Protocol Version 1.0 and Statistical Analysis Plan

Supplementary Material to Accompany the Manuscript:

Effect of Intraoperative Dexamethasone on Major Complications and Mortality Among Infants Undergoing Cardiac Surgery: The DECISION Randomized Clinical Trial

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Protocol Synopsis

SPONSOR	E.N. Meshalkin National Medical Research Center
PROTOCOL TITLE	Intraoperative **D**examethasone in p**E**diatric **C**ardiac **S**urgery (**DEC**i**S**ion): a randomized, double-blind, placebo-controlled clinical trial
PROTOCOL TYPE	Investigator initiated ClinicalTrials.gov Identifier: NCT02615262
STUDY POPULATION Main selection criteria:	INCLUSION CRITERIA - planned elective repair of congenital heart defects under cardiopulmonary bypass; - age ≤12 months; - written informed consent signed by parent or guardian. EXCLUSION CRITERIA - emergency surgery; - hypoplastic left heart syndrome; - use of inotropes before surgery; - steroids use in the preceding 30 days; - mechanical ventilation before surgery; - bacterial, viral or fungal infection in the preceding 30 days; - gestational age <37 weeks; - perinatal central nervous system injury; - participation in conflicting randomized trials.
STUDY HYPOTHESIS	Intraoperative administration of dexamethasone reduces complication rates and improves clinical outcomes in infants undergoing repair of congenital heart defects under cardiopulmonary bypass.
STUDY DESIGN	Multicenter, randomized, double-blind clinical trial.
SAMPLE SIZE	384 patients with 1:1 randomization.
DURATION OF THE STUDY	36 months or longer if required to achieve the estimated sample size. Follow-up will be scheduled at 30 days since enrolment or at the end hospitalization if this is longer than 30 days.
TREATMENT REGIMEN(S)	One-half of the patients will be randomly allocated to receive 1 mg/kg of dexamethasone immediately after induction of anesthesia and one-half will be allocated to equivolume of 0.9% sodium chloride at the same time point.
INVESTIGATIONAL PRODUCT(S) Formulation(s): - dexamethasone; - 0.9% sodium chloride (henceforth referred to as saline). Route(s) of administration: intravenously.	
STUDY ENDPOINTS	**Primary**: composite of major complications: **a)** all-cause 30-days or hospital mortality; **b)** myocardial infarction (cTn values >10 x 99th percentile during the first 48 h, occurring from a normal baseline cTn value, either new pathological Q waves or new left bundle branch block, or angiographically documented new native coronary artery occlusion, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality); **c)** need for extracorporeal membrane oxygenation; **d)** cardiopulmonary resuscitation;

	e) acute kidney injury (at least pRIFLE "injury" stage - estimated creatinine clearance decrease by 50%, urine output <0.5 mL/kg/hr for 16 h); **f)** prolonged mechanical ventilation (i.e. ≥24 hours); **g)** new neurologic injury (stroke, seizures, coma).
	Secondary: - individual components of the composite endpoint; - duration of mechanical ventilation; - maximum inotropic index during the first 24 hours after surgery; - inotropic index greater than 10 for 24 hours or more at 5 for 48 hours after the operation; - use of pacemaker; - drainage blood loss in the first day after surgery; - number of transfused blood components in the first day after surgery; - postoperative infection (sepsis - SIRS resulting from or occurring in the presence of proven infection, pneumonia, mediastinitis, wound infection); - reason for randomization code break, where applicable; - intensive care unit (ICU) stay; - re-admission to the ICU; - length of hospitalization.
SAFETY CRITERIA	- postoperative infection (sepsis, pneumonia, mediastinitis, wound infection).
STUDY PROCEDURES	The active group will receive dexamethasone at a dose of 1 mg/kg of body weight immediately after anesthesia induction. The control group will receive saline at a dose of 0.25 ml/kg at the same time point. The anesthetist, intensivist, patient's legal representative, caregiver and data analyst will be blinded to treatment allocation.
NUMBER OF SITES	4 sites in Brazil, China and Russia.
INTERIM ANALYSES	No.

Investigator Statement

I have read the protocol and agree that it contains all necessary information for me and my staff to conduct the study. I will personally oversee the conduct of this study and will make a reasonable effort to complete the study within the time designated.

I will provide the personnel under my supervision with copies of the protocol and access to all information provided by the Sponsor. I will ensure they are well informed about the conduct of the study. I am aware that before the commencement of this study, the local Institutional Review Board must approve this protocol in the clinical facility where it will be conducted. I agree to make all reasonable efforts to adhere to the attached protocol.

I agree to provide all subjects with informed consent forms, as required by government and International Conference of Harmonization regulations. I agree to report all adverse experiences in accordance with the terms of this protocol.

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(Signature of Principal Investigator) (Date)

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2. INTRODUCTION AND RATIONALE

Cardiac surgery under cardiopulmonary bypass is accompanied by systemic inflammatory response (SIRS), which is associated with adverse clinical outcomes[1]. Deleterious effects of the SIRS are most severely expressed in infants.[2] It was demonstrated that administration of steroids reduces systemic inflammatory response in infants with congenital heart disease (CHD) undergoing cardiac surgery under cardiopulmonary bypass.[3] However, data on the effects of steroid application on clinical end points, such as mortality, acute kidney injury, acute ischemic stroke and infection remain controversial.[4,5] Limited evidence of the impact of steroids on perioperative complications in pediatric cardiac surgery has been received mainly in observational studies and therefore has a low value. A recent meta-analysis of two randomized studies acknowledged the absence of compelling evidence that would allow to make definitive conclusions on the issue.[6] Nevertheless, intraoperative use of steroids to reduce complication rates in pediatric cardiac surgery remains a routine practice worldwide. Therefore, a randomized clinical trial of the use of steroids for pediatric cardiac surgery is essential.

STUDY HYPOTHESIS

Intraoperative administration of dexamethasone reduces complication rates and improves clinical outcomes in infants undergoing repair of congenital heart defects under cardiopulmonary bypass.

MAIN EXPECTED RESULTS AND IMPACT

The results of this study can support or refute the use of dexamethasone in pediatric cardiac surgery worldwide. If dexamethasone reduces major complication rates, we will have a justification for its use which is lacking at the moment.

If dexamethasone and placebo are similar in terms of their effects on major complications, this will make it redundant in routine use and thus reduce polypragmasia in pediatric cardiac anesthesia which is common.

3. STUDY OBJECTIVES

3.1 PRIMARY

Composite of 30-days or hospital all-cause mortality, myocardial infarction, need for extracorporeal membrane oxygenation (ECMO), cardiopulmonary resuscitation, acute kidney injury, prolonged mechanical ventilation, and new neurologic injury (stroke, seizures, coma) in intra- and postoperative period.

3.2 SECONDARY

- individual components of the composite end point;
- duration of mechanical ventilation;
- maximum inotropic index during the first 24 hours after surgery;
- inotropic index greater than 10 for 24 hours or more at 5 for 48 hours after the operation;
- use of pacemaker;
- drainage blood loss in the first day after surgery;
- number of transfused blood components in the first day after surgery;
- postoperative infection (sepsis - SIRS resulting from or occurring in the presence of proven infection, pneumonia, mediastinitis, wound infection);
- reason for randomization code break, where applicable;
- intensive care unit (ICU) stay;
- re-admission to the ICU;
- duration of hospital stay.

4. STUDY DESIGN

4.1 DESCRIPTION OF THE PROTOCOL

This will be a double-blind placebo-controlled superiority clinical trial.

4.2 DURATION OF THE STUDY

The estimated duration of the study is 36 months or longer if required to achieve the estimated sample size.

5. SELECTION OF PATIENTS

5.1 POPULATION

On a daily basis, children under 12 months of age inclusive, scheduled for elective cardiac surgery with CPB, will be identified from the institutional electronic records. Potential candidates will be screened against inclusion and exclusion criteria and consecutive eligible patients will be enrolled.

5.2 INCLUSION CRITERIA

- planned elective repair of congenital heart defects under cardiopulmonary bypass;

- age ≤12 months;
- written informed consent signed by parent or guardian.

5.3 EXCLUSION CRITERIA

- emergency surgery;
- hypoplastic left heart syndrome;
- use of inotropes before surgery;
- steroids use in the preceding 30 days;
- mechanical ventilation prior to surgery;
- bacterial, viral or fungal infection in the preceding 30 days;
- gestational age <37 weeks;
- perinatal central nervous system damage;
- participation in conflicting randomized trials.

6. TREATMENTS

6.1 INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

The experimental group will receive dexamethasone at a dose of 1 mg/kg of body weight intravenously immediately after anesthesia induction.
The control group will receive an equivolume (i.e. 0.25 ml/kg of body weight) of saline intravenously immediately after anesthesia induction.
Steroids may be administered after randomization code break, which must be documented and communicated to the Sponsor.

6.2 STANDARD CARE

The patients must receive the best available care. No additional interventions or laboratory tests are required by the study protocol.

6.3 ALLOCATION CONCEALMENT AND BLINDING

Personnel involved in the care of the trial's participants, including outcome assessors, as well as patients' legal representatives will be blinded to treatment allocation. The staff members responsible for randomization and administration of the study drug will not be involved in the care of the trial's participants. All the statistical analyses will be performed by the biostatistician not involved in treatment allocation. The study drugs are identical in color, appearance and volume, both study drugs will be prepared in a separate room and arrive to the operation room in an unmarked syringe.

6.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

Patients deemed eligible (target n=384) will be randomly allocated to receive either dexamethasone (active group) or placebo (control group). The randomization will be performed by a biostatistician, using a computer-based randomization service (www.sealedenvelope.com), using of a permuted-block technique with varying block size. To ensure balanced distribution by the variables deemed important, the randomization will be stratified by center, gender and age (with the cut-off at 30 days). Each participating center will receive a set of sequentially numbered sealed opaque envelopes containing treatment allocation, to be opened after patient's admission to operation room.

6.5 UNBLINDING

The unblinding will take place after all the statistical analyses have been completed and reviewed. Otherwise, the reasons for breaking randomization code will be: allergic reaction, aspiration, concern for airway edema, cardiopulmonary resuscitation. All events of code breaks along with the reasons must be communicated to the Sponsor within 24 hours.

6.6 IMP ACCOUNTABILITY AND COMPLIANCE

All steroids must be withheld from routine use in operating room. All deviations from the protocol must be communicated to the Sponsor within 24 hours and reflected in the electronic Case Report Form (eCRF). There is no drug company involved in the study.

7. SAFETY

No risk for the study subjects is expected. The study design is simple and all patients will receive the best available treatment. The study drugs are safe and have been administered to thousands of patients every year.

7.1 SAFETY INSTRUCTIONS

Both IMPs included in this study have been routinely used for decades in thousands of patients worldwide and there is no safety concern.

7.2 DEFINITIONS OF ADVERSE EVENT, ADVERSE DRUG REACTION AND SERIOUS ADVERSE EVENT, SERIOUS ADVERSE REACTIONS

Pediatric cardiac surgery has a relatively high mortality rate (3 to 10%) and several possible complications. Some of them have been included in the eCRF: multiple transfusion of blood products due to poor hemostasis, high dose inotropic drugs, mechanical circulatory support (e.g. ECMO), myocardial infarction with or without hemodynamic complications, neurologic deficits, sepsis, mediastinitis, wound infection, acute renal failure, surgical revision for bleeding, hospital readmission and death. Others have not been included in the eCRF but are frequently observed after cardiac surgery, can be considered disease progression and will not considered to be adverse events: low cardiac output syndrome causing end organ failure, embolic events, difficult to wean patient, etc.

7.3 PHARMACOVIGILANCE PROCEDURE

Steroids included in this study have been routinely used for decades in thousands of patients worldwide and there is no safety concern. At the same time, all the complications that occur after cardiac surgery can be considered either disease progression or complication of surgery. We will notify the Ethics Committee of all adverse events that will occur in the study patients within 48 hours.

8. TEMPORARY OR DEFINITIVE TREATMENT DISCONTINUATION

Does not apply.

9. STATISTICAL CONSIDERATIONS

9.1 DETERMINATION OF SAMPLE SIZE

For sample size estimation, we used local registry containing data on 378 patients operated at E. Meshalkin National Medical Research Centre in the preceding 18 months. In the registry population, steroids use was restricted to allergic reaction, aspiration, concern for airway edema, or cardiopulmonary resuscitation. Based on the above, the absolute risk of primary endpoint was estimated to be 40%. Hence, it was calculated that a total of 306 patients (153 in each group) would be sufficient to detect an absolute risk difference of 15% for the primary endpoint with probability of type I error of 5% and power 80%. To compensate for incomplete data, the estimated sample size was increased by 25%. The resulting total sample size is 384 patients (192 patients in each group).

9.2 DATA COLLECTION AND STORAGE

Baseline and clinical data will be collected prospectively, reversibly anonymized and entered into the eCRF by a dedicated research team member at each center. After obtaining follow-up information, the data will be irreversibly anonymized, such that re-identification of previously anonymized subjects will be impossible. Security measures (storage in a secure electronic environment, restricted access) will be put in place to protect patient privacy and data integrity. Baseline and clinical data will be collected for randomized patients only. At the coordinating center (i.e. Sponsor), a dedicated research team member not otherwise involved in the study will be responsible for the data entry to the electronic database. On a monthly basis, the data will be cross-checked for consistency by the study biostatistician. Access to the database will be restricted to the two aforementioned persons. All changes in the database will be tracked. After the study completion (i.e. obtaining follow-up information for last enrolled patient), the participating centers will have 30 days to respond to data queries before database lock, after which no further changes to the database will be possible.

9.3 ANALYSIS

Categorical variables will be reported as absolute numbers and percentages. Unadjusted univariable analyses, to compare the two treatment groups, will be based on Fisher exact test. Relative risks and 95% confidence intervals will be calculated by means of the two-by-two table method with the use of log-normal approximation. Continuous variables will be reported as mean ± standard deviation or median and interquartile range. Between-group differences will be evaluated using unpaired t-test or Wilcoxon signed rank test. Generalized regression models, adjusting for clinically important variables and their suitable transformations, will be used to estimate the treatment effect (and associated 95% confidence interval) with respect to the primary and secondary endpoints. To account for late exclusions, a time-to-event analysis will be conducted for the primary end point. Periods at risk will be defined in days for each participant, starting the day of randomization and ending with an event or censoring (withdrawal, loss to follow-up, or end of the study period). The survival times will be estimated using the Kaplan-Meier estimator and compared using log-rank test. All analyses will be according to both per-protocol and the intention-to-treat principles, however, the latter will be the primary analysis. A sensitivity analysis will be conducted after excluding events likely unrelated to the intervention, and the judgement for such exclusions will be provided.

The following variables will be used for subgroup analyses: gender, age ≤30 days, use of antegrade cerebral perfusion, circulatory arrest, left-to-right shunting, right-to-left shunting, surgery on fibrillating heart. Missing

data will not be imputed. Additionally, reasons for code breaking will be summarized by study arm and reviewed. Statistical significance will be set at the two tailed 0.05 level.
All the analyses will be done using R software (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.).

9.4 INTERIM ANALYSIS

No interim analysis will be executed, unless demanded by the Data Monitoring Committee (DMC).

10. MONITORING OF THE STUDY

Independent auditors will verify adherence to required clinical trial procedures and will confirm accurate data collection according to the Good Clinical Practice guidelines on a quarterly basis. Each center will regularly complete and send a screening log to the coordinating center. At the coordinating center, a DMC will be formed, consisting of an anesthesiologist, an intensive care specialist and a cardiac surgeon not involved in the study, supported by an independent biostatistician. The DMC will consider blinded data split by study arm on a quarterly basis to assess recruitment pace, data quality and safety issues (e.g. adverse events, unexpectedly high complication rates, etc.). The DMC will have a right to demand randomization code break and to recommend termination of the study due to a safety concern. No formal statistical analyses will be performed until the study completion, unless required by the DMC.

11. ETHICAL AND REGULATORY CONSIDERATIONS

This clinical trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for Good Clinical Practice. This clinical trial will be conducted in compliance with all international laws and regulations, and national laws and regulations of the country in which the clinical trial is performed, as well as any applicable guidelines.

11.1 INFORMED CONSENT

The investigator (according to applicable regulatory requirements), or a person designated by the investigator, and under the investigator's responsibility, will fully inform the patient’s legal representative of all pertinent aspects of the clinical trial. All patients’ legal representatives will be informed to the fullest extent possible about the study, in language and terms they are able to understand. Prior to a patient’s participation in the clinical trial, their legal representative MUST sign the written Informed Consent Form. It will also be made clear to the patient’s legal representative that he/she can withdraw from the study at any time without giving reasons and that he/she will not be in any way disadvantaged by this. Any Informed Consent will be part of Investigator’s file and retained with it. A copy of the signed and dated written Informed Consent Form will be provided to the legal representative.

11.2 INDEPENDENT ETHICS COMMITTEE APPROVAL (IRB/IEC)

This clinical trial protocol as well as the Informed Consent will be submitted to the Ethics Committee, and the written and dated approval/ favorable opinion, signed by the chairman with ethics committee(s) composition will be obtained.

11.3 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The investigator undertakes to perform the clinical trial in accordance with this clinical trial protocol, ICH /Good Clinical Practice and the applicable regulatory requirements.
The investigator ensures compliance with all procedures required by the clinical trial protocol and with all study required procedures. The investigator agrees to provide all information requested in the Case Report Form (CRF) in an accurate and legible manner.

11.4 RESPONSIBILITIES OF THE SPONSOR

Does not apply.

12. DATA MANAGEMENT

12.1 SOURCE DOCUMENTS

According to the ICH /Good Clinical Practice, the monitoring team must check the Case Report Form entries against the source documents.

12.2 CASE REPORT FORMS (CRFS)

It is the responsibility of the investigator to maintain adequate and accurate web based CRFs. All CRFs will be completed electronically in their entirety to ensure accurate interpretation of data.

13. DATA PROTECTION

Data will be stored in electronic database without indicating the name of the patients (a numeric code will be used).

14. CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a publication reporting the study findings.

15. BIBLIOGRAPHIC REFERENCES

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