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RATIONALE AND DESIGN OF THE STERIODS TO REDUCE SYSTEMIC INFLAMMATION AFTER INFANT HEART SURGERY (STRESS) TRIAL

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Abstract

For decades, physicians have administered corticosteroids in the perioperative period to infants undergoing heart surgery with cardiopulmonary bypass (CPB) to reduce the post-operative systemic inflammatory response to CPB. Some question this practice because steroid efficacy has not been conclusively demonstrated and because some studies indicate that steroids could have harmful effects. STRESS is a randomized, placebo-controlled, double blind, multi-center trial designed to evaluate safety and efficacy of perioperative steroids in infants (age < 1 year) undergoing heart surgery with CPB. Participants (planned enrollment = 1200) are randomized 1:1 to methylprednisolone (30mg/kg) administered into the CPB pump prime versus placebo. The trial is nested within the existing infrastructure of the Society of Thoracic Surgeons Congenital Heart Surgery Database (STS-CHSD). The primary outcome is a global rank score of mortality, major morbidities and hospital length of stay with components ranked commensurate with their clinical severity. Secondary outcomes include several measures of major post-operative morbidity, post-operative hospital length of stay and steroid-related safety outcomes including prevalence of hyperglycemia and post-operative infectious complications. STRESS will be one of the largest trials ever conducted in children with heart disease and will answer a decades old question related to safety and efficacy of perioperative steroids in infants undergoing heart surgery with CPB. The

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pragmatic “trial within a registry” design may provide a mechanism for conducting low cost, high efficiency trials in a heretofore-understudied patient population. Trial Registration Number:

Keywords

congenital heart disease; perioperative steroids; trial; cardiopulmonary bypass

INTRODUCTION

Despite major advances in management, congenital heart disease (CHD) requiring surgery during infancy is associated with relatively poor outcomes; National registry data document operative mortality in ~4% of infants undergoing CPB operations with major morbidities including neurologic injury, renal failure, unplanned reoperation, cardiac arrest and need for post-operative mechanical circulatory support, in ~20–30%.^(1–4) These outcomes are often associated with a severe systemic inflammatory response to cardiopulmonary bypass (CPB).^(5–8) To reduce the post-CPB inflammatory reaction, many centers routinely administer pre- or intra-operative steroids.^(9–17) This approach has been utilized for decades yet existing data on the safety and efficacy of perioperative steroids in infants with CHD are limited and often conflicting.⁽¹⁸⁾ Consequently, registry and survey data demonstrate wide variability in practice patterns with some practitioners routinely administering perioperative corticosteroids, some routinely avoiding corticosteroids, and some employing a selective approach depending on case complexity, and patient age.^(19–21)

A large scale, randomized, controlled trial (RCT) is needed to evaluate the safety and efficacy of steroids in infants in the perioperative setting. However, there are major challenges to conducting RCTs in children with CHD including high costs, the broad heterogeneity of CHD diagnoses and interventions, and a litany of difficulties associated with consenting and enrolling children with CHD in clinical trials.⁽²²⁾ The STRESS (STeroids to REduce Systemic inflammation after infant heart Surgery,) trial aims to overcome these barriers by leveraging the resources of the Society of Thoracic Surgeons Congenital Heart Surgery Database (STS-CHSD). The STRESS trial is a pragmatic “trial within a registry” using the existing infrastructure of the STS-CHSD; a key objective is to facilitate an efficient and cost effective RCT. Here we present the rationale and design of the STRESS trial.

PRIOR STUDIES

Inflammatory response to cardiopulmonary bypass and use of perioperative corticosteroids

Cardiac surgery with CPB elicits a systemic inflammatory cascade stimulated by the body’s immune response to surgical injury, the effects of hypothermia, hemodilution, shear stress within the CPB circuit and cell activation from exposure to both CPB circuit surfaces and transfused blood products.^(8,23) The systemic inflammatory response is broad with both hyper activation and inhibition of immunocompetent cells, stimulation of the complement and coagulation systems as well as increased cytokine production, and endothelial

dysfunction.(8,23) Conventional wisdom is that younger children experience a more pronounced systemic inflammatory response to CPB than adolescents and adults. Low cardiac output syndrome, the most prominent clinical manifestation of systemic inflammation, is seen in less than 10% of adults undergoing CPB but is three to six fold more common in neonates and infants.(5,7,8,18,24,25) The relatively larger size of the CPB circuit is believed to be a major contributing factor; the priming volume of a neonatal circuit is approximately equivalent to the total blood volume of the neonate.(26) In addition the immature immune system is hyper-responsive to CPB-related inflammatory stimuli.(27) Anti-inflammatory steroids have been promoted for decades as a potential therapeutic strategy in children and adults undergoing heart surgery with CPB. Notably there are other hypothetical indications for perioperative corticosteroids. Some providers advocate for use of perioperative corticosteroids to treat “relative adrenal insufficiency” in critically ill infants including those undergoing cardiopulmonary bypass. Adrenal insufficiency is characterized by inappropriately low serum cortisol levels and is hypothesized as one mechanism contributing to post-operative low cardiac output syndrome in some infants. However investigations have been hampered by the absence of any clear consensus on the definition of “relative adrenal insufficiency” and therefore there is no consensus on indications for treatment. Others advocate for the use of perioperative corticosteroids as neuroprotective agents to ameliorate the effects of deep hypothermic circulatory arrest. This effect is more controversial with very limited data to guide appropriate practice.(28)

Late phase adult steroid trials

Several large trials have evaluated the safety and efficacy of perioperative steroids in adults undergoing surgery with CPB. The Dexamethasone for Cardiac Surgery (DECS) trial (29) randomly assigned 4,494 patients > 18 years undergoing cardiac surgery with CPB to receive intraoperative dexamethasone or placebo. There was no significant difference in the prevalence of the primary trial endpoint, a composite mortality or major morbidity measure, between dexamethasone (prevalence = 7%) and placebo groups (prevalence = 8%) (RR 0.83, 95% CI 0.67–1.01, p=0.07). The subsequent Steroids In cardiac SuRgery (SIRS) (30) trial randomized 7,507 patients age > 18 years undergoing cardiac surgery with CPB to placebo versus low dose (~5mg/kg) intraoperative methylprednisolone. Methylprednisolone, compared with placebo, did not reduce the risk of death at 30 days after surgery (154 [4%] vs 177 [5%] patients; relative risk [RR] 0.87, 95% CI 0.70–1.07, p=0.19) or the risk of death or major morbidity (909 [24%] vs 885 [24%]; RR 1.03, 95% CI 0.95–1.11, p=0.52).

Previous steroid trials in children

Existing data on the safety and efficacy of steroids during the perioperative period in children are conflicting. Several randomized, controlled human studies (9–11,13–15,17,31,32) have demonstrated that perioperative steroids reduce post-CPB inflammatory markers. A meta-analysis of the six most well formulated of these trials included only 232 steroid and control children (12). This analysis demonstrated a non-significant trend towards improved post-operative mortality in steroid-treated neonates (4.7% vs 1.7% OR = 0.41 [95% CI 0.14–1.15] p=0.089) and a reduced incidence of post-operative renal dysfunction (8% versus 54% OR = 0.07 [95% CI 0.01–0.38] p = 0.002). However, the six included studies evaluated a range of different steroid formulations (dexamethasone, hydrocortisone

and methylprednisolone), dosing regimens and timing of steroid administration (pre-, peri- and post-operative administration). Moreover, these studies were conducted over more than three decades during which time there has been dramatic evolution in CPB practices, including changes that likely impact the systemic inflammatory response to CPB and therefore potentially affect the risk-benefit profile of perioperative corticosteroids. More recently, Graham and colleagues completed a double blind, randomized, placebo controlled trial at two centers to determine whether intraoperative methylprednisolone improves postoperative recovery in neonates undergoing CPB surgery.(17) Their analysis included 176 subjects (n = 81 methylprednisolone, n= 95 placebo) and they found no difference in the primary outcome, a composite of in-hospital death, mechanical circulatory support, cardiac arrest, hepatic injury, renal injury or rising lactate level ($>5\text{mmol/L}$) (OR = 0.63 [95% CI 0.31–1.3], $p=0.21$). However, methylprednisolone was associated with reductions in vasoactive inotropic requirements. Moreover, there was a significant interaction between treatment effect and center with methylprednisolone protective at 1 center, (OR = 0.35 [95% CI: 0.15 to 0.84], $p = 0.02$), and not so at the other center (OR = 5.13 [95% CI: 0.85 to 30.90], $p = 0.07$). (17)

Registry studies in children

Pasquali and colleagues have conducted two registry-based analyses of corticosteroid efficacy and safety. The first was a propensity-matched analysis of 46,730 children (< 18 years) from 38 centers included in the Pediatric Health Information Systems (PHIS) Database (19). In this analysis, 54% of the overall study cohort received pre- and/or intra-operative corticosteroids while 46% received no corticosteroid therapy. They found no significant differences in mortality when comparing corticosteroid recipients and non-recipients. However, corticosteroid use was associated with significantly longer post-operative ICU length of stay (mean difference, 2.2 days; 95% confidence interval 1.62 to 1.74), higher likelihood of perioperative infection (odds ratio 1.27; 95% confidence interval, 1.10 to 1.46), and greater use of insulin (odds ratio, 2.45; 95% confidence interval 2.24 to 2.67). Subsequently they analyzed linked data from PHIS and the STS-CHSD from 3,180 neonatal CPB surgeries performed from 2004 to 2008 at 25 U.S. centers. Although the study population was smaller than the initial PHIS analysis, the STS-CHSD includes more granular demographic, procedural and outcomes data allowing better adjustment for case-mix variability. In multivariable analysis, steroid administration was not associated with any mortality or length of stay benefit. There was no overall association between steroid administration and post-operative infection, however a subgroup analysis demonstrated increased risk of infection for neonates undergoing lower complexity (Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery [STAT] levels 1–3) operations (odds ratio for infection = 2.6; 95% CI 1.3–5.2). (20)

Current practices

Starting in 2014, pre- and intra-operative steroid administration has been included as a data collection variable in the anesthesia module of the STS-CHSD. Not all STS-CHSD centers participate in the anesthesia database so the data are limited, but do provide some measure of current practice. Of 6,242 infant CPB operations, pre- or intraoperative steroids were administered for 3198 (51.2%) with the majority (n=3016, 94.3%) receiving intra-operative

steroids only. A recent survey of pediatric cardiac anesthesiologists practicing in the United Kingdom demonstrated similarly heterogeneous practices with 35% reporting that they never use corticosteroids, 46% reporting selective use and 19% reporting that they use corticosteroids for every pediatric CPB cases.(33)

Summary of rationale for a trial

The neonatal and infant response to CPB is different from adults; neonates and infants demonstrate both a more pronounced inflammatory reaction and a different post-operative complication profile.(7,25) Low cardiac output syndrome is more commonly seen in neonates and infants than in adults.(5,7,8,18,24,25) For these reasons, it is inappropriate to extrapolate data from adult trials to the pediatric population. Moreover, as summarized above, data from childhood studies of perioperative corticosteroids are both limited and conflicting.(10,12–14,16–20,24,29,31,32,34) Perioperative steroids are currently administered by some providers to neonates and infants undergoing heart surgery with CPB, but others believe that this practice is flawed. Taken together, these data support the need for a large and definitive safety and efficacy trial.

PRAGMATIC TRIAL WITHIN A REGISTRY APPROACH

Although randomized clinical trials (RCT) have been the mainstay of clinical research, traditional RCTs are often slow and expensive, and these challenges are amplified when studying rare diseases in children.(35) The pragmatic “trial within a registry” approach used in STRESS aims to leverage existing registry resources to reduce trial costs and improve trial efficiency.(36) Previous adult trials have demonstrated the potential cost-savings and efficiency benefits of this approach. (37,38) These benefits occur at multiple levels in the STRESS trial. First, registry data including patient demographic information, diagnoses and key outcome measures, mirror our ultimate trial data collection variables. Consequently, we were able to use registry data to evaluate inclusion and exclusion criteria, and we performed Monte Carlo trial simulations to evaluate trial design features such as outcome measures, analytic approaches and study power (trial design described below). Second, we used existing registry data to evaluate site eligibility. The STS-CHSD was initiated in 1994 and currently captures data from nearly all hospitals (>95%) performing CHD surgery in the United States. (25) Using registry data we were able to project patient enrollment at potentially eligible trial sites instead of using traditional “survey” approaches that more often than not represent a best guess of site enrollment potential. Third, because registry data are already collected into the STS-CHSD, the cost of database builds and data collection are markedly reduced with a reduced likelihood of database glitches that might require costly redesigns and updates. STS-CHSD data collection forms are now in their 5th generation and include diagnostic and procedural codes that match the International Pediatric and Congenital Cardiac Code. (39) STS-CHSD data element definitions are familiar to data collection personnel at participating sites and the database has existing quality control measures to ensure data reliability. Nathan et al. recently demonstrated overall registry data accuracy of > 98% across 56,500 data elements (500 subjects, 113 unique fields) when compared with data elements extracted by experienced study coordinators conducting chart review. (40) Fourth, many registries have years of experience with registry-specific analytics.

The STS-CHSD analytic approaches, including mechanisms for risk stratification and case-mix adjustment, have all been validated in previous STS-CHSD publications and provide a mechanism to account for the broad heterogeneity of CHD diagnoses, baseline risk factors and procedural complexity (analytic approach described below).(3,4,41,42) Importantly, demographic, operative and most of the trial outcomes data will be collected using the existing STS-CHSD elements using processes already in place at participating centers. Use of the STS-CHSD registry will greatly reduce the data entry burden for site investigators and monitors. Finally, endpoint adjudication can be simplified by leveraging existing registry infrastructure. The STS-CHSD conducts routine site audits to validate key metrics and ensure appropriate data collection. By focusing trial endpoints on audited data at sites with a proven track record of quality data submission, site-monitoring costs can be significantly reduced. There are also disadvantages to a pragmatic trial design using registry data. Although STRESS will collect a small subset of ancillary data, the majority of data will be limited to variables currently collected within the STS-CHSD. A limited subset of ancillary blood biomarker data will be collected but restricted to routinely performed, clinically indicated laboratory data compiled from the electronic health record; no additional study-specific laboratory data will be collected. Moreover, STRESS has no core lab functionality and will rely entirely on clinician coding of outcomes in the STS-CHSD; echocardiographic data will not be collected and other imaging assessments will not be used to verify key outcomes beyond imaging data performed as part of routine clinical care. Finally, STRESS outcomes will be limited to those that occur during the post-surgical hospitalization or within 30 days of surgery with no capacity to capture longer-term outcomes.

FINAL TRIAL DESIGN

The STRESS trial is a randomized, double blind, placebo-controlled, multi-center trial evaluating the safety and efficacy of single-dose intraoperative methylprednisolone 30mg/kg versus placebo in infants (< 1 year of age) undergoing cardiac surgery with CPB. Planned enrollment is for 1200 subjects, including a targeted minimum of 400 neonates (< 30 post-natal days), at a minimum of 25 centers that currently contribute data to the STS-CHSD and have passed data quality checks to ensure consistency of the reported data (Figure 1). The number of arms, sample size, and details of the primary endpoint were based, in part, on Monte Carlo trial simulations performed using existing STS-CHSD data from 35,967 infant index CPB operations performed at 103 centers from 2011 to 2015. Data from these simulations are being reported separately. Briefly, they demonstrated increased power to detect efficacy and safety signals using a two-arm trial design (study drug vs placebo) with a global rank endpoint consisting of mortality and major complications as well as post-operative hospital length of stay (further details on power and outcome measures outlined below).

Trial population

Neonates and infants (< 1 year of age) undergoing cardiac surgery with CPB are eligible for enrollment. Additional inclusion and exclusion criteria are outlined in Table 1. As of November 5th, 2019 the STRESS trial has enrolled 478 subjects at 18 centers in the United States.

Study drug and administration

Neonates and infants are randomized centrally to methylprednisolone 30mg/kg administered into the cardiopulmonary bypass pump prime versus placebo (Table 2).

A block randomization scheme is employed to ensure equal allocation by study site. The dose regimen (30mg/kg administered into the pump prime) was developed based on a pharmacokinetic (PK) and pharmacodynamics (PD) analysis of samples from a previous methylprednisolone trial (PI Eric Graham, [ClinicalTrials.gov](https://clinicaltrials.gov) identifier).(13) To briefly summarize, this analysis included 65 participants randomized to a single intraoperative dose of methylprednisolone (30mg/kg, n = 30 subjects) versus preoperative + intraoperative methylprednisolone (30mg/kg/dose, n=35 subjects). Results of the PK/PD analysis demonstrated reduced inflammatory markers in response to methylprednisolone but with no differences in post-operative PK or PD parameters when comparing the two-dose regimen to the single dose intraoperative regimen.(13,14)

Primary and secondary outcome measures

A global rank score (Table 3) was selected as the primary endpoint. The score was developed by the investigative team and tested using trial simulations with data from the STS-CHSD.(43) The global rank score was agreed upon by all members of the internal steering committee and then was reviewed/approved by the external steering committee, members of the Data Monitoring Committee (DMC) and the study sponsor. The makeup of these various oversight committees are summarized below in the section on “Trial Organization, Funding and Regulatory Oversight”. There were several reasons for the choice of a global rank score as the primary outcome measure; Like traditional composite endpoints, ranked outcomes can increase the number of events observed or the incidence of the outcome, thereby increasing power to detect clinically meaningful differences. However, unlike traditional composite endpoints, ranked outcomes permit sorting of events according to clinical importance or relevance. For example, our score ranks operative mortality ahead of permanent neurologic injury, which in turn is ranked ahead of post-operative mechanical circulatory support. Finally, the global rank approach permits combinations of binary and continuous outcome measures (e.g. hospital length of stay), which is not feasible with traditional composite scores.

In STRESS, the primary endpoint consists of 98 possible rank scores (Table 3). Endpoints contributing to the global ranking are captured in the STS-CHSD with formal data element definitions that are reviewed with site data entry coordinators at the time of site initiation. Subjects will receive a rank score based upon the worst outcome (highest rank score) that they experience during the study trial (i.e., during hospitalization or 30 days after study drug/placebo administration, whichever is longer). Importantly, in trial simulations, inclusion of length of stay in the composite increased study power by 28 percentage points.

STRESS trial secondary outcome measures include: 1) operative mortality; 2) death or major complication as defined by an outcome in one of the 6 highest global ranking categories (Table 3, numbers 92 to 97); 3) post-operative hospital length of stay; 4) occurrence of prolonged (> 7 days) post-operative mechanical ventilation; 5) occurrence of

post-operative low cardiac output syndrome or severe cardiac dysfunction, and 6) need for administration of hydrocortisone within the first 72 hours of surgery.

STRESS Trial safety outcome measures include: 1) occurrence of any STS-CHSD-defined post-operative complication; 2) hyperglycemia necessitating insulin administration within the first 24 hours of surgery; 3) drug-related serious adverse events (SAEs); and 4) occurrence of an STS-CHSD defined post-operative infectious complication including infective endocarditis, pneumonia, sepsis, deep wound infection or mediastinitis.

Trial Organization, Funding and Regulatory Oversight

The STRESS trial () is funded by a grant from the National Centers for Advancing Translational Sciences (NCATS, 1U01TR001803-01). Additional support is provided through collaborations with the NCATS-sponsored Trial Innovation Network (<https://ncats.nih.gov/ctsa/projects/network>, assisting with trial start-up, contracting and central IRB coordination) and the NICHD-sponsored Pediatric Trials Network (<https://pediatrictrials.org/>, assisting with PK/PD analyses). The Duke Clinical Research Institute is the primary data-coordinating center and Vanderbilt University serves as the central IRB. The trial is being conducted under the auspices of an FDA-issued Investigational New Drug Application (#129,266) from the Division of Cardiovascular and Renal Products and written informed consent is obtained from parents or an authorized legal guardian before enrollment of each infant in the trial. An internal steering committee consisting of four pediatric cardiothoracic surgeons, four pediatric cardiologists, a pediatric cardiac intensivist and a patient advocate, provide continuous trial monitoring and oversight, while a four member external steering committee, including a pediatric cardiologist, pediatric cardiothoracic surgeon, pediatric cardiac intensivist and a patient advocate provide biannual trial review and oversight. An unblinded statistician is assigned to monitor trial safety. A DMC consisting of a pediatric cardiologist, pediatric clinical trial specialist and a biostatistician with expertise in congenital heart surgery will provide biannual, and as needed safety oversight in accordance with a DMC charter prepared and agreed upon prior to trial initiation.

Mechanisms for data capture

STRESS is designed as a “trial within a registry” with a principal objective to design an efficient, low cost trial evaluating a clinically meaningful trial endpoint. Following randomization, trial coordinators will enter the study participant’s randomization subject identifier into their local STS database using the STS-CHSD trial participant identifier. All trial demographic, operative and most outcomes data will be extracted from the STS-CHSD following site submission to the data warehouse. Primary and secondary efficacy endpoints all represent data elements already collected by the STS-CHSD. A small subset of additional safety and laboratory variables are not currently collected by the STS-CHSD. These variables will be captured into a separate, limited IBM Clinical Development (regulatory compliant) study database that will be linked with the STS-CHSD using the participants randomization subject identifier (Figure 2). Serious unexpected suspected adverse reactions (SUSARs) will be reported within 24 hours of the event consistent with FDA standards.

Treatment protocol and follow up

Other than study drug, participants enrolled in the STRESS trial will receive routine post-operative care consistent with local standards. Post-operative steroid administration is permitted at the discretion of the local providers but will be tracked as a secondary outcome measure. Participants will be followed for the duration of their hospitalization following cardiac surgery. Post-discharge mortality will be captured if occurring before the end of the 30th postoperative day.

STATISTICAL CONSIDERATIONS

Sample size

The sample size of 1,200 (600 per group) 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, assuming that the distribution of global ranking categories in STRESS is similar to the STS registry and that outcomes in the steroids group will be shifted toward lower ranking categories by the amounts depicted in Table 3. This distribution assumes a 1.2 percentage point reduction in operative mortality (category 97), a 4.9 percentage point reduction in death or major complications (categories 92–97), and a 6.2 percentage point increase in the proportion of patients who survive without major complications and are discharged within 6 days (categories 0–6). The sample size also provides high power under various distributions that differ from Table 3. If “win probability” denotes the likelihood that a participant from the steroids group has a lower ranking (better) outcome compared to a participant from the placebo group and “loss probability” denotes the likelihood that a participant from the steroids group has a higher ranking (worse) outcome compared to a participant from the placebo group, then a sufficient condition for >90% power under any outcome distribution is that the difference between the win probability minus the loss probability is at least 11 percentage points. Thus, under a broad range of study assumptions, the sample size provides robust power to detect a clinically relevant improvement in the probability of a better outcome with steroids compared to placebo.

Analysis Population

The primary analysis will follow the intention to treat principle meaning that participants will be analyzed according to the group to which the participants were randomized, regardless of subsequent medications or treatment crossover. Because eligibility is defined with respect to surgery, and because the endpoints are defined with respect to the receipt of study drug/placebo (see below), subjects will be considered to be “enrolled” in the trial if they undergo surgery and receive study drug/placebo. Thus, for demographic/baseline, safety, efficacy, and additional analyses, only participants who are randomized and receive the study drug/placebo will be included.

Primary endpoint analyses

The trial's global ranking endpoint outcome is an ordinal categorical variable having 98 levels, where category 97 represents the worst possible outcome (e.g. death) and category 0 represents the best possible outcome (e.g. discharged on the day of surgery without death or major complications) according to a pre-specified subjective global ranking algorithm. The distribution of ordinal global ranking categories will be compared across treatment groups using the Wald or score chi-square test statistic from a proportional odds logistic regression model with a treatment group indicator variable and an indicator variable for site. To account for heterogeneity among trial participants, the model will be adjusted for a pre-specified set of prognostically important baseline covariates to include prematurity, age at surgery, weight at surgery, and STAT mortality category (41).

A small p value for the treatment group variable in this model will suggest that there is a difference in outcomes between the treatment groups, but it will not determine the magnitude of the effect. To estimate the magnitude of the treatment effect of study drug versus placebo, we will present summary measures of the frequency distribution of ranking categories by treatment group and estimate the probability that a randomly selected steroids group participant will have a better or worse outcome than a randomly selected placebo group participant with the Win Ratio(44). Ninety-five percent confidence intervals for the win ratio will also be obtained.

Secondary Endpoint Analyses

Differences in all secondary endpoints except time to operative mortality and post-operative length of stay among treatment groups will be analyzed via regression modeling with adjustment for covariates (described above) and site. Logistic regression will be used for secondary endpoints that are binary. For time to operative mortality, the null hypothesis of equal distributions in the two treatment groups will be tested with a Cox proportional hazards model with adjustment for the same covariates as the primary endpoint. For the post-operative hospital length of stay (PLOS) outcome, the Fine and Gray (1999) competing risks regression analysis will be performed with death counted as a competing risk and with adjustment for covariates. Though several secondary analyses will be conducted, we will not adjust the 0.05 level of significance for multiple comparisons. The actual p-values for each comparison will be reported to aid in the overall interpretation, however, we will be conservative in our interpretation of all of these analyses.

Interim Analysis and Stopping Rules

Formal interim treatment group comparisons will focus on comparing the distribution of the primary global ranking endpoint categories by treatment group using the covariate-adjusted proportional odds model described above. 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. A single planned interim analysis using alpha spending will be targeted to occur

after completion of data collection for the first ~600 to 800 subjects depending on timing of the biannual STS-CHSD data harvest. Additional interim analyses are not currently planned but may be performed upon request by the data monitoring committee.

Discussion

For decades perioperative steroids have been administered to patients undergoing cardiopulmonary bypass in hopes that they might reduce the post-bypass inflammatory response and thereby improve outcomes. Two recent large adult trials (DECS and SIRS) have failed to demonstrate a beneficial effect of perioperative steroid administration (13,30). However, the DECS trial demonstrated benefit in a pre-specified high-risk subgroup. Graham and colleagues recently completed an RCT evaluating intraoperative methylprednisolone versus placebo in 176 neonates and, although they did not meet their primary endpoint, they found differential effects at the two enrolling centers with secondary outcome signals suggesting a possible methylprednisolone benefit.(17) No large scale, randomized controlled corticosteroid trial has ever been completed in children undergoing CPB operations. There is strong rationale to support such a trial; past experience has consistently demonstrated that children respond differently to drugs than their adult counterparts and it is generally recognized as inappropriate to extrapolate data from adult trials to young children. Moreover children, and in particular neonates and infants, have an exaggerated inflammatory response to CPB when compared to their adult counterparts. (7,23) Neonates and infants also have a higher risk of post-operative mortality and major morbidity.(25) Finally, registry and survey data demonstrate clear evidence of equipoise with an approximately even split between providers who routinely administer perioperative steroids and those that do not. (18–21,33)

The STRESS trial overcomes several major hurdles that have previously prevented completion of larger-scale randomized controlled clinical trials in neonates undergoing CPB operations. By leveraging the existing infrastructure of the STS-CHSD, the trial will be conducted with maximal efficiency, and at the lowest possible cost. Moreover, existing STS-CHSD data were used in trial simulations to determine the optimal trial design and approach including to determine eligibility criteria, evaluate potential site readiness for trial participation, evaluate potential primary and secondary endpoints, and design the optimal analytic approach. The STRESS trial also leverages collaborations with major NIH-sponsored trial networks including the NCATS-sponsored Trial Innovation Network and the NICHD-sponsored Pediatric Trials Network.

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Figure 1.

The STRESS Trial Network currently includes 27 STS-CHSD sites in the U.S.

Figure 2.
STRESS Trial Data Integration

Table 1.

STRESS trial inclusion and exclusion criteria

Inclusion Criteria	
< 1 year of age	
Undergoing surgery with cardiopulmonary bypass	
Not previously enrolled in the STRESS trial	
Exclusion Criteria	
< 37 weeks adjusted gestational age at time of surgery	
Any oral or intravenous steroid treatment within two days of surgery;	
Previous enrollment in the STRESS trial	
Infection contraindicating steroid use	
Preoperative mechanical circulatory support or active resuscitation at the time of randomization	
Any patient receiving any of the following medications within 2 days of surgery: Amphotericin B, aminoglutethiamide, anticholinesterases, warfarin, CYP3A4 inducers including (but not limited to) carbamazepine, phenobarbital, phenytoin, rifampin, bosentan and nafcillin, CYP3A4 inhibitors including (but not limited to) clarithromycin, voriconazole, itraconazole, ketoconazole, ciprofloxacin, diltiazem, fluconazole, erythromycin (oral or intravenous but exclusive of topical applications), azithromycin and verapamil	

Table 2.

Drug dosing

Group	N	Study drug
1	600	IV methylprednisolone (30mg/kg) administered directly into CPB prime
2	600	Placebo (normal saline)

Table 3.

The Global Rank trial endpoint

Endpoint	Global rank (rank hierarchy)
Post-operative mortality	97
Heart transplant	96
Renal failure with permanent dialysis	95
Neurological deficit persistent at discharge	95
Respiratory failure requiring tracheostomy	95
Post-op mechanical circulatory support	94
Unplanned cardiac reoperation	94
Reoperation for bleeding	93
Unplanned interventional cardiac catheterization	93
Delayed sternal closure	93
Cardiac arrest	92
Multi-system organ failure	92
Renal failure with temporary dialysis/hemofiltration	92
Post-op prolonged ventilator support (> 7 days)	92
Post-operative length of stay 90 days	91
Post-operative length of stay in days	1–90

Table 4.

Change in outcomes for Power calculations

	GRS 0–6	GRS 7–14	GRS 15–91	GRS 92	GRS 93	GRS 94	GRS 95	GRS 96	GRS 97
Steroids	34.2%	30.1%	16.1%	4.8%	4.3%	4.6%	1.1%	0.8%	3.9%
Placebo	28.1%	29.4%	18.0%	5.7%	5.3%	5.8%	1.4%	1.0%	5.2%
Difference	6.2%	0.7%	–1.9%	–0.9%	–1.0%	–1.2%	–0.3%	–0.2%	–1.2%

GRS represents “Global Rank Score” and corresponds with the rank hierarchy in Table 2