Review Type/Type dévaluation:	Committee Member 1/Membre de comité 1
Name of Applicant/Nom du chercheur:	MENON, Kusum
Application No./Numéro de demande:	311832
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2013-09-16 Operating Grant/Subvention de fonctionnement
Committee/Comité:	Randomized Controlled Trials/Essais contrôlés randomisés
Title/Titre:	Steroid Use in Pediatric Fluid and Vasoactive Infusion Dependent Shock (STRIPES)

Assessment/Évaluation:

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

PI: Menon

Reviewer: 1 (first submission)

Summary/Background:

The investigators propose a multi-centre pilot randomized controlled trial to determine the feasibility of doing a full trial on the comparative effects of steroids versus placebo in children with fluid and vasoactive infusion dependent shock.

Feasibility objectives:

1) To estimate the rate of patient recruitment and understand barriers to recruitment;

2) To assess adherence to the proposed specific treatment protocol;

3) To document the frequency of and understand the reasons for open label steroid use.

The primary outcome measure will be the patient accrual rate over one year.

Secondary outcome measures will include: 1) Barriers to recruitment; 2) Adherence to the protocol; and 3) Use of open label steroids

Need for trial (right question, consistent with current knowledge, generalizable beyond study):
Approximately 20,000 children per year present to emergency departments, pediatric wards and intensive care units in North America with fluid and vasoactive infusion dependent shock. This severe type of shock results in significant morbidity and carries a 2-10% mortality rate depending on the setting in which it occurs. This form of shock is thought to arise from dysfunction of the hypothalamic-pituitary-adrenal axis through a variety of mechanisms, and has been referred to as relative adrenal insufficiency or critical illness related adrenal insufficiency.

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Assessment/Évaluation:

Many clinicians believe that corticosteroids improve outcomes in such patients and therefore use them when confronted with a critically ill child with fluid and vasoactive infusion dependent shock. Although fluid and vasoactive agents are the mainstay of therapy, the high morbidity caused by this condition has led clinicians to utilize corticosteroids as their next line of treatment. However, although the use of steroids in this setting has been widely debated in the literature for over 40 years, there is still no clear evidence to support this practice

The investigators provide arguments concerning

- the benefits of stress dose corticosteroids in some patients with shock secondary to adrenal insufficiency

- the absence of tests for clinicians to identify these specific patients with shock that lead to empirical decisions

- the literature supporting the hemodynamic benefits of steroids in shock patients, but also some evidence suggesting that steroid administration in critically ill patients may be associated with adverse effects, including gastrointestinal bleeding and immunosuppression.

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. Therefore, in collaboration with the Canadian Critical Care Trials Group, they propose to conduct a pilot randomized controlled trial on the use of steroids in pediatric shock prior to going forward with a larger, much needed, trial powered for clinically important outcomes.

Primary Research Question: What is the effect of hydrocortisone versus placebo on the timing of discontinuation of vasoactive agents among pediatric patients with fluid and vasoactive infusion dependent shock?

Secondary Research Questions: In patients with fluid and vasoactive infusion dependent shock what is the effect of hydrocortisone versus placebo on 1) PICU mortality 2) duration of mechanical ventilation 3) new onset of organ dysfunction 4) PICU length of stay and 5) incidence of adverse effects.

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Assessment/Évaluation:

Previous Data/Pilot work (if available):

1) recent survey of pediatric intensive care physicians in Canada (32) reported that 87% of respondents felt that the role of steroids in pediatric shock needed to be clarified

2) systematic review of steroids in pediatric shock: 8 small RCTs, limited literature, problem with quality, heterogeneity

3) retrospective multicentre cohort study (in progress) documents: use of steroids in 50% of shock patients, mostly hydrocortisone, adrenal axis testing in 7%

Response to Previous reviews (if relevant):

- Not relevant

Two RCTs on www.clinical.trials.gov

- 1 prematurely stopped because of difficulty with recruitment, complexity of the protocol:

- Another one does not seem active (no response from the PI)

Important differences will contribute to success:

- Background work

- Large network including specialists

- Deferred consent model in 5/7 centres

- Pragmatic trial design based on the usual physicians approach to shock patients

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Assessment/Évaluation:

Many challenges to conducting RCTs in pediatric critical care

small numbers of eligible patients

difficulty in obtaining consent in vulnerable populations

inability to locate legal guardians for time sensitive research

use of protocols that require extensive amounts of blood work, investigations or additional tests and medications to confirm eligibility or maintain enrolment.

Attempt to minimize the impact of these potential barriers to feasibility: 1) minimizing additional tests and interventions for study patients and 2) providing the Surviving Sepsis Guidelines for the administration of fluids, antibiotics and vasoactive agents to the treating physician but not mandating their use. Although they will encourage attending teams to avoid open-label steroid use and carefully record any such occurrence, they will not refer to open-label use as a protocol violation so as not to deter enrolment and to encourage buy-in. Furthermore, the ability of treating physicians to use open label steroids if they wished was mandated by the Research Ethics Board in order for them to approve use of a deferred consent model.

This pragmatic approach has several advantages: 1) it will mimic the manner in which clinicians manage patients with shock thus encouraging recruitment and generalizability of the results; 2) there is insufficient evidence on the use of specific vasoactive agents in shock to justify protocolizing them and 3) there is precedent for this approach in critical care trials.

Interventions
Pragmatic trial to compare intravenous hydrocortisone versus an intravenousnormal saline placebo

Centralized permuted block randomization will be web-based and stratified by centre.

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Assessment/Évaluation:

Inclusion Criteria will include: 1) Children aged newborn to 17 years and 2) On any dose of any vasoactive infusion for ≤ 6 hours.

Exclusion Criteria will include: 1) Known or suspected hypothalamic, pituitary or adrenal disease; 2) Those who received systemic steroids for more than 10 days in the previous month; 3) Those who are expected to have care withdrawn; 4) Premature infants; 5) Patients who are pregnant; 6) Patients post cardiac surgery; 7) Patients for whom primary cardiogenic shock is suspected; 8) Patients for whom spinal shock is strongly suspected; and 9) Patients for whom hemorrhagic or hypovolemic shock is strongly suspected.

Primary objective: recruitment of 60 patients from seven sites per year (estimate of 72 patients over one year)

Secondary
Adherence to the protocol:
- 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);

- Weaning of drug to q8h when hemodynamically stable (goal is to wean within 12 hours of no escalation of therapy);

- Discontinuation of drug when off all vasoactive medications (goal is to discontinue between 12 and 18 hours of vasoactive medications being stopped);

Adherence to the protocol adequate if criteria a to c are met in 80% of enrolled patients (approximately 48/60).

Open label steroid use:

- Frequency of open label steroid use

- Clinical parameters of patients when open label steroids are given.

Number of patients started on open label steroids acceptable if it occurs in fewer than 10% of patients (approximately 6/60).

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Assessment/Évaluation:

Incidence of the following clinical outcomes in the two groups:

- Time to discontinuation of vasoactive infusions, the primary outcome of the full STRIPES trial and mortality, secondary outcome (blinded to allocation);

- 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.

Blood sampling for mechanistic studies

- The percentage of patients from whom blood samples are sent

- The percentage of blood samples that are successfully received and analyzed in their respective labs.

Assessment:

Research Approach (including methods and feasibility): The methodology is appropriate to the research question, and likely to minimize bias. Given the barriers and the small numbers of patients available and difficulty of managing the co- intervention, it is important to conduct of a pilot study.

Interventions are well described in both groups. Use of open-label steroids is an outcome. They will use the same pragmatic approach in both groups, same time window for recruitment as well as assess adrenal axis testing, steroid dosing regimen, feasibility of mechanistic studies.

Originality: Clearly a question that has not previously been answered.

Applicant: Excellent group with appropriate expertise and background

Environment: Tertiary care centres, experienced with research.

Impact of the Research: Feasibility study for a full trial

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Assessment/Évaluation:

Strengths:

1. Very important practice guidelines question

2. Strong group, multiple expertise,

3. Protocol based on consensus and previous works

4. Clear objectives of feasibility

5. Monitoring of protocol adherence in real time

6. Costs well detailed

7. Well written, well designed

Weaknesses:

1. Insufficient detailing on the frequency of open label steroid use : critical outcome as it will influence the *Time to discontinuation of vasoactive infusions*

Is the criteria for the number of patients started on open label corticoids : *acceptable if it occurs in fewer than 10% of patients (approximately 6/60)* realistic, taking into account they mentioned data reporting an effect of corticoids and a use of steroids in 50% of shock patients in a cohort in progress.

2. Feasibility of the main trial: Next step should be better frameworked. Investigators need to give more information and detailing of the primary outcome of the main trial

Concern about the primary outcome and sample size of the full trial: no definitive decision on the primary outcome and no definitive calculation of the sample size but anticipate that it might be *Time to discontinuation of vasoactive infusions*

- Mortality as outcome not feasible (rate of 2-8%)

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Assessment/Évaluation:

- Sample size of the main trial is actually based on *Time to discontinuation of vasoactive infusions*:

Need for 185 patients (final 232) based on a mean of 70h in placebo, 46h in steroid group

External Reviews: None

Analytic Plan: mainly descriptive

Feasibility (sample, intervention etc): good.

Budget: $816,082.02
Feasibility of decreasing the number of centres in order to reduce pilot trial costs?

Large proportion of the needed number of participants of the main trial will be already recruited in the pilot

KT:

Economic analysis: not part of study

Review Type/Type dévaluation:	Committee Member 2/Membre de comité 2
Name of Applicant/Nom du chercheur:	MENON, Kusum
Application No./Numéro de demande:	311832
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Competition/Concours:	2013-09-16 Operating Grant/Subvention de fonctionnement
Committee/Comité:	Randomized Controlled Trials/Essais contrôlés randomisés
Title/Titre:	Steroid Use in Pediatric Fluid and Vasoactive Infusion Dependent Shock (STRIPES)

Assessment/Évaluation:

Title: STRIPES Pilot

Nominated PI: Kusum Menon

Summary

Refractory shock may become less refractory in the presence of glucocorticoids. There is a body of biologically plausible evidence and some mixed results from RCTs in adults. Overall there is a substantial amount of background work by the investigators to suggest such a therapy is reasonably likely to be effective. One of the major issues in the past has been determining an appropriate dose of glucocorticoids – this remains unresolved but probably can't be resolved outside of an RCT(s).

Methods

Patients

Pediatric patients with vasopressor and fluid dependent shock from any cause within 6 hours of developing shock. Excluded are patients with cardiogenic or hypovolemic shock (which suggests to me this will mostly be a trial of septic shock).

Intervention

2mg/kg hydrocortisone bolus then 1 mg/kg every 6 hours until stable vasopressor and fluid use for 12 hours (max 7 days therapy). Restart infusions for increased fluid and vasopressor use. Drug is most common in class for this disease/patient group and dose is approximately median of current doses used. I perhaps would have erred on the low side since adverse effects with glucocorticoids appear very dose dependent.

Control

Volume matched normal saline

Outcome

Pilot trial: feasibility objectives of recruitment rate (clear goal for success), barrier assessment (not quite clear

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Assessment/Évaluation:

how this will be done but not much of a concern to me), protocol adherence (clear goal)

Main trial: mortality, MODS, LOS, etc

Time

Follow-up to hospital discharge (? Maximum time frames)

Strengths

Area of demonstrated equipoise and potential to change practice if pilot successful and able to fund full trial. Strong background work. Pilot is crucial and seems well planned out.

Limitations

Dose and duration of intervention leave room for question in the event of a “negative” study.

Ability to assess feasibility goals not that well substantiated by sample size. Full study sample size not really explained. The outcome of time on vasopressor as an outcome is weak and a minimally clinically important difference not explained.

Budget

$800K for 72 patients with almost half the budget in on-call money. Were alternatives to on-call considered? How many patients would be missed by restricted on-call duty or by simply changing the per patient recruitment fee for on-call vs not on-call patients (ie. Don’t pay to just carry the pager if no patients recruited)?

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Assessment/Évaluation:

The pilot project seems to be somewhat redundant. In some of the references the investigators make, they have data on potential number of patients (as in table 1 of their Appendix 2 or as in their table on section 2.12 or about barriers in 2.2.3).

Given the questions posted by the investigators:

1) To estimate the rate of patient recruitment and understand barriers to recruitment;

2) To assess adherence to our specific treatment protocol; and

3) To document the frequency of and understand the reasons for open label steroid use.

There are some issues:

For 1) no measure of “understanding of barriers” or listing of how a barrier will be identified.

For 2) adherence is adherence of staff following protocol, not real adherence of patients complying with treatment as all treatment is given only while in hospital and they state a 100% follow up.

Further ahead they mention:

3) To assess the appropriateness of our eligibility criteria for the full trial; there is no description on how they will assess appropriateness, only that reasons for non consent will be documented.

These all spill over to the statistical plan. In order to have, even “descriptive analysis” as planned by the investigators, you need to have a well-defined outcome.

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Assessment/Évaluation:

Regarding their analysis on this pilot to inform the full trial they state: " Other Sources of Bias: Time to first antibiotic dose, volume of resuscitation fluid and red cell transfusions and vasopressor score (64) will be recorded and compared to determine if these cointerventions which are felt to influence the outcome of shock are similar between the two groups." If they believe there could be sources of bias it would be then more appropriate to match based on these and then present the differences.

Regarding the analysis plan for their Secondary Outcomes:

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); "

I believe that this outcome has nothing to do with being in control or treatment group, this only has to do with the logistics and organization of the staff. This could be considered a potential source of confounding or Bias to address regarding the actual outcome, as delay in this would potentially mean delay on reaching the outcome.

"b. Weaning of drug to q8h when hemodynamically stable (goal is to wean within 12 hours of no escalation of therapy);" same happens here, these are logistical issues not really drug or control issues.

" c. Discontinuation of drug when off all vasoactive medications (goal is to discontinue between 12 and 18 hours of vasoactive medications being stopped); "

Same issue here. One thing is that the outcome of time to discontinuation (let's say time to Dr ordering discontinuation) is reached, another is the time they will take to stop the treatment drug after this has been ordered.

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Assessment/Évaluation:

Regarding their sample size:

The investigators state that with a sample size of 60, based on 80% adherence, their Margin of Error (MOE) would be that of 10%. Which is right, but there is no reason to believe that adherence would be 80%; matter of fact the pilot is being conducted to assess this, so they should go on with a worst case scenario of no information (assuming p=. 5) and their MOE would be12.7% with 60 people.

The sample size calculated for the full trial is stated as that of comparison of means, but they do not state SDs for this and hence their calculations can not be verified or trusted to be correct. Regarding time to discontinuation, since they said they would follow for up to 7 days, could be censored and so they should be doing time-to-event analysis and look at median time to outcome. Their outcome is, even if not censored (assuming all patients reach outcome within follow up time) highly skewed and hence a test for difference in means (t-test) would not be the most appropriate.

Also, there is no mentioning of whether or not a site effect could be thought of or negligible …no discussion at all on it.

Overall I think this proposal needs revision on the measurement operational definitions of their outcomes to then be able to follow a decided analysis plan (time to event? Mean time?, etc.) and following that, the corresponding sample size calculation.

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Assessment/Évaluation:

The committee expressed considerable enthusiasm for this multi-centre pilot RCT. The investigators are part of an impressive, well-established clinical trials network. A recent survey by the investigators documents that the main trial question is of high importance that will inform clinical practice guidelines.

The proposal needs revision to further clarify the feasibility of the main trial.

January/Janvier 07, 2014
DCO150GP

Canadian Institutes of Health Research/Instituts de recherche en santé du Canada
Notice of Recommendation/Avis de recommandation

Application Number/Numéro de la demande: 311832
Committee Code/Code du comité: RC1

Applicants/Candidats: Dr. Kusum MENON

With/Avec: Mr. A. ACHARYA, Dr. K. CHOONG, Mrs. L. KHALAF, Dr. M. LAWSON, Dr. L. MCINTYRE, Dr. J. MCNALLY, Dr. T. RAMSAY, Dr. H. WONG

Institution paid/ Établissement payé: Children's Hospital of Eastern Ontario (Ottawa)

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

Primary Inst./Inst. principal: Circulatory and Respiratory Health
Other Related Inst./ Autres inst. connexes: Human Development, Child and Youth Health

Competition /Concours: Operating Grant
September/Septembre 16, 2013

Number in competition/Nbre de demandes dans le concours: 2528

Peer Review Committee Recommendation, for your information and use/ Recommandation du comité d'examen par les pairs, pour fins d'information et d'utilisation:

Committee/Comité:	Randomized Controlled Trials
Number reviewed/ Demandes examinées:	30
Application rank within the committee/ Rang de la demande dans le comité:	5
Percent Rank within the committee / Rang en pourcentage au sein du comité:	16.67%
Rated / Cote:	4.17
Recommended Term/ Durée recommandée:	2 years/ans 6 months/mois
Recommended average annual operating amount/ Montant annuel moyen recommandé pour le fonctionnement:	$326,433
Recommended equipment amount/ Montant recommandé pour les appareils:	$0

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An application rated below 3.50 is ineligible for CIHR funding. For applications rated 3.50 and above, please note that it is the application's rank within the peer review committee that determines whether it is funded, rather than its absolute rating. The final funding decision will be communicated in the Notice of Decision.

Document à titre d'information seulement.
Une demande cotée en dessous de 3,5 n'est pas admissible au financement des IRSC. En ce qui a trait aux demandes cotées 3,50 ou plus, veuillez noter que l'on détermine l'attribution des fonds en fonction du classement obtenu au sein du comité d'examen par les pairs plutôt qu'en fonction du classement absolu. La décision finale relative au financement sera communiquée dans l'Avis de décision.