

**Steroids to Reduce Systemic inflammation after neonatal heart Surgery  
(STRESS trial)**

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## 1 OVERVIEW

Congenital heart diseases (CHD) are the most common birth defects, occurring in nearly 1% of live births. Every year, an estimated 40,000 infants born in the U.S. suffer from CHD. Despite advances in surgical management, CHD requiring neonatal surgery is associated with poor outcomes; national registry data demonstrates post-operative major morbidity in 23% and 10% do not survive to hospital discharge.[1-4]

Poor outcomes after neonatal heart surgery are often attributable to a severe systemic inflammatory response to cardiopulmonary bypass (CPB).[5-8] CPB is necessary for most neonatal CHD surgeries. Therefore, to reduce the post-CPB inflammatory reaction, many surgeons administer pre-or intra-operative steroids.[9-15] Steroids have been shown to reduce inflammatory markers after neonatal heart surgery.[13, 16] However, steroids also have potential harmful effects including an increased risk of post-operative infection.[17] The recent SIRS trial evaluated the safety and efficacy of steroids after CPB in adults and demonstrated no beneficial effect of steroids but increased risk of post-CPB myocardial infarction and other major adverse events.[18, 19]

Adult trial results cannot be reliably extrapolated to neonates because the neonatal response to CPB is markedly different to that seen in adults; neonates demonstrate both a more pronounced inflammatory reaction and a different post-operative complication profile. For these reasons approximately 2/3rds of congenital heart surgeons continue to administer perioperative steroids to neonates undergoing heart surgery.[17] Yet this practice is not evidence based as no safety/efficacy trial has ever evaluated steroids in neonates undergoing heart surgery with CPB. Several smaller steroid trials (all enrolling < 75 patients) have focused on surrogate outcome measures, but none have provided conclusive data.[16, 20]

The major barrier to performing a steroid trial in neonates with CHD has been the high cost associated with trial conduct for these relatively rare defects. To overcome this barrier, we will use a novel approach leveraging existing registry infrastructure at CHD surgical sites that participate in the Society of Thoracic Surgeons Congenital Heart Surgery Database (STS-CHSD). Sites participating in the STS-CHSD collect data into their institutional databases using standardized case report forms (see Appendix A) so that the data can be exported to the STS-CHSD. These sites already employ data coordinating specialists to capture patient demographics, procedural variables, and post-operative outcomes (including a list of over 60 complication variables) using strict and consistent data element definitions. By leveraging these site-specific resources we project that we can reduce trial costs by >75%.

## 2 PROTOCOL SYNOPSIS

<b>Protocol Title</b>	<b><u>S</u>teroids to <u>R</u>educe <u>S</u>ystemic inflammation after neonatal heart <u>S</u>urgery (STRESS trial)</b>
<b>US IND Number</b>	129266
<b>Grant number</b>	UO1TR001803-01
<b>Product</b>	Intravenous methylprednisolone
<b>Objectives:</b>	To determine the pharmacokinetics (PK)/pharmacodynamics (PD), safety and efficacy of methylprednisolone in neonates undergoing heart surgery with cardiopulmonary bypass
<b>Study Design:</b>	This is a prospective, double blind, multi-center, placebo-controlled safety and efficacy study. Blood samples will be collected from a subset of enrolled study participants to evaluate multiple dose methylprednisolone PK/PD. After informed consent is obtained, participants will be randomized in a 1:1 fashion to intravenous methylprednisolone versus placebo. Study drug/placebo will be administered 8 to 12 hours before the anticipated start time of surgery and in the operating room at the time of initiation of cardiopulmonary bypass. Patients will be followed for primary and secondary outcomes for the duration of their hospitalization. Serious study drug-related adverse events will be collected for 7 days after the last dose of study drug.
<b>Rationale for study design</b>	The study design will allow for evaluation of safety and efficacy to neonates receiving the drug. The proposed design will also allow for characterization of multiple dose methylprednisolone PK/PD.
<b>Study Population:</b>	Up to 1500 neonates ages < 30 days undergoing heart surgery with cardiopulmonary bypass.
<b>Number of Sites:</b>	Up to 15
<b>Duration of Subject Participation:</b>	Until hospital discharge
<b>Dose ranges to be studied</b>	Intravenous methylprednisolone will be administered using a preservative free formulation. The dosage in this study will be 30 mg/kg
<b>Dose Schedule:</b>	<ol style="list-style-type: none"> <li>1. Pre-operative steroids/placebo administered 8 to 12 hours before anticipated surgical start time as a continuous IV infusion over 1hr</li> <li>2. Intraoperative methylprednisolone/placebo administered as a single IV dose into the cardiopulmonary bypass pump prime</li> </ol>
<b>Diagnosis and Main Criteria for Inclusion</b>	<p><u>Inclusion criteria:</u></p> <ol style="list-style-type: none"> <li>1. Age &lt; 30 days at the time of surgery</li> <li>2. Undergoing heart surgery with CPB as part of standard clinical care.</li> <li>3. Availability and willingness of the parent/legally authorized representative to provide written informed consent.</li> </ol> <p><u>Exclusion criteria:</u></p> <ol style="list-style-type: none"> <li>1. &lt; 37 weeks adjusted gestational age at time of surgery</li> <li>2. Any oral or intravenous steroid treatment within two days of surgery</li> <li>3. Infection contraindicating steroid use</li> </ol>

	<ol style="list-style-type: none"> <li>4. Any patient receiving any of the following medications within 2 days of surgery: Amphotericin B, aminoglutethimide, anticholesterases, warfarin, P450 3A4 inducers including (but not limited to) carbamazepine, phenobarbital, phenytoin, rifampin, bosentan and nafcillin or P450 3A4 inhibitors including (but not limited to) clarithromycin, voriconazole, itraconazole, ketoconazole, ciprofloxacin, diltiazem, fluconazole, erythromycin and verapamil.</li> <li>5. Preoperative mechanical circulatory support or active resuscitation at the time of randomization</li> <li>6. Emergent surgery precluding steroid administration 8 hours before surgery.</li> </ol>
<b>Estimated Start:</b>	July 2017
<b>Estimated Finish:</b>	June 2021
<b>Primary endpoints</b>	<p>Primary efficacy and safety outcome measures will be compared between neonates receiving any methylprednisolone and placebo.</p> <p><u>Primary endpoint - efficacy:</u> The primary outcome measure will consist of a composite mortality, major morbidity and length of stay global rank endpoint with endpoints ranked according to severity. For this endpoint each randomized patient will be assigned a rank based upon their most-severe outcome.</p>
<b>Secondary endpoints</b>	<p><u>Efficacy:</u></p> <ul style="list-style-type: none"> <li>• Mortality including in-hospital mortality or mortality after hospital discharge but within 30 days of the last dose of study drug</li> <li>• Death or major complication as previously defined and reported by the STS-CHSD[21] and including any one or more of the following: <ul style="list-style-type: none"> <li>○ In-hospital mortality</li> <li>○ Mortality after hospital discharge but within 30 days of the last dose of study drug</li> <li>○ Postoperative acute renal failure requiring permanent dialysis</li> <li>○ Postoperative neurologic deficit persisting at discharge</li> <li>○ Postoperative AV block requiring permanent pacemaker</li> <li>○ Postoperative mechanical circulatory support</li> <li>○ Phrenic nerve injury/paralyzed diaphragm</li> <li>○ Unplanned reoperation</li> </ul> </li> <li>• Post-operative hospital length of stay</li> <li>• Duration of mechanical ventilation</li> <li>• Occurrence of post-operative low cardiac output syndrome</li> </ul> <p><u>Safety:</u></p> <ul style="list-style-type: none"> <li>• Occurrence of any one or more of the following major post-operative infectious complications: <ul style="list-style-type: none"> <li>○ Postprocedural infective endocarditis</li> <li>○ Pneumonia</li> <li>○ Sepsis</li> <li>○ Deep wound infection</li> <li>○ Mediastinitis</li> </ul> </li> <li>• Other post-operative complications will be collected from the start of study drug administration until hospital discharge.</li> </ul> <p><u>PK/PD/Biomarkers:</u></p>

	<ul style="list-style-type: none"> <li>• Time to maximum concentration (<math>T_{max}</math>)</li> <li>• Maximum concentration (<math>C_{max}</math>)</li> <li>• Clearance (CL)</li> <li>• Volume of distribution (Vd)</li> <li>• Post-operative blood markers of inflammation</li> </ul>
<b>PK/PD/Biomarkers:</b>	Blood samples will be obtained from patients at various time points after the intravenous infusion. PK parameters will be estimated by non-compartmental analysis using WinNonLin software. Study participants as well as enrolling centers will be given the opportunity to not participate in the PK/PD and/or Biomarker studies as these require needle sticks. Therefore it is expected that PK/PD and/or biomarker data will not be collected on every participant enrolled in the STRESS trial
<b>Criteria for evaluation</b>	<p><u>Safety/Efficacy:</u> Safety and efficacy data will be collected at participating sites using their existing surgical databases (STS-CHSD). The majority of efficacy and safety outcomes represent data elements that sites are currently collecting for submission to the STS-CHSD. A separate clinical database will be used for expedited reporting of any study drug-related serious adverse events. An independent Data Monitoring Board (DMC) will monitor the conduct of the trial for performance (e.g., recruitment, flow and quality control of data, adherence to the protocol) and patient safety. The DMC may review the data at any time. At any time and for any reason, the DMC may recommend to the sponsor that the trial be interrupted or discontinued.</p> <p><u>Pharmacokinetics:</u> Methylprednisolone concentrations will be measured in plasma. Samples will be measured at a central lab using a validated bioanalytical assay.</p>
<b>Statistical Consideration:</b>	This protocol has sufficient enrollment to evaluate PK/PD, safety and efficacy of IV methylprednisolone

### 3 BACKGROUND INFORMATION

#### 3.1 Summary of Experience in the Perioperative Setting in Children with CHD

Some surgeons/centers currently administer perioperative high dose (20mg to 60mg) intravenous methylprednisolone before neonatal heart surgery with CPB. In a national registry study of > 3000 neonates with data capture spanning 2004 to 2008, 62% of neonates undergoing surgery with CPB received perioperative methylprednisolone while 38% did not. Of those receiving methylprednisolone, 22% received methylprednisolone on both the day before, and day of surgery, 12% on the day before surgery only, and 28% on the day of surgery only. Results of a survey of surgeons from the Congenital Heart Surgeon's Society were similar; 28% did not routinely use steroids for neonatal heart surgery. Of the 72% that did routinely use steroids, ~1/3rd administered steroids pre-operatively and intra-operatively and the remainder gave intra-operative steroids only.[22]

Several previous small translationally focused clinical trials have evaluated the safety and efficacy of methylprednisolone. In the largest contemporary trial, neonates scheduled for cardiac surgery were prospectively randomized to receive either 2-dose (8 hours preoperatively and operatively, n = 39) or single-dose (operatively, n = 37) methylprednisolone at 30 mg/kg IV per dose in a prospective double-blind trial. Neonates receiving pre-operative methylprednisolone therapy demonstrated significantly reduced pre-operative pro-inflammatory cytokines including interleukin-6 and 8. There were no differences between the two groups in post-operative pro-inflammatory markers and no differences in the incidence of post-operative low cardiac output syndrome. [13, 14] Methylprednisolone was well tolerated with no adverse drug reactions. The overall incidence of post-operative infection was 13% (10/76) and 4% (3/76) received a post-operative insulin infusion for hyperglycemia.

A meta-analysis evaluated six previous steroid trials in children undergoing heart surgery with CPB. The combined enrollment of these six trials was 232 participants including 116 receiving peri-operative steroids; two of these studies used methylprednisolone at doses of 30mg/kg IV per dose (n=67 patients). The results of this meta-analysis demonstrated a nonsignificant trend of reduced mortality in steroid-treated patients (11 [4.7%] vs 4 [1.7%] patients; odds ratio, 0.41; 95% CI, 0.14–1.15; p = 0.089). Steroids had no effects on mechanical ventilation time ( $117.4 \pm 95.9$  hr vs  $137.3 \pm 102.4$  hr; p = 0.43) and ICU length of stay ( $9.6 \pm 4.6$  d vs  $9.9 \pm 5.9$  d; p = 0.8). Perioperative steroid administration reduced the prevalence of renal dysfunction (13 [54.2%] vs 2 [8%] patients; odds ratio, 0.07; 95% CI, 0.01–0.38; p = 0.002). There were no significant differences in the adverse event profiles for patients receiving steroids versus placebo.[20]

The conclusions of the aforementioned studies, as well as several associated editorials have all been that a large, randomized, controlled trial is needed to evaluate the safety and efficacy of perioperative steroids for neonatal heart surgery with CPB.[13, 14, 16, 20]

## 4 TRIAL DESIGN AND METHODS

### 4.1 Overview

This study is a prospective, double-blind, multi-center, placebo-controlled safety and efficacy study of methylprednisolone in neonates undergoing heart surgery with CPB. The study will enroll up to 1500 neonates (< 30 days of age) and the total study duration is expected to be approximately 48 months. An ancillary PK/PD/Biomarker study will enroll subjects at select centers. This study is unique in that it is designed to leverage existing registry infrastructure at participating sites so as to reduce trial costs. Participants will be randomized and will receive a randomization ID. This ID will also serve as a unique patient identifier allowing us to crosslink datasets. Participants will then receive two doses of study drug/placebo. The first dose will be administered 8 to 12 hours before anticipated heart surgery and the second dose will be administered into the pump prime during cardiopulmonary bypass. All study participants will then receive routine post-operative care. Participating centers will enter all demographic, preoperative, operative and outcomes data into their existing institutional databases for submission to the STS-CHSD as they currently do. These data will be used to evaluate trial outcomes.

### 4.2 Procedures to Minimize/Avoid Bias

#### 4.2.1 Randomization

Eligible participants will be randomized prior to their electively scheduled surgery in a 1:1 fashion to the treatment groups summarized in table 2 below. A block randomization scheme will be employed to ensure equal allocation by study site. Randomization assignments will be generated by a web-based system at the data coordinating center (DCC), after confirmation of trial eligibility. Trial sites will enter the randomization number into three separate databases that will be used for this trial (see section 6.4): the participating center's surgical database (for submission to the STS-CHSD), an eCOS database that will be used to capture some adverse event data, timing of drug delivery and timing of PK samples (for participating centers only) and a REDCap database that will be used to capture a subset of laboratory values from the electronic health record.

**Table 2. Study Drug dosing**

Group	N	Pre-operative	Intra-operative
1	up to 750	IV methylprednisolone over 1 hour	IV methylprednisolone in the CPB prime
2	Up to 750	Placebo	Placebo

#### 4.2.2 Masking

The study medication and the placebo will be identical in appearance to assure masking of study medication. The randomization assignment will be seen only by the statistician at the DCC and the investigational pharmacist preparing the study medication. The family/subject, study coordinator and investigators will remain masked as to treatment group assignment until after all trial data are analyzed.

#### 4.3 Study measures

Study outcomes were determined after trial simulations. Based upon these data we selected the following primary and secondary outcome measures.

##### 4.3.1 Primary Endpoint

A composite mortality, major morbidity and length of stay global rank endpoint with endpoints ranked according to severity. The global rank score has been previously described.[23] Subjects will receive a rank score based upon the lowest ranking (worst) endpoint that they experience during the study trial.

##### 4.3.2 Secondary Endpoints (see section 11.2 for data element definitions)

###### Efficacy:

- Mortality including in-hospital mortality or mortality after hospital discharge but within 30 days of the last dose of study drug
- Death or major complication as previously defined and reported by the STS-CHSD[21] and including any one or more of the following:
  - In-hospital mortality
  - Mortality after hospital discharge but within 30 days of the last dose of study drug
  - Postoperative acute renal failure requiring permanent dialysis
  - Postoperative neurologic deficit persisting at discharge
  - Postoperative AV block requiring permanent pacemaker
  - Postoperative mechanical circulatory support
  - Phrenic nerve injury/paralyzed diaphragm
  - Unplanned reoperation
- Post-operative hospital length of stay
- Duration of mechanical ventilation
- Occurrence of post-operative low cardiac output syndrome

###### Safety:

- Occurrence of any one or more of the following STS-CHSD-defined major post-operative infectious complications:
  - Postprocedural infective endocarditis
  - Pneumonia
  - Sepsis
  - Deep wound infection
  - Mediastinitis
- Other post-operative complications will be collected from the start of study drug administration until hospital discharge.

###### PK/PD/Biomarkers:

- Time to maximum concentration ( $T_{max}$ )

- Maximum concentration ( $C_{max}$ )
- Clearance (CL)
- Volume of distribution (Vd)
- Post-operative blood markers of inflammation

PK/PD and Biomarker data will only be collected at select centers and in those patients whose parent/legally authorized representative have granted consent to blood draws. An opt in/out clause is included in the informed consent forms for study participants and centers will be allowed to participate in this part of the study if they prefer. Parent/legally authorized representative of participants may elect to participate in the PK/PD, the Biomarker studies or both. Time points for blood collection will be the same for both the PK/PD and biomarker studies. Biomarkers being collected represent blood markers of inflammation.

#### 4.3.3 Timeframe for collection of safety and efficacy endpoints

With respect to primary and secondary outcome measures, participants will be followed for the duration of their hospitalization. Data will be collected consistent with standard STS-CHSD reporting protocol. Participants that are discharged within the first 30 days after their initial cardiac surgery will be followed to assess for mortality through 30 days after surgery consistent with current STS-CHSD protocol. If patients remain hospitalized for > 6 months after the final study subject has been enrolled then they will be assigned the worst rank outcome that they have encountered to that point. Serious study drug-related adverse events will be collected through 7 days after the last dose of study drug. Based upon an 18 hour estimated half life of methylprednisolone, this duration of follow up (> 10 half lives) will ensure collection of all potentially study drug-related serious adverse events but avoids capturing unnecessary serious adverse events in this high morbidity patient population.

#### 4.4 Schedule of events

Participants will be enrolled at the time of their electively scheduled surgery. Sites will receive a randomization ID that will be entered into the three relevant databases: the sites' surgical database (STS-CHSD), an eCOS clinical database, and a REDCap database. The first dose of study drug/placebo will be administered 8 to 12 hours prior to the anticipated start time of electively scheduled surgery. The second dose of study drug/placebo will be administered in the CPB pump prime at the time of initiation of CPB. Participants will then undergo surgery with CPB per standard of care. Participants will receive routine post-operative care. Post-operative outcomes including post-operative hospital length of stay, discharge mortality, and complication data will be recorded in the sites institutional surgical database (STS-CHSD) consistent with current practices at the enrolling sites. STS-CHSD data element definitions of particular relevance to the STRESS trial are included in Section 11.2. A subset of additional safety endpoints will be collected into a separate clinical database, eCOS and select safety laboratory values will be collected from the electronic health record into the REDCap database (see section 6.4). Plasma samples including PK/PD/Biomarker samples will be evaluated in a subset of enrolled patients at select centers using a limited sampling scheme. Sample acquisition, handling, and shipping instructions are outlined in Appendix C.

**Table 3. Schedule of events**

Procedure	Pre-	Day 1	Day 2	Day 3	Day 4-7	Hospitalization
Informed Consent	X					
Demographics	X					
Physical Exam	X					
Medical History	X					
Elective surgery with CPB		X				

Administer study drug <sup>1</sup>	X	X				
Timed PK/PD/Biomarker Samples <sup>2</sup>		X	X			
Study drug-related SAEs	X	X	X	X	X	
STS-CHSD data (1° / 2ndary endpoints)		X	X	X	X	X

<sup>1</sup> Study drug/placebo will be administered 8-12 hours prior to surgery and at the time of initiation of CPB

<sup>2</sup> Specific times of PK/PD/Biomarker sampling TBD based upon preliminary analysis of an on-going population

## 5 SELECTION AND WITHDRAWAL OF SUBJECTS

### 5.1.1 Inclusion criteria

- Age < 30 days at the time of surgery
- Undergoing heart surgery with CPB as part of standard clinical care.
- Availability and willingness of the parent/legally authorized representative to provide written informed consent.

### 5.1.2 Exclusion criteria

- < 37 weeks adjusted gestational age at time of surgery
- Any oral or intravenous steroid treatment within two days of surgery
- Any patient receiving any of the following medications within 2 days of surgery: Amphotericin B, aminoglutethimide, anticholesterases, warfarin, P450 3A4 inducers including (but not limited to) carbamazepine, phenobarbital, phenytoin, rifampin, bosentan and nafcillin or P450 3A4 inhibitors including (but not limited to) clarithromycin, voriconazole, itraconazole, ketoconazole, ciprofloxacin, diltiazem, fluconazole, erythromycin and verapamil.
- Infection contraindicating steroid use
- Preoperative mechanical circulatory support or active resuscitation at the time of randomization
- Emergent surgery precluding steroid administration 8-12 hours before surgery.

### 5.1.3 Subject withdrawal

#### 5.1.3.1 Indications for Discontinuation of Study Drug

Study drug may be discontinued, but subjects should remain in the trial and complete all study data collection. Study drug may be discontinued for the following reasons:

- An adverse experience including failure to tolerate study medication that, in the judgment of the investigator or primary physician requires drug discontinuation.
- Voluntary discontinuation of study drug by parent/legally authorized representative.

All information regarding any temporary stop and restart of study drug will be recorded.

### 5.1.4 Recruitment/enrollment procedures protocol

Expected duration of accrual of subjects is approximately 48 months. Recruitment will be conducted using standard procedures. To help with recruitment, information describing the study will be developed for print, electronic, and social media. Subjects will be approached for participation, either in person or by telephone, by site study coordinators or investigators, who will obtain parental consent following standard procedures. The specific procedures will be in compliance with the requirements of each site's Institutional Review Board.

## 6 STUDY PROCEDURES

### 6.1 Preoperative Assessment – Screening Procedures and Baseline Measurements

- Obtain a signed and dated Informed Consent Form (ICF) prior to any study related procedures.

2. Enter all demographic, preoperative risk factor and past medical/surgical history data into the STS-CHSD as per routine
3. Obtain a unique subject randomization ID from the eCOS database. This randomization ID will also serve as a unique patient identifier allowing cross-linking across databases. It must also be entered into the site's surgical database under the study identifier tab as the "STS-related clinical trial ID" and it must be entered into the study REDCap database (see section 6.4). In addition the STS "participant ID" must be entered into all 3 databases and will serve as a double check in the event that the randomization ID is incorrectly entered into any one of the 3 databases.
4. Perform routine preoperative assessment

## **6.2 Baseline/Pre-Dose Assessment**

After the parent or legally authorized representative has signed the IRB-approved informed consent form, and after it has been determined that the patient satisfies all inclusion and exclusion criteria, the following evaluations will be performed and entered directly into the study database (STS-CHSD):

1. Baseline demographics (race, gender, date of birth, age, weight, age and weight at surgery)
2. Fundamental cardiac diagnosis as defined by the STS-CHSD
3. Presence of any of the 41 STS-CHSD defined preoperative risk factors including mechanical ventilation to treat cardiorespiratory failure, sepsis, stroke, renal failure or hepatic dysfunction as defined by the STS-CHSD.
4. Presence of any non-cardiac anatomic abnormality, genetic syndrome or chromosomal anomaly as defined by the STS-CHSD.

## **6.3 Study Procedures During Study Drug Administration**

The following procedures or evaluations will be performed during and immediately following the drug administration and the data recorded as indicated:

1. Record study drug dosing information including dose and timing of drug administration into the eCOS database.
2. Immediately (within 1 business day of first becoming aware of the adverse event) enter all serious, study drug-related adverse events into the eCOS database.

## **6.4 Study Procedures After Study Drug Administration During Hospitalization**

The following information will be collected using the standard STS-CHSD data collection forms consistent with usual institutional practice:

1. Record all post-operative complications using standard STS-CHSD data element definitions (see section 11.2 for definitions)
2. Record all subsequent surgeries (CPB or non-CPB cardiovascular or non-cardiovascular)
3. Record duration of mechanical ventilation
4. Record post-operative hospital length of stay
5. Record discharge mortality (in-hospital death or death after hospital discharge but within 30 days of surgery)

All other aspects of care, including administration of clinically indicated medications can be provided per routine standard of care.

Serious, study drug-related adverse events may require expedited reporting and must be submitted into the eCOS database. Sites must report these events within 1 business day of first becoming aware of the event.

The variables listed in Table 4 are not collected by the STS-CHSD and will need to be collected directly from the Electronic Health Record. These variables must be entered directly into the relevant databases as specified in Table 4.

**Table 4: Additional variables to be captured from the electronic health record**

Variable	Definition	Database
Post-operative highest blood glucose	Enter the highest post-operative blood glucose within 72hrs of surgery	REDCap*
Post-operative insulin administration	Was insulin administered within 24 hours of surgery?	eCOS
Post-operative adrenal suppression	Was hydrocortisone administered within 72 hours of surgery?	eCOS
Preoperative creatinine	Enter the last serum creatinine level obtained prior to surgery	REDCap*
Highest post-operative creatinine	Enter the highest serum creatinine within 72 hours of surgery	REDCap*
Lowest post-operative potassium	Enter the lowest post-operative potassium within 72 hours of surgery	REDCap*
Highest post-operative AST	Enter the highest AST within 72 hours of surgery	REDCap*
Highest post-operative ALT	Enter the highest ALT within 72 hours of surgery	REDCap*
Highest post-operative lactate	Enter the highest lactate within 72 hours of surgery	REDCap*
Lowest post-operative serum cortisol	Enter the lowest serum cortisol level obtained within 72hrs of surgery	REDCap*

\*Some sites may choose not to implement the REDCap dynamic data pull mechanism which facilitates rapid capture of the laboratory data from the electronic health record. These sites will enter all laboratory data into the eCOS database.

## 6.5 PK/PD/Biomarker sampling procedures (select sites)

A limited PK/PD/Biomarker sampling scheme will be employed such that no more than 5600 µl (7 samples, 800 µl per sample) of blood is obtained (Table 5). Blood samples will be collected in 800 µL aliquots. Children who have only 1 evaluable PK sample will be included in the analysis, but additional participants may be enrolled to ensure at least 100 children with < 4 adequate PK samples.

**Table 5. PK/PD/Biomarker sampling scheme**

Sample Number*	Per Patient Prioritization	Time	Per patient blood collection
1	Please always try to collect this	Pre- 1 <sup>st</sup> dose	4 x 200 uL = 800 uL
2	Collect a minimum of 2 of any of these 5 time points to collect a minimum total of 3 time points per participant.	0-30 minutes after the start of CPB	4 x 200 uL = 800 uL 4 x 200 uL = 800 uL
3		0-30 minutes after MUF	
4		1-2 hours after completion of CPB	
5		4-6 hours after completion of CPB	
6		16-24 hours after completion of CPB	
7	If participating in the biomarker arm, then please always try to collect this	36-48 hours after completion of CPB	4x 200 uL = 800 uL

### Timed PK/PD/Biomarker sample handling procedures (plasma):

Assays to measure methylprednisolone concentrations and measures of the inflammatory response to CPB in plasma will be conducted at a central lab using validated bioanalytical assays. The date and time will be recorded for the administration of study drug, and the acquisition time of the PK sample.

## **7 TREATMENTS TO BE ADMINISTERED**

### **7.1 Description of Study Treatments**

Eligible subjects will be randomized prior to their electively scheduled surgery in a 1:1 fashion to IV methylprednisolone (30mg/kg) versus placebo as summarized in table 2 above and including preoperative + intraoperative methylprednisolone, and preoperative + intraoperative placebo. The dosages for administration (30 mg/kg) are based upon expert consensus regarding current practice. Intravenous methylprednisolone is available in a **preservative free** single use “Act-O-Vial System” containing powder (40mg, 125mg, 500mg and 1000mg options are available) and diluent. Study drug will be provided “off the shelf” by study sites and prepared following local pharmacy protocols. Only preservative-free solutions will be used for this trial due to safety concerns with the administration of benzyl alcohol preservatives in neonates. Study drug will be mixed with isotonic saline in a syringe to create a solution. Placebo preparations will consist of isotonic saline only and will be prepared in identical syringes so as to be physically indistinguishable from study drug.

### **7.2 Route of Administration**

For the purposes of this trial methylprednisolone will be administered in two forms: 1) as an intravenous infusion given over 1 hour (all preoperative administrations); and 2) as a bolus dose administered directly into the CPB priming solution (intraoperative administration).

### **7.3 Storage and Administration**

Study drug/placebo will be prepared by the site investigational pharmacy and delivered to the bedside or operating room from the investigational pharmacy on the day of study drug administration. All co-investigators, staff administering study drug and other care providers will be blinded to study drug allocation. Start and stop times of study drug administration must be documented by the investigational pharmacy in the eCOS database.

## **8 STUDY DRUG ACCOUNTABILITY**

### **8.1 Medications/Treatments Permitted and Not Permitted during the Study**

#### **8.1.1 Rescue Medication, Emergency Procedures and Additional Treatments(s)**

Management would be symptomatic treatment (e.g., severe hypertension) or observation and monitoring (e.g., mild hyperglycemia). For preoperative administration, infusion may be temporarily halted for up to 2 hours for side effects. Study drug may be resumed on resolution of symptoms or side effects if considered safe in the judgment of the investigators and the subject’s primary physician and with consent of subject.

#### **8.1.2 Restrictions regarding concomitant treatment**

Subjects may be treated with other medications at the discretion of their physicians.

### **8.2 Emergency Unblinding**

An emergency code break can be requested from the site research pharmacist after full discussion with the STRESS PI. This code break may be used in rare life-threatening or emergency situations when the identity of the study drug must be known to the investigator in order to provide appropriate medical treatment or if required to assure safety of trial participants. If the code break for a subject is required, the DCC must be informed within one working day of the event. The reason for breaking the code must be documented in the eCOS database on the appropriate eCRF along with the date and the initials of the person who broke the code.

## 9 SAFETY ASSESSMENTS AND MONITORING

### 9.1 Collection and Reporting

Due to the unique study design, most adverse events will be recorded as complications and/or other adverse event data variables specifically captured by the site's surgical database using STS-CHSD data element definitions (see Section 11.2).

Serious, study drug-related adverse events will be reported by site investigators or qualified designee from the time of study drug administration through 7 days after the last dose of study drug in the eCOS database within 1 business day of first becoming aware of the event. The site investigator's reported relationship assessment to study drug will be confirmed or assessed otherwise by a Safety Medical Monitor at the Duke Clinical Research Institute.

### 9.2 Definitions of Adverse Events (AEs), Suspected Adverse Reaction and Serious Adverse Events

The FDA Final Rule on IND Safety Reporting Requirements [<http://edocket.access.gpo.gov/2010/pdf/2010-24296.pdf>] provides the following definitions:

**Adverse events (AEs)** An AE is any untoward medical occurrence associated with the use of a drug in a subject whether or not considered drug- or biologic-related. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a pharmaceutical product or biologic.

A **suspected adverse reaction (SAR)** is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. A "reasonable possibility" suggests there is a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

**Serious adverse events:** An adverse event or suspected adverse reaction is considered serious if, in the view of either the site investigator or the IND sponsor, it results in any of the following outcomes:

1. Death
2. Life-threatening AE: Places the subject at immediate risk of death at the time of the event as it occurred. It does not include an AE that, had it occurred in a more severe form, might have caused death.
3. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
4. Inpatient hospitalization or prolongation of existing hospitalization
5. Congenital anomaly or birth defect
6. An important medical event that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition above. This determination is based on the opinion of either the investigator or sponsor (e.g., if either believes it is serious, it must be considered serious).

Laboratory abnormalities are not specifically captured by institutions as part of their STS-CHSD and will not be considered AEs unless they result in a post-operative complication that sites report to the STS-CHSD. In this case, the clinical diagnosis rather than the laboratory term will be used by the reporting investigator (e.g., renal failure versus elevated creatinine).

### 9.3 Assessment of Severity

The determination of severity rests on medical judgment of a medically qualified investigator. For adverse events captured by the site's surgical database, the data monitoring committee will review these events every 6-months following transfer of data to the data coordinating center at the Duke Clinical Research Institute. For suspected unexpected serious adverse reactions, monitoring will be performed continuously and event severity will be graded by the study sponsor. The severity of suspected adverse reactions and study drug related SAEs will be graded using the following definitions as defined by the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (<http://ctep.cancer.gov>):

1. **MILD:** Participant is aware of symptoms or has minor findings but tolerates them well and no or minimal intervention required.
2. **MODERATE:** Participant experiences discomfort enough to cause interference with usual activity and may warrant intervention.
3. **SEVERE:** Participant experiences symptoms that are incapacitating with inability to do usual activities or that significantly affect clinical status and warrant intervention.

Study personnel will enter the study drug-related serious adverse event data into the eCOS database. The STRESS Trial PI / IND sponsor will be responsible for adjudicating severity and relatedness of these events and determining which events should be reported in expedited fashion to FDA. The IND sponsor or designee will submit expedited safety reports (IND Safety Reports) to the FDA and other regulatory agencies as necessary, and will inform the investigators of such regulatory reports. Investigators must submit safety reports as required by their Institutional Review Board (IRB). Documentation of the submission to and receipt by the IRB should be retained for each IND safety report.

### 9.4 Assessment of Causal Relationship

A medically qualified investigator must assess the relationship of any adverse event to the use of the study drug, based on available information using the following guidelines:

1. **Not related:** There is not a reasonable causal relationship to the investigational product and the adverse event.
2. **Unlikely related:** No temporal association, or the cause of the event has been identified, or the drug or biologic cannot be implicated.
3. **Possibly related:** There is reasonable evidence to suggest a causal relationship between the drug and adverse event.
4. **Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. Relatedness to these complications will not be specifically assigned by the Data Monitoring Committee unless they are separately reported as suspected unexpected serious adverse reactions (SUSARs).

#### **Expectedness**

The expectedness of an adverse event or suspected adverse reaction shall be assessed by a DCRI Safety Medical Monitor according to the package insert. Any AE that is not identified in nature, severity, or specificity in the current package insert is considered unexpected. Events that are not mentioned in the package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but not specifically mentioned as occurring with the particular drug under investigation, are considered unexpected.

### 9.5 Identification of Safety Events

As subjects in this study may have pre-existing medical conditions and will be currently hospitalized, those pre-existing conditions will not be considered as adverse events unless they worsen or increase in frequency or

intensity after administration of study drug. New events that occur or the worsening in frequency or intensity of pre-existing conditions will be reported as adverse events or, if serious reporting criteria are met, serious adverse events. Events that do *not* qualify as an Adverse Event for the STRESS trial and should not be recorded in the eCOS clinical database are:

- Medical or surgical procedures (e.g. surgery, transfusion); however, the condition that required the procedure is considered an adverse event if the situation developed or worsened due to study drug administration
- Pre-existing diseases or baseline conditions present or detected before the start of study drug that do not worsen in frequency or intensity due to study drug administration
- Any events considered to be related to the patients underlying heart disease or recovery from his/her cardiac surgery, including any of the post-operative complications listed in the STS-CHSD.

#### **9.6 Serious Adverse Events that are assessed by the site investigator as Not related or Unlikely related to study drug Study-specific Endpoints and Adverse Events of Interest**

Specific events in this study are Endpoints or Adverse Events of Interest, both of which will be recorded in the site's institutional surgical database, STS-CHSD.

- The following Endpoints will **also** be recorded on the eCOS Serious Adverse Event eCRF if assessed as related to study drug by the site investigator:
  - Death (cause of death)
  - Multi-system organ failure
- The following Adverse Events of Interest will **also** be recorded on the eCOS Serious Adverse eCRF page if assessed as related to study drug by the site investigator:
  - Events Pulmonary hypertension or Pulmonary hypertensive crisis,
  - Arrhythmia,
  - Respiratory failure,
  - Seizure,
  - Stroke

#### **9.7 Safety Monitoring**

The data coordinating center (DCC) will monitor safety during the conduct of the study. The study sponsor will review all potential unexpected study drug related serious adverse events at the time of SAE notification by DCRI Safety Surveillance and confirm whether the event is a suspected unexpected serious adverse reaction (SUSAR). The data monitoring committee (DMC) will monitor safety every 6 months as per the DMC charter. Annual and expedited reports will be submitted to the FDA as required.

#### **9.8 Dose Interruptions for Serious Adverse Events**

If the patient experiences an SAE thought to be related to study drug, subsequent doses may be held at the discretion of the site investigator. The decision will be discussed with the study PI / IND sponsor. For an SAE not thought to be due to study drug, no interruption is necessary.

## 9.9 Halting Rules

All patients who receive study medication will be followed for safety. An independent data monitoring committee consisting of three physicians will conduct an internal review of study safety every 6-months of study enrollment. The safety review will include all SAEs and all AEs captured in either the STS-CHSD or the separate eCOS clinical database that the data monitoring committee determine are possibly or probably related to the study drug and all patients who discontinued participation in the study early. Study halting criteria will include:

1. Five or more instances of any study drug related AE.
2. Serious adverse reactions occur in  $\geq 2$  subjects in any study drug group

If the study is halted, the AEs will be thoroughly evaluated and study enrollment will not resume until the safety review is completed.

## 9.10 Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multi-Center Clinical Trials

The site Investigator or designee is responsible for reporting all serious adverse events to the local IRB/REB in accordance with local policies and procedures.

## 9.11 Follow-up of Subjects after Adverse Events

For Serious AEs with a positive causal relationship to the study drug, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator.

## 9.12 Study Suspension

Study enrollment and administration of study drug will be stopped for a safety review if:

- $>3$  subjects experience **active** (not placebo) **study drug-related** SAEs of the same Preferred Term (MedRA coding) or
- at the discretion of the study PI.

# 10 STATISTICS

## 10.1 Planned Sample Size

The trial's sample size was formulated to provide high power ( $>90\%$ ) for detecting a clinically important treatment benefit in patients randomized to steroids versus placebo as measured by the trial's primary global ranking endpoint categories with testing based on the Wilcoxon rank sum test or, equivalently, the proportional odds logistic regression model score test [24]. The magnitude of the hypothesized treatment effect of steroids versus placebo was quantified by the win difference  $P_1 - P_0$  where  $P_1$  is the probability that a randomly selected patient in the steroids group will have a better outcome (higher global ranking category) than a randomly selected patient in the placebo group and  $P_0$  is the probability that a randomly selected patient in the steroids group will have a worse outcome (lower global ranking category) than a randomly selected patient the placebo group. As shown in Table 6, a sample size of approximately 1,200 participants will provide approximately 85% power if the win difference is 0.10 and will provide 95% power if the win difference is 0.12. Thus, the study has good power

to detect a meaningful improvement in the probability of a better outcome with steroids compared to placebo. For an alternative perspective on the study's power, the treatment effect of steroids versus placebo may be quantified by specifying the extent to which the odds of having an outcome in one of the  $k$  lowest (worst) global ranking categories is reduced in patients randomized to steroids versus placebo, where  $k \leq 1$  refers to the odds of death,  $k \leq 2$  refers to the odds of death or heart transplant, etc. Specifically, the treatment effect may be quantified by the set of odds ratios

$$OR_{\leq k} = \frac{\text{odds of having an outcome in category } \leq k \text{ if randomized to steroids}}{\text{odds of having an outcome in category } \leq k \text{ if randomized to placebo}}, k = 1, 2, \dots, 96,$$

where for simplicity we may assume that  $OR_1 = OR_2 = \dots = OR_{96} (\equiv OR)$ . As shown in Table 6, a sample size of 1,200 participants will provide approximate 82% power if the odds ratio is 0.75 (i.e. a 25% reduction in the odds) and approximately 95% power if the odds ratio is 0.70 (i.e. a 30% reduction in the odds). Thus, the study is well powered under a range of clinically relevant and plausible risk reduction scenarios. For simplicity, power statements above are based on approximate power using a Wilcoxon test ignoring baseline covariates. However, to increase statistical power, analysis of the primary endpoint will be adjusted for baseline covariates, as described in Section 10.3 below. Based on Monte Carlo simulations, a covariate adjusted analysis will increase power by an amount ranging from 3 to 5 percentage points compared to an unadjusted analysis under assumptions consistent with 80%-90% power for the unadjusted analysis.

**Table 6. Estimated power as a function of the effect size as quantified by the win difference or odds ratio assuming N = 1,200 (600 per group)**

Effect Size Parameter	Win Difference ( $P_1 - P_0$ )			Odds Ratio (OR)		
Numerical Effect Size	0.10	0.11	0.12	0.75	0.725	0.70
Power (N = 1,200)	85%	91%	94%	82%	90%	95%

Assumptions: Based on two-sided  $\alpha=0.05$ . Power was calculated as  $\Pr[X_{n,\Delta}^2 > 3.841]$  where  $X_{1,n,\Delta}^2$  denotes a chi-squared random variable with 1 degree of freedom and non-centrality parameter  $n\Delta$ , where  $n = 1200$  and  $\Delta = 3(P_1 - P_0)^2 / (4\rho)$  (derived from formulas in Zhao et al.[25]) or  $\Delta = \log(OR) / (12\rho)$  (derived from formulas in Whitehead [26]) where  $\rho$  is the probability that 3 randomly selected trial participants will not all have outcomes in the same global ranking category. The quantity  $\rho$  reflects the reduction in variance due to ties and was set to its maximum possible value ( $\rho = 1$ ) in order to obtain a conservative lower bound approximation of power. Calculations do not account for an expected slight loss of power after decreasing alpha to account for interim analyses.

## 10.2 Statistical Analysis Plan

All major treatment comparisons between the randomized groups will be performed according to the principle of "intention-to-treat"; that is, subjects will be analyzed (and endpoints attributed) according to the group to which subjects were randomized, regardless of subsequent medications or treatment crossover. Statistical comparisons will be performed using 2-sided significance tests.

## 10.3 Analysis of the Primary Endpoint

The trial's global ranking endpoint outcome is an ordinal categorical variable having  $K$  levels, where category 1 represents the worst possible outcome (e.g. death) and category  $K$  represents the best possible outcome (e.g. a short hospital stay free of death or major complications) according to a pre-specified subjective global ranking algorithm (see above). The observed distribution of ranking categories will be compared across treatment groups using a stratified non-parametric Wilcoxon rank sum test (also known as the van Elteren test [27]) with stratification by categories of pre-randomization predicted mortality or morbidity risk or by using a regression-based analog of the van Elteren test which allows adjusting for multiple pre-randomization prognostic factors in order to maximize statistical power [28]. Covariates for stratification or covariate adjustment will be determined

prospectively and will be pre-specified in the statistical analysis plan. The level of significance for the assessment of the primary endpoint will be  $\alpha=0.05$  (two-sided). The magnitude of the treatment effect will be described by presenting summary measures of the frequency distribution of ranking categories by treatment group and by estimating the probability that a randomly selected steroids group participant will have a better or worse outcome than a randomly selected placebo group participant (e.g. the win ratio [29]). If the data provide evidence of an overall difference in outcome between treatment groups, we will further examine whether the therapeutic effect is similar for all participants, or whether it varies according to specific participant characteristics, which will be pre-specified in the statistical analysis plan. These analyses will use ordinal regression models and will involve testing for interactions between treatment and these specific baseline variables. Effect estimates for subgroups will be carefully (conservatively) interpreted in conjunction with the formal interaction tests.

#### **10.4 Analysis of Secondary Safety and Efficacy Endpoints**

Secondary endpoints will be analyzed via regression modeling with adjustment for pre-randomization covariates. For secondary endpoints that are binary (e.g. mortality, composite mortality or major complications, low cardiac output syndrome), the form of the model will be a logistic regression comparing the endpoint event rate across the two treatment groups. For continuous outcomes with skewed distributions (e.g., post-operative hospital length of stay, duration of mechanical ventilation) the outcome will be approximated by a skewed distribution such as log-normal, Weibull or negative binomial. For safety analyses, we will summarize the number of adverse events overall, by severity, and by each Medical Dictionary for Regulatory Activities system organ class and preferred term. We will tabulate adverse event data by procedural risk cohort (STAT levels).

#### **10.5 Interim Analyses**

Interim examination of clinical endpoints and key safety events will be performed at regular intervals during the course of the trial. An independent Data and Safety Monitoring Board (DSMB) will monitor participant safety and review performance of the trial. The primary objective of these interim analyses will be to ensure the safety of the participants enrolled in the trial and evaluate the accumulating endpoint data by treatment group to test for possible differences favoring either of the two randomized management strategies. In addition, interim monitoring will involve a review of participant recruitment, compliance with the study protocol, status of data collection, and other factors which reflect the overall progress and integrity of the study.

Formal interim treatment group comparisons will focus on comparing the distribution of the primary global ranking endpoint categories by treatment group. To account for repeated significance testing of the accumulating data, the group sequential method of Lan and DeMets will be used as a guide for interpreting these interim analyses. Monitoring boundaries for the primary endpoint will be based on a two-sided symmetric O'Brien-Fleming type spending function with an overall two-sided significance level of  $\alpha = 0.05$ . The O'Brien-Fleming approach requires large critical values early in the study but relaxes (i.e., decreases) the critical value as the trial progresses. These proposed monitoring boundaries are intended as a guide for interpreting the interim analyses and not as a strict rule for early termination. The first interim analysis using alpha spending will be targeted to occur after completion of data collection for the first 600 subjects. Additional interim analyses will be performed at intervals determined by the DSMB.

## 10.6 Data Safety and Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be appointed by the trial's leadership to monitor participant safety and to review performance of the trial. A DSMB charter that outlines the operating guidelines for the committee and the procedures for the interim evaluations of study data will be developed by the trial's leadership and agreed upon by the DSMB. Reports will be prepared regularly in accordance with the plan outlined in the charter and as requested by the DSMB chair, and will include interim analyses of primary and secondary endpoints; additional safety events; and other information as requested by the committee. After each meeting, the DSMB will make recommendations to the trial's leadership about the continuation of the study. After approval by trial leadership, a summary of the DSMB report and recommendations will be forwarded to site investigators for submission to their local IRB.

## 10.7 Population for Analysis

- Efficacy: All participants who are randomized.
- Safety: All participants who receive at least 1 dose of study drug.
- PK/PD/Biomarkers: All participants who receive at least 1 dose of methylprednisolone and have at least 1 evaluable PK sample.

# 11 DATA MANAGEMENT

## 11.1 Data entry

The majority of data for the STRESS trial will be captured via the STS-CHSD. Sites must enter the randomization ID into the participating subjects STS-CHSD record under the “STS-related clinical trial ID” tab. This identifier must be entered into the STS database, as well as all other trial databases (see below for descriptions) immediately after it is assigned. This identifier will be used to link the three databases. For other variables, the STS-CHSD includes specific data element definitions that must be closely followed (see section 11.2).

Serious, unexpected, study drug-related adverse events may require expedited reporting and therefore must be collected in an expedited fashion. Since the STS-CHSD data are only harvested every 6-months, a separate eCOS database has been developed to capture these events. Study drug-related serious adverse events must be submitted into the eCOS database within 1 business day of first becoming aware of the event. The eCOS database will also be used to capture a select subset of additional variables including timing of medication administration, adverse events of interest that are felt to be study drug-related (see section 9.2) and timing of PK/PD/Biomarker sample collection (for participating sites).

In addition, a small subset of select post-operative laboratory administration variables (Table 4) need to be captured but are not incorporated into the STS-CHSD. These data must be collected from the electronic health record. Some sites will be using the RedCap Dynamic Data Pull (DDP) mechanism to facilitate capturing these variables. These sites will receive training before implementation of the RedCap DDP. Sites not using DDP will enter the data directly into the eCOS database.

As summarized above, the STS-related clinical trial ID will be used to link the three databases. As a safety control, sites will also enter the “STS participant ID” into the eCOS database and the REDCap DDP database. In

the event that the STS-related clinical trial ID is mis-entered into one of the databases, the participant ID will be used to ensure accurate linkage.

## 11.2 Data Element Definitions

All STRESS data element definitions are based upon the STS-CHSD data element definitions which are available on-line at: [http://www.sts.org/sites/default/files/documents/CongenitalDataSpecsV3\\_3\\_Updated.pdf](http://www.sts.org/sites/default/files/documents/CongenitalDataSpecsV3_3_Updated.pdf). Some specific definitions of particular relevance to the STRESS trial are listed below:

**Fundamental diagnosis:** The fundamental diagnosis is a diagnosis that is carried with a patient throughout life, through all operations and hospitalizations. *The fundamental diagnosis is the most complex cardiac anomaly or condition (congenital or acquired) of the patient.* Most frequently, the primary diagnosis will also be the fundamental diagnosis. For some operations, however, the fundamental diagnosis and primary diagnosis will be different. For example, consider a child who underwent repair of subaortic stenosis, subsequently develops complete atrioventricular (AV) block, and undergoes pacemaker placement within the same hospitalization. The primary diagnosis for the pacemaker surgery is “Arrhythmia, Heart block, Acquired”, while the fundamental diagnosis is “Aortic stenosis, Subvalvar”. Similarly, a patient who has a complete AV canal defect and undergoes either palliation or repair of the defect has a primary and fundamental diagnosis of “AVC (AVSD), Complete CAVSD”. Subsequently, the child develops mitral insufficiency and is re-hospitalized for mitral valve replacement. The primary diagnosis for the mitral valve replacement operation is “Mitral regurgitation”, but the fundamental diagnosis is “AVC (AVSD), Complete CAVSD.” The utilization of the fundamental diagnosis field, it is hoped, will clarify designation of a primary diagnosis, and enable greater specificity in the lesion specific report analyses.

### STS-CHSD data element definitions for primary outcome measures:

**Death:** For the purposes of STRESS, we will use the STS-CHSD definition of operative mortality which includes: (1) all deaths, regardless of cause, occurring during the hospitalization in which the operation was performed, even if after 30 days (including patients transferred to other acute care facilities); and (2) all deaths, regardless of cause, occurring after discharge from the hospital, but before the end of the thirtieth postoperative day.

**Heart transplantation:** Includes any technique, allograft or xenograft.

**Renal failure requiring permanent dialysis at discharge:** Renal failure - acute renal failure (ROOT Definition) + with new postoperative/postprocedural requirement for dialysis, including peritoneal dialysis and/or hemodialysis. Code this complication if the patient requires dialysis at the time of hospital discharge or death in the hospital. (This complication should be chosen only if the dialysis was associated with acute renal failure.) {"Renal failure - acute renal failure" ROOT Definition = Acute renal failure is defined as new onset oliguria with sustained urine output < 0.5 cc/kg/hr for 24 hours and/or a rise in creatinine > 1.5 times upper limits of normal for age (or twice the most recent preoperative/preprocedural values if these are available), with eventual need for dialysis (including peritoneal dialysis and/or hemodialysis) or hemofiltration. Acute renal failure that will be counted as an operative or procedural complication must occur prior to hospital discharge or after hospital discharge but within 30 days of the procedure. The complication is to be coded even if the patient required dialysis, but the treatment was not instituted due to patient or family refusal.

**Neurological deficit persisting at discharge:** Newly recognized and/or newly acquired deficit of neurologic function leading to inpatient referral, therapy, or intervention not otherwise practiced for a similar unaffected inpatient, with a persisting neurologic deficit present at hospital discharge. In other words, new (onset

intraoperatively or postoperatively – or intraprocedurally or postprocedurally) neurological deficit persisting and present at discharge from hospital.

**Respiratory failure, requiring tracheostomy:** Failure to wean from mechanical ventilation necessitating the creation of a surgical airway.

**Renal failure requiring temporary dialysis:** Acute renal failure (ROOT Definition) + With new postoperative/postprocedural requirement for temporary dialysis, including peritoneal dialysis and/or hemodialysis. Code this complication if the patient does not require dialysis at the time of hospital discharge or death in the hospital. (This complication should be chosen only if the dialysis was associated with acute renal failure.) {"Renal failure – acute renal failure" ROOT Definition = Acute renal failure is defined as new onset oliguria with sustained urine output < 0.5 cc/kg/hr for 24 hours and/or a rise in creatinine > 1.5 times upper limits of normal for age (or twice the most recent preoperative/preprocedural values if these are available), with eventual need for dialysis (including peritoneal dialysis and/or hemodialysis) or hemofiltration. Acute renal failure that will be counted as an operative or procedural complication must occur prior to hospital discharge or after hospital discharge but within 30 days of the procedure.

**Postoperative/Postprocedural mechanical circulatory support:** Utilization of postoperative/postprocedural mechanical support, of any type (IABP, VAD, ECMO, or CPS), for resuscitation/CPR or support, during the postoperative/postprocedural time period. Code this complication if it occurs (1) within 30 days after surgery or intervention regardless of the date of hospital discharge, or (2) after 30 days during the same hospitalization subsequent to the operation or intervention.

**Unplanned cardiac operation during the postoperative or postprocedural time period, exclusive of reoperation for bleeding:** Any additional unplanned cardiac operation occurring (1) within 30 days after surgery or intervention in or out of the hospital, or (2) after 30 days during the same hospitalization subsequent to the operation or intervention. A cardiac operation is defined as any operation that is of the operation type of "CPB" or "No CPB Cardiovascular". The following operations will always be coded as "Planned Reoperation": (1) Delayed Sternal Closure, (2) ECMO Decannulation, (3) VAD Decannulation, (4) Removal of Broviac catheter. The following operations will always be coded as "Unplanned Reoperation": (1) Mediastinal exploration for infection, (2) Mediastinal exploration for hemodynamic instability, (3) Emergent mediastinal exploration for initiation of ECMO or VAD, (4) Reoperation for residual or recurrent lesion. Mediastinal exploration for bleeding is always coded separately as "Bleeding, Requiring reoperation".

**Reoperation for bleeding:** Postoperative/postprocedural bleeding requiring reoperation.

**Unplanned non-cardiac reoperation:** Any additional unplanned non-cardiac operation occurring (1) within 30 days after surgery or intervention in or out of the hospital, or (2) after 30 days during the same hospitalization subsequent to the operation or intervention.

**Unplanned interventional cardiovascular catheterization procedure:** Any unplanned interventional cardiovascular catheterization procedure occurring (1) within 30 days after surgery or intervention in or out of the hospital, or (2) after 30 days during the same hospitalization subsequent to the operation or intervention.

**Cardiac arrest:** A cardiac arrest is the cessation of effective cardiac mechanical function. This complication should be selected if the cardiac arrest developed after OR Entry Date and Time. Do not select this complication for patients under hospice care or DNR.

**Multi-System Organ Failure:** *Note – this is the only complication variable where the STS-CHSD definition has been modified. The current STS-CHSD definition is non-specific therefore we have developed the following definition for specific use during the STRESS trial.*

Multi-system Organ Failure requires two or more of the following to be present:

- Neurologic dysfunction: any permanent or transient neurologic injury including clinical seizure
- Renal dysfunction: serum creatinine > 2 times baseline or temporary or permanent dialysis
- Hepatic dysfunction: AST or ALT > 2 times normal
- GI dysfunction: Any surgical or medically treated episode of Necrotizing enterocolitis
- Respiratory dysfunction: Mechanical ventilation > 7 days

Please code the individual organ system failures as well. If multi-system organ failure is associated with sepsis as well, please also code: "Sepsis, Multisystem Organ Failure".

**STS-CHSD data element definitions for infectious complications**

**Pneumonia:** A “respiratory disease characterized by inflammation of the lung parenchyma (including alveolar spaces and interstitial tissue), most commonly caused by infection”. Pneumonia is diagnosed by appropriate clinical findings (such as fever, leukopenia or leukocytosis, and new onset of purulent sputum) and one or more of the following: positive cultures (of sputum or pulmonary secretions) and / or pulmonary infiltrate on chest xray. An endotracheal tube culture may or may not be positive. Patients commonly demonstrate an evolving area of focal lung consolidation accompanied by fever (>38.5). Pneumonia (pneumonitis) may affect an entire lobe (lobar pneumonia), a segment of a lobe (segmental or lobular pneumonia), alveoli contiguous to bronchi (bronchopneumonia), or interstitial tissue (interstitial pneumonia). These distinctions are generally based on x-ray observations.

**Sepsis:** Evidence of serious infection accompanied by a deleterious systemic response. In the time period of the first 48 postoperative or postprocedural hours, the diagnosis of sepsis requires the presence of a Systemic Inflammatory Response Syndrome (SIRS) resulting from a proven infection (such as bacteremia, fungemia or urinary tract infection). In the time period after the first 48 postoperative or postprocedural hours, sepsis may be diagnosed by the presence of a SIRS resulting from suspected or proven infection. During the first 48 hours, a SIRS may result from the stress associated with surgery and/or cardiopulmonary bypass. Thus, the clinical criteria for sepsis during this time period should be more stringent. A systemic inflammatory response syndrome (SIRS) is present when at least two of the following criteria are present: hypo- or hyperthermia (>38.5 or <36.0), tachycardia or bradycardia, tachypnea, leukocytosis or leukopenia, and thrombocytopenia.

**Deep wound infection:** A deep wound infection involves the deep soft tissues (e.g., fascial and muscle layers) of the incision AND the patient has at least ONE of the following numbered features: 1) Purulent drainage from the deep portion of the incision (but not from the organ / space component of the surgical site and no evidence of sternal osteomyelitis), 2) The deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has ONE of the following lettered signs or symptoms (unless the incision is culture negative): A) fever, B) localized pain, or C) tenderness, 3) An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination, or 4) A diagnosis of a deep wound infection by a surgeon or by an attending physician.

**Wound infection-Mediastinitis:** The diagnosis of mediastinitis must meet one of the following criteria: Criterion 1: Patient has organisms cultured from mediastinal tissue or fluid that is obtained during a surgical operation or by needle aspiration. Criterion 2: Patient has evidence of mediastinitis by histopathologic examination or visual evidence of mediastinitis seen during a surgical operation. Criterion 3: Patient has at least ONE of the following numbered signs or symptoms with no other recognized cause: 1) fever, 2) chest pain, or 3) sternal instability AND at least one of the following numbered features: 1) purulent mediastinal drainage, 2) organisms cultured from mediastinal blood, drainage or tissue, or 3) widening of the cardio-mediastinal silhouette. Criterion 4: Patient ≤ 1 year of age has at least one of the following numbered signs or symptoms with no other recognized cause: 1) fever, 2) hypothermia, 3) apnea, 4) bradycardia, or 5) sternal instability AND at least one of the following

numbered features: 1) purulent mediastinal discharge, 2) organisms cultured from mediastinal blood, drainage or tissue, or 3) widening of the cardio-mediastinal silhouette. Infections of the sternum (sternal osteomyelitis) should be classified as mediastinitis. Sternal instability that is not associated with a wound infection or mediastinitis is documented as "Sternal instability".

**Postprocedural infective endocarditis:** Infective endocarditis in the setting of a heart which has been altered by surgery or intervention. Duke Criteria for the Diagnosis of Infective Endocarditis (IE): The definitive diagnosis of infective endocarditis requires one of the following four situations: 1) Histologic and/or microbiologic evidence of infection at surgery or autopsy such as positive valve culture or histology; 2) Two major criteria; 3) One major criterion and three minor criteria; 4) Five minor criteria. The two major criteria are: 1) Blood cultures positive for IE 2) Evidence of endocardial involvement. Blood cultures positive for IE requires: 1) Typical microorganism consistent with IE isolated from 2 separate blood cultures, as noted in number two below (viridans streptococci, *Streptococcus bovis*, *Staphylococcus aureus*, or HACEK group [*HACEK*, *Haemophilus* species {*H. aphrophilus* and *H. paraprophyllus*}, *Actinobacillus actinoinyctemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*.]) or (Community-acquired enterococci in the absence of a primary focus); 2) Microorganisms consistent with IE isolated from persistently positive blood cultures defined as: (At least 2 positive cultures of blood samples obtained > 12 hours apart) or (All of 3 or a majority of 4 or more separate cultures of blood, the first and the last sample obtained > 1 hr apart); 3) Single blood culture positive for *Coxiella burnetii* or an antiphase I IgG antibody titer of >1 :800. Evidence of endocardial involvement requires 1) Positive results of echocardiography for IE defined as: (Oscillating intracardiac mass on the valve or supporting structures in the path of regurgitant jets or on implanted material in the absence of an alternative anatomic explanation) or (Abscess) or (New partial dehiscence of a valvular prosthesis) or 2) New valvular regurgitation (worsening or changing or preexisting murmur not sufficient). The six minor criteria are: 1) Predisposing heart disease or injection drug use (IVDA); 2) Temperature of > 38C; 3) Vascular phenomenon (major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial or conjunctival hemorrhage, Janeway's lesions); 4) Immunologic phenomenon (glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor); 5) Microbiologic evidence (a positive blood culture that does not meet a major criterion as noted above) or serologic evidence of active infection with an organism consistent with IE; 6) Echocardiographic findings that are consistent with IE but do not meet a major criterion as noted above. References: 1) Dhawan VK Infectious Endocarditis in Elderly Patients. Clin. Infect. Dis. 2002;34:806- 812. 2) Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. Am. J. Med. 1994;96:200-209. 3) Li IS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin. Infect. Dis. 2000;30:633-638. 4) <http://gold.aecom.yu.edu/id/almanac/dukeendocarditis.htm>, accessed July 5, 2006.

### **Select STS-CHSD data element definitions of particular relevance**

**Cardiac dysfunction resulting in low cardiac output:** Low cardiac output state characterized by some of the following: tachycardia, oliguria, decreased skin perfusion, need for increased inotropic support (10% above baseline at admission), metabolic acidosis, widened Arterial – Venous oxygen saturation, need to open the chest, or need for mechanical support. If the cardiac dysfunction is of a severity that results in inotrope dependence, mechanical circulatory support, or listing for cardiac transplantation, please also code as "Cardiac failure (severe cardiac dysfunction)". A patient will be considered to have "inotrope dependence" if they cannot be weaned from inotropic support (10% above baseline at admission) after any period of 48 consecutive hours that occurs after the time of OR Exit Date and Time, and either (1) within 30 days after surgery in or out of the hospital, and (2) after 30 days during the same hospitalization subsequent to the operation. If patient meets criteria for severe cardiac dysfunction, only code "severe".

## **12 ETHICS AND HUMAN SUBJECTS CONSIDERATION**

### **12.1 Institutional Review Board/Independent Ethics Committee Approval**

Prior to its implementation, this protocol, including any subsequent amendments, must be IRB approved at each respective site, according to federal regulations.

### **12.2 Signed Informed Consent / Authorization**

Prior to any study-related procedures, the investigator or designee will obtain from the patient's legally authorized representative (i.e., parent/legal guardian), a signed and dated written Informed Consent/Authorization consistent with FDA/ICH regulations, the HIPAA Privacy Rule. A HIPAA Privacy Rule Authorization language will be included in the Informed Consent/Authorization Form (where the Informed Consent and Authorization are combined in one document) and it will be IRB approved.

### **12.3 Duties of the Investigator**

The investigator is obligated to conduct this study in accordance with U.S. federal regulation 21 CFR 312.60-69 as specified on the signed form FDA 1572, applicable state laws, and the International Conference on Harmonization: Good Clinical Practice: Consolidation Guideline. The investigator is responsible for informing the IRB of any safety issues related to the study and the study drug including reports of serious adverse events, if required, and all IND safety reports.

### **12.4 Records of the Study**

A STS-CHSD will be used to record all patient data including all historical subject information and study data as specified by this protocol. The STS-CHSD data entry must be completed by designated and trained study personnel.

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, e-mail correspondences, computer printouts, laboratory data and recorded data from automated instruments.

It will be the responsibility of the Investigator(s) to assure that the study file at the site is maintained. The study file will contain, but will not be limited to:

- Current Package Insert and all previous versions over course of study
- Final study protocol
- Protocol Amendments (if applicable)
- Operations Manual (if applicable)
- Informed Consent Form (blank)
- Revised Informed Consent forms and/or all addenda (blank)
- DHHS Number for IRB or other documentation of IRB compliance with FDA regulations (if applicable)
- Documentation of IRB approval of protocol, consent form, any protocol amendments and any consent form revisions.
- Annual IRB updates and approvals
- All correspondence between the Investigator and IRB

## **12.5 Patient Privacy / Authorization**

The principal investigator will ensure that the use and disclosure of protected health information obtained during a research study complies with the HIPAA Privacy Rule. The Rule provides U.S. federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of patients participating in Clinical Trials. “Authorization” is required from each research patient, i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual’s protected health information. A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization will be combined in the Informed Consent document (approved by the IRB).

## **12.6 Informed Consent**

Informed consent will be obtained and documented in accordance with U.S. 21 CFR Part 50.25, §§ 116, 117 and 408 of 45 CFR Part 46 and all other applicable regulatory requirements. Prior to any study procedures being performed, the investigator or his/her designee will inform the subject’s legally authorized representative (e.g., parent, guardian) of all aspects pertaining to study participation. Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB. The subject’s legally authorized representative (parent or guardian) must be given ample opportunity to inquire about details of the study. The description of the study procedures will include the purpose of the research and procedures, risks and benefits of the research, alternative procedures, confidentiality, legal rights, parental or guardian permission, the contact person and phone number if there are any questions, and the voluntary nature of participation. It will be emphasized that participation is voluntary and participants may withdraw from the study at any time without any effect on standard care. Both the investigator or his/her designee, and the subject’s legally authorized representative must sign and date the informed permission form prior to the subject being enrolled in the study. An original signed informed consent will be retained in the site study records. The subject’s legally authorized representative will receive a copy of the signed and dated informed permission form and a copy of the signed assent (if applicable).

Permission forms must be in a language fully comprehensible to the subject’s legally authorized representative. Permission shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject’s legally authorized representative. The written parental/legal guardian permission document will embody the elements of informed consent as described in the Declaration of Helsinki, the Code of Federal Regulations, and the ICH Guidelines and will comply with local regulations. This form may be read to the subject’s legally authorized representative, but, in any event, the investigator shall give the representative adequate opportunity to read it before it is signed and dated. Permission must be documented by the dated signature of the subject’s legally authorized representative. The signature confirms the permission is based on information that has been understood. Each signed permission form must be kept on file by the investigators for possible inspection by Regulatory Authorities.

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### **13 PHARMACOLOGY AND TOXICOLOGY INFORMATION**

The Sponsor has not and will not conduct non-clinical studies of methylprednisolone. Information on its pharmacology and toxicology can be found in the sample product label, see Section 10.3

## **14 PREVIOUS HUMAN EXPERIENCE**

Please refer to product label (Appendix B).

## **15 APPENDICES**

**15.1 Appendix A1: Case report form for the STS-CHSD**

**15.2 Appendix A2: Data element definitions for the STS-CHSD**

### **15.3 Appendix B: Package insert for intravenous methylprednisolone**

#### **15.4 Appendix C: Plasma PK sampling and handling**

Timing of samples will treat the time of initial drug administration as time (0). The date and time will be recorded for the time of drug administration and for the acquisition time of the PK sample. The PK/PD/Biomarker samples will be obtained in sodium heparin collection tubes.

1. For the scheduled pharmacokinetic draws, one 800uL blood sample will be collected from a peripheral IV or central line site into the provided sodium heparin tubes, and placed on ice.
2. Immediately, within one-half hour of the blood draw, centrifuge at 3,500 g for 5 minutes at approximately 4°C.
3. Transfer plasma into the provided polypropylene screw cap transfer tubes.
4. Transfer tubes should be labeled with a pre-printed label containing site, patient number, and protocol collection time. Ensure that the pre-printed label corresponds to the recorded date and time of collection on the CRF.
5. Immediately freeze the specimens (-70°C) in an upright position. Notify the Protocol Chair immediately if the samples become thawed or damaged.
6. Ship frozen at times specified, to the designated specialty laboratory.