This document contains study protocol and statistical plan for

14798	NCT02320669	Phase 3 Triiodothyronine Supplementation for Infants After Cardiopulmonary Bypass (TRICC-2)

TRICC-2: TRIIODOTHYRONINE SUPPLEMENTATION IN INFANTS UNDERGOING CARDIOPULMONARY BYPASS

IND 55367

A randomized, double blind, placebo controlled study of the effects of Triiodothyronine in Infants Undergoing Cardiopulmonary Bypass

Research Study Protocol

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Study Product: Triiodothyronine (trade name: Triostat)

Date: **30 September 2015**
Amendment #: **4**

Signatures:

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Study Sponsor/Study Principal Investigator **Date**

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Site Principal Investigator **Date**

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List of Abbreviations

AE	Adverse Event
CAVC	Complete Atrioventricular Canal
CICU	Cardiac Intensive Care Unit
CoA	Coartctation of Aorta
COV	Closeout Visit
CPB	Cardiopulmonary Bypass
CRF	Case report forms
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DSC	Delayed Sternal Closure
ECMO	Extracorporeal Membrane Oxygenation
FDA	US Food and Drug Adminstration
HIPAA	Health Insurance Portability and Accountability Act
HLHS	Hyperplastic Left Heart Syndrome
HLV	Hypoplastic Left Ventricle
ICU	Intensive Care Unit
ICU-LOS	Intensive Care Unit Length of Stay
IMV	Interim Monitoring Visit
IND	Investigational New Drug Application
ITT	Intention to Treat
LACH	Los Angeles Children's Hospital
LPCH	Lucille Packard Children's Hospital
NIH	National Institutes of Health
NR	Not Responsible
OOPD	Office of Orphan Product Development

PHN	Pediatric Heart Network
QoL	Quality of Life
R-ICU	Readiness for ICU Discharge
SAE	Serious Adverse Event
SCH	Seattle Children's Hospital
SIV	Site Initiation Visit
SVC-PA	Superior Vena Cava to Pulmonary Artery Shunt
T3	Triiodothyronine
T4	Thyroxine
TAPVD	Total Anomalous Pulmonary Venous Drainage
ToF	Teratology of Fallot
TGA	Transposition of Great Arteries
TSH	Thyroid Stimulating Hormone
TTE	Time to Extubation
VSD	Ventricular Septal Defect

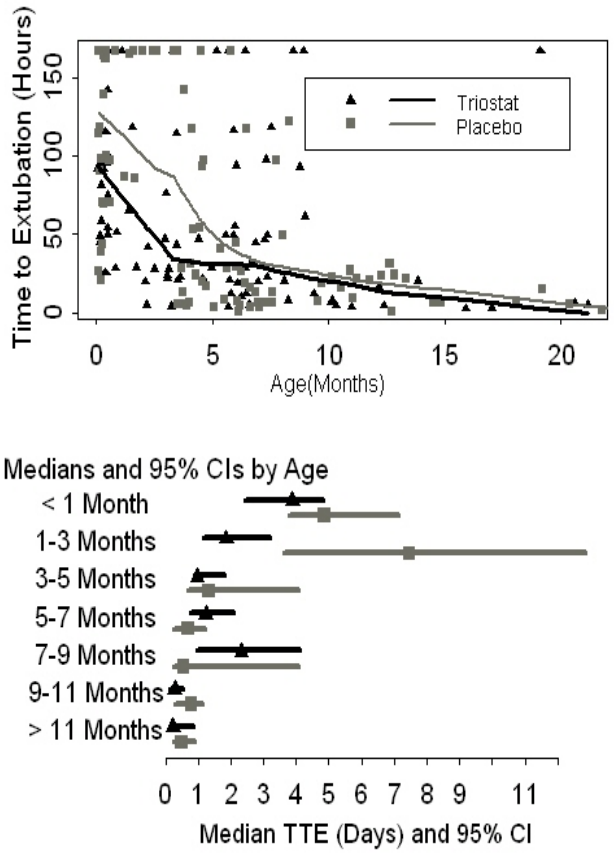
Significance

Congenital heart disease occurs in approximately 32,000 infants per year. The American Heart Association estimates that 300,000 children under age 21 have a congenital heart defect, and approximately thirty-eight percent of these will have one or more surgical procedures. This cohort of infants undergoing cardiac surgery represents an orphan disease population by NIH and FDA definitions. Over the past 20 years increasing numbers of patients have undergone cardiopulmonary bypass for correction of congenital heart defects and or palliation of single ventricle type anatomy. Technical advances have been made in these surgical procedures. However, progress has been limited with regard to pharmacological management of infants during the postoperative period. **Rapid extubation strategies have been applied at many centers in older infants and children[2, 3] in attempts to reduce morbidity associated with prolonged intubation. However cardiac surgery and cardiopulmonary bypass in neonates and young infants still results in long periods in the cardiac intensive care units. Long CICU stay is often due to prolonged time on mechanical ventilation with associated acute and long term morbidities.** Relatively few randomized clinical trials have evaluated agents provided to these infants after cardiopulmonary bypass. The recent Triiodothyronine Supplementation in Infants and Children Undergoing Cardiopulmonary Bypass (TRICC) clinical trial performed under IND # 55367 demonstrated a fairly straightforward and safe pharmacological approach to reducing mechanical ventilation time[5]. However, further data is required in order to apply for the labeling change for triiodothyronine (liothyronine), which would impact current standard of care.

Cardiopulmonary Bypass disturbs thyroid hormone homeostasis in adults and children[6, 7]. Initially, these disturbances were considered physiological adaptations to surgical stress, which would modify oxygen consumption. However, emerging evidence shows that inflammation initiated by CPB circuits inhibits the thyroid hormone axis at multiple levels [8 9 10]. Thus, marked and persistent depression of circulating hormones after CPB is directly caused by this procedure which stimulates cytokine storm. Circulating triiodothyronine levels related directly to clinical outcome in many studies in both adult and pediatric populations[6, 7]. Several manipulations in the CPB circuitry such as addition of ultrafiltration as well as steroids have been used to reduce the impact of this inflammatory response with variable overall effects[11, 12]. Accordingly, specific therapy targeted at correcting disturbances in thyroid hormone homeostasis is warranted. Preclinical trials in animal models show that triiodothyronine supplementation improves cardiac function after reperfusion[13]. The mechanisms of action still require elucidation. Recent studies in our laboratory indicate that thyroid hormone modulates substrate utilization to provide increased energy for contractile function[13]. Controlled clinical trials performed in adults undergoing CPB have shown that T3 supplementation produces remarkably positive effects on clinical outcome parameters[7, 14, 15]. In particular, T3 supplementation reduces atrial excitability in the postoperative period, manifested by reduced incidence of atrial fibrillation in the treated study population[14]. Despite these positive clinical outcome parameters triiodothyronine supplementation has not gained standard of care status in the adult population undergoing cardiopulmonary bypass. The reasons for this lack of general acceptance are unclear but may relate to the generic status of triiodothyronine (marketed as liothyronine) and absence of a particular champion pharmaceutical company.

Infants exhibit particularly profound abnormalities in thyroid hormone homeostasis, which will be detailed in preliminary data. Unexplained myocardial stunning occurs after CPB which relates directly to thyroid hormone levels, and prolongs time on mechanical ventilation after surgery. Data from several small clinical trials of T3 supplementation in general populations of children undergoing surgery for congenital heart defects (age: 0 – 18 years) suggested that T3 supplementation might be helpful in postoperative period[1, 16, 17]. These results should be considered in the context of the state of clinical trials and the use of drugs for children undergoing cardiopulmonary bypass. Approximately 80% of drugs used in children are not approved for pediatric indications. Most of the drugs used routinely in the intensive care unit have not been evaluated via randomized clinical trials in a pediatric population. In fact, careful review of the literature shows evidence that some of these agents, for example dopamine and dobutamine, have poor benefit to safety ratios. Dobutamine and dopamine are highly arrhythmogenic[18]. Only milrinone has been evaluated in a controlled clinical trial in children[19]. Although this drug has received labeling status by FDA and appears safe, the data supporting its use are weakened by a composite outcome parameter that has never been validated.

Figure 1. TRICC trial data. Relationship between time to extubation and age in months (top panel). Smoothed regression lines for Placebo and Triostat groups converge just above 5 months of age. Median TTE with confidence intervals is shown by age groups (lower panel).



The Triiodothyronine during Cardiopulmonary bypass in Infants and Children (TRICC) clinical trial tested the hypothesis that triiodothyronine supplementation reduces time on mechanical ventilation after cardiopulmonary bypass. The FDA Office of Orphan Product Development funded the trial. The double blind, placebo controlled, multi-center study randomized almost 200 children under the age of 2 years, making it the largest drug trial performed in this population[5]. Triiodothyronine supplementation did not significantly influence the primary clinical endpoint, the time to extubation, in the entire study cohort. However, we, the investigators, planned a priori analyses by age. We determined that the T3 effect is not heterogeneous over all ages from birth to 2 years, as evidenced by a significant treatment by age interaction when the study population was divided at the median age of 5 months. Post-hoc analyses (Figure 1 and 2) revealed that T3

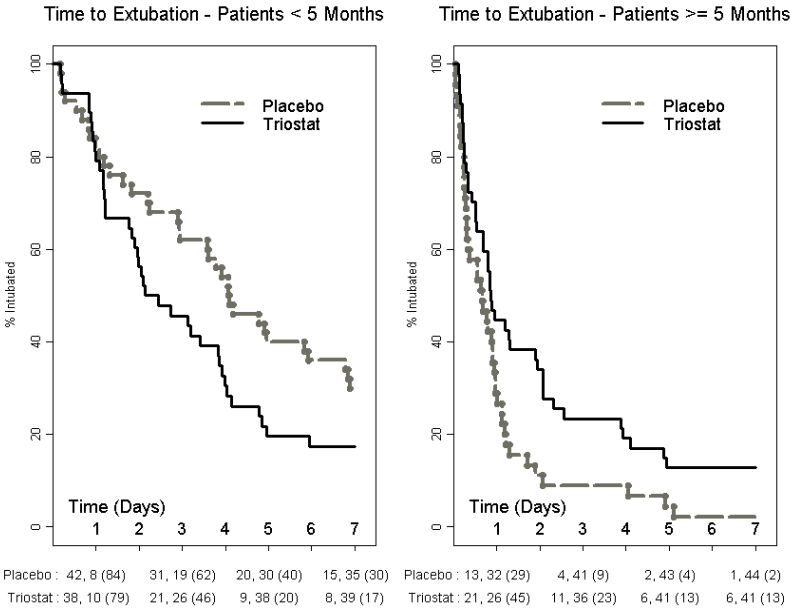


Figure 2. TRICC trial data. Kaplan-Meier curves for subjects < 5 months age and subjects age > 5 months. (Statistics by Cox Proportional Hazards): Hazard Ratio for the Triostat group among patients < 5 months was 1.72 (p=0.0216), and for > 5 months 0.60 (p = 0.0220). Below the graph are N at risk, number of extubations, (% intubated).

substantially benefited patients less than 5 months of age by reducing the median time to extubation by 43 hours when compared to placebo (T3-treated median-55 hours; 95% CI, 44–92; Placebo 98 hours; 95% CI, 71–142). The study linked the positive clinical outcome to two potential mechanisms. First, T3 treatment improved cardiac function as assessed by echocardiographic parameters. Second, T3 supplementation promoted a decrease in inotropic agent use even though cardiac function improved (Figure 3). In addition to these results, the trial demonstrated the overall safety of T3 supplementation. TRICC provided data which can and likely has impacted care in these very young patients undergoing surgery for congenital heart diseases. However, the FDA denied application for a labeling change to include this indication as we did not demonstrate efficacy in the entire trial cohort, and the analysis by age was not a pre-specified primary endpoint (0 – 2 years of age was the prespecified primary endpoint). The FDA would not consider a Triostat label change for cardiac surgery based on post-hoc analyses of a specific subgroup. Nor would they consider change in labeling regarding safety without demonstrating efficacy in the entire cohort. Accordingly, the FDA suggested that another prospective trial in the specific age group with potential to benefit from treatment was necessary to apply for a labeling change. Thus, we propose performing a second trial in infants less than 5 months of age. The primary efficacy endpoint will be the affect of T3 supplementation on all patients less than 5 months of age. Randomization will be stratified based on age (< or ≥ 4 weeks). The age strata will be considered separately as secondary analyses.

Study Design and Innovation

We will determine if triiodothyronine supplementation after cardiopulmonary bypass reduces time on mechanical ventilation in infants less than age 5 months.

Innovation resides in the clinical study design, which will capture time to extubation, cardiac intensive care unit (CICU) days, discharge feeding tube use, and other endpoints so that the results can be evaluated in terms of clinical benefit, resource use, and quality of life components. Consideration of this treatment strategy from a clinical, cost/value and Quality of Life stand-point will show the entire picture. Based on our TRICC results, we expect to find a meaningful effect on TTE, a slight decrease in resource use (CICU days), an increase in QoL (more discharges on full oral feeds) associated with T3 supplementation; all for a therapy which has a minimal cost.

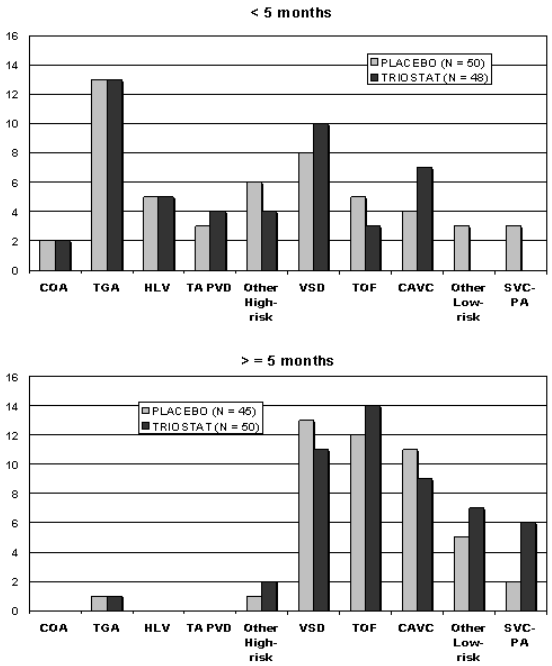


Figure 3. Diagnosis distribution between age groups in TRICC. First 5 groups are High Risk by Aristotle Score > 10. CoA, infant coarctation; TGA, arterial switch for transposition; HLV, stage I palliation for hypoplastic left heart; TAPVD, total anomalous pulmonary venous drainage; VSD, ventricular septal defect; TOF, Tetralogy of Fallot; CAVC, complete atrioventricular canal; SVC-PA, superior vena cava to pulmonary artery shunt or Glenn.

Study Population

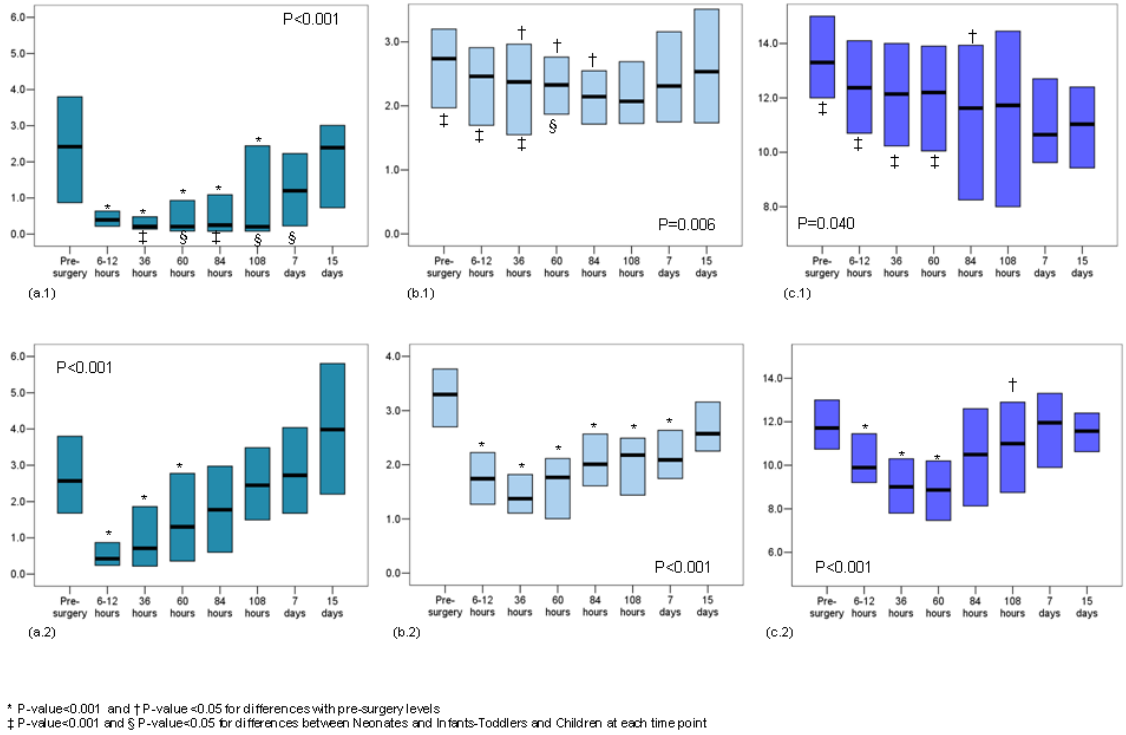
The TRICC study identified patients < 5 months as those with the most potential benefit from triiodothyronine supplementation. In TRICC we used Aristotle score to quantify the complexity and risk of the surgical procedure.[20-22]. High risk was defined as an adjusted Aristotle score greater than 10. The profile for study patients according to this diagnosis stratification is shown in Figure 3. This figure shows that with increasing age, the population shifts towards lower risk categories. From these profiles it is clear that patients less than 5 months of age have increased risk not only due to younger age but also due to greater surgical complexity. The age related findings from the TRICC trial were presented at the Annual Sessions of the American Heart Association in 2010. Physicians in attendance, who care for these children, questioned whether the response in neonates differed from older infants. TRICC was not designed to answer this question.

STRATIFICATION DESIGN

Accordingly, we have designed TRICC 2 with age strata: less than 4 weeks and greater than or equal to 4 weeks in order to have sufficient numbers of younger and older patients to address whether the affect is different in neonates. The logic behind the stratification is a combination of published and preliminary data.

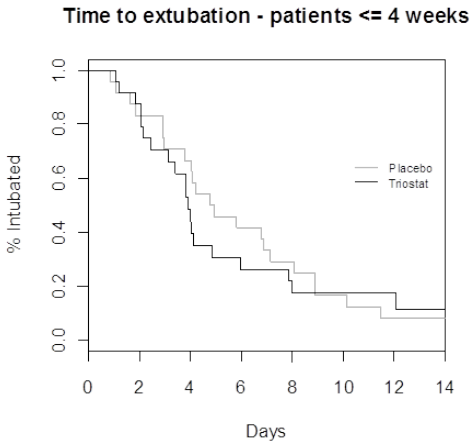
Justification for Age Strata

Recently published data obtained by the PI in collaboration with M. Cantinotti et al show that infants less than 4 weeks old demonstrate differences in thyroid hormone profile both before and after cardiopulmonary bypass compared to older children (Figure 5). Although declinations in TSH, T3, and T4 are not as profound as those in older children, they persist longer after CPB, suggesting that response to T3 supplementation might be different in neonates < 4 weeks old. The TRICC trial was not powered to perform more detailed age stratification and separate out the neonatal group. However, the Kaplan-Meier curves for patients intubated versus time show the logic of the stratification design. This figure shows the cumulative percent of patients still requiring intubation versus time in the TRICC study. While the patients older than 4 weeks show a substantial benefit, the benefit is reduced in patients less than 4 weeks. It is unknown due to the small sample size whether these graphs demonstrate a true difference in the magnitude in the effect, or simply show the variability in outcomes in this youngest and sickest population. The stratification of TRICC- 2 was designed to enable us to distinguish between the two possibilities.

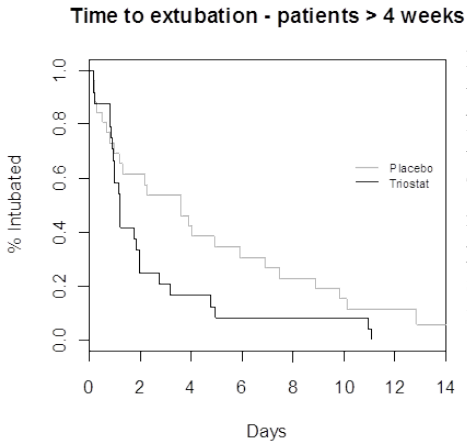


* P-value<0.001 and † P-value <0.05 for differences with pre-surgery levels
‡ P-value<0.001 and § P-value<0.05 for differences between Neonates and Infants-Toddlers and Children at each time point

Figure 4. TSH, free T3 and free T4 values for neonates (< 4 weeks, n = 57) in top panels and older infants and toddlers (n = 105) in bottom panels. Neonates show lower preoperative values, though postoperative decline in T3 is less severe [4].



TTE- Placebo 116.7 (70.7, 168); Triostat 93.3 (54, 168); p = 0.308



TTE- Placebo 70.1 (18.2, 168); Triostat 28 (21.1, 47); p = 0.100

Figure 5. TRICC trial data for 2 age groups under 5 months old. For patients <=4 weeks: N = 25, Placebo; 25 Triostat. For patients >4 weeks: N = Placebo 25, and Triostat 23. Though not adequately powered, data suggest more potent treatment impact in the older patient group. These data support age stratification design in our study. Data below figures reflect median (25,75%tile)

The target sample size (total 220 enrolled) was calculated to provide statistical power of >80% to identify a treatment effect corresponding to a hazard ratio of 1.55 with an overall type I error level of 0.05 (2-sided). Patients will be block-randomized by risk and age, with a minimum of 100 patients who are > 4 weeks of age. Based on the age distribution in TRICC, we expect about 60% of patients will be greater than or equal to 4 weeks, which will provide adequate numbers in each of the age groups. If for some reason high numbers of neonates are enrolled, we may cap enrollment of neonates so that at least 100 patients are ≥ 4 weeks. Patients will be randomized to T3 or placebo in a 1:1 ratio.

Primary Clinical Endpoint

Time to extubation (TTE) will be the primary clinical endpoint in this study. FDA regulators agree that this endpoint is appropriate to apply for a labeling change for Triostat. Studies of children undergoing surgery for congenital heart disease conducted at single centers with uniform hospital utilization have shown that decreasing TTE results in overall reduced hospital stay and cost [3]. Time to extubation in infants also relates to longer term quality of life indicators. For instance, most congenital heart centers report that the majority of these infants demonstrate continuing oral feeding difficulties at discharge. Between 50 and 60% are discharged from the hospital with either full or supplemental feeds through nasogastric tubes or gastrostomy[23, 24] After discharge, nasogastric feeding continues at home with substantial increased cost, and detriment to the quality of life of the infants and their parents. Several studies have reported that prolonged time to extubation is the single most important predictor for discharge on nasogastric feeds. [23, 24] This specific quality of life indicator, discharge of full oral feeds will be used as secondary endpoint indicator.

Composite endpoints have been used in pediatric intensive care studies with variable and limited success[19] [1]. Validity of these composite endpoints is often questioned. Frequently used endpoints such as time in intensive care unit and hospital stay are burdened by variable practice in a multi-center study. Additionally transfers require staff availability, which is not always feasible. For instance, some of the participating centers in the TRICC trial discharged patients to home directly from the intensive care unit. TTE is considered an important clinical endpoint and benchmark in pediatric cardiac surgical series. Mechanical ventilation is an important source of anxiety for parents with children in the intensive care unit[25] . Furthermore, we successfully detected differences in TTE in TRICC, establishing that T3 supplementation affects this endpoint. Therefore TTE was selected as an objective outcome measure for this study. We recognize this endpoint has limitations, due to

ambiguity of start and stop time. First, time 0, the start of the intubation period, has been poorly defined in multiple analyses evaluating pediatric cardiac surgery. Start time has been defined as initial time to intubation prior to surgery, entrance into the operating room, or surgical completion. None of these time-points have relevance to surgical outcome, and are influenced by factors such as the complexity of the procedure and skill of the surgeon. Therefore, time from aortic cross-clamp removal will be defined as time 0 (start time) because under this definition it can be objectively measured.

In TRICC-2, all participating investigators will commit to reducing non-patient related delays in extubation and document the time of readiness to extubate along with any reason for delay, if a delay cannot be avoided. **For the calculation of the primary endpoint, the actual extubation time will be used.** It is essential that treating physicians are blinded to treatment assignment to prevent bias in deciding appropriate extubation time.

Delayed sternal closure (DSC) is an effective approach to the management of neonates and infants at risk for hemodynamic, respiratory, or hemostatic instability early after cardiac surgery [26]. However, DSC is an important confounding influence on time to extubation, and must be considered in this study design. Use of DSC varies among institutions but a multi-center retrospective study showed that it contributes to longer length of hospital stay and higher postoperative infection rates in patients undergoing stage 1 palliation for hypoplastic left heart syndrome (HLHS)[27]. At centers involved in the study, surgeons often make the decision for DSC prior to operative repair or palliation. In our own series (SCH) DSC prolongs time to extubation by a median of 2.5 days in HLHS patients compared to patients with standard chest closure, yielding a bimodal distribution for time to extubation. We will adjust for whether DSC actually occurs in the primary analysis Cox Proportional Hazards Model.

Secondary Endpoints

FDA regulators suggested that mortality and/ or additional morbidity parameters would provide important supportive data. However, mortality in this population is extremely low, and generally caused by factors which would not be improved by pharmacological therapy, such as surgical mishaps, and extremely high risk surgery. Furthermore, with mortality rate at 5.3% in placebo group from TRICC and 3% in treatment group, our study would require a several fold increase in sample size to be adequately powered. The consensus of ICU physicians at the 3 centers participating in this trial is that extubation and removal from the ventilator is the primary acute goal for these patients. Parent groups also report that extubation is the most important parameter. We have evaluated adverse events as potential morbidity endpoints, but these are numerous, diverse, subjective, and therefore are not suitable for a composite endpoint. Hospital length-of-stay was considered as a potential outcome parameter; however this is influenced by center-specific protocols, readiness of family to have the child come home, and other variables which are clearly beyond the effect of T3. ICU length-of-stay (ICU-LOS) is used universally as an outcome parameter in adult and pediatric studies. Studies employing this outcome parameter are generally based on a large population, which is necessary due to the non-patient related issues and events. We have evaluated ICU-LOS as a potential secondary endpoint. The median ICU- LOS in TRICC patients $\leq$ 4 weeks old was 7.5days (IQR 6-14) with Triostat, and 8.5 days (IQR 7-13.5) with Placebo. The values for patients >4 weeks were 4.5 days (IQR 4.0-9.0) with Triostat and 7 days (IQR 4.0- 16.5) Placebo. T3 supplementation may influence ICU-LOS among the older patients, although less likely to influence this parameter in the younger neonatal group.

We will use ICU-LOS as a secondary endpoint. This will not eliminate problems related to step-down unit availability etc. We therefore introduce another secondary endpoint, which is a composite value similar to that used by Mackie et al. This endpoint will be termed **"ready for ICU discharge",** and defined as the number of

hours from termination of cardiopulmonary bypass to readiness for ICU discharge. The intensivists and investigators agreed to record this endpoint (R-ICU) when both of the following parameters are reached: 1) all inotropic drugs terminated; 2) patient extubated and in no respiratory distress, only oxygen supplied by nasal cannula or mask; 3) If on high flow nasal cannula Max O_2 4L (0-90d old) or 6L (91d-2y), FiO2 ≤ 50%:

As noted previously, delayed TTE is a direct predictor of "oral feeding difficulty" resulting in hospital discharge on alternate feeding modes such as nasogastric tube[23, 24]. Discharge with nasogastric tube reduces quality of life for infants and families. Therefore we will use **discharge on full oral feeds as a secondary quality of life end point.**

In order to assess cardiac endpoint parameters we will **use Low Cardiac Output Syndrome (LCOS) as another secondary endpoint.** This assessment will be competed on a separate CRF for LCOS for the first 36 hours after ICU admission and will include 1) identifying clinical signs/symptoms present in LCOS; 2) identifying all interventions involved in the treatment of LCOS; 3) Pharmacologic Assessment of inotropes/vasopressures

Summary of secondary endpoints

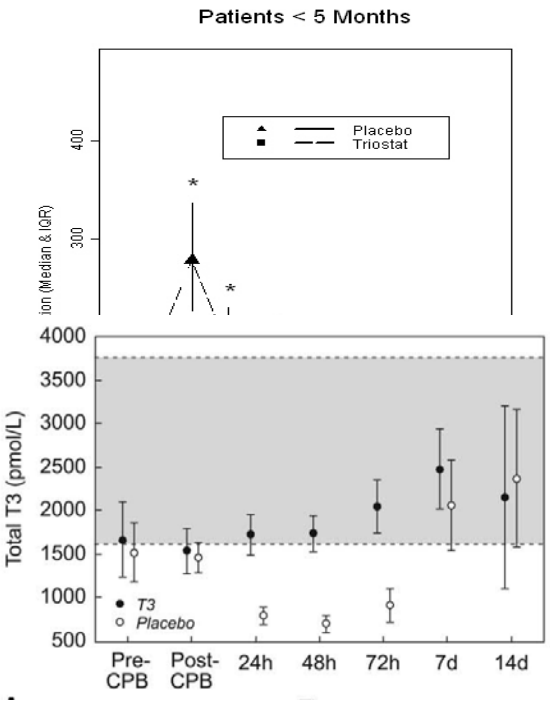
1) **ICU-LOS**
2) **R-ICU**
3) **Discharge on Oral feeds**
4) **LCOS**
5) Mortality*
6) Mortality and/or mechanical circulation (ECMO)*
   - *The PI anticipates that the study is inadequately powered to detect differences in these endpoints between treatment groups, but they were suggested by the FDA regulators.
7) Time to sternal closure for patients with delayed surgical closure

Echocardiography was performed as part of the protocol in the TRICC trial. Echocardiography, as noted previously, established a treatment effect on cardiac contractile function. However, echocardiography parameters were secondary endpoints. Performance of echocardiography burdened the study with regards to enrollment due to staffing issues (sonographer unavailability at protocol time points) and is prohibitively expensive at U.S. centers. We considered the benefit of echocardiography as part of the protocol versus the cost. Accordingly, echocardiography will not be performed as part of protocol, although performance of the study will not impact standard of care studies. A previous review observed this point, and suggested that we use data obtained for clinical purposes outside of the protocol. However, these evaluations are ordered based on clinical necessity. As such the sickest patients might have echo data and the others would not, creating a biased sample.

Triostat Dosing

Triostat ® (liothyronine sodium injection), 10µg/mL, 1mL vial is currently distributed by JHP Pharmaceuticals. Supplementation elevated total triiodothyronine levels in the TRICC trial as noted in Figure 6. For TRICC the dosing strategy was 0.4µg/kg prior to CPB and immediately after cross-clamp release and 0.2µg/kg every 3 hours thereafter for 3 doses, thereby supplying a total 1.4µg/kg over an approximate 10 hour period. This strategy was effective in patients less than 5-months oldbut did not provide steady-state levels, and maintained levels above the placebo group for only 24 hours, by 24 hours levels in both placebo and treatment groups were well below baseline. Additionally, the strategy produced substantial peaks in serum T3 levels, although these were not associated with adverse events. The primary reason for bolus was concern regarding liothyronine incompatibility with other drugs, and the limited number of infusions available in these small patients. These have been obviated with newer types of lines and infusion pumps. Liothyronine is compatible with drugs given in the ICU. Prior studies have used liothyronine (Triostat) infusion in this vulnerable population with no drug incompatibility reported. Data from the TRICC trial and a smaller trial performed by our Lucille-Packard co-investigator support bolus dosing followed by infusion. Dr. Stephen Roth published pharmacokinetic data from a series of neonates undergoing surgical procedures requiring CBP. In his study, Triostat infusion (0.06 µg/kg/hour) initiated immediately after terminating CPB prevented total T3 decline to below normal levels in many but not all patients. The infusion produced optimum levels within the normal range by 24 to 48 hours (n = 23). These data strongly support a composite protocol using initial bolus to prevent early decline in T3, and then followed by the established maintenance infusion.

Figure 6. A. Dosing strategy in TRICC trial raised total T3 levels with peak at 1 hour with slow decline reaching placebo group levels after 24 hours. Because of persistent low levels shown below for at least 72 hours and in Figure 5, the new trial strategy is to extend T3 infusion, supported by data in B published by collaborator Stephen Roth [1].



Accordingly, we will use a strategy with an initial loading dose 0.4µg/kg validated in TRICC after cross clamp removal or similar time point surrogate followed by an infusion totaling approximately 3 µg/kg infused as 0.06 µg/kg/hr for 48 hours or until extubation in the CICU, whichever time is shorter (validated by Mackie et al, (Stephen Roth)[1]. This dose is intended to prevent the initial decline and maintain relatively steady-state levels well within the normative range for the 48-hour time period; data from TRICC as well as our preliminary data in infants younger than 4 weeks show persistence of the hypothyroid period extending through 48 hours.

Study Conduct and Procedures

Study Recruitment and Screening

Subjects will be recruited from admissions at participating centers scheduled to undergo a cardiac procedure requiring CPB. Potential subjects will be screened for study suitability by the research staff in cooperation with the clinical care team. A screening log will be kept at each site. If the family shows interest in the study, they will undergo informed consent procedures which will be conducted by the research team. The study will be described verbally to the patient and family. After the introduction and description of the study, the family will be given adequate time to read and review the written consent forms. Time will be allotted for questions and additional discussion, if necessary. Family friends, relatives or additional support persons (at the request of the parent/guardian) may also be present to hear and read what is being asked of the family.

Early Withdrawal of Subjects

When and how to withdraw subjects: Subject may be withdrawn from the study prior to the expected completion of that subject for health, logistical, or personal reasons (i.e. serious adverse events, subject consent withdrawal, disease progression, etc.). No safety consequences are anticipated with early withdrawal from the study since Triostat is adjunctive therapy.

Data Collection and Follow-up for Withdrawn Subjects: Subjects who receive study medication and are withdrawn will be followed through the duration of the study for that subject. Subjects who withdraw consent will be asked if study data can be collected for the duration of the study. Subjects who completely withdraw consent and do not wish to have further data collected will not be followed past the point of withdrawal of consent.

Emergency Blind Breaking: At the beginning of the study, each site will be instructed on the method for emergency blind-breaking. Blinding codes may be broken in emergency situations if this is required for clinical management. The Principal Investigator at the site will contact Dr. Portman to assess the necessity for un-blinding. In the unlikely event that Dr. Portman is unreachable, the site Principal Investigator will be responsible for making the decision to unblind the patient. The study investigator will instruct the participating site pharmacy to break the blind to the treating physician only. The study investigators at the site as well as Dr. Portman are to remain blinded to protect the integrity of the data.

Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Informed Consent obtained
2. Male and female patients <5 months (152 days) of age
3. Patients undergoing cardiopulmonary bypass

Exclusion Criteria:

1. Known thyroid disease (Down Syndrome is not an exclusion criterion unless the patient has thyroid disease)
2. Trisomy 13 and 18

3. Prolonged preoperative ventilator support which would not be impacted by cardiac surgery (Lung disease: bronchopulmonary dysplasia, hypoplastic lungs associated with diaphragmatic hernia)
4. Any other condition as determined by the PI causing prolonged ventilator support which is unlikely to respond favorably to cardiac surgery
5. Prior participation in the clinical trial

Schedule of Events

1. Prior to Surgery
    a. Informed Consent
    b. Inclusion/Exclusion
    c. PK/thyroid hormone Blood Sample
    d. Demographics
2. Prior to first bolus of Triostat/Aortic Cross Clamp
    a. PK/thyroid hormone Blood Sample
3. Triostat Bolus/Release of Aortic Cross Clamp
    a. Triostat Bolus – 0.4μg/kg
    b. Triostat infusion started – 0.06 μg/kg/hr
4. 6 hours post 1st Triostat bolus
    a. PK/thyroid hormone Blood Sample (±1hour)
    b. Echo
5. 12 hours post 1st Triostat bolus
    a. PK/thyroid hormone Blood Sample (±1hour)
    b. Record a charted Blood Pressure measurement (±1 hour)
6. 24 hours post 1st Triostat bolus
    a. PK/thyroid hormone Blood Sample (±1hour)
    b. Record I/O for previous 24 hours
    c. Echo
7. 48 hours
    a. Record I/O for previous 24 hours
    b. Stop Triostat infusion (either here or at extubation, whichever is sooner)
8. 72 hours post 1st Triostat bolus
    a. PK/thyroid hormone Blood Sample (±1hour)
    b. Record I/O for previous 24 hours
    c. Echo
9. 30 day follow-up (Chart Review – to be completed 30 days post stoppage of medication)
    a. AE assessment
    b. Vital Status
    c. Feeding Status
10. Endpoints: Date and time to be recorded for the following (if applicable)
    a. Primary
        i. Extubation
    b. Secondary
        i. ICU discharge/ready for ICU discharge
        ii. Feeding tube stop time
        iii. Time of sternal closure
        iv. Death (if applicable)
        v. ECMO start (if applicable)

11. Timepoints to be recorded
    a. Aortic Cross Clamp time
    b. Release of Aortic Cross Clamp time
    c. ICU discharge time/ready for ICU discharge time
    d. Feeding tube stop time
    e. Time of sternal closure
    f. Death (if applicable)
    g. ECMO start (if applicable)

- The aortic cross clamp removal time used should be the first instance of cross clamp removal. The cross clamp may be removed and reclamped, however the schedule of events is timed off of the first cross clamp removal time.
- Blood draw windows apply only if there are vascular lines in place that can be drawn from. In the event that lines have been discontinued, it is acceptable to have study samples drawn at the time of the closest clinical draw (non study-driven blood draw) to a timepoint. Missing or late blood draws due to a lack of a vascular line or no timely clinical blood draws will not be considered a deviation. This most likely applies to the 72 hour blood draw timepoint.
- The medication bolus and infusion will be given in the 1 hour window after cross clamp removal.
- The medication infusion will be stopped in a ± 2 hour window after either extubation or 48 hours after cross clamp removal, which ever comes first.
- Concomitant medications include medications taken in the 4 weeks prior to hospitalization and continue through 30 day follow-up discharge of the index hospitalization.
- Capture of hemodynamic parameters & lactate levels will be captured as part of standard of care measurements and will not be driven by the protocol. Hemodynamic parameters will be captured for the duration of the study
- Echoes are done per Standard of care and are not driven by the study. While the schedule of events specifies an echo at 6, 24, and 72 hours, it is not a deviation if one of these is missed or late. The echo most closely correlating to this timing will be used at each timepoint.
- All PK/thyroid hormone samples taken require 2ml of blood in a red top tube at each timepoint.

	Prior to Surgery	Release of Aortic Cross Clamp	6 hours	12 hours	24 hours	48 hours	72 hours	30d f/u (Chart Review)
Informed Consent	X							
Inclusion/Exclusion	X							
Blood Sample	X	X	X	X	X		X	
Demographics	X							
Triostat Bolus		X						
Start Triostat Infusion		X						
Stop Triostat Infusion						X		

Echo			X		X		X	
Intake/Output (I/O)					X	X	X	
f/u - Chart Review								X

Data to Capture from Subject Medical Record

Various data points are recorded on each subject as a part of routine clinical care. Some of those data points are desired to be captured in the TRICC2 study. Accompanying CRFs guide the capture of additional desired data from the subject's medical record.

Participating Centers and Eligible Population

Three centers will participate in this study. Investigators at Seattle Children's Hospital (SCH), Stanford University Lucille Packard Children's Hospital (LPCH) and Los Angeles Children's Hospital (LACH) will participate. Seattle Children's has recently had a personnel change with exit of a surgeon. Surgical volume has increased and complexity remains at high level since that surgeon's departure. All three principal investigators (M Portman, R. Mainwaring, L. Hastings), at the individual sites participated as site PI for the original TRICC trial, although Stanford will be a new site for this study. Dr. Steve Roth, Co-PI performed a single center clinical trial using Triostat at Boston Children's, and has relocated to Stanford. Therefore, all the investigators are extremely experienced in conducting clinical trials in this population, and all have previously used this drug in clinical trials. The three centers are the major tertiary centers for Pediatric Cardiac surgery for the entire U.S. West coast. Together these centers provide a potential surgical volume of near 400 patients per year within the age group for recruitment. Enrollment rate for the TRICC trial was near 70% of patients approached. Therefore, we are optimistic that we can complete enrollment within the time frame of the grant (4 years).

Table 2. Summary of Potential Eligible Patients per Year

SITE	SCH	LPCH	LACH	TOTAL
PI	MP	RM	LH	
< 5 MONTHS	93	120	178	391
< 4 weeks	56	81	158	295

Blinding and Randomization

All treating physicians will be blinded to study treatment. All intensive care treating physicians will agree to terminate mechanical ventilation based on patient related parameters and to minimize non-patient related delays. Clinical practice regarding use of inotropic agents will not be specified in the protocol and will be left to standard of care at each participating institution. Randomization will be performed by site pharmacy staff, who will be unblinded. Randomization will be blocked to maintain equal numbers divided between Triostat and placebo groups at individual centers, and equal numbers of patients between treatment and placebo for the following strata:

1. Less than or equal to 30 days of age
2. Greater than 30 days of age, less than 152 days of age

Blood samples for Total T3, free T3, and TSH levels (in that order of priority if there are timepoints with insufficient volume) will be drawn prior to surgery, just prior to the first infusion and 6 ± 1, 12 ± 1, 24 ± 1, and 72 ± 1 hours after cross clamp removal or surrogate time point if patient does not undergo cross-clamping Samples for free T3, total T3, and TSH levels will be forwarded to a central laboratory (SCH) for processing and analyses.

Data Recording

All data will be recorded on clinical research forms continuously until the patient is discharged or 30 days, whichever is shorter. Echocardiograms are not required by protocol, but data will be extracted from clinically indicated and performed echocardiograms.

Statistical Analysis

Time to extubation (TTE) for the entire population is the primary clinical endpoint. The target sample size (total 220 enrolled) was calculated to provide statistical power of >80% to identify a treatment effect on TTE corresponding to a hazard ratio of 1.55 with an overall type I error level of 0.05 (2-sided). Patients will be block-randomized into age groups < 4 weeks and > or equal to 4 weeks, with a minimum of 100 patients who are ≥ 4 weeks of age. These requirements will provide sufficient numbers for subgroup analyses (see below).

The primary analysis will be performed using Cox Proportional Hazards, including terms for stratification factors, and delayed sternal closure. Patients will be included in analyses if they were randomized and received at least one dose of study drug according to the principal of Intention-to-Treat (ITT). Occasionally patients are randomized and then surgery is cancelled or rescheduled due to scheduling conflicts, and not due to patient related issues. This can rarely result in the patient missing the study medication when the operation is rescheduled at the last minute. However, since this study is double-blind, the ITT principal is preserved because the treatment assignment is blinded and so unknown to persons responsible for these decisions. As stated in *ICH-E9, Statistical Principles for Clinical Trials posted on the FDA website: "Subjects who fail to satisfy an entry criterion may be excluded from the analysis without the possibility of introducing bias only under the following circumstances: In some situations, it may be reasonable to eliminate from the set of all randomized subjects any subject who took no trial medication. The intention-to-treat principle would be preserved despite the exclusion of these patients provided, for example, that the decision of whether or not to begin treatment could not be influenced by knowledge of the assigned treatment." http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073137.pdf*

Thus, patients randomized but not receiving study medication will not be included in the analysis. Counting patients who receive at least 1 dose of study drug will improve the scientific validity of the study, and reduce the overall cost and duration of this trial. Patients who receive at least 1 dose will be analyzed according to randomization assignment regardless of the treatment actually received. The TTE distributions will be compared across treatment groups using the Log-Rank test. Time zero will be defined as the time of cross-clamp removal, and span until to the first of death, extubation or 21 days. Patients who die will be censored at the earliest of 21 days or death, and patients who are still intubated at 21 days post-cross clamp removal will be censored at 21 days. Medians and 95% confidence intervals for TTE will be based on the Kaplan-Meier estimate to account for censoring. A sensitivity analysis adjusting for non-patient-related delays will also be performed to determine the impact of these delays, which we expect to be few, on the primary efficacy analysis. Differences in death will be compared using Fisher's Exact Test.

Secondary endpoints as previously described will be analyzed using similar methodology. Endpoints with censored observations will be addressed using survival analysis techniques to account for censoring.

This study is powered to detect a hazard ratio of 1.8 with respect to TTE in patients less than 4 weeks of age (assuming half of the total sample is in this age range). The effect in patients < 4 weeks of age is an important clinical outcome as these are the sickest patients in the population, and reduction in their relatively long intubation times provides more opportunity for benefit. There will be no Type I error adjustment for this subgroup analysis in order to maximize power for the primary outcome, but the sample size was determined considering the need to report the effect in the youngest patients. Thus, this analysis will be considered supportive and will be described as such in subsequent publications.

Patient characteristics and adverse events will be compared using the chi-square test or Fisher's Exact test as appropriate. Continuous characteristics and outcomes will be compared using the T-test or ANOVA for repeated measures. Point estimates for hazard ratios and 95% (2-sided) confidence intervals will be reported.

Safety endpoints include arrhythmias, infection rate, serious, and non-serious adverse events. Only treatment-emergent events with signs or symptoms that begin or worsen after the first dose of study drug will be reported.

Total T3 levels will be analyzed to determine half-time using a single compartmental pharmacokinetic model similar to previously published methodology by the PI [29].

Safety

Adverse Event (AE) Reporting

Reporting of adverse events in cardiac surgical trials in infants is complicated as there is no regulatory guidance specific to conducting clinical research in critically ill children. The Pediatric Heart Network reported a new method of reporting using predefined "sentinel events" in place of serious adverse events (SAEs). All other adverse events were reported as "complications". The standard definitions using "Common Terminology Criteria for Adverse Events" (CTCAE), developed by the National Cancer Institute does not carry enough appropriate pediatric codes to cover the complexity of the postsurgical population. The Pediatric Heart Network (PHN) launched the Single Ventricle Reconstruction Trial and midway switched from standard reporting to their new system identifying "sentinel events"[30, 31]. This system reduced administrative burden and improved quality of safety reporting. However, their study which evaluated surgical techniques against one another was not performed under IND and according to PHN investigators their system has not been reviewed by the FDA. On query regarding the appropriateness for using the PHN published method for reporting adverse events in a drug trial the FDA responded: "*Our goal is to understand the effect of said study treatment on adverse events, i.e., "adverse reactions" (to study drug), not to catalog all bad things that happen to subjects. In this respect, the process PHN followed may or may not be reasonable. One would need to think through whether the experimental treatment had any likelihood of affecting the common adverse events associated with surgery and whether the investigators were likely to be able to distinguish study treatment-related events from "normal" (clinically expected) ones. "*

As TRICC-2 will be performed with IND requirements, we will need to report adverse events (AEs) using FDA standards revised by the common rule amendments of 21 CFR Parts 312 and 320 (April 2011). The common rule does reduce reporting requirements somewhat as long as expected AEs and SAEs are predefined in the study protocol (see Appendix 1). A summary of adverse events reported for the TRICC trial appears in Table 3. This shows that the majority of patients show AEs, though relatively few have SAEs using standard reporting methodology. Thus, the greatest burden for reporting may not be related to SAEs but to reporting of common procedural complications as AEs regardless of severity. Using literature review and expert consensus, the PHN developed lists defining common and specific AEs which occur in this infant population undergoing cardiac surgery. Protection of Human Subjects (section 6) contains a list adapted from the PHN,

which defines expected surgical complications or AEs. For instance pleural effusion is defined as an adverse event when drainage exceeds 7 days after surgery. This definition will reduce reporting of pleural effusions. In an effort to address the issue raised by the FDA with regard to affect on common adverse events in this population, we have numerically coded the complication table generated by the PHN (section 6).

Summary of Adverse Events from Time of Surgery to the First of Hospital Discharge, 30 Days Post-procedure or Death for entire cohort and < 5 months						
	Placebo Total (N=95)	Triostat Total (N=98)	P	Placebo, < 5 months (N=50)	Triostat, < 5 months (N=48)	P
At Least One AE	82 (86.3%)	80 (81.6%)	0.376	45 (90.0%)	42 (87.5%)	0.695
At Least One Serious AE	12 (12.6%)	14 (14.3%)	0.736	8 (16.0%)	8 (16.7%)	0.929
At Least One Unexpected AE	40 (42.1%)	40 (40.8%)	0.856	25 (50.0%)	22 (45.8%)	0.68
At Least One Possibly Treatment-Related AE	45 (47.4%)	57 (58.2%)	0.151	26 (52.0%)	34 (70.8%)	0.065
Death (any time on study)	5 (5.3%)	3 (3.1%)	0.493	4 (8.0%)	3 (6.3%)	1
Death or Mechanical Life Support	5 (5.3%)	3 (3.1%)	0.493	4 (8.0%)	3 (6.3%)	1
Arrhythmia AE	9 (9.5%)	11 (11.2%)	0.69	7 (14.0%)	7 (14.6%)	0.934
JET	7 (7.4%)	8 (8.2%)	0.837	5 (10.0%)	5 (10.4%)	0.946
SVT	2 (2.1%)	3 (3.1%)	1	2 (4.0%)	2 (4.2%)	1
VT	1 (1.1%)	0 (0.0%)	0.492	1 (2.0%)	0 (0.0%)	1

Table 3. TRICC data. Table shows no significant difference in rates of adverse events between placebo and Triostat groups. Postoperative arrhythmias served as an index safety factor.

Compliance and Monitoring

IND # 55367 has been assigned by the FDA, which has instructed the PI that amendment and modification only is needed for performance of TRICC-2, rather than new IND. IND amendment was submitted on December 8. We will subcontract with an independent clinical research organization (CRO) to perform monitoring for our study. The CRO, Clinical Research Staff Support Core (CRSSC), has considerable experience in monitoring the conduct of clinical trials in children. The TRICC-2 study will be performed under the Guidelines of Good Clinical Practices as outlined in FDA document “Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance”.

We will list the study on ClinicalTrials.gov. Dr. Portman as PI and holder of the IND will serve as sponsor. Division of responsibilities between the PI and the CRO are included in the table below. The PI will be supported by experienced study personnel at the Seattle Site. X = responsible; NR –not responsible, SIV – site initiation visit, IMV, interim monitoring visit, COV- close out visit.

Table 4. Division of Interim Monitoring Duties between Sponsor (M. Portman) and Clinical Research Organization (CRSSC).

Monitoring	PI	CRO
1. Qualify sites	X	NR
2. Provide Monitoring services (SIV, IMV, COV) at US sites; 200 patients; First IMV after enrollment of 2 patients; subsequent visits after enrollment of 5 patients at each site.	NR	X
3. Provide monitoring reports and follow up letters to sites after each visit	NR	X
4. Final review and approval of monitoring reports	NR	X
5. Conduct drug accountability at site during IMVs (see below)	NR	X
6. Review SAEs during IMVs	NR	X
Regulatory		
1. Collect required essential documents including CRFs from each site	NR	X
2. Review and approve essential documents	NR	X
3. Provide essential regulatory documents (e.g. CV of PI, FDA1572 Form, IRB approval) to Dr. Portman for submission to regulatory agency (FDA)	NR	X
4. Submit essential documents to regulatory agency	X	NR
5. Track regulatory documents for all sites	NR	X
6. Assist sites with regulatory submission to IRBs	NR	X
7. Submit SAEs to regulatory agency	X	NR
8. Prepare IND safety reports for submission to sites, DMC, and regulatory agency	X	NR
9. Track IND safety reports	x	NR

Monitors will be blinded. Therefore, they cannot perform on-site drug accountability monitoring. This task will be performed by the Seattle Children's Investigational Drug Service pharmacist for all sites.

Data Management

Seattle Children's Hospital and Research Institute will serve as the central site and data repository. The CRO will oversee completion of clinical research forms (CRFs) and transfer original CRFs to SCH for input into the central data base. Dr. Portman's staff will generate final queries to each site. The Research Electronic Data Capture (REDCap) database created at Vanderbilt University will be used as the study database. We will use a double entry to avoid input errors. Data will be stripped of identifiers (according to HIPAA) prior to transfer. Each patient will be assigned a study number with code to identifiers kept securely at each individual site. The database will undergo intermittent internal audit to ascertain that CRF data are correctly inputted. The auditor, not yet assigned, will be a different individual than Database manager.

Data Monitoring Committee

The DMC will be an independent multidisciplinary group consisting of clinicians with collective experience in the management of infants after cardiopulmonary bypass and in the conduct and monitoring of clinical trials. DMC members will be pediatric cardiologists, pediatric cardiac surgeons and/or pediatric cardiac intensivists, and a bioethicist. A biostatistician will also serve on the DMC to advise the committee on the interpretation of statistical data provided by the independent statistician. Members will be appointed by the DMC Chair in consultation with Dr. Portman. Blinded and unblinded data reports will be produced by an independent statistician at Axio Research. This statistician will be available to present unblinded analyses in the closed sessions of the DMC meeting. The DMC will ratify a charter at their first meeting.

Appendix 1: Listing of Expected AE's

1. Cardiac General
   - 1.1 Arrhythmia (recorded if requires medication or treatment)
     - 1.1.1 Atrial fibrillation
     - 1.1.2 Atrial flutter
     - 1.1.3 Supraventricular tachycardia
     - 1.1.4 Junctional ectopic tachycardia
     - 1.1.5 Sinus node dysfunction (requiring pacing)
     - 1.1.6 Atrioventricular block(second or third degree)
     - 1.1.7 Ventricular tachycardia
     - 1.1.8 Ventricular fibrillation
   - 1.2 Mediastinum
     - 1.2.1 Hemopericardium (requiring intervention, includes postoperative mediastinal hemorrhage)
     - 1.2.2 Pericardial effusion (requiring drainage)
     - 1.2.3 Postpericardiotomy syndrome (requiring treatment)
   - 1.3 Cardiac performance
     - 1.3.1 Hypotension (<40 mm Hg for neonates; <50mm Hg after stage II surgery)
     - 1.3.2 Hypertension (requiring long-term therapy, ie, >30 days after discharge, therapy should be at the therapeutic doses and specifically prescribed for the treatment of hypertension)
     - 1.3.3 RV dysfunction(requiring escalation or initiation of therapy, not to include immediate postoperative dysfunction routinely associated with cardiopulmonary bypass)
     - 1.3.4 Semilunar valve insufficiency or stenosis (requiring treatment initiation or escalation)
     - 1.3.5 Atrioventriuclar valve insufficiency or stenosis (requiring treatment initiation or escalation)
     - 1.3.6 Prosthetic valve dysfunction
   - 1.4 Great vessels
     - 1.4.1 Superior vena cava stenosis (anatomic, symptomatic, "superior vena cava syndrome")
     - 1.4.2 Superior vena cava occlusion
     - 1.4.3 Inferior vena cava occlusion
     - 1.4.4 Other cardiovascular
2. Respiratory
   - 2.1 Chronic respiratory failure (intubated for >2 weeks after surgery)
   - 2.2 Chylothorax (postoperative accumulation of chylous fluid in the pleural space requiring intervention whether by evacuation, dietary change, and /or medical treatment)
   - 2.3 Hemothorax (requiring drainage)
   - 2.4 Phrenic nerve injury/diaphragmatic paralysis (newly elevated diaphragm on chest x-ray film)
   - 2.5 Pleural effusion (requiring drainage >7 days after surgery, other)
   - 2.6 Pneumothorax (requiring tube insertion)
   - 2.7 Tracheal injury
   - 2.8 Vocal cord injury (direct visualization)
   - 2.9 Airway obstruction (requiring a significant intervention)
   - 2.10 Hypoxia (requiring readmission or escalation of care)
   - 2.11 Other respiratory
3. Neurologic
   - 3.1 Choreoathetosis/posturing (moderate involuntary movements interfering with function)
   - 3.2 Coma

3.3 Intracranial bleeding (confirmed by imaging)
3.4 Seizure(s) (confirmed by electroencephalogram or obvious motor signs)
3.5 Stroke (confirmed by imaging study)
3.6 Hydrocephalus (report if CTCAE grade >2)
3.7 Neurologic deficit persisting at discharge not attributed to any of the above diagnoses
3.8 Other neurologic

4. Gastrointestinal
   4.1 Direct bilirubin >4 umol/L
   4.2 Liver failure (AST, ALT, or GGT > 500 U/L)
   4.3 Necrotizing enterocolitis, confirmed (pneumatosis or free air)
   4.4 Necrotizing enterocolitis, suspected (NPO, antibiotics started)
   4.5 Other esophageal or bowel perforations not associated with necrotizing enterocolitis
   4.6 Upper gastrointestinal bleed, requiring treatment
   4.7 Stricture/stenosis (CTCAE > grade 2)
   4.8 Other gastrointestinal
5. Infectious
   5.1 Empyema
   5.2 Endocarditis
   5.3 Gastroenteritis or enteritis
   5.4 Line infection, bacterial (positive blood cultures)
   5.5 Line infection, fungal (positive blood cultures with initiation of therapy)
   5.6 Pneumonia, respiratory infection, viral (requiring the initiation of therapy)
   5.7 Mediastinitis/wound infection, deep (requiring incision and drainage; sternal instability)
   5.8 Wound infection, superficial (erythema, possible tissue separation and drainage)
   5.9 Sepsis, confirmed (positive blood cultures, not line infection)
   5.10 Sepsis, clinical with negative cultures
   5.11 Urinary tract infection
   5.12 Other infection
6. Renal
   6.1 Acute renal failure (creatinine> 1.5mg/dL (133umol/L) or tripling of baseline value for <7 days; temporary dialysis)
   6.2 Chronic renal failure (creatinine >1.5mg/dL (133 umol/L) or tripling of baseline value for >7 days; long-term dialysis)
   6.3 Other renal
   6.4 Hematologic Anemia (hemoglobin <10 gm/L)
   6.5 Thrombocytopenia (platelets < 50 x 10(9)/L)
   6.6 Hematoma (CTCAE grade > 2)
   6.7 Hemorrhage, gastrointestinal (CTACE grade >2; hemepositive stools)
   6.8 Hemorrhage, genitourinary (CTCAE grade > 2)
   6.9 Hemorrhage, pulmonary/upper respiratory (CTCAE grade > 2)
   6.10 Other hematologic
7. Vacular
   7.1 Thrombus/thromboembolism
   7.2 Vascular, other
8. Other complication
   9.1 Other

RV, Right Ventricular; CTCAE, Common Terminology Criteria for Adverse Events; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; NPO, nothing by mouth.

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