STRIPES

SOP Title:	**STRIPES – Pharmacy Standard Operating Procedures** (from STRIPES Study SOP Manual)
SOP Version:	Version 6
SOP Date:	24-Nov-2015 (taken from STRIPES Study SOP Manual)

1. Regulation

The STRIPES Pilot Study is considered a Phase IV study. As such, conduct of this study must 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:

C.05.006 Authorization: A clinical trial application for authorization by Health Canada is not required for 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 dug is appropriate for the trial. **The label information should not compromise the blinding** and the expiration date needs to be identifiable.

2. Pharmacy Procedures

The specific pharmacy procedures will vary for each site according to local pharmacy Standard Operating Procedures. There is no central pharmacy for this study; however, if a site pharmacy has questions concerning the STRIPES Study, they can contact the Study Coordinator or the Manager of Drug Distribution at the Study Coordinating Centre (SCC):

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3. Ordering Study Drug

Each site pharmacy will be responsible for procuring and storing the study drug and necessary supplies for their site. Recruitment will be capped at 24 patients per site, however, it is expected that each site will recruit between 6-12 patients over the one-year recruitment period.

4. Preparing Study Drug

Each site pharmacy will prepare the hydrocortisone and placebo solutions for the patients enrolled at their centre. The hydrocortisone will be made up as a 10 mg/ml intravenous solution. The placebo will be a normal saline solution and should be made up in equivalent volume. The active drug and placebo (hydrocortisone and normal saline) should be identical in appearance, volume and smell as hydrocortisone is made up in normal saline and dissolves completely with no visible precipitate.

5. Study Drug Storage

Hydrocortisone (the STRIPES Study drug) 10 mg/mL is stable for 9 days in the fridge and 30 hours at room temperature, as per the new guidelines for USP 797 regarding the compounding of sterile products which state:

"Medium-risk conditions—If you compound or pool multiple doses of sterile products for administration to multiple patients or to a single patient on multiple occasions and the compounding process involves more than single volume transfer or takes a long time (such as complete dissolution or homogenous mixing), the process will usually be considered medium-risk. Generally, medium-risk CSPs do not have broad-spectrum bacteriostatic substances and are administered over multiple days. Without passing a sterility test, medium-risk CSPs may be stored for 30 hours at room temperatures of 25 to 40 degrees Fahrenheit, 9 days at cold temperatures and 45 days if frozen solid and held at -20 degrees or less. Medium-risk compounding examples include compounded total parenteral nutrition fluids that require multiple injections, detachments and attachments of nutritional products to a device that delivers all the nutritional components to the final sterile container as well as filling injection or infusion devices with multiple sterile drug products and evacuation of air from the device reservoirs before filling." (from: http://blog.pharmacyonesource.com/usp-797-a-breakdown-of-low-medium-and-high-risks).

6. Study Drug Dosing

6.1. Hydrocortisone

Hydrocortisone will be administered to study participants as follows:

- Patients randomized to the hydrocortisone arm will receive a **2 mg/kg** hydrocortisone IV bolus on enrolment

- Thereafter, the patient will receive **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 q8h** 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 (168 hours) after which weaning of the hydrocortisone will not be required

- Note: There is no maximum weight-based dose because the dosing range for hydrocortisone is so large.
- Note: For obese patients, dosing should be based on <u>actual</u> weight and <u>not</u> on ideal body weight.

6.2. Placebo

Patients will receive placebo consisting of normal saline equivalent in volume to the appropriate dose of hydrocortisone according to the dosing schedule above.

7. Duration of Study Drug

The duration of treatment will range from a minimum of 14 hours (loading dose plus one dose 6 hours later followed by one q8h dose) to a maximum of 7 days (168 hours) of study drug.

8. Timing of First Dose

The first dose of the study drug must be administered within 8 hours of the patient meeting the study eligibility criteria (i.e. the time when the patient was first started on a vasoactive infusion). Before the Site Research Coordinator enters the patient information into the web-based randomization system, the Site Research Coordinator must contact the pharmacy to ensure that the study drug can be dispensed within the given timeframe. When the Site Research Coordinator submits the study drug order form to the pharmacy, the Coordinator will remind pharmacy staff of the time before which the first dose of study drug must be administered to the patient.

In the event that the study drug is given outside of the 8 hour window, the Site Research Coordinator will record this as a protocol violation and inform the SCC.

9. Randomization

At enrolment, the Site Research Coordinator will obtain a study ID number for each patient through the web-based randomization system. Each site pharmacy will be provided with a master randomization list. The Site Research Coordinator will submit the study drug order to the pharmacy with the study ID number recorded on the order sheet. Pharmacy staff will match the study ID number on the study drug order to the number on the master randomization list to determine treatment allocation. Therefore, the pharmacy staff will not be blinded.

10. Blinding

The randomization lists will only be accessible to the Methods Centre at the Ottawa Hospital Research Institute and to the pharmacy staff at each site and should not be seen by anyone else directly involved with the study. If possible at your site, the clinical pharmacist should also be blinded to the study group assignment. If the clinical pharmacist cannot be blinded, please ensure that they are aware of the importance of not revealing the patient's allocated study treatment to the patient's healthcare team.

The pharmacy must maintain a list of randomized patients and treatment allocation. The pharmacy staff should not reveal the randomization code unless notified by the Site Investigator or delegate as per the unblinding procedures (see next Section).

Pharmacy staff should ensure that any labels used on the study drug package do not unblind the participant.

11. Unblinding Procedures

Blinding may only be broken at the request of the patient's MRP. If unblinding is required, the MRP must first contact the Site Investigator. The Site Investigator will contact the pharmacy to unblind the participant. If the Site Investigator decides to delegate this task to another member of the study team, this must be documented in the study delegation log, and the pharmacy staff must be made aware of any additional study personnel who can request unblinding.

12. Pharmacy Hours of Operation for Enrollment

The hours during which patients can be enrolled into the study will vary from site to site depending on the availability of the on-call research coordinator and the hours of operation of the pharmacy. Prior to initiation of the study, the Site Research Coordinator should meet with the site pharmacy team to determine during which hours study patients can be enrolled. Please consider the 8-hour limit to dispense the study drug when determining the time window for study enrolment at your site.

If your site pharmacy is not available 24/7 and/or the cost for having pharmacy staff available 24/7 is not feasible given the study budget, the following is proposed:

- The site pharmacy prepares numbered medication kits following the randomization list and stores them in PICU (numbered with the study ID numbers assigned to your site).
- Depending on the expiry time for hydrocortisone 10mg/mL refrigerated at your site, the kits would need to be re-made at the end of the storage duration as per Section 5 "Study Drug Storage".
- These kits would be stock solutions rather than patient-specific volumes, therefore, the nurse administering the study drug would have to withdraw the appropriate volume required for the bolus dose (2mg/kg).

- Once the patient is enrolled the pharmacy would take over preparing the doses when they opened.