STRIPES

Steroids in Pediatric Fluid and/or Vasoactive Infusion Dependent Shock

Data Management Plan

Protocol Title: Steroid Use in Pediatric Fluid and Vasoactive Infusion Dependent Shock (STRIPES)

Purpose: The purpose of this document is to provide detailed information about the processes used for the STRIPES Pilot Study with respect to data systems design and implementation, collection, maintenance, security and confidentiality of data.

Principal Investigator: Kusum Menon, MD

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Signatures of Approval:

Name (printed)	Study Role	Signature	Date
Dr. Kusum Menon	Principal Investigator		
Yael Kamil	REDCap Administrator		
Tinghua Zhang	Statistician		
Katie O'Hearn	Study Coordinator		

Protocol Summary:

Title	Steroid Use in Pediatric Fluid and Vasoactive Infusion Dependent Shock
Short Title	STRIPES
Protocol Number	STRIPES – Version 1, 05 May 2014
Phase	Phase IV
Methodology	Pragmatic, multi-centre, double blinded, randomized controlled trial of hydrocortisone versus placebo in fluid and vasoactive infusion dependent shock.
Study Duration	Estimated study duration (from start of recruitment period to end of data analysis and manuscript preparation period) is 36 months
Study Center(s)	1. Study Coordinating Centre: Children's Hospital of Eastern Ontario 2. Sub Sites: o Alberta Children's Hospital (ACH) o British Colombia Children's Hospital (BCCH) o IWK Health Centre (IWK) o CHU Sainte Justine (SJ) o McMaster Children's Hospital (McCH) o Montreal Children's Hospital (MCH)
Primary Objective	Primary Objective – The primary feasibility objective will be the patient accrual rate over one year. Our goal is to recruit 72 patients over one year. However, we will consider patient accrual to be adequate if we recruit 60 patients from seven sites within this time.
Secondary Objectives	Secondary study objectives – *1)* *Adherence to the protocol:* a. Time to administration of the first dose of study drug (goal is <8 hours from starting a vasoactive medication, i.e. randomization within 6 hours and drug administration complete within 8 hours); b. Weaning of drug to q8h when hemodynamically stable (goal is to wean within 12 hours of no escalation of therapy); c. Discontinuation of drug when off all vasoactive medications (goal is to discontinue between 12 and 18 hours of vasoactive medications being stopped); We will consider adherence to our protocol to be adequate if criteria a to c are met in 80% of enrolled patients (approximately 48/60). *2)* *Open label steroid use:* a. Frequency of open label steroid use and b. Clinical parameters of patients in whom open label steroids are administered. c. We will consider the number of patients started on open label steroids to be acceptable if it occurs in fewer than 10% of patients (approximately 6/60). 3) *Incidence of the following clinical outcomes in the two groups*: a. Time to discontinuation of vasoactive infusions and mortality (blinded to allocation); b. Adverse events (specifically: severe bleeding, secondary infections and use of insulin infusions). The time to discontinuation of vasoactive agents will be used to better estimate the sample size for the full study. The mortality rate and incidence of adverse events will be also measured in aggregate (i.e. the whole cohort) in order to provide a better baseline estimate of these outcomes in our study population. *4)* *Blood sampling for mechanistic studies* a. The percentage of patients from whom blood samples are sent b. The percentage of samples sent that are successfully received and analyzed in their respective labs.
Number of Subjects	The projected enrollment is 72 patients.

Diagnosis and Main Inclusion Criteria	Children aged newborn to 17 years with fluid and vasoactive infusion dependent shock who have been on any vasoactive agent for between 1 to 6 hours.
Study Product, Dose, Route, Regimen	The randomization list will be stratified by site in order to account for site specific practice variation. Patients will be randomized 1:1 using random variable block sizes (2-4 patients/block) to avoid substantial imbalance in the number of patients assigned to each group given the small size of this pilot study. Participants will be randomized to receive either hydrocortisone or a placebo. Hydrocortisone: Patients randomized to the hydrocortisone arm will receive a 2 mg/kg hydrocortisone IV bolus on enrolment followed by 1 mg/kg of hydrocortisone IV q6h until the patient has not had an escalation in therapy (as defined by an increase in their vasoactive infusions or a fluid bolus such as normal saline, albumin or any other blood product) for at least 12 hours. If they meet these criteria their hydrocortisone will be weaned to 1 mg/kg every 8 hours which will be continued until they are off all vasoactive infusions for 12 hours. If following the initial hydrocortisone wean, the patient requires fluid boluses and/or an increase in their vasoactive infusion(s), their hydrocortisone will be increased back to 1 mg/kg of hydrocortisone IV q6h until they meet stability criteria again. Hydrocortisone will be continued for a maximum of 7 days after which weaning of the hydrocortisone will not be required. Placebo: Patients will receive placebo consisting of normal saline equivalent in volume to the appropriate dose of hydrocortisone. The remainder of the protocol will be as per the experimental group.
Duration of administration	The study drug will be administered in the PICU within 8 hours of the patient being started on any vasoactive agent. Study drug duration will range from a minimum of 14 hours (loading dose + one q6h dose + one q8h dose) to a maximum of 7 days (168 hours).
Reference therapy	Corticosteroids are currently used for ~50% of the patients that would be enrolled in this trial. Therefore patients in both arms of the trial will be treated by regimens that fall within the current standard of care.

Statistical Methodology	To meet the feasibility objectives of this pilot RCT we have planned descriptive analyses. We will present point estimates of recruitment, feasibility events (including adherence to protocol) and open label steroid use, as proportions with 95% confidence intervals. We will present continuous data as means and standard deviations, or medians and inter-quartile ranges, as appropriate. With respect to patient recruitment, our goal is to enroll a minimum of 60 patients at 7 sites over a one-year period. Failure to do so will prompt us to modify our plans for a future trial. If our recruitment rate is as anticipated, or better, we will not modify eligibility criteria. If our recruitment rate is marginal (that is, barely achieves our goals), we will examine the number of patients excluded on the basis of each exclusion criterion, and will reconsider the necessity for any criterion that has resulted in a large number of excluded patients. We will record the number of eligible non-randomized patients and reasons for non-enrolment, and on the basis of these results we will consider deterrents to randomization and methods to enhance enrolment of eligible patients. With regards to protocol adherence, we will collect a great deal of relevant data, and will monitor a subset of these data in real-time. We will analyze protocol violations with a view to possible modifications of study procedures and protocols. With respect to open label steroid use, we will calculate the proportion of patients in each group who receive open label steroids. We will review respiratory and hemodynamic variables at the time of open label steroid use, along with clinician notes, in an effort to improve upon future compliance.

Roles/Responsibilities:

1) Principal Investigator (PI): Kusum Menon
2) Study Coordinator: Katie O'Hearn
3) Statistician: Tinghua Zang
4) REDCap Administration: Yael Kamil
5) Site Investigators: Elaine Gilfoyle (ACH), David Wensley (BCCH), Gavin Morrison (IWK), Marisa Tucci (SJ), Karen Choong (McCH), and Ronald Gottesman (MCH)
6) Site Research Coordinators: Dori-Ann Martin (ACH), Gordon Krahn (BCCH), Gina Vaninetti (IWK), Mariana Dumitrascu (SJ), To be determined (McCH), and Maryse Dagenais (MCH)

Data Management Plan:

The flow sheet explains the process for electronic Case Report Form (eCRF) data collection. The following steps provide a detailed outline:

1) **Electronic CRF:** The eCRF will be set up according to the study protocol. Design and creation of the database will be a collaborative effort of the Study Coordinator, Principal Investigator and REDCap Administrator. REDCap forms will be developed by Katie O'Hearn with input from Dr. Menon and Yael Kamil. Dr. Menon will approve the forms. The forms will be tested by Katie O'Hearn.

2) **Data confidentiality:** All personal health information is kept confidential unless release is required by law. Representatives of the funding agency or government regulators such as representatives of CHEO Research Ethics Board, as well as the CHEO Research Institute (CHEO RI) may review the original relevant medical records under the supervision of the study PI for audit purposes. A Quality Improvement Reviewer may review relevant medical records under the supervision of the Investigator and staff to ensure that all research standards and

guidelines/regulations are met. Study procedures and data collection will only commence once the subject meets the study eligibility criteria (enrolled via deferred consent). If the legal guardian is present and has the capacity to consent, or in centres where a deferred consent model is not used, procedures and data collection will only commence once the subject's parent or legally acceptable representative has signed the Informed Consent Form. The following identifiable information will not be collected: name, initials, MRN, or address.

Participants will not be identifiable in any publication or presentation resulting from the trial. No identifying information will leave the CHEO RI. All information which leaves CHEO RI will be coded with an independent study number. It is the responsibility of the PI and the Site Investigators to keep the study records for 25 years as required by Health Canada for Phase IV studies.

3) **Data collection process:** The following data will be entered directly into the REDCap eCRF by the Site Research Coordinators(s):
   - Data collected from the participant's medical chart (includes standard of care lab results)
   - Documentation of participant eligibility and informed consent process
   - Economic information obtained from the participant's caregivers (i.e. where legal guardian is staying, work status while child is admitted to PICU) and from PICU staff (nurse:patient ratio)
   - Individual Subject Serious Adverse Event Reports
   - Protocol Deviations and Violations

   Lab results for bloodwork that are obtained strictly for research purposes will be entered into the eCRF by the Study Coordinating Centre (SCC). Any data that is collected on paper first (i.e. sites that prefer to collect data on a paper CRF) will be entered into REDCap and the source document will signed, dated and filed in the participant's study file. Lab result sheets for research bloodwork will be reviewed by the Principal Investigator and filed in the regulatory binder at the SCC.

4) **Tracking data entry and data modification:** The Site Research Coordinators or delegated research assistants will be primarily responsible for inputting the data into REDCap. This should be documented on each sites study Delegation Log. The REDCap database contains an audit trail which is time stamped for every user who accesses and edits the database. Each REDCap user will have their own individual user ID and password.

5) **Data query, data clarification and correction plan:** The Data Resolution Workflow application in REDCap will be used for data queries. The user rights for this application will be set as follows:
   - View only – Dr. Menon
   - Respond only to opened queries – Site Research Coordinators/assistants, Site Investigators
   - Open, close, and respond to queries – Statistician, Study Coordinator

   This allows the Methods Centre and SCC to generate queries, and will show the status of any queries (e.g. Data Verified, Closed). REDCap can also be used to generate a daily report to inquire if any users have made changes to the data.

6) Software and hardware to be used to collect and process data: REDCap (Research Electronic Data Capture) is a secure, web-based application designed exclusively to support data capture for research studies. REDCap is developed and maintained by a team at Vanderbilt University and licensed free of charge to research institutions. REDCap provides an intuitive user interface for data entry (with data validation), and 128-bit data encryption.

7) **Version control for the eCRF – Data validation Plan:** Once the database has been developed, the eCRFs for three mock patients will be entered to test and validate the system while it is still in Development Mode. This ensures that the forms are functioning properly and that there are no errors in branching logic. Any errors or problems will be resolved before the project is moved to Production Mode.

   Where applicable, eCRF fields will be programmed with validation checks (otherwise known as edit checks). Based on an understanding of the data collection forms these checks will:
   - Alert the data entry users to missing data
   - Check that numeric variables are within reasonable ranges
   - Alert the data entry user to incorrect formatting of data (e.g. dates, times)
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   After data entry for 10 patients has been completed, one case will be randomly selected for validation. This case will be re-entered in REDCap by an individual who did not enter the original data. The "Data Comparison Tool" in REDCap will be used to check for discrepancies between the two copies of the CRF. This process will be repeated for every 10 patients completed. Alternately, once data entry for all study participants has been completed, 10% of cases will be randomly selected for validation (as described above). Every difference that arises will be noted in a discrepancy list and accounted for in the calculation of an error rate. If the error rate is greater than 0.01 (1%), discrepancies will be investigated and the Principal Investigator will decide if re-entry is necessary.

8) **Security and protection of data:** The CRU's REDCap servers are housed in a dedicated, locked server room within the CHEO Hospital main site, which is secured with 24-hour on-site security guards. The CRU coordinates its network infrastructure and security with CHEO Information Services (CHEO IS). This provides the CRU with segregated and redundant firewalls and switches, HVAC, malware and anti-virus support, data backup and recovery support, and server hardware and software support within CHEO IS. Network equipment includes two servers connected to redundant gigabit switches. Administrative user authentication to the servers is centralized to the CHEO IS Active Directory while the application authentication uses an internal table-based authentication method. Communication over public networks and between the web application is encrypted using secure socket layer (SSL) with 256-bit encryption or higher. Access between the web application and database is protected by a firewall.

   Direct access to CHEO computers is only available while physically located inside the facility, or via Citrix remote access. All servers and desktops are scanned for malware and antivirus threats, and our IS staff is notified of alerts. Security is maintained using active directory security. Users are required to change their passwords every 180 days, and workstations time out after 10 minutes of inactivity. All files are protected at group and user levels; database security is handled in a similar manner with group level access to databases, tables, and views in MySQL Server.

   The REDCap data collection application will be used for study data management. REDCap, developed by an NIH-funded consortium of institutional partners, provides a secure, web-based application for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry. The system offers data manipulation with audit trails for reporting, monitoring and querying patient records, and an automated export mechanism to statistical applications. REDCap was developed specifically around HIPAA security guidelines

and has a proven track record with over 1000 academic clinical research centres hosting the application.

The investigators and CRU staff are fully committed to the security and confidentiality of all research data. All CRU personnel have signed confidentiality agreements concerning all data encountered in the center. Violation of these agreements may result in termination from employment at the CHEO Research Institute. In addition, all personnel involved with CRU data systems have completed GCP training and are governed by CRU standard operating procedures that address data management, privacy and security.

9) **Data Archiving & Record Retention:** All research records for this trial (as it falls under Health Canada Division 5 regulations) will be retained for a minimum of 25 years after study closure. At the SCC, study files in the Regulatory binder will be kept in the office of the study coordinator (Katie O'Hearn) in CHEO Research Institute II, Room R2109a. Electronic copies of any study records will be housed on the secured "V" drive of CHEO, in a password protected dedicated STRIPES study folder. This folder is only accessed by Drs. Menon and McNally (Co-PI), and the current study coordinator (Katie O'Hearn or to be determined). No other individuals will have access to this folder. The identifying documents such as the subject list or the consent forms will be stored separately from the de-identified study documents.

Quality Assurance:

Conduct of this study will adhere to the Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS), the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), and Health Canada Food and Drug Regulations with the following exceptions for Phase IV studies:

- *C.05.006 Authorization*: A clinical trial application for authorization by Health Canada does not apply to phase IV studies.

- *C.05010 (j) Good manufacturing practices (GMP):* do not apply. This is the responsibility of the Manufacturer (company).

- *C.05.012 (e) Records respecting shipment, receipt, disposition, return and destruction of the drug*: Only (a) phase I through III trials and (b) studies where a marketed drug is being used outside its approved indications, must do drug accountability.

- *C.05.011 Labelling*: It is acceptable for the marketed drug to be labelled in accordance with its marketing authorization provided that the labelling on the marketed drug is appropriate for the trial. The label information should not compromise the blinding and the expiration date needs to be identifiable.

The protocol, including the informed consent document and all recruiting materials, will be submitted to the CHEO Research Ethics Board (REB) at the SCC and to the local REB at each site for review and approval. A REB review form will also be submitted to the Maternal Infant Child & Youth Research Network (MICRYN) REB committee. The MICRYN REB committee will not conduct the REB review, but will facilitate communication between site REB chairs. No changes will be made to the protocol or study documentation without REB approval, except where necessary to eliminate apparent immediate hazards to participants. The parent or legally acceptable representative will be able to withdraw their consent to participate at any time without prejudice. Additionally, the investigators may withdraw a participant if, in the investigator's clinical judgment, it is in the best interest of the child.

A site monitoring visit may be conducted by the SCC up to 3 times during the course of the study. These visits may take place in person, or via teleconference. An additional for cause monitoring visit may result if a major protocol violation occurs at your site. The purpose of these visits is to provide support and clarification for the site study staff. The monitoring visits/teleconferences will take place:

- At study start up
- Mid-way through the recruitment period
- At study close out

During the monitoring visit/teleconference, the SCC will ensure that the protocol is being followed, and all required data is being collected. Additionally, the SCC will identify any items missing from the Regulatory Binder. The consent document will be reviewed for content to ensure it contains the required (and additional, as applicable) regulatory elements. The consent document will be compared to the protocol and REB procedures for informed consent documentation to ensure agreement between the two documents.

Regulatory Documents:

The following documents will be collected and kept in the STRIPES Study Regulatory Binder at each site:

- Protocol and Amendments
- Approved Informed Consent Forms and other approve study documents
- Ethics Committee Documentation
- SAE and Safety Reports
- Study SOPs
- Case Report Form sample and Instructions
- Study Staff Information
- Subject Accountability Records
- Monitoring Documentation
- General Correspondence
- Investigator Brochure
- Biological Samples and Laboratory Documentation
- Investigational Product Documentation
- Other (as applicable)