Randomized Controlled Trial of Inferior Vena Cava Ultrasonography in the Management and Disposition of Pediatric Patients Undergoing Evaluation for Sepsis and Dehydration
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	Protocol Name:	**Randomized Controlled Trial of Inferior Vena Cava Ultrasonography in the Management and Disposition of Pediatric Patients Undergoing Evaluation for Sepsis and Dehydration**
	Principal Investigator:	Elizabeth Haines 516-946-9742 ejhaines@gmail.com or elizabeth.haines@mssm.edu
	Primary Contact Name/Contact Info:	Elizabeth Haines 516-946-9742
	Date Revised:	2/10/2015
	Study Number:	IF1733382

MSSM Protocol Template HRP-503a

Instructions:

1. *Prepare a document with the following sections. Note that, depending on the nature of your research, certain sections below may not be applicable. Indicate N/A as appropriate, explaining where possible.*
2. *For any items described in the sponsor's protocol, grant application or other source documents submitted with the application, you may reference the title and page numbers of these documents rather than cutting and pasting into this document.* ***Do NOT refer to any derived documents, such as the Sample Consent document, or other internal documents required with the submission.***
3. *If you reference page numbers, attach those pages to this protocol.*
4. *When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.*

Brief Summary of Research (250-400 words):

1) Objectives:

The primary objective of this study is to assess the utility of early versus delayed ultrasonography of the inferior vena cava in pediatric patients undergoing emergency department evaluation of sepsis and dehydration

2) Background

Ultrasound is a widely accepted and highly useful clinical tool. It carries the additional advantage of being rapid, painless and non-radiating. It has long been used to assess cardiac output and vascular pathologies. More recently emergency and trauma clinicians have been using it to assess hydration status, shock/sepsis states and fluid responsiveness (nguyen). Using sonography to look at the inferior vena cava gives clinician a rapid view of vascular collapsibility that has been previously demonstrated to correlate with MAP and CVP (Sinonson/schiller, Stone/Huang). Previously Jones et. al. completed an RCT in adults greater than age 17 evaluating the goal directed utility of early versus delayed inferior vena cava sonography for patients presenting with non traumatic hypotension to the emergency department. This study found improved outcomes and more accuracy in diagnostic etiology of in those undergoing immediate IVC imaging.

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3) **Setting of the Human Research-** The Emergency Department of Mount Sinai Hospital

4) Resources Available to Conduct the Human Research –

Internal resources from the Department of Emergency Medicine.

5) Study Design – A randomized controlled trial of IVC Ultrasonography in pediatric patients 0-21 year of age.

a) Recruitment Methods

All patients, regardless of age or gender, who present to the Emergency Department who trigger triage STOP SEPSIS ALERT (based on triage vital signs and chief complaint), vomiting requiring zofran or diarrhea with concern for dehydration/hypovolemia , whom the treating physician believes would benefit from intravenous fluids will be eligible for inclusion into this study. The "treating physician" refers to one of the Pediatric Emergency Medicine attendings or fellows, all of whom are listed as co-investigators on the application form submitted with this protocol. Only if and when a patient or parent expresses interest in participating in the study, the Attending or Fellow caring for the patient will determine if the patient is eligible. If the patient is eligible, and has no criteria that would exclude them from the study, written informed consent will be obtained from the guardian and assent will be obtained in children $\geq$ 7 years old. The patient will be enrolled in the study and randomized to either the immediate ultrasonography group (US of the IVC first with before the clinician fully assesses the patient and places rehydration orders) or the control group (Ultrasonography at 15 minutes into the assessment and management of the patient).

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b) Inclusion and Exclusion Criteria

Inclusion criteria for enrollment in study:

All patients, regardless of age or gender, who present to the Emergency Department who:

A. Trigger triage STOP SEPSIS ALERT (based on triage vital signs and chief complaint)
   And/OR
B. Present with vomiting requiring Zofran
   And/OR
C. Present with diarrhea with concern for dehydration/hypovolemia

whom the treating physician believes would benefit from intravenous fluids will be eligible for inclusion into this study.

Exclusion criteria for enrollment in study:

(1) Unstable patients with life-threatening injuries who require ongoing resuscitation.
(2) Patient undergoing traumatic resuscitation

c) Number of Subjects

Using the following equation to calculate sample size for proportional outcomes in randomized controlled trials and using data from a 2012 study by Paul et. al. citing a 58% overall compliance with PALS severe sepsis target times:

$$m \text{ (size per group)} = c \times \frac{\pi_1(1-\pi_1) + \pi_2(1-\pi_2)}{(\pi_1-\pi_2)^2}$$

where **c** is set at 7.9 for a power of 80%

π_1 is current percent success rate on standard protocol

π_2 is the current percent success plus the anticipated treatment effect percent

We have calculated the total number of subjects in the sepsis arm to be: 82 per group or 164 total patients for a power of 80% and a type I error set at 5%

For the gastroenteritis and dehydration arm we have established a sample size using a the following power calculation for continuous (time) outcomes

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$$\text{Total sample size} = \frac{c}{\delta^2} + 2$$

where **c** is set at 7.9 for a power of 80%

δ^2 is set for a 10% size treatment effect (reduction in time)

We would need 200 subjects per group or a total of 400 patients in the gastroenteritis arm of the study.

d) Study Timelines

Currently the Mount Sinai Pediatric Emergency Department sees approximately 30,500 patients on an annual basis. Of this total census about 200 trigger the Stop Sepsis alert upon registration. Based on this we have set the enrollment period over 12 months.

Current census data predicts approximately 3000 Mount Sinai annual emergency department visits for vomiting and dehydration requiring antiemetic therapy. In order to collect a convenience sample of 400 patents and adjust for seasonal variability, the study period will enroll over a six month period between June 2015 and November 2015.

e) Study Endpoints

For the Sepsis arm endpoints include:

Primary

- Secured second vascular access point- type (IO, second IV, CV access) within 15 min of physician evaluation
- Inotrope/Vasopressor use
- Antibiotic within 60 min

- 60 ml/kg Normal Saline bolus administered within 60 minutes

Secondary

- Disposition- PICU, Floor, Discharge
- Length of ED stay (from sepsis alert to admission/discharge order entry)
- Return ED Visit for same illness
- Survival to hospital discharge
- 30 day mortality
- Left ventricular function
- Source of sepsis

For the Gastroenteritis/Dehydration arm endpoints include:

Primary

- Type of rehydration: oral versus intravenous
- Total amount of fluids given (ml amount)
- Total ED length of stay from triage time to disposition time (order to admit/discharge)

f) Procedures Involved in the Human Research

Allocation of patients to intervention and control arms will be accomplished by a computer generated randomization application Sherlock MD©. Randomization will be separate for sepsis cohort and gastroenteritis cohort. Within sepsis and gastroenteritis cohorts, subjects will be stratified by disease severity. Specifically they will meet criteria for severe sepsis or meet criteria for severe dehydration based on standard clinical severity scoring (e.g. SIRS criteria, Clinical Dehydration Score).

Subjects randomized to either arm will receive diagnostic imaging of the inferior vena cava with ultrasound. Subjects randomized to the investigational arm will undergo IVC ultrasound immediately

upon arrival and clinician evaluation. Those subjects randomized to the control arm will undergo IVC ultrasound after a timed 15 minute delay. The IVC will be scanned in both longitudinal and transverse planes. All study clinicians will undergo brief 20 minute standardized training session to review which images to obtain.. Still and dynamic images will be recorded and saved. Imaging procedure involves a credentialed ultrasound clinician using an ultrasound machine to visualize the inferior vena cava in order to assess the collapsibility and respiratory variation. This vessel is visualized by placing the ultrasound probe on the subxiphoid area of the abdomen using transducer gel. Images will be obtained in two axes (transverse and sagittal). Images/video will be recorded and stored using a unique study subject number to assure that health information remains confidential and de-identified. Treatment and management decisions will be at the discretion of the treating clinician. The enrolling clinician will be responsible for obtaining consent, randomization and completing the data collection forms. As indicated by the study inclusion criteria, all participants who have triggered the electronic Severe Stop Sepsis notification or have clinically suspected dehydration due gastroenteritis or vomiting will be screened and consented by the enrolling clinician. Given the published data that suggests inferior vena cava ultrasound may help clinicians more effectively and efficiently treat sepsis and dehydration, the main objective of this study is to see if it can reliably improve outcomes as well as improve compliance with targeted treatment goals. We believe that clinical care of subjects who undergo Inferior vena cava US is unlikely to be altered in a negative way.

g) Specimen Banking

Not applicable

h) Data Management and Confidentiality

During the process of data collection, patient identifiers will be collected (first and last name, MR#, age, birth date, date of visit. This identifying information is necessary for US will be located on only 1 form. This form will be kept in a locked file cabinet in a locked office remaining on the medical campus of Mount Sinai Hospital at all times.

Data forms will be kept in a secure locked file. HIPAA-sensitive Personal Health Information (PHI) will not be reused or disclosed to any other person or entity, except as required by regulation and law or for authorized oversight of the research project.

The ultrasound images and clips are not saved in the permanent medical record in EPIC. However, all images are saved in an ultrasound archive supported and secured by Mount Sinai Medical Center IT Department and is HIPAA compliant.

i) Provisions to Monitor the Data to Ensure the Safety of subjects

In order to ensure that adequate provisions are in place for monitoring the data to ensure the safety of subjects, ultrasound image review for quality assurance (QA) will occur weekly during the study. Images will be reviewed to determine the presence or absence of total inferior vena collapse and presumed severe dehydration (as well as other pathology). If the 2nd (QA) interpretation is positive for pathology. The EPIC record will be reviewed to see if the patient was treated with appropriately given the QA read findings. If there are any discrepancies or pathological findings noted on the image review, there is a procedure in place to contact patients and institute any changes in treatment, if necessary. Previous studies site good interobserver agreement with a Cohen's Kappa = 0.64. In accordance we anticipate that a discrepancy between ultrasound interpretations will happen rarely.

A DSMB will be formed from personnel not participating in this trial. This board will include a senior scientist and an ethicist. To monitor for safety problems, adverse events will be reported to the DSMB. An interim data analysis is planned when study enrollment reaches (25% enrollment) 40 patient in the sepsis arm and 100 in the gastroenteritis arm to ensure no excess rates of adverse events are observed in the intervention group compared with the control group.

The primary responsibility of the DSMB is to ensure the safety of the patients. None of the members will be investigators in the study.

The DSMB may meet in person or by telephone conference. Routine business may also be addressed via email. The work of the DSMB, however, will be conducted in complete isolation from any of the investigators of this study. Breaches of this confidence by any member of the DSMB that might impair investigator blinding will be strictly avoided.

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MSSM Principal Monitor: Elizabeth Haines, DO and James Tsung, MD

Indicate whether this person is the PI, a Team Member, or is Independent: Co PI

DSMB chair:

Name: Richardson
First Name: Lynne
Academic Title: Associate Professor of Emergency Medicine, Vice Chair for Academic, Research, and Community Programs
Department: Emergency Medicine
Mailing Address: [redacted], New York, NY 10029
Phone: 212-824-8066
Fax: 212-426-1946
E-mail: lynne.richardson@mssm.edu

Dr, Richardson is a nationally recognized Emergency Medicine health services researcher; her areas of interest are access and barriers to care, and improving effective utilization of health care resources. She is actively involved in several NIH funded trials and holds a vast number of publications and research based advocacy roles. She has a commitment to patient safety and equality, she is well equipped to assess risk to the research subject's health and well being. In monitoring this study she will

- Monitor for adverse outcomes, poor outcomes and subject withdraw rates
  The committee will meet to review results at when 25% enrollment has occurred to ensure no excess rates of adverse events are observed in the intervention compared with the control group.
- If excess rates of adverse events (e.g. higher frequency of unscheduled healthcare visits, longer length of stay, higher admission rates) are observed in the intervention compared with the control group, the DSMB may interrupt or alter the study design.
- This study does not involve medications. Dose selection procedures do not apply.
- During the process of data collection patient identifiers will be collected (first and last name, MR#, age, birth date, date of visit, notes regarding medication and fluid orders). This identifying information is necessary for US will be located on only 1 form. This form will be kept in a locked file cabinet in a locked office within Mount Sinai Hospital at all times
- Should adverse events be noted by the oversight board a suspension of this study will occur and the PPHS and IRB will be fully informed immediately of such occurrence.

MSSM Additional DSMB Member:
Indicate whether this person is the PI, a Team Member, or is Independent: Independent

Last Name: Newman
First Name: David
Academic Title: Associate Professor of Emergency Medicine
Department: Emergency Medicine
Mailing Address: 1 Gustave Levy Place, Box 1620, New York, NY 10029
Phone: 212-824-8065
Fax: 212-426-1946
E-mail: davidnewman@mountsimai.org

j) Withdrawal of Subjects

If a patient or parent expresses that they unable to tolerate the procedure, the ultrasound exam will be stopped immediately and the patient will be removed from the study. There are no infectious risks from the use of ultrasound in this study. The machine will be cleaned per routine procedure after each examination.

6) Risks to Subjects

There are no known risks to ultrasound, with no reports of adverse events in over 65 years of clinical use. The use of ultrasound is painless by avoiding contact of the ultrasound probe with the body part (solely maintaining contact with the ultrasound gel). The ability of patients to tolerate ultrasound without pain, is well documented in the literature.

7) Provisions for Research Related Injury

None

8) Potential Benefits to Subjects

More accurate diagnosis of dehydration and severe sepsis requiring emergent fluid resuscitation

9) Provisions to Protect the Privacy Interests of Subjects

Potential subjects will be approached in the privacy of the ED exam room, in which all personal, private, and sensitive information will be kept confidential as during any

routine doctor-patient exchange. The subject can decline participation at any point in the study.

10) Economic Impact on Subjects

There is no additional cost to the patient nor to the hospital. There is no charge for the performed inferior vena cava US to the patient.

11) Payment to Subjects

none

12) Consent Process

Consent will be obtained either from the potential participant if age 18 years or greater or the parent/guardian of the potential participant aged less than 18 years. Consent will be obtained in a private setting in the examination room of the Emergency Department prior to performing the ultrasound. The person providing consent will be allowed to consider the request free of time constraints and sense of obligation or white coat pressure. They will be given the opportunity to review the consent document and discuss it with whomever they like. Assent will be obtained for all potential participants greater than or equal to age 7 years and will be documented on the last page of the child consent form.

13) Process to Document Consent in Writing

Written consent with a paper based form will use basic language that is easy to understand (5th grade level. To ensure that the subject understands, they will be asked to reiterate in their own words the purpose of the research, what they will need to do as participants in the study, and what the potential risks and alternatives are.

14) Vulnerable Populations

The population of interest in this study includes patients < 18 years old (i.e vulnerable subjects). All efforts will be made to protect these children during this study. As previously listed, ultrasound emits no radiation and is a painless procedure; therefore this study presents no risk to these patients. If the patient/child or parent expresses any discomfort from the ultrasound or procedure, the procedure will be immediately discontinued and the patient will be removed from the study.

When subjects with diminished mental capacity are to be enrolled, there will be an independent assessment of capacity to sign consent. If a potential participant does not have the capacity to sign consent, permission of a surrogate and assent of the potential participant if aged 7 years or greater will be obtained. If permission of the surrogate is not obtained, the potential participant will not be enrolled in the study. It is important that persons with diminished capacity be included in this study. Dehydration is clinically important and common morbidity in young children with diminished capacity (e.g. those with mental retardation/cerebral palsy). This population is particularly vulnerable to sepsis and moderate to severe dehydration requiring resuscitation and should be allowed to participate in the study.

Assent from the potential participant will be obtained for all potential participants greater than or equal to age 7 years. Consent will be obtained from parents/guardians of potential participants who are younger than 18 years of age.

15) Multi-Site Human Research (Coordinating Center)

Not applicable in this study

16) Community-Based Participatory Research

Not applicable in this study

17) Sharing of Results with Subjects

Relevant information and findings from the ultrasound imaging studies will be shared as per standard of care in the Emergency Department

18) IRB Review History

Primary application- no applicable history

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19) Control of Drugs, Biologics, or Devices

Note: The IDS has its own forms that must be completed and a review process that must be followed before the IDS representative will sign off on Appendix B for submission to the PPHS.

*****Please see attached FDA 510-approved device brochure- specific to the ultrasound equipment used in this study**