maternal infant child & youth research network

réseau de recherche en santé des enfants et des mères

MATERNAL INFANT CHILD YOUTH RESEARCH NETWORK

RESEARCH ETHICS REVIEW

1. **PROJECT TITLE** **Steroid Use in Pediatric Fluid and Vasoactive Infusion Dependent Shock (STRIPES) - Pilot Study**

2. **STUDY START AND END DATES** **June 2014 to October 2016**

3. **STUDY LEAD**

indicate the name and location of the overall national or international study lead

Name Kusum Menon Department/Division Department of Pediatrics, Division of Critical Care
Institution Children's Hospital of Eastern Ontario (CHEO) Address 401 Smyth Road, Ottawa, ON K1H 8L1
Discipline *ie. Medicine, Psychology* Medicine
Signature Kusum Menon

4. **PRIMARY CONTACT FOR THE STUDY OVERALL**

Name Katie O'Hearn Position Study Coordinator
Institution Children's Hospital of Eastern Ontario Address 401 Smyth Road, Ottawa ON, K1H 8L1
Email kohearn@cheo.on.ca Phone 613-737-7600 ext. 4006 Fax 613-738-4287

5. **FUNDING SOURCE**

5.1 Research Granting Agency, please specify source and type of award: Canadian Institutes of Health Research (CIHR) Operating Grant

5.2 Date of Funding commencing or Period of Funding? June 2014 to October 2016

5.3 Other funding sources, please specify: No other funding sources

5.4 Study both funded and initiated by an Industry (Pharmaceutical or other), specify company name:

Not applicable

5.5 For Industry sponsored trials, please provide the name and address of contact person/company in order for us to invoice the company for the REB Review fee: Not applicable

A fee of $XXXXXX Canadian will be charged for the review of any research project partially or fully funded by private industry, and is applied whether the study is submitted to full Board or delegated/expedited review. Consideration will be made for exemption from the review fee, on a case-by-case basis. Requests for an exemption must be made in writing to the Chair. This review fee is not normally applied to investigator-initiated studies.

☒ Funded proposals are generally considered to have successfully undergone independent, scientific peer review. Copies of these reviews must be appended to the full Board submission.

For unfunded projects OR those that have received funding without prior independent scientific peer review, please specify the source of scientific peer reviews (two) which are included with the submission:
Not applicable

6. TYPE OF INVESTIGATION AND APPROVALS

6.1. Clinical Trial

6.1.1. ☒ Clinical Drug Trial

☐ Phase I ☐ Phase II ☐ Phase III ☒ Phase IV

*Health Canada must approve all Phase I, II and III clinical drug trials **prior to** their commencement. Please refer to the HPFB website (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/index_e.html) for further information. The Clinical Trial Application (CTA) can be obtained through this website. A Clinical Trial Application must be filed with Health Canada **prior to** submission to the board. A copy of the Health Canada Non-Objection Letter must be forwarded to the REB office prior to final approval of the protocol.*

☐ Health Canada Non-Objection Letter attached. Date of Letter: _____
Control #:_____

☐ Yes, the Clinical Trial Application (CTA) has been submitted to Health Canada on: *(date)*

Name the sponsor/institution/investigator responsible for filing a Clinical Trial Application (CTA) or Investigational Testing Authorization (ITA) with Health Canada or Other. *Not applicable*

A. Enter the generic name of any investigational drug(s) not yet approved or any marketed drug(s) used outside of its approved indication. *Not applicable*

B. Enter the name of any marketed drug(s) used within its approved indication. *Hydrocortisone sodium succinate (Solu-Cortef)*

C. Enter the name of any Natural Health Products used. *Not applicable*

D. Enter the name of any positron-emitting radiopharmaceuticals (PERs). Not applicable

6.1.2. ☐ Clinical Device Trial (name)

☐ Class I ☐ Class II ☐ Class III ☐ Class IV

Class I devices present the lowest potential risk (e.g. thermometers) and do not require investigational testing authorization from Health Canada. Class II, III, and IV devices present higher risks to the individual and do require such authorization. Health Canada maintains a directory of all devices approved for use in Canada http://webprod.hc-sc.gc.ca/el-le/index-eng.jsp

6.1.3. ☐ Clinical Trial (Other)

Please specify nature of intervention being studied:

6.1.4. **Is the above trial placebo-controlled? ☒ Yes ☐ No**

The Board adheres to the guidelines proffered by the TCPS – 2nd edition and the National Placebo Working Committee on the Appropriate Use of Placebos in Clinical Trials in Canada (July 2004) http://www.cihr-irsc.gc.ca/e/25139.html

All clinical trials must be registered at either (please check one):

Registration is to be completed prior to the first patient enrolled in the overall study.

☒ http://www.clinicaltrials.gov ☐ http://www.controlled-trials.com

Registration Number: *NCT02044159*

6.1.5. This is a Department of Health and Human Services (US Federal Agencies) grant

☐ **yes** ☒ **no**

6.1.6. There is a requirement for this research to comply with USA regulations for research ethics

☐ **yes** ☒ **no**

If yes, please indicate whether or not FDA (Investigational New Drug) number (drug studies) or an FDA Investigational Device Exception (IDE) is required for the research and provide documentation from the Sponsor or the FDA verifying the IND/IDE number, or explaining the study exemption status,
Not applicable

6.2. **Pandemic planning:** The trial holds out the prospect of immediate (physiologic) benefit (that relates to improved disease state / morbidity etc) to the research subject. ☐ **Yes** ☒ **No**

6.3. The trial involves the provision of optimal care to research subjects that would otherwise not be available off – study. ☐ **Yes** ☒ **No**

6.4. **Non-Interventional Research** ☐ **yes** ☒ **no**
Please specify nature of study: *This trial is an interventional pilot study that will investigate the safety and effectiveness of hydrocortisone versus a placebo in children with fluid and/or vasoactive infusion dependent shock.*

7. SITES INVOLVED AND PRINCIPAL OR QUALIFIED INVESTIGATORS (PI)

Check Institutions and complete box. PIs must be permanent members of the Site staff

☒ Institution BC Children's & Women's Health Center; University of BC;s erved by CW REB

PI Name David Wensley Department/Division Department of Pediatrics

Discipline *ie. Medicine, Psychology, Nursing* Medicine

Signature **See next page**

☐ Institution Calgary Children's Hospital, Alberta, served by the AB REB

PI Name Department/Division

Discipline *ie. Medicine, Psychology, Nursing*

Signature

☒ Institution Children's Hospital of Eastern Ontario served by CHEO REB

PI Name Kusum Menon Department/Division Department of Pediatrics, Division of Critical Care

Discipline *ie. Medicine, Psychology, Nursing* Medicine

Signature Kusum Menon

☒ Institution Hamilton Health Sciences Center, served by McMaster University REB

PI Name Karen Choong Department/Division Department of Pediatrics

Discipline *ie. Medicine, Psychology, Nursing* Medicine

Signature Karen Choong

☒ Institution L'Hôpital de Montréal pour enfants, McGill University, served by MUHC REB

PI Name Ronald Gottesman Department/Division Department of Pediatrics

Discipline *ie. Medicine, Psychology, Nursing* Medicine

Signature **See next page**

7. SITES INVOLVED AND PRINCIPAL OR QUALIFIED INVESTIGATORS (PI)

Check Institutions and complete box. PIs must be permanent members of the Site staff

☒ Institution BC Children's & Women's Health Center; University of BC;s erved by CW REB

PI Name David Wensley Department/Division Department of Pediatrics

Discipline *ie. Medicine, Psychology, Nursing* Medicine Division of Critical Care

Signature

☐ Institution Calgary Children's Hospital, Alberta, served by the AB REB

PI Name Department/Division

Discipline *ie. Medicine, Psychology, Nursing*

Signature

☒ Institution Children's Hospital of Eastern Ontario served by CHEO REB

PI Name Kusum Menon Department/Division Department of Pediatrics, Division of Critical Care

Discipline *ie. Medicine, Psychology, Nursing* Medicine

Signature Kusum Menon

☒ Institution Hamilton Health Sciences Center, served by McMaster University REB

PI Name Karen Choong Department/Division Department of Pediatrics

Discipline *ie. Medicine, Psychology, Nursing* Medicine

Signature **See previous page**

☒ Institution L'Hôpital de Montréal pour enfants, McGill University, served by MUHC REB

PI Name Ronald Gottesman Department/Division Department of Pediatrics

Discipline *ie. Medicine, Psychology, Nursing* Medicine

Signature **See next page**

7. SITES INVOLVED AND PRINCIPAL OR QUALIFIED INVESTIGATORS (PI)

Check Institutions and complete box. PIs must be permanent members of the Site staff

☒ Institution BC Children's & Women's Health Center; University of BC;s erved by CW REB

PI Name David Wensley Department/Division Department of Pediatrics

Discipline *ie. Medicine, Psychology, Nursing* Medicine

Signature **See previous page**

☐ Institution Calgary Children's Hospital, Alberta, served by the AB REB

PI Name Department/Division

Discipline *ie. Medicine, Psychology, Nursing*

Signature

☒ Institution Children's Hospital of Eastern Ontario served by CHEO REB

PI Name Kusum Menon Department/Division Department of Pediatrics, Division of Critical Care

Discipline *ie. Medicine, Psychology, Nursing* Medicine

Signature Kusum Menon

☒ Institution Hamilton Health Sciences Center, served by McMaster University REB

PI Name Karen Choong Department/Division Department of Pediatrics

Discipline *ie. Medicine, Psychology, Nursing* Medicine

Signature **See previous page**

☒ Institution L'Hôpital de Montréal pour enfants, McGill University, served by MUHC REB

PI Name Ronald Gottesman Department/Division Department of Pediatrics

Discipline *ie. Medicine, Psychology, Nursing* Medicine

Signature

☒ Institution CHU Sainte Justine, Université de Montreal, served by CHU REB

PI Name Catherine Ferrell | Department/Division Department of Pediatrics

Discipline *ie. Medicine, Psychology, Nursing* Medicine

Signature Catherine Ferrell

☒ Institution IWK, Halifax, Dalhousie University, served by IWK REB

PI Name Gavin Morrison | Department/Division Department of Pediatrics

Discipline *ie. Medicine, Psychology, Nursing* Medicine

Signature

8. LAY ABSTRACT

Approximately 500 words. This must be submitted in lay terms

Approximately 20,000 children per year in North America present to the hospital with severe shock. Children who develop this condition have very low blood pressures and as a result may suffer damage to their internal organs and may even die. This type of shock is responsible for ~5% of pediatric intensive care admissions, and can cause significant long-term health issues. Some children with this condition may significantly benefit from the use of steroids, but there may also be some side effects. The guidelines for using steroids in children with shock state that there is no strong evidence either for or against the use of steroids in these children, so the decision about whether or not to use steroids is left to the doctor. As a result, the treatment for children with severe shock varies from doctor to doctor, as some physicians strongly believe that steroids are helpful for this condition, and others do not. Therefore, it is important to study the use of steroids carefully in these children. We propose a study that will examine the effectiveness and safety of steroids in children with severe shock by comparing children who are treated with the steroid, hydrocortisone, versus children who are not treated with steroids. Participants will be randomized to receive either hydrocortisone or a placebo. We will measure how long children in these groups require medication and other treatments, how long they stay in the hospital, and if they have side effects that could be related to steroids such as bleeding in the stomach or bowels, or new infections. Before conducting a large, randomized controlled trial (RCT) in multiple hospitals across Canada, we will conduct a pilot study (STRIPES Pilot Study). The STRIPES Pilot Study will enroll 72 patients from 7 pediatric centres in Canada, and will allow us to test our protocol in a smaller group of patients. Following successful completion of the STRIPES Pilot Study, the next phase of this study will be conducted in a larger group of children in several pediatric hospitals across Canada.

9. STUDY SCOPE, OBJECTIVES AND HYPOTHESIS

Description of the research questions

Corticosteroids are used for the treatment of pediatric shock without sufficient evidence to support this practice. While there is scientific rationale and limited data supporting their use in this setting, there is also evidence from other populations suggesting potential harm. A randomized controlled trial on the use of steroids in this condition is long overdue. Therefore, in collaboration with the Canadian Critical Care Trials Group, we will conduct a pilot randomized controlled trial on the use of steroids in pediatric fluid and vasoactive infusion dependent shock prior to going forward with a larger, much needed, trial powered for clinically important outcomes.

The full STRIPES Trial will seek to answer the following research questions: (i) What is the effect of hydrocortisone versus placebo on the time to discontinuation of vasoactive agents among pediatric patients with fluid and vasoactive infusion dependent shock, and (ii) In patients with fluid and vasoactive infusion dependent shock, what is the effect of hydrocortisone versus placebo on PICU mortality, duration of mechanical ventilation, new onset of organ dysfunction, PICU length of stay, and incidence of serious adverse events. Prior to conducting the full trial to address these questions, the STRIPES Pilot Study has four specific feasibility objectives:

1) To estimate the rate of patient recruitment and understand barriers to recruitment
2) To assess adherence to our specific treatment protocol
3) To assess the appropriateness of our eligibility criteria for the full trial
4) To assess the feasibility of collecting and shipping blood samples in this population.

10. BACKGROUND, RATIONALE AND SCHOLARLY SIGNIFICANCE

Please limit to a few sentences

Given the poor methodological quality of the existing pediatric randomized controlled trials, the variability in target populations and steroid dosing regimens studied, contradictory results from adult trials, and the

lack of information on potential adverse effects, it has been difficult to develop evidence-based guidelines for critically ill children with shock. The management of these patients remains highly variable with many critical care physicians having strongly held beliefs both for and against the use of steroids in this population. Ultimately, a pragmatic trial, carefully designed with broad-based input, is necessary to provide clinicians with the best possible evidence on which to base the decision of whether or not to use steroids in the management of these pediatric patients.

11. FOR CLINICAL TRIALS OF DRUGS, BIOLOGICS, NATURAL HEALTH PRODUCTS OR DEVICES, OR FOR RESEARCH INTO MECHANISMS OF DISEASE INVOLVING INVASIVE PROCEDURES.

Have the methods been used in the following subjects, and if not, is it feasible to do so?

	It has been studied	It is feasible	No/not applicable
Adult experimental animal	☒	☐	☐
Experimental animal at analogous stage of development	☐	☐	☒
Adult human	☒	☐	☐
Older children where relevant Healthy children	☐	☐	☒

12. BASIC STUDY DESIGN

Specifics of treatments or procedures

The STRIPES Pilot Study is designed as a pragmatic, multi-centre, double-blinded, RCT that will compare hydrocortisone versus a placebo in 72 children. The prescriptive component of the protocol will be limited to the administration of the study drug. The fluid and vasoactive infusion management in both arms will not be dictated by the study protocol, but will be left up to the treating physician. The requirements for intubation, mechanical ventilation, sedation and analgesia, use of hemodynamic triggers and endpoints, and red cell transfusions will also be left to the discretion of the treating physician. Patients randomized to the hydrocortisone arm will receive a 2mg/kg hydrocortisone IV bolus on enrolment followed by 1mg/kg of hydrocortisone IV q6h until the patient has not had an escalation of therapy for at least 12 hours. As escalation of therapy is defined as an increase in their vasoactive infusions or a fluid bolus such as normal saline, albumin or any other blood product. If the patient has not had an escalation of therapy for more than 12 hours, their hydrocortisone will be weaned to 1mg/kg q8h. This dose will be continued until they are off all vasoactive infusions for 12 hours. If, following the initial wean, the patient requires fluid boluses and/or an increase in vasoactive infusion(s), their hydrocortisone will be increased back to 1mg/kg 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. Patients randomized to the placebo group will receive normal saline equivalent in volume to the appropriate dose of hydrocortisone, according to the same dosing regimen described above. Outcome data, including survival status, frequency of adverse events, and PICU course will be collected daily until death or hospital discharge.

13. OUTCOME VARIABLES

Describe endpoint measurements

Primary outcome:

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 period. We will also assess potential barriers to recruitment including lack

of a deferred consent model, physician and guardian related consent issues, availability of research personnel and the narrow recruitment window.

Secondary Outcomes:
There are four secondary outcomes for the STRIPES Pilot Study.
1) Adherence to the protocol: We will consider adherence to our protocol to be adequate if the following criteria are met in 80% of enrolled patients: (i) 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); (ii) weaning of drug to q8h when hemodynamically stable (goal is to wean within 12 hours of no escalation of therapy); and (iii) discontinuation of drug when off all vasoactive medications (goal is to discontinue between 12 and 18 hours of vasoactive medications being stopped).
2) Open label steroid use: We will record the frequency of open label steroid use, and the clinical parameters of patients in who open label steroids are administered. We will consider the number of patients started on open label steroids to be acceptable if it occurs in fewer than 10% of patients.
3) Incidence of the following clinical outcomes in the two groups: (i) time to discontinuation of vasoactive infusions and mortality (blinded to allocation); and (ii) 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: We will determine the percentage of patients from whom blood samples are sent, and the percentage of samples sent that are successfully received and analyzed in their respective labs.

14. SAMPLE SIZE AND CALCULATION

Indicate total projected participants and indicate expected recruitment at each site.

A. CASES Study Total 36

C&W, BC 3 Calgary, AB 0, not applicable
CHEO, ON 6 Hamilton, ON 6 MUHC, QU 6
Ste Justine, QU 6 IWK, HX 3 (+ 6 cases at Alberta Children's Hospital)

B. CONTROLS Study Total 36

C&W, BC 3 Calgary, AB 0, not applicable
CHEO, ON 6 Hamilton, ON 6 MUHC, QU 6
Ste Justine, QU 6 IWK, HX 3 (+ 6 cases at Alberta Children's Hospital)

C. What considerations led to your proposed control group (or lack of one)? For trials involving the use of placebos please explain what considerations led to your proposed use (ref. TCPS article 7.4)

This trial will compare the safety and effectiveness of hydrocortisone (intervention) versus a placebo (control). A placebo was necessary to show that any differences between the hydrocortisone and control group are due to hydrocortisone itself and not other factors. It is important to note that: (i) According to our recent survey of Canadian pediatric intensivists, doctors would use hydrocortisone to treat children with vasoactive and/or fluid dependent shock ~50% of the time. By participating in this trial, children have a 50% chance of receiving hydrocortisone or a placebo. Therefore, patients in both arms of the trial will still be treated by regimens that fall within the current standard of care model. (ii) Physicians will be given the option to use open label steroids if they are concerned about a patient's condition. If patients were to

receive steroids after randomization to the steroid arm, their total hydrocortisone dose would still fall well within the recommended acceptable dosing range for shock (1 to 50 mg/kg).

D. Indicate the methods used to calculate sample size

We expect to enroll 72 patients. This target number will allow us to assess our feasibility objectives over a reasonable time period (one year) and will allow each centre to recruit between 6 and 24 patients. This will allow us to test the acceptability of our eligibility criteria as well as open label steroid use at 7 sites and with exposure to 50 different clinicians. With 60 patients, we will have the ability to detect an adherence rate of 80% ± 10% (meaning 80% ± 10% of study patients will have fewer than 10% of monitored values as violations).

15. STANDARD OF CARE

There is no established standard of care for the use of steroids in children with shock. Our recently completed retrospective cohort study demonstrated that steroids were used in 35.7% of patients with slightly lower illness severities than our current proposal. Furthermore, in our recent survey approximately 50% of physicians in Canada stated they would use steroids for patients with the inclusion criteria outlined in our proposal and 50% would not. Finally, and perhaps most importantly, 84.3% of respondents in the survey stated that they would be willing to randomize patients that met our inclusion criteria into a study of steroids versus placebo in shock. The above findings clearly show that equipoise exists in the pediatric critical care community on the use of steroids in this patient population.This research also offers a realistic possibility that the participants may benefit from receiving steroids. There is strong physiologic evidence and some clinical evidence to support the premise that administration of steroids improves outcomes in shock.

16. DATA ANALYSIS

Methods of analysis, secondary analysis

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.

17. TARGET POPULATIONS

Inclusions and exclusions

Inclusion Criteria

1) Children newborn to 17 years; and 2) on any dose of any vasoactive infusion for between 1 to 6 hours.

Exclusion Criteria

Patients: 1) who have known or suspected hypothalamic, pituitary or adrenal disease; 2) who received more than one dose of systemic steroids is the last 10 days, or any dose of systemic steroids in the last 24 hours; 3) who are expected to have treatment withdrawn; 4) who are premature infants <38 weeks corrected gestational age; 5) who are pregnant; 6) post cardiac surgery; 7) who received their first dose of vasoactive infusion more than 24 hours after PICU admission; 8) who are no longer on a vasoactive infusion at the time of study enrollment, and/or are expected to no longer be on a vasoactive infusion when the first dose of study drug would be administered; 9) for whom primary cardiogenic shock is strongly suspected; 10) for whom spinal shock is strongly suspected; and 11) for whom hemorrhagic or hypovolemic shock is strongly suspected

18. RECRUITMENT AND IDENTIFICATION

A. Identification of potential participants:

- ☒ Physician or other care-provider of patient
- ☐ Health Record
- ☐ Existing database/clinic registry
- ☐ Other (describe)

B. Access to potential research participants

Describe in detail how initial contact will be made with prospective participants (i.e. in person, phone, letter)

This study will employ a deferred consent model. The available time between identification of the patient and the cut-off for enrolment will determine whether informed consent or deferred consent is used. If the legal guardian is present when the patient is identified, and if there is sufficient time available for study staff to approach the legal guardian and fully explain all aspects of the study, and sufficient time available for the legal guardian to read the consent form, ask questions, and truly consider study participation, informed consent will be obtained prior to participant enrollment. A member of the patient's healthcare team would first ask the legal guardian if the study team can speak to them about the study. Once permission is obtained, the study team will approach the family for consent. If, on the other hand, the available time would not allow for true informed consent, or if the legal guardian is not present, the patient will be enrolled using the deferred consent model. In the deferred consent model, the first contact with the family will occur as follows: a member of the health care team will present the family with a deferred consent pamphlet explaining that their child has been enrolled in the study and that a member of the study team will speak to them as soon as possible about continuing study participation. The pamphlet will also encourage families to have the health care team page the study team if they are ready to talk about consent before the study team has made contact. A poster will also be placed at the patient's bedside to say that they have been enrolled in the STRIPES study and with the study team contact information. As soon as the most responsible physician (MRP) feels it would be appropriate for the study team to speak to the family about on-going consent, a member of the healthcare team will ask the family if they study team can approach them about the study. The study team will then speak to the legal guardian about consent. In sites where a deferred consent model is not used, the patient's healthcare team will first approach the family and ask if the study team can speak to them about a research study.

C. Who will make the initial contact (must be known to the participant/guardian) A member of the patient's healthcare team (physician, nurse) will first make contact with the legal guardian and ask if a member of the study team can approach them.

19. **PROCEDURES/INTERVENTIONS**

Include information about biological specimen storage, labeling methods, accessibility of samples, questionnaires and data collection forms used in the study

Intervention	How & by whom	Reference to Protocol Page number and paragraph
Special clinic visit (number and timing)	*Not applicable*	
Diagnostic imaging (type, number and timing)	*Not applicable*	
Blood tests (taken with routine or by separate blood work)	*A total of 3ml blood will be collected from existing lines or with clinically-indicated bloodwork. If a patient does not have lines in place, and is not having clinically-indicated bloodwork, this sample will not be collected. The sample will be collected prior to the initiation of study drug. If access for blood sampling is not available before study drug is started, but becomes available within 24 hours of hospital admission, then a blood sample will still be collected. The blood sample will be collected by the patient's healthcare team.*	*page 6, paragraph 3 page 7, paragraph 6 to page 8, paragraph 1 Appendix 4, Appendix 6*
Questionnaire (number and timing)	Not applicable	
Interviews (number and timing)	Not applicable	
Other (specify	Not applicable	
How long will each participant be studied	*From study enrollment to hospital discharge or death, whichever occurs first*	*Section 2.7, page 9, paragraph 7*

20. CONSENT

A. Specify who will explain the consent form and invite the subject to participate. Include details of where the consent will be obtained, and under what circumstances.

Once a patient's study eligibility has been confirmed, the study team will determine if the patient's legal guardian is present. If there is sufficient time available for study staff to approach the legal guardian and fully explain all aspects of the study, and sufficient time available for the legal guardian to read the consent form, ask questions, and truly consider study participation, informed consent will be obtained prior to participant enrollment. If, on the other hand, the available time would not allow for true informed consent, the patient will be enrolled using the deferred consent model. The deferred consent model will also be used if the legal guardian is not present when the patient is identified for the study.

In the deferred consent model, the patient will be enrolled and randomized once eligibility is confirmed. As soon as a legal guardian is available, the healthcare team will provide the legal guardian with a

pamphlet that outlines the study into which their child has been enrolled and contains information on how to contact the study research assistant and the study site investigator for further information and to discuss consent for ongoing participation in the study. The pamphlet will also contain a statement encouraging the family to ask the healthcare team to page the study research assistant when they are ready to speak with them. A simple poster will also be placed on the wall in the patient's room in PICU stating that the child has been enrolled in the STRIPES study and containing the relevant contact information. In addition, the study research assistant will contact a member of the patient's healthcare team when the patient is settled in PICU to ask them about an appropriate time to speak with the family. Once the MRP determines that it is appropriate, and the health care team has asked the family if study staff can approach, the study research assistant/coordinator will approach the family for consent. If consent for subsequent participation is declined, the patient will not receive further study drug, data already collected in the case report form will be retained in the database and research assistants will ask legal guardians for permission to continue with data collection to the end of the study period (hospital discharge or death), and to analyze any collected blood samples. If the legal guardian refuses, data collection will stop, and any collected blood samples will be destroyed.

In the event that a patient enrolled using deferred consent dies before study staff speaks to the family about consent, the family will still be notified by the MRP of their child's enrollment into the study. As soon as the MRP determines that it would be appropriate, the MRP will ask the family if the Site Investigator can speak to them. The Site Investigator will then approach the family to fully explain the study, and ask the family whether they would like their child's data to remain in the study database or be destroyed. If the family decides that their child's data can be included in the study, the Site Investigator will have the legal guardian sign the consent form.

In the centres without deferred consent, consent from the legal guardian will be requested as soon as the patient is deemed eligible and as soon as a guardian is available.

B. If you are asking for a waiver or an alteration of the requirement for subject informed consent please justify the waiver or alteration and confirm that the study meets the criteria on the right.

This study plans to enroll participants within 6 hours of being started on any vasoactive agent. Experience from the Canadian Critical Care Trials Group has shown that this will be problematic without a deferred consent model. Based on these observations, deferred consent has been approved at the Principal Investigator's site, and will be sought in four of the remaining six participating study sites. A deferred consent model has previously been used at each of these 5 sites, and preliminary discussions with the local research ethics boards at these sites have been supportive. The Tri-Council Policy Statement for Ethical Conduct for Research Involving Humans outlines criteria that must be met in order to utilize deferred consent: As summarized below, this study meets the following requirements.

1. A serious threat to the prospective participant requires immediate intervention: Fluid and vasoactive infusion dependent shock is responsible for ~5% of pediatric intensive care admissions, results in significant morbidity and can carry a mortality rate of 2-10%. The goal of treatment for this condition is to prevent shock from progressing to a final irreversible stage that results in organ and tissue injury and leads to permanent disability and even death. It is critical, therefore, that any treatment be given early. Adult studies have shown that when steroids were administered within 8 hours, they reduced the risk of death in patients with septic shock and relative adrenal sufficiency, but the same effect was not found when steroids were administered within 72 hours. Given the importance of early treatment, we have chosen a 6 hour cut-off for enrolment and 8 hours for completion of initial treatment with study drug. Delaying treatment longer than 8 hours could put the patient at risk for poorer outcomes and could lead to inaccurate data regarding the efficacy of steroids as a treatment for pediatric shock.

2. Either no standard efficacious care exists or the research offers a realistic possibility of direct benefit to the participant in comparison with standard care: There is no established standard of care for the use of steroids in children with shock. Our recently completed retrospective cohort study demonstrated that steroids were used in 35.7% of patients with slightly lower illness severities than our current proposal. Furthermore, in our recent survey approximately 50% of physicians in Canada stated they would use steroids for patients with the inclusion criteria outlined in our proposal and 50% would not. Finally, and perhaps most importantly, 84.3% of respondents in the survey stated that they would be willing to randomize patients that met our inclusion criteria into a study of steroids versus placebo in shock. The above findings clearly show that equipoise exists in the pediatric critical care community on the use of steroids in this patient population.

This research also offers a realistic possibility that the participants may benefit from receiving steroids. There is strong physiologic evidence and some clinical evidence to support the premise that administration of steroids improves outcomes in shock.

3. Either the risk is not greater than that involved in standard efficacious care, or it is clearly justified by the prospect for direct benefits to the participant: Patients eligible for this study will be seriously ill and therefore at high risk for potential adverse events regardless of participation in this study or treatment with steroids. This trial, however, poses no incremental risk to the safety of participants compared to usual care. Patients in both arms of the trial will be treated by regimens that fall within the current standard of care and therefore do not incur an added risk by participating in this trial. Treating physicians would retain the ability to use open-label steroids if they felt it was clinically indicated. Even if patients randomized to the steroid arm were to also receive open-label steroids, their total hydrocortisone dose would still fall within the acceptable dosing range for pediatric shock (1 to 50mg/kg). It is also important to note that note that the only relevant RCT in children, involving only 38 patients, did not find a significant difference in the incidence of secondary infections and significant gastrointestinal bleeding between those who did and did not receive hydrocortisone 12. Similarly, our retrospective cohort study did not find an association between steroid use and gastrointestinal bleeding, infections or insulin infusion use. However, all potential adverse events will be reviewed by an independent DSMB.

4. The prospective participant is unconscious or lacks capacity to understand the risks, methods and purposes of the research project: The participants in this study are children aged newborn to 17 years suffering from severe shock which results in decreased perfusion to the brain rendering these children incapable of providing consent or assent based on age and/or clinical condition. Consent will be obtained on the patient's behalf from their legal guardian.

5. Third party authorization cannot be secured in sufficient time, despite diligent and documented efforts to do so: Given the critical importance of early treatment for fluid and vasoactive infusion dependent shock, the enrolment window for this study has been set at 6 hours. As a result, it is most likely that a legal guardian will not be reached within the required time period 13, and/or that the legal guardian would be too distressed to truly give informed consent 14. Therefore consent will be sought as soon as it is convenient and desirable as judged by the family and their healthcare team following the patient's admission to PICU. The support for this approach is as follows:

a) There is evidence to support the fact that the surrogate decision makers are too stressed to provide informed consent in the 24 to 48 hour period following admission of their loved one to an ICU.

b) Other pediatric critical care trials have had this model approved by Research Ethics Boards in Canada in the last 10 years (Head Injury and Hypothermia Trial published in the New England Journal in 2008 which used deferred consent in 6 Canadian Pediatric Centres including CHEO, Dr. Melissa Parker's fluid

resuscitation trial in shock patients in Hamilton and Dr. Gonzalo Guerres' study on Impact of Early Parenteral Nutrition Completing Enteral Nutrition in Pediatric Critically Ill Patients which are currently recruiting).

c) If deferred consent was only implemented for patients in whom a legal guardian was not available at the time of potential enrolment, it would create a two tiered consent process whereby certain patients (for example those from up north) would almost always have consent obtained later whereby local patients would be more likely to have consent sought prior to enrolment.

The patient's legal guardian would be advised of the trial as soon as possible by being given an information sheet on the study and posters on the wall in their child's room, and consent would be sought retroactively. The legal guardian would retain the right to withdraw their child and the child's data from the trial, and decline further participation in the trial at any time. In the event that a patient enrolled using deferred consent dies, written consent would still be sought retroactively, and families would retain the right to withdraw their child's data from the trial.

6. No relevant prior directive by the participant is known to exist. Prospective patients would not have relevant advance directives on the use of steroids as a treatment for pediatric shock and most minors would not have established prior directives for research in general.

Since a deferred consent model is used less frequently, the principal investigator has worked with the CHEO REB to develop specific reporting protocols for this study. Any adverse events that occur during the conduct of the study that could be attributed to the deferred consent model will be reported to the Principal Investigator, and to the REB at the Study Coordinating Centre (Children's Hospital of Eastern Ontario). If requested, a copy of this REB report will also be sent to the REB at other participating sites. In addition, the Principal Investigator will submit a report to the CHEO REB with the first annual renewal, or after the first 5 patients have been enrolled (whichever occurs first) to summarize the operationalization of the deferred consent model. If the CHEO REB has any concerns with the report, the deferred consent model may be adjusted to rectify identified issues. If requested, a copy of this REB report will also be sent to the REB at other participating sites.

C. How long after receiving the consent form will the subject have to decide whether or not to participate? If this will be less than twenty-four hours, provide an explanation.

If the legal guardian is approached for consent prior to patient enrollment, the legal guardian will have up to 6 hours to decide whether or not to participate. The 6 hour window has been set due to the emergency nature of severe shock. Shock is a progressive process characterized by an early compensated phase in which adaptive mechanisms act to maintain blood pressure and maintain tissue perfusion, an uncompensated phase where the compensatory mechanisms fail and the patient requires, and may still respond to, therapeutic interventions and a final irreversible stage where shock progresses to organ and tissue injury leading to permanent disability and even death. The goal of shock therapy is to prevent progression to the third stage where irreversible organ damage occurs; therefore it is critical that any potential therapy, including steroids, be given early which is why we have chosen a 6 hour cut-off for enrolment. When a patient is enrolled using deferred consent, and the family is given the consent form for ongoing consent, the study team will follow up with the family in 24 hours to see if they have made a decision about continuing. If required, families can be given more time to make the decision.

D. Will every subject be competent to give fully informed consent on his/her own behalf? Please click Select to complete the question and view further details

Subjects in this study will not be competent to give full informed consent on his/her behalf. The age range for this study is 38 weeks gestational age up to 17 years of age. Therefore, a large proportion of the participants will be too young to consent. Even for children old enough to consent, their medical condition at the time of enrollment prevents them from being able to consent on their own behalf. As a result, consent will be obtained from the patient's legal guardian.

E. Describe any situation in which the renewal of consent for this research might be appropriate, and how this would take place. *Patients will be followed up only from the time of enrollment until hospital discharge. Given the relatively short follow up period, it is unlikely that renewal of consent for this research would be appropriate.*

F. What provisions are planned for subjects, or those consenting on a subject's behalf, to have special assistance, if needed, during the consent process (e.g. consent forms in Braille, or in languages other than English).

The consent form and deferred consent pamphlet will be translated into French. If a family speaks another language (other than French and English) a translator will be used. The translator will sit with the study team and the family and explain the consent form. If the family gives their consent, the translator will also sign the consent form as a witness and to state that they have accurately explained everything contained in the consent form to the family.

21. **RISKS/BENEFITS**

Potential harms, inconveniences, and benefits

A. For each study intervention describe the probability and magnitude of potential harms, discomfort and inconveniences

This trial poses no incremental risk to the safety of participants compared to usual care. As demonstrated by our multi-centre chart review as well as our published survey, 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 and therefore do not incur an added risk by participating in this trial. Even if patients were to receive open label steroids following randomization to the steroid arm, their total hydrocortisone dose would still fall within the recommended acceptable dosing range for shock (1 to 50 mg/kg). The incidence of potential adverse effects of steroids including secondary infection, gastrointestinal bleeding and hyperglycemia will be recorded in all participants. Hydrocortisone can have side effects. Common side effects include hyperglycemia and gastritis. Uncommon side effects include irritability, fluid retention, hyponatremia, and minor stomach bleeding. Rare side effects include severe bleeding in the stomach or bowel that requires surgery, gastric perforation, or new infections. There is a small risk that patients randomized to the placebo group would have benefitted from the administration of hydrocortisone. For this reason, physicians are allowed to give open label steroids if they are concerned about a patient's condition. Even if steroids are given to a patient who was randomized to the steroid arm, their total hydrocortisone dose would still fall well within the range prescribed for shock (1 to 50 mg/kg).

B. For each study intervention, describe the probability and magnitude of potential benefits to participants *Patients in both arms of this trial will be treated by regimens that fall within the current standard of care. Therefore, participating in this trial does not present additional benefits to the patient.*

C. For each study intervention, describe the probability and magnitude of potential benefits to society *The current guidelines for the treatment of pediatric vasoactive and/or fluid dependent shock state that there is not enough evidence to determine whether or not steroids benefit this group. Results from this pragmatic trial, comparing hydrocortisone and placebo, can be used to inform evidence-based guidelines on whether or not to use steroids in children with severe shock.*

22. COMPENSATION/COSTS/RECOGNITION

Describe compensation or reimbursement. Indicate if this is the same across sites for all participants, or whether there are site-specific differences and why.

Patients will not be compensated for their participation. There are also no costs to the patient that would need to be reimbursed.

23. **SECURITY & CONFIDENTIALITY OF PERSONAL HEALTH INFORMATION & RESEARCH DATA**

Describe how the identity of the subjects will be protected both during and after the research study, including how subject will be identified on data collection forms.

Are any sensitive issues raised in this study or its publication which could result in harm (el cause embarrassment, refusal of employment or insurance coverage, stigmatization) and therefore require participant consent? ☐ yes ☒ no

If "yes" please specify how such consequences will be addressed *Not applicable*

☐ Personal identifying information will be collected. Justify the need for it to be collected.

☒ Confirm that identifying information is delinked

Use of study participant names, initials, hospital or health authority numbers, and any other identifying information is strictly prohibited on study data collection forms, adverse event reports, and other research participant-specific documents. Participants must be assigned a unique identification code. The code-breaking information must be kept separate from the data extraction files. It is the responsibility of the PI at each site to ensure that the code-breaking information is totally inaccessible to individuals who are not on the research team.

☒ Records and computers are secured

Method: ☒ Patients Coded ☒ Files/Folders passworded ☒ Computer passworded

☒ Computer in locked office only

☒ Other (specify) Secure, web-based electronic data capture system (REDCap). Each user will have their own unique login name and password to access REDCap.

☒ Chart/Computer Access limited to the research team

Method: ☒ Cabinet/Office keys only with research personnel

☒ Computer password only with research personnel

☐ Other (specify)

☒ A current list of the names of study personnel (including co-investigators) and their delegated tasks will be maintained in the study file. If a list will not be maintained, please explain.

Describe limits on the protection of confidentiality (e.g., mandatory reporting obligations under the law; sponsor personnel, audits by an internal or external auditor or, for clinical trials, regulatory authorities such as Health Canada)

Each study patient's personal information will be kept strictly confidential, except as required or permitted by law. Representatives of the local Research Ethics board will have access to the patient's personal information. The patient's medical records may be reviewed by the investigators or delegates of the Research Ethics Board for the purpose of verifying clinical trial procedures and/or data. Internal monitoring research staff may review the patient's research chart and medical records for quality improvement purposes. A Quality Improvement Reviewer may review the patient's medical records under the supervision of the Investigator and staff to ensure that all research standards and guidelines/regulations are met. Further, there may be instances where risk to a study participant is

identified. In this case, information will be shared with appropriate medical personnel in order to initiate care.

24. DATA SOURCES AND STORAGE

A. Identify all sources of data (eg. Database, registry, health record, clinic files, physician office files etc) *Study data will be abstracted from each patient's health record.*

B. Where will the data be stored? (eg. Computerized file, hard copy, audio/video recording, PDA etc)

All hard-copy source documents will be stored in a locked filing cabinet in a locked office. Study data will be entered direclty into a web-based electronic data capture program (REDCap) and stored on a secure server at the study coordinating centre. Data exported from REDCap will be stored on a password protected computer at CHEO in a password protected folder. This folder will only be accessable to the principal investigator and members of the steering committee.

C. How will the data be stored and protected while in storage? Describe the safeguards in place to protect the confidentiality and security of the data

The Clinical Research Unit (CRU) will be used as a central location for data processing and management. The CRU will store the data 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 Systems (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 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. Data exported from REDCap will be stored on the CHEO server in a password protected folder.
Hard-copy documents will be stored at each site in a locked cabinet in the study coordinator/site coordinators office. Participants will be indentified by an ID number on the study source documents. Any papers identifiying the participant by name (i.e. consent form, master participant list) will be stored seperately from the rest of the study documents.

D. If any data or images are to be kept on the Web, what precautions have you taken to prevent it from being copied? See above

E. At the end of the study, for how long will the data be stored? 25 years

F. Who will have access to the data in the future and for what purpose? *Only the principal investigator and members of the study steering committee will have access to the study data for the purpose of disseminating study results.*

G. What plans are in place to ensure that the stored data will remain 'viewable' (eg. Integrity of printer or FAX ink, changing digital technology)? Note that for high-risk research, such as drug trials, records should be stored for a minimum of twenty-five (25) years as required by Health Canada. For research in pregnant women or young children records must be stored for 10 years past the age of majority of the child which may vary by province *The dataset will be stored in*

REDCap, where it will remain viewable over the storage period. Prior to storage, the data set will be locked so that is cannot be altered in any way. Any paper documents (e.g. consent forms) will be printed using a high-quality printer and securly stored in a locked office in the site coordinator's office.

H. When and how will the data be destroyed? *Data will be destroyed 25 years after the last participant completes the trial. At the end of the retention period, all paper records will be disposed of in confidential waste or shredded, and all electronic records will be deleted.*

25. DATA SHARING AND LINKAGE

A. Do you plan on linking local data with any other data set (including provincial or national administrative health data)? ☐ yes ☒no

If yes, identify the data set and indicate why these linkages are required, identify how the linkage will occur, and provide a list of data items contained in it Not applicable

B. Will data be sent outside of the Institution where it is being collected? ☐ yes ☒no

If yes, please describe the type of data to be transferred, who the data will be transferred to, where the data will transferred, and how the data will be sent.
Data will not be sent from participating institutions to the study coordinating centre. Instead, data will be entered into REDCap and stored directly onto a secure server housed at the CHEO CRU (see above). The type of data that will be collected includes patient demographics and medical history, clinical course while in the PICU, mortality, serious adverse events, and economic information (e.g. nurse to patient ratio during PICU stay). No identifying data will be collected. Each site will enter study data direclty into REDCap, and will only be able to see data from their site. The Study Coordinating Centre (CHEO) will be able to access the study data for all participating sites.

C. Will the researchers be receiving data from other sites? ☒ yes ☐no

If yes, please describe the type of data that will be received, who it will be received from, where it will be received from, and how the data will be received
Data will not be sent from site to site, but will be entered directly into the study case report form in REDCap. Each site will only be able to access study data from their respective site. The Study Coordinating Centre (CHEO) will have access to data from all sites.

D. Is there a contract/research or data-sharing agreement involved? ☒ yes ☐no
If yes, include a copy of the signature page with other attachments

26. PROPOSED MONITORING OF RESEARCH STUDY

A. Describe the provisions made to break the code of a double-blind study in an emergency situation, and indicate who has the code.
In the event of an emergency, blinding can be broken at the request of clinical service. The randomization code and list of randomized participants will be stored at each site pharmacy. If unblinding is required, clinical service will first contact the Site Investigator, who will then contact the pharmacy to unblind the participant. As per requirements from the CHEO REB, the treating physician will also be able to use open-label steroids if they feel it is necessary. Even if patients were to receive open label steroids following randomization to the steroid arm, their total hydrocortisone dose would still fall within the recommended acceptable dosing range for shock (1 to 50 mg/kg).

B. Describe data monitoring procedures while research is ongoing. Include details of planned interim analyses, Data and Safety Monitoring Board, or other monitoring systems.

The Data Monitoring and Safety Committee (DSMC) will include a senior biostatistician (Dr. Dean Fergusson, DMSC Chair), a pediatric endocrinologist (Dr. Alex Ahmet) and a pediatric intensive care specialist (Dr. Ari Joffe) all with expertise in clinical trial methodology. The DMSC will review all serious adverse events and will communicate directly with the principal investigator. There will be no stopping rules; however, the DMSC can make recommendations to the principal investigator who will communicate back to the Steering Committee at the end of the trial regarding any safety concerns for the full trial. The DMSC will meet every 3 months during the conduct of the study. If deemed necessary, the DMSC may meet more frequently. Between meetings, the DSMC will receive information concerning post-randomization serious adverse events from all participating centers. For each meeting, the Steering Committee will provide the DSMC with tabulated information on serious adverse events by intervention group and by study center (blinded as group A and B). After each meeting, the DSMC chair will provide the principal investigator with a letter stating the general outcome of the meeting and any suggested changes to the design or conduct of the study. The rationale for recommendations will be included when appropriate. This report will NOT include confidential information. This meeting summary report will be forwarded to the principal investigator within 2 weeks of the meeting. At completion of the trial, the Steering Committee will provide the DMSC with analyses by group. These analyses will include relative rates of gastrointestinal bleeding, infections and hospital mortality. The analyses will be controlled for centre and will provide both unadjusted analyses and analyses adjusted for age and PRISM score.

C. Describe the circumstances under which the study could be stopped early. Should this occur, describe what provisions would be put in place to ensure that the subjects are fully informed of the reasons for stopping the study

There would be no circumstances under which the study would be stopped early since it is a pilot study with a known substance (hydrocortisone) for an approved indication.

27. DISCLOSURE OF INFORMATION

A. *Plan for dissemination of research results to research study participants, and who will do this*

The prinicipal investigator and study coordinator will prepare a report of the study results in lay terms. This report will be made available to any interested study participants.

B. *Plan for dissemination of results to communities (scientific, advocacy) and who will do this*

Study results will be presented at the Canadian Critical Care Trials Group Scientific Meeting. The results will also by synthesized into a manuscript and submitted for publication to a peer-reviewed journal.

28. DOCUMENTATION TO BE ATTACHED

☒ Protocol

☐ Health Canada regulatory approval (receipt will be acknowledged)

☐ FDA IND or IDE letters (receipt will be acknowledged)

☒ Investigator Brochures/Product Monographs

☒ Scientific Review

☐ If a Web site is part of this study, enter the URL http://stripes.ccctg.ca/

Since URL's may change over time or become non-existent, you must also attach a copy of the documentation contained on the web site to one of the sections above or provide an explanation.

☐ Data sharing agreement signature page (if applicable)

Note that certain clauses in the following will be subject to site/jurisdiction-specific approval

☒ Consent Forms

☐ Assent Forms

☒ Advertisement to recruit subjects

☐ Questionnaire, questionnaire cover letter, tests, interview scripts, etc.

☐ Letter of initial contact