0 Study Timelines*

9.1 An individual study subject's participation in the study should last approximately 5 years.

9.2 All study subjects should be enrolled within 5 years of study start.

9.3 The study should be completed within 10 years of study start.

10.0 Inclusion and Exclusion Criteria*

10.1 Inclusion: Patients less than one year of age and outside the neonatal period who are undergoing repair of atrial septal defect (ASD), ventricular septal defect (VSD), atrioventricular septal defect (AVSD), tetralogy of fallot (TOF) or biventricular repair with left to right shunting physiology will be recruited.

10.2 Exclusion: Patients with the diagnosis of AVSD and pulmonary hypertension. Patients less than 1 year and requiring any of the following repairs: HLHS, Aortic arch reconstruction, Arterial switch, TOF with pulmonary atresia. Patients diagnosed with developmental delays or any syndrome associated with developmental delays.

10.3 We are including children, and will not include:

- Adults unable to consent
- Pregnant women
- Prisoners

11.0 Vulnerable Populations*

11.1 The research involves greater than Minimal Risk to subjects, but presents the prospect of direct benefit to the individual subjects.

11.2 Because of the prospect of direct benefit, permission of one parent is sufficient even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.

12.0 Local Number of Subjects

12.1 50

13.0 Recruitment Methods

13.1 Potential subjects will be recruited from the cardiology clinic or from preadmission testing (PAT) clinic.

13.2 Subjects will be patients undergoing cardiac surgery here at NCH.

13.3 Potential subjects will be identified by looking at the surgery schedule or the PAT clinic schedule in EPIC.

13.4 Subjects will receive $10 for the baseline visit and $25 for each subsequent study visit: prior to discharge from the hospital, 1-3 months, six months and one year postoperatively. They'll also receive $25 for the visit at 5 years of age. All payments will be via ClinCard.

14.0 Withdrawal of Subjects*

N/A

15.0 Risks to Subjects*

15.1 The most common side effect of receiving Dexmedetomidine is temporary high blood pressure when the dose is started, but treatment of the high blood pressure is rarely needed. In studies with adults, common side effects were low blood pressure (28%), high blood pressure (16%), nausea (11%), slow heartbeat (7%), fever (5%), vomiting (4%), difficulty breathing (4%), fast heartbeat (3%), and anemia (3%).

15.2 The most common side effects of Fentanyl are reduced air flow into the lungs, breathing that slows or stops, muscle tightness, and slow heartbeat that requires treatment. Fentanyl may also cause high blood pressure, low blood pressure, dizziness, blurred vision, nausea, vomiting, excessive sweating, uncontrolled tightening of the vocal cords that makes breathing difficult, excessive happiness, shrinking of the eye pupils, and tightening of the airways. Rarely, it can cause air flow into the lungs to be reduced again after surgery as the drug wears off.

16.0 Potential Benefits to Subjects*

16.1 The potential benefits are a reduction in stress response during cardiac surgery and early extubation leading to less post-operative morbidity and mortality and better outcomes.

17.0 Data Management* and Confidentiality

17.1 **Aim 1 Statistics and Data Analysis**: One-way repeated ANOVA will be used to test differences of neurodevelopmental Bayley scores at discharge, 1 month - 3 months, 6 months and one year of age. For repeated two group comparison, we can conduct a paired-t test or Wilcoxon signed rank sum test, where appropriate. One-way ANOVA or Kruskal Wallis test will be used to detect group differences. Association between Neurodevelopmental scores and S100ß / NSE levels will be assessed using Pearson linear correlation or Spearman's rank correlation, where appropriate. Multivariate stepwise regression models will be used to evaluate the predictive power of the different stress markers on the different clinical outcomes including postoperative mortality, cardiac arrest requiring resuscitation, arrhythmias, sepsis, DIC, clinical evidence of seizures, reintubation (if patient was extubated in the OR), length of ventilator use in the CTICU, inotropic scores, length of CTICU stay and length of hospital stay. Logistic stepwise models will be used for dichotomous outcomes including; postoperative mortality, cardiac arrest requiring resuscitation, arrhythmias, sepsis, DIC, clinical evidence of seizures, reintubation (if patient was extubated in the OR) and inotropic scores. Linear stepwise regression models will be used for the continuous outcomes of length of ventilator use, length of ICU stay and length of hospital stay.

17.2 **Aim 2 Statistics and Data Analysis**: Descriptive statistics will be computed to summarize all variables of interest. For continuous variables, mean and standard deviation will be provided for normally distributed data or median and range for non-normally distributed data. Count with frequency and percentage will be estimated for categorical variables.

Two sample t-test or Wilcoxon rank-sum test, where appropriate, will be used to test effect differences for stress response markers and other continuous clinical variables such as age, weight and induction time, etc…, between the two groups in each of the five point measurements. A Chi-square test or Fisher Exact Test with Bonferroni Correction (based on data observations) will evaluate the relationship for categorical clinical data. A mixed model will also be used to estimate overall difference and time trend for these stress biomarkers with repeated measurements. Type I error will be strongly controlled at $\alpha=0.05$ for single comparisons and with adjustment for multiple comparisons.

17.3 Research records will be stored in a locked cabinet and password protected computer. Only certified research personnel will be given access to identifiable subject information.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

18.1 The study will be monitored in compliance with the relevant parts of 21 CFR and according to the ICH GCP Guidelines. The procedures outlined in the protocol and case report forms will be carefully reviewed by the PI and staff prior to study initiation to ensure appropriate interpretation and implementation. No deviations from the protocol shall be made except in emergency situations where alternative treatment is necessary for the protection, proper care and wellbeing of subjects.

18.2 All subjects will be clinically monitored as it pertains to routine anesthetic care during the surgical procedure. This includes the use of standard ASA (American Society of Anesthesiology) monitors which measure ventilation (end tidal C02, inspired anesthetic gases), oxygenation (pulse oximetry), temperature and circulation (heart rate, blood pressure and EKG assessments). In addition, all subjects will have BIS (Bispectral Index) monitoring used to assess the depth anesthetic as well as guide titration of anesthetic agents.

18.3 Amendments will be submitted to the Nationwide Children's Hospital IRB for their review and approval prior to implementation. When an amendment to a protocol substantially alters the study design or increases potential risk to the study subject, the Informed Consent Form will be revised and if applicable, subject's consent to continue participation will again be obtained.

19.0 Provisions to Protect the Privacy Interests of Subjects

19.1 Subject information will not be given to any other investigators. Subjects and their information will be closely monitored and guarded by study staff; there will be limited access to patients and their information by trained study staff; and subject information will only be shared and discussed between study staff specific to this study.

19.2 Subject recruitment will be cleared through the cardiothoracic nurse practitioners prior to approaching the patient to ensure that the family is not being overwhelmed by multiple study teams.

20.0 Compensation for Research-Related Injury

20.1 None

21.0 Economic Burden to Subjects

21.1 None.

22.0 Consent Process

22.1 We will be following "SOP: Informed Consent Process for Research (HRP-090)".

22.2 The consent process will begin in the PAT clinic by PI, Sub-Investigators, Study Coordinators, and/or trained research staff.

22.3 The study will be thoroughly explained to the patient's family. There will be ample time allotted for questions and answers. An explanation of voluntary participation will take place, and the family will be asked if they are interested in participating in the study. If the parent(s), or legal guardian agrees to participate they will be asked to sign consent forms. The patient will then be enrolled in the study with the understanding that they can elect to stop the study and be withdrawn from the study at any time.

23.0 Process to Document Consent in Writing

23.1 We will be following "SOP: Written Documentation of Consent (HRP-091)."

24.0 Setting

24.1 Potential subjects will be identified and recruited from the cardiology or PAT clinic. Research procedures will be performed in the main OR, CTICU, and biobehavioral core.

25.0 Resources Available

25.1 The department of Anesthesiology and Pain Medicine has 2 research coordinators and 2 research associates that will be enrolling subjects for this study. All study staff will be trained on the study procedures.

25.2 We will also be utilizing the psychologists and research associates from the biobehavioral core for the neurodevelopmental testing.

26.0 Multi-Site Research*

26.1 N/A

27.0 Protected Health Information Recording

1.0 Indicate which subject identifiers will be recorded for this research.

- ☒ Name
- ☐ Complete Address
- ☒ Telephone or Fax Number
- ☐ Social Security Number (do not check if only used for ClinCard)
- ☒ Dates (treatment dates, birth date, date of death)
- ☒ Email address , IP address or url
- ☒ Medical Record Number or other account number
- ☐ Health Plan Beneficiary Identification Number
- ☐ Full face photographic images and/or any comparable images (x-rays)
- ☐ Account Numbers
- ☐ Certificate/License Numbers
- ☐ Vehicle Identifiers and Serial Numbers (e.g. VINs, License Plate Numbers)
- ☐ Device Identifiers and Serial Numbers
- ☐ Biometric identifiers, including finger and voice prints
- ☐ Other number, characteristic or code that could be used to identify an individual
- ☐ None (Complete De-identification Certification Form)

2.0 Check the appropriate category and attach the required form* on the Local Site Documents, #3. Other Documents, page of the application. (Choose one.)

- ☒ Patient Authorization will be obtained. (Include the appropriate HIPAA language (see Section 14 of consent template) in the consent form OR attach the HRP-900, HIPAA AUTHORIZATION form.)
- ☐ Protocol meets the criteria for waiver of authorization. (Attach the HRP-901, WAIVER OF HIPAA AUTHORIZATION REQUEST form.)
- ☐ Protocol is using de-identified information. (Attach the HRP-902, DE-IDENTIFICATION CERTIFICATION form.) (Checked "None" in 1.0 above)
- ☐ Protocol involves research on decedents. (Attach the HRP-903, RESEARCH ON DECEDENTS REQUEST form.)
- ☐ Protocol is using a limited data set and data use agreement. (Contact the Office of Technology Commercialization to initiate a Limited Data Use Agreement.

***Find the HIPAA forms in the IRB Website Library, Templates.**

Attach the appropriate HIPAA form on the "Local Site Documents, #3. Other Documents", page of the application.

3.0 How long will identifying information on each participant be maintained?

Following publication of study results, research records will be stored for a period of 3-5 years and then will be destroyed by placing in a secure shredding bin.

4.0 Describe any plans to code identifiable information collected about each participant. None

5.0 Check each box that describes steps that will be taken to safeguard the confidentiality of information collected for this research:

☒ **Research records will be stored in a locked cabinet in a secure location**

☒ **Research records will be stored in a password-protected computer file**

☐ **The list linking the assigned code number to the individual subject will be maintained separately from the other research data**

☒ **Only certified research personnel will be given access to identifiable subject information**

6.0 Describe the provisions included in the protocol to protect the privacy interests of subjects, where "privacy interests" refer to the interest of individuals in being left alone, limiting access to them, and limiting access to their information. (This is not the same provision to maintain the confidentiality of data.)

Subject information will not be given to any other investigators. Subjects and their information will be closely monitored and guarded by study staff; there will be limited access to patients and their information by trained study staff; and subject information will only be shared and discussed between study staff specific to this study.

Confidential Health Information

1.0 Please mark all categories that reflect the nature of health information to be accessed and used as part of this research.

☒ Demographics (age, gender, educational level)
☒ Diagnosis
☒ Laboratory reports
☐ Radiology reports
☒ Discharge summaries
☒ Procedures/Treatments received
☒ Dates related to course of treatment (admission, surgery, discharge)
☐ Billing information
☒ Names of drugs and/or devices used as part of treatment
☐ Location of treatment
☐ Name of treatment provider
☐ Surgical reports
☒ Other information related to course of treatment

☐ None

2.0 Please discuss why it is necessary to access and review the health information noted in your response above.
It is necessary to meet the objectives of the study and to analyze the data.

3.0 Is the health information to be accessed and reviewed the minimal necessary to achieve the goals of this research? ☒ Yes ☐ No

4.0 Will it be necessary to record information of a sensitive nature? ☐ Yes ☒ No

5.0 Do you plan to obtain a federally-issued Certificate of Confidentiality as a means of protecting the confidentiality of the information collected? ☐ Yes ☒ No