Clinical Study Protocol

Detection and Management of Non-Compressible Hemorrhage by Vena Cava Ultrasonography

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Primary Investigator: Jay Doucet MD FACS
Associate Professor of Trauma
Division of Trauma, Surgical Critical Care, and Burns
Department of Surgery, University of California San Diego

UCSD Medical Center
200 W Arbor Drive
San Diego, CA 92103-8896

Office 619.543.7200
Fax 619.543.7202
e-mail jdoucet@ucsd.edu

Study Coordinator: Terry Glenn Curry RN
Clinical Research Coordinator
Division of Trauma, Surgical Critical Care, and Burns
University of California, San Diego Medical Center
4230 First Ave. #1
San Diego, Ca 92103-8896

Office 619-543-7455
Page 619-290-2323
Fax 619-543-7366
e-mail: tcurry@ucsd.edu

Granting Agency: National Trauma Institute
8000 IH 10 West, Suite 600
San Antonio, TX 78230
(210) 524-7739

Protocol Video: http://youtu.be/bpaMTqqqGdw

1. Project Abstract

This is a prospective, observational, clinical trial of major trauma victims presenting at academic trauma centers using bedside ultrasound to identify patients with evidence of hypovolemia as determined by inferior vena cava (IVC) collapsibility within 20 minutes of admission. All patients with or without significant IVC collapsibility will be enrolled and receive the institutions' standard of care resuscitative intravenous solutions. Patients will be stratified at a second ultrasound IVC exam 30-40 minutes after admission by response or non-response to an intravenous fluid challenge. Enrolled patients will have a third ultrasound exam when considered resuscitated, but not later than 24 hours. Our objective is to demonstrate whether such non-responder patients identified by serial IVC ultrasound examinations have significant shock physiology as determined by markers of shock such as lactate, base deficit and complications. Demographics, mechanisms of injury, diagnoses, fluids and transfusions given, interventions required, complications, mortality and discharge disposition will be recorded. Prior small studies of ultrasonographic assessment of IVC diameters and collapsibility demonstrated it to be a sensitive detector of blood volume loss and hemorrhagic shock. This technique may also predict those patients who will require transfusions, surgery or angiographic embolization. This technique may also allow better triage of major trauma victims and thereby avoid delay in therapy and complications. This study will also provide an opportunity to demonstrate the ability of handheld ultrasound devices to detect and monitor hemorrhagic shock in initial trauma care and in the ICU. The study has significant military relevance as handheld ultrasound is readily available to forward echelons of combat casualty care and can provide clinical decision support when evaluating casualties with hemorrhagic shock.

1A. Non-proprietary Lay Person Summary

This is a study of patients admitted with major traumatic injuries. Such patients may develop inadequate circulation to the organs as a result of internal blood loss. Early detection of internal blood loss can be difficult as physical examination alone may miss patients with significant blood loss. Some patients with internal bleeding will arrive with low blood pressure; these patients are usually given 2 liters of intravenous fluid to determine if their blood pressure will recover. If the blood pressure does not rise or if it drops again later, the blood loss can be assumed to be severe, and the patient will likely need transfusions, surgery and other interventions. However, this fluid treatment method can lead to delays and complications as some patients may initially respond but then continue to bleed. The inferior vena cava is the large vein draining blood from the lower body to the heart. The inferior vena cava is known to empty when the patient has had significant blood loss. The vena cava diameter can be seen using ultrasound. This study intends to perform ultrasound to examine the vena cava diameter on patients just after arriving with major trauma and low blood pressure. After the patient has been given the 2 liter intravenous fluid treatment, the inferior vena cava diameter will be measured again. A third examination 8-24 hours after admission will determine if the inferior vena cava diameter has returned to normal. We propose that measuring the inferior vena cava in this manner can predict those patients who are likely to continue bleeding and require interventions such as surgery. Early detection in these patients may avoid delays in treatment, complications and excess mortality. Because this examination is done with handheld ultrasound machines, it could be done outside hospitals and in military combat casualty care.

2. Study Synopsis

Name of Sponsor	UCSD/NTI
Intervention	Abdominal Ultrasonography in Trauma Patients
Title of Study	Detection and Management of Non-Compressible Hemorrhage by Vena Cava Ultrasonography
Study Centers	Multicenter Study in approximately 4 Level I Trauma Centers
Indications	Suspected Adult Blunt Abdominal Trauma
Study Duration	Up to 3 imaging studies in 24 hours and observation to discharge
Study Objectives	
The aims of the study are 1) Determine the sensitivity, specificity and accuracy of USA of IVCe, IVCi and IVC-CI with the classic clinical parameters hypotension (SBP<90) or tachycardia (HR>108), indicative of hemorrhagic shock. 2) Compare USA of IVCe, IVCi and IVC-CI with base deficit or serum lactate levels upon admission.3) Determine the sensitivity, specificity, PPV and NPV of USA of IVCe, IVCi and IVC-CI to predict the need for blood transfusion or hemostatic interventions such as surgery or angioembolization.	
Study Endpoints	
Primary Endpoint	IVC collapsibility and IVC response to resuscitation in two imaging studies as an indicator or predictor of SBP<90
Secondary Endpoint	• IVC Collapsibility as an indicator of mortality • IVC Collapsibility as indicator of transfusion need • IVC Collapsibility as a predictor of base deficit >6 • IVC Collapsibility as a predictor of surgical or IR intervention
Study Design	
Methodology	This study is a prospective, multi-institutional observational human trial in major trauma patients presenting to a Level I trauma center. The study group will be major trauma victims with suspected abdominal trauma undergoing trauma team assessment and FAST ultrasound. The independent variable is the IVCe, IVCi and IVC-CI on admission FAST. The primary dependent variables include admission SBP < 90, Base Deficit > 6 in the first 24 hours, serum lactate > 20 mg/dl, need for packed red cell transfusion within 24 hours. Other variables to be collected include subsequent vital signs, type and volume of fluids given intravenously in the first 24 hours, requirement and volume of blood transfusions, urine output, body weights, standard of care arterial blood gases in the first 24 hours including Base Deficit or lactate, hematocrit measurements, need for a hemostatic procedure (i.e. laparotomy, thoracotomy, angiographic embolization), ventilator days, hospital and ICU length of stay, hospital charges, complications, discharge disposition and mortality. A small Control group (25 per site) of major trauma victims without hypotension will be used to obtain reference values of IVCe, IVCi and IVC-CI for each site.
Number of Subjects	The planned total number of subjects is 500

Diagnosis and Main Criteria for Inclusion	1. Major Trauma Victims at Level I Trauma Center (i.e. ISS ≥ 15) 2. Significant IVC collapsibility (>75%) on initial FAST
Exclusion Criteria	1. Pregnancy after 20 weeks gestation, 2. Less than 18 years of age, 3. Prisoners and others prohibited from participating in clinical trials and 4. Patients with severe Traumatic Brain Injury who at admission are deemed by treating surgeons as having non-survivable brain injuries.
Interventions	1. Admission FAST with IVC windows 2. Standard of care trauma resuscitation 3. Repeat FAST with IVC windows or CT abdomen with I.V. contrast following initial trauma assessment and resuscitation
Enrollment	1. Patients with continued collapsibility (≥ 75%) are non-responders, those with decreased collapsibility (< 75%) are responders 2. Enrollment procedures, consent obtained 3. Followup FAST after consent, 8-24 hours after admission when patient considered "resuscitated", but NLT 24 hours.
Criteria for Evaluation	
Data to be collected	See datasheet.
Primary Efficacy Analysis	The primary efficacy variable is prediction shock (SBP>90) during the first 24 hours after admission. If the p-value from the test of the null hypothesis is less than 0.0003 at interim analysis, it will be concluded that loss of IVC collapsibility is statistically significant from continued collapsibility.
Sample Size Justification	Published data indicates that USA of IVC diameter for a 450ml blood loss in blood donor volunteers is highly sensitive[5]. About 7% of patients admitted to Level I Trauma Centers present with a systolic blood pressure less than 90mmHg, most of these should have significant IVC collapsibility. Participating Trauma centers would admit 2500 trauma patients per year, which would mean approximately 175 patients would be admitted annually with SBP < 90 mmHg. To detect a difference in mortality of 10% in between Responder and Non-responder IVC-CI groups with a beta-error of 20% or less and alpha of 0.05, about 492 study patients would be required. To complete the proposed study in one year would require 4 trauma centers contributing about 125 study patients each.
Baseline Data Analysis	Baseline comparability of the groups (responder and non-responder) for the most important prognostic factors (age, GCS, base deficit, vital signs, mechanism of injury) will be summarized descriptively using means and standard deviations, medians and tabulations as

	appropriate. Comparisons will be done by Fisher's exact test for binomial variables, Chi-Square test for categorical variables and T-test for continuous variables.
Safety Monitoring/DSMB	A DSMB committee will review safety and efficacy data from the trial. The Data will be provided at about 100 patient intervals.
Interim Analysis	Interim Analysis will be performed at intervals of 200 patients. At the planned analysis a two-sided test will be conducted to detect an increase or decrease in the common odds ratio.
Safety Analysis	All AEs and SAEs will be summarized by counts of subjects with AEs and individual occurrences coded by type of event.

3. Research Plan:

A) Title of project

Detection and Management of Non-Compressible Hemorrhage by Vena Cava Ultrasonography

B) Hypothesis and Specific Aims:

The hypothesis of the proposed study is that an ultrasonic assessment (USA) protocol of inferior vena cava (IVC) diameter and collapsibility can detect and aid management of non-compressible hemorrhage in major trauma victims.

Specific aims of the study include:

1) determine the sensitivity, specificity and accuracy of ultrasonic assessment (USA) of IVC diameters in detecting traumatic shock at admission as compared to vital signs,

2) determine the ability of USA of IVC diameters to detect preclinical shock states defined by elevated arterial blood gas (ABG) Base Deficit or lactate in trauma patients without hypotension (SBP less than 90) at admission,

3) correlate the restoration of IVC diameters and collapsibility to achievement of endpoints of shock resuscitation in the ICU, such as correction of Base Deficit or lactate, evidence of improved organ perfusion such as urine output and avoidance of multiple organ dysfunction or death.

C) Background and Significance

Scientific rationale

Clinicians are unable to reliably determine intravascular volume status in trauma patients by clinical examination alone[1]. Major trauma victims undergo intensive investigation including invasive monitoring, blood gas analysis, intravenous fluid challenges, hourly urine outputs, serum lactates and other tests in attempting to determine the intravascular volume status and its trajectory. The central venous pressure is typically used in trauma patients arriving in the ICU to estimate intravascular volume status and response to intravenous fluid adminstration[2].

Investigations to rule out hemorrhagic shock require time and advanced equipment and are not typically available in prehospital environments or in the forward echelons of military combat casualty care. The Focused Assessment with Sonography for Trauma (FAST) is used for the initial assessment of trauma patients, and has almost replaced the diagnostic peritoneal lavage (DPL) for the rapid bedside assessment for hemoperitoneum in an unstable trauma patient[3, 4]. FAST can also detect hemopericardium and hemothorax. The inferior vena cava (IVC) can also be readily seen during FAST, either from a subxiphoid transabdominal sonographic window or through a mid-axillary liver sonographic window. The IVC diameter has been shown to correlate with intravascular volume. The large veins of the torso are sometimes

described as "capacitance vessels", and approximately 2/3 of the total blood volume is contained in the venous circulation. Lyon et al. performed a study of healthy blood donors and measured IVC diameters. They revealed that a 5 mm decrease in IVC diameter was seen after donation of 450ml of blood[5]. In hemodialysis patients, IVC diameter has been successfully used to estimate the blood volume status[6]. However, as with central venous pressure, there are no absolute normal values of IVC diameter that can be applied without exception to every patient.

Under normal conditions in healthy, spontaneously breathing, supine patients the IVC will nearly or completely collapse with inspiration and expand with expiration. Ultrasonographic assessment of the diameter of the inferior vena cava in expiration (IVCe) and in inspiration (IVCi) allows assessment of the collapsibility of the inferior vena cava (IVCe-IVCi). Another measurement of intravascular volume status is the IVC collapsibility index (IVC-CI). The IVC-CI is calculated using a standard formula IVC-CI = (IVCe) – (IVCi)/(IVCe) x100%, where IVCe is the maximum IVC diameter at expiration and IVCi is the minimum IVC diameter at inspiration[7]. Respiratory variation in IVC diameter has been found to be more pronounced in hypovolemia with abnormally low CVP being increasingly likely as IVC-CI approaches 100%[7, 8]. However there is not yet an exact cutoff value determined for IVC-CI for hypovolemia, although 75% has been suggested as the cutoff for hypovolemia[9].

Similarly to central venous pressure measurements, techniques of IVC measurement have many of the same inaccuracies of CVP measurements. Positive pressure ventilation can invert the normal inspiratory-expiratory minimal and maximum size relationship, and high PEEP levels may reduce venous inflow to the chest and distend the IVC. Increased right atrial pressures are seen in right heart failure, valvular disease and pulmonary hypertension and may cause increased IVC diameter that is not reflective of an increased volume status. However, these conditions would not be expected in acute combat casualties or in most civilian trauma admissions. Another issue with IVC diameter may be the effect of increased abdominal pressure such as seen in abdominal compartment syndrome (ACS) causing narrowing of the IVC[10]. However, ACS is rarely present at admission in major trauma patients, and when it is present at admission is usually accompanied by overt clinical signs that indicate immediate surgical intervention.

Body habitus can also affect the measurement of IVC diameter, this has been accommodated by incorporating patient height or BMI in a conversion factor multiplied by the IVC diameter[11].

Following IVC diameters after initial therapeutic fluid challenge of the blunt trauma patient with hypotension may improve the utility of FAST in trauma patients. Yanagawa et al., in a study of 30 trauma patients presenting with shock (systolic BP < 90mmHg) followed patients into two groups: a transient responder group (n=17) in which shock recurred after an initial 2 L intravenous crystalloid fluid bolus in the emergency room and a responder group (n = 13) in which blood pressure remained stable. Both groups had similar IVC diameters on arrival, however after two liters crystalloid fluid resuscitation the transient responder group was significantly smaller: 6.5 ± 0.5 mm vs. 10.7 ± 0.7 mm, (mean ±SE), $p < 0.05$. In other words, in the responder group there was a significant increase in mean IVC diameter (ΔIVC) after fluid administration which did occur in the transient responder group. IVC diameter predicted patients who would become hypotensive later despite equivalent fluid resuscitation. It also predicted those likely to need emergent hemostatic inventions such as laparotomy or angiography - the

transient responder group contained a greater proportion of patients who underwent such procedures than the responder group (47.0% vs. 7.6%, $p < 0.05$)[11].

D) Methodology:

Design

This study is a prospective, multi-institutional, observational human trial in major trauma patients presenting to a trauma center. Patients selected for study are major trauma victims who have evidence of increased collapsibility (IVC-CI ≥ 75%) on initial FAST examination. Responders and Non-responder cohorts will be selected on IVC-CI response to interventions in the Trauma Bay after forty minutes. Responders will have restoration of IVC-CI to euvolemic levels (IVC-CI ≤ 60%). The primary dependent variables include hospital mortality, need for hemostatic interventions such as surgery or angiography, need for ICU admission, need for ventilation, need for blood product transfusion within 24 hours, multiorgan failure and complications. Other variables to be collected include vital signs including SBP, type and volume of fluids given intravenously in the first 24 hours, urine output, body weights, standard of care arterial blood gases in the first 24 hours including Base Deficit and/or lactate, hematocrit measurements, ventilator days, hospital and ICU length of stay, hospital charges, complications, and discharge disposition. A small Control group (25 per site) of major trauma victims without hypotension will be used to obtain reference values of IVCe, IVCi and IVC-CI and ensure standardization of the protocol for each site

Study measurements

Patients will undergo a modified FAST within 20 minutes of admission to the trauma bay with an additional imaging window – a video clip of the USA of the patient's inferior vena cava during inspiration and expiration will be saved. This will be used to calculate measurements of IVCe and IVCi and collapsibility. Within 40 minutes of admission but more than 20 minutes after the first FAST, a second modified FAST examination will be obtained to determine the patient's response to initial resuscitation.

Imaging technique

Patients undergoing FAST with IVC diameter measurement are examined in the supine position. If the patient is breathing spontaneously the diameter of the IVC is measured at both end inspiration and end expiration. If the patient is on positive-pressure ventilation, the usual relationship between the respiratory cycle and IVC diameter may be inverted; minimal and maximal IVC diameters are used[12]. The exact portion of the IVC to be measured varied in prior studies. Locations used included the IVC-Right atrial junction, the area just below the hepatic veins or at the level of the renal veins. A study in healthy volunteers compared measurements of respiratory variation in IVC diameters at the level of the left renal vein and at 2 cm caudal to the hepatic vein inlet to be consistent[13]. Measurements taken at the junction of the right atrium and

IVC were not equivalent to the other sites. The authors recommended that the IVC diameter at the right atrium-IVC junction not be used. For this project we will normally use a site 2 cm caudal to the hepatic vein inlet, this site is readily adapted to the FAST exam via the mid-axillary window, and less affected by bowel gas.

Sample characteristics

Inclusion criteria for subjects enrolled in the first year of this study will be major trauma patients brought to Level I Trauma Centers. Selected patients for the study will be those presenting with admission SBP less than 90mmHg or with IVC collapsibility on modified-FAST at admission. The centers selected for participation routinely utilize clinician-performed Focused Assessment with Sonography for Trauma (FAST) at admission. Exclusion criteria includes pregnancy after 20 weeks gestation, those under 18 years of age, prisoners and others prohibited from participating in clinical trials and patients with severe traumatic brain injury who at admission are deemed by treating surgeons as having non-survivable brain injuries. Pregnant women after the mid-second trimester (>20 weeks since LMP) will be excluded. This is because starting late in the second trimester, the diameter of the inferior vena cava (IVC) dramatically decreases with maternal positional change from the left lateral position to the supine position as the gravid uterus compresses the IVC. This effect is not always completely negated by the use of a bump or bolster placed under right side of the trauma backboard. This effect would likely make it difficult or impossible to interpret the IVC diameter, collapsibility or response to fluid administration.

Patients selected for study will be separated into cohorts depending on the response to initial standard-of-care resuscitation by institutional trauma protocols as measured by a subsequent modified FAST exam – those whose show reduced IVC collapsibility will be the "Responder" group, those will continued IVC collapsibility will be the "non-Responder" group.

Sample size

Published data indicates that USA of IVC diameter for a 450ml blood loss in blood donor volunteers is highly sensitive[5]. About 7% of patients admitted to Level I Trauma Centers present with a systolic blood pressure less than 90mmHg, most of these should have significant IVC collapsibility. Participating Trauma centers would admit 2500 trauma patients per year, which would mean approximately 175 patients would be admitted annually with SBP < 90 mmHg. To detect a difference in mortality of 10% in between Responder and Non-responder IVC-CI groups with a beta-error of 20% or less and alpha of 0.05, about 492 study patients would be required. To complete the proposed study in one year would require 4 trauma centers contributing about 125 study patients each.

Recruitment and consent

All centers will operate under human research protection protocols from their respective Institutional Review Boards. The Institutional Review Board letters of approval for UC San Diego is attached at the appendices.

Major trauma victims are typically unable to provide study time consent at admission. The study will be done under a Waiver of Informed Consent as described in 45 CFR 46.116(d). This is permissible as the FAST ultrasound exam is already done routinely as part of the standard of care; the additional view of the IVC adds no significant risk for discomfort, delay of care or radiation, no decisions will be made based on the ultrasound results and this study is purely observational. All ultrasound devices to be used are approved under a FDA 501(k) license for abdominal sonography. Notices of the study will be made to the public and participants in accordance with IRB directions.

Timeline of Patient Interventions

(1) Major Trauma Patient admitted to trauma bay.
   (a) ATLS Primary Survey and Secondary Survey performed.
   (b) Intravenous fluids started.
   (c) **FAST ultrasound with IVC diameters within 20 minutes of arrival**.
   (d) Patient receives Standard-of-care resuscitation per institutional protocols.
   (e) Patient identified as having significant IVC-CI.
   (f) Unique study ID assigned.
   (g) Study data initial capture including demographics, mechanism, admission diagnoses, enroute and trauma bay vitals, fluids and transfusions given, admission ABGs, hemoglobin, hematocrit, time of intubation, chest tubes, and imaging diagnoses.
   (h) Second FAST ultrasound with 40 minutes of admission but more than 20 minutes after first exam.
(2) Patient leaves trauma bay and goes to ICU, CT, OR, or Interventional radiology.
(3) Patient is admitted to ICU, Step-down unit or equivalent.
   (a) Study data captured includes vital signs, body weights, ABG results, urine output, ventilator use and settings, transfusions, Input/output, hemoglobin, hematocrit, time of intubation, fluids and transfusion given, CT scans of chest or abdomen in the first 24 hours if indicated, APACHE, SAPS II and MODS scores.
(4) The patient is discharged from hospital or dies.
   (a) Discharge disposition, discharge diagnoses, length of stay, length of ICU stay, length of ventilation, ISS, RTS, AIS scores, procedures performed, complications, organ failure are recorded.
   (b) Data and images are submitted to data collection website.

Subsequent care and follow-up imaging

Patients will be treated according to the local institutions' trauma protocols, which typically include intravenous fluid resuscitation, blood product transfusions, vasoactive drugs, hemostatic interventions such as surgery or interventional radiology and other treatments as considered clinically appropriate. Arterial blood gases will be obtained on admission and in the ICU as clinically indicated. CT scans of the chest or abdomen that are ordered as part of the subject's clinical care will be saved to measure IVC diameters for correlation to USA of IVC diameters.

Imaging equipment

Participating centers will use FDA-approved small bedside and handheld ultrasound machines that are typically utilized by nonradiologist clinicians in performing their daily FAST exams. The models used will be the same or similar to those used in military deployed medical treatment facilities and civilian Level I and II in Trauma centers. The use of high-end ultrasound machines, such as those costing over $75,000 will not be permitted. Centers will have an ultrasound machine set-up that has a highly reliable method of collecting ultrasound video. This would include a digital-video-recorder (DVR) with optical backup or via a video server. Centers lacking these devices will be provided with a DVR with optical backup by the study.

Data collection

Each prospective study candidate will be assigned a unique, anonymous, numeric identifier admission. Data collected will include demographics, trauma mechanism, ISS and regional AIS scores, prehospital and admission vital signs, Apache, SAPS II and MODS scores. Outcome variables will include volume and type of fluids required to be given intravenously in the first 24 hours, requirement and volume of blood transfusions, urine output, body weights, admission arterial blood gases including Base Deficit or lactate, subsequent blood gases for 48 hours, CBC results, procedures performed, ventilator days, hospital and ICU length of stay, hospital charges, complications, discharge disposition and mortality. Imaging data to be collected will be the IVCe/IVCi video clips at admission.

Differences in outcome variables will be compared between ranges of IVCe, IVCi and collapsibility. Multivariate analysis will be used to validate the predictive ability of IVCe, IVCi and collapsibility to detect need for transfusion, MODS, complications, mortality and other shock sequelae. UCSD will be the Data Collection Center for this study. Data will be entered in the AAST-MITC online data entry system (for data sheet with complete data fields see Appendix D). The AAST-MITC data entry system is a secure system, in which de-identified data as well as imaging files are entered and stored in a secure server. The PI (Dr. Doucet) and the Co-PI and AAST-MITC Chair (Dr. Coimbra) are the only persons with access to the full database.

Training of investigators

To ensure reproducibility and standardization in imaging and measurements, participating AAST-MITC Centers will receive training in obtaining the correct ultrasound views of the IVC. Training material will include videos demonstrating machine settings, proper probe positioning, model images, troubleshooting, and methods of calculating IVCe, IVCi and collapsibility. For training, participating centers will use typical handheld or small bedside ultrasound units as used by clinicians in Level I and II Trauma Centers and in military deployed medical treatment facilities. Participating investigators will be required to submit images of at least 10 patients demonstrating proficiency in imaging acquisition and ultrasonographic technique prior to first patient enrollment.

Training material will be created at the UC San Diego Division of Trauma Educational and Research Media office, which has a dedicated Production Manager.

Adverse Events and Unanticipated Problems

Unanticipated problems are those problems that are not described in the study protocol or other study documents. Any adverse events and/or unanticipated problems will be reported promptly as outlined in the approval letter from the US Army Medical Research Material Command (USAMRMC) Human Research Protection Office (HRPO).

For serious adverse events, we will include in the initial adverse event report the name of the person submitting the report, if different from the PI, name of the study, the number of subjects enrolled to date, and the number and type of serious and unexpected adverse events previously reported in the study. The HRPO and/or HSRRB will evaluate reported information to determine if changes are warranted in the research protocol or protocol-related documents or in the information provided to research subjects. Any changes required by the local IRB should be communicated immediately to the HRPO.

The HRPO requires that the following language appear in all protocols:

"Unanticipated problems involving risk to volunteers or others, serious adverse events related to participation in the study, and volunteer deaths related to participation in the study should be promptly reported by phone (301-619-2165), by e-mail (hsrrb@amedd.army.mil), or by facsimile (301-619-7803) to the U.S. Army Medical Research and Materiel Command's (USAMRMC) Office of Research Protections, Human Research Protections Office. A complete written report should follow the initial notification. In addition to the methods above, the complete report can be sent to the USAMRMC, ATTN: MCMR-ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012."

Study Timeline

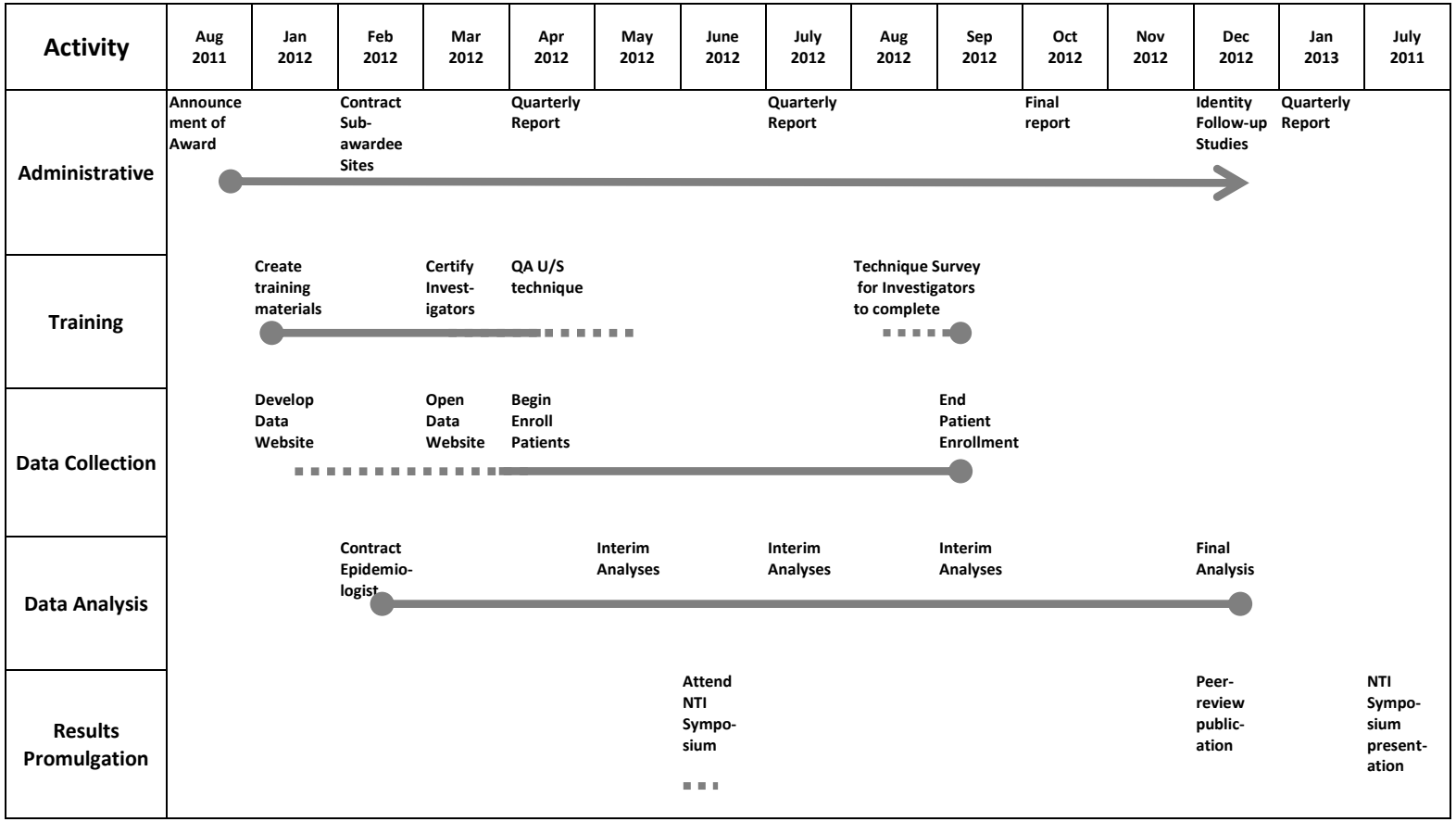
An expected timeline for the proposal is shown at Table 1. In the first few months after grant award, the sub-awardee multi-institutional sites will be contracted to the proposal and the training material for site investigators created. The vendor who will construct the AAST-MITC data collection web will be contracted. Patient enrollment would be expected to commence in July 2010 and end on or before June 30, 2011.

Future Years

A future year study could include repeated measurements of IVC diameter in trauma patients presenting in shock (systolic BP < 90mmHg) at admission, after initial fluid administration and then after stabilization in the ICU. Repeated measurements of IVC diameter could also include CT scans of the abdomen or thorax; these may allow a subsequent measurement of IVC diameters when the patient has apparent normalization of vital signs. These could be reviewed to examine the utility of detecting change in IVC diameters between the time of admission FAST and the CT scan on the outcome variables. Additional USA of IVC studies could be done later in

the hospital course if informed consent can be obtained. Future studies could also include creation of resuscitation algorithms based on the validated IVC measurements. These could be used to prospectively provide clinical decision support for intravenous fluid resuscitation, blood transfusion and hemostatic adjuncts such as surgery or angiographic embolization in civilian and military trauma care.

Study Timeline



E) Analysis of Results

Data will be collected in a secure electronic database via the AAST-MITC study data website. Analysis will be performed after testing data quality. Statistical software (SAS ®) will be used for statistical analysis and a project-funded PhD epidemiologist will be consulted for the data analysis.

The ability of the protocol to detect non-compressible hemorrhage will be determined by the difference in outcomes between the Responder and Non-Responder Groups, including differences in adjusted mortality rate, need for hemostatic interventions, need for blood product transfusions, need for ventilation or ICU admission. These frequencies will be analyzed by Chi-Square. The exact cutoff values of admission USA of IVCe, IVCi and IVC-CI that will indicate hypotension (SBP<90), metabolic acidosis (Base Deficit > 6, lactate > 20 mg/dl) or need for blood cell transfusion are not known. A receiver operating characteristic (ROC) curve will be constructed for initial IVCe, IVCi and IVC-CI to determine the optimal cutoff values to detect admission SBP < 90 and mortality[14]. The ROC two-dimensional graph will display the sensitivity versus (1- specificity) using multiple cut off points to allow the optimal cut off to be selected. Accuracy of the cut off may be expressed as the area under the curve. A value of 0.7 - 0.9 will be considered a good cut off. Confidence intervals for the area under the ROC also will be calculated. This is a well-accepted method to assess a new imaging technique[15]. This method will be repeated to determine the cutoff values for admission Base Deficit > 6 or serum lactate > 20 mg/dl. Similarly, this method will be used to determine cutoff values of IVCe, IVCi and IVC-CI that will predict the need for blood cell transfusions. Sensitivity, specificity, PPV and NPV will be calculated using 2 x 2 contingency tables for the cutoff values of determined for IVCe, IVCi and IVC-CI.

F) Military relevance:

There is little clinical decision support except for vital signs available at Echelon I and II levels of care for detection of hemorrhagic shock[16]. Unequivocal clinical signs of hemorrhagic shock such as hypotension or loss of radial pulses appear notoriously late in wounded, physically fit soldiers. Handheld ultrasound units are already available in Echelon II facilities that would allow USA of IVC diameters. Detection of hemorrhagic shock via USA of IVC diameters before overt hypotension occurs can aid decisions for prioritization for rapid evacuation to surgical treatment facilities, use of hemostatic adjuncts and need for fluid resuscitation or blood product transfusion. USA of IVC diameters may also have utility when assessing multiple casualties for priority for moves to surgical care. The skills to perform a limited USA of IVC diameters can be readily acquired by non-physician caregivers such as deployed Independent Duty Corpsmen and combat medics. Ultrasonographic measurements of IVC diameters may also provide a method of detecting hemorrhagic shock during waits for evacuation and while en route to Echelon III facilities.

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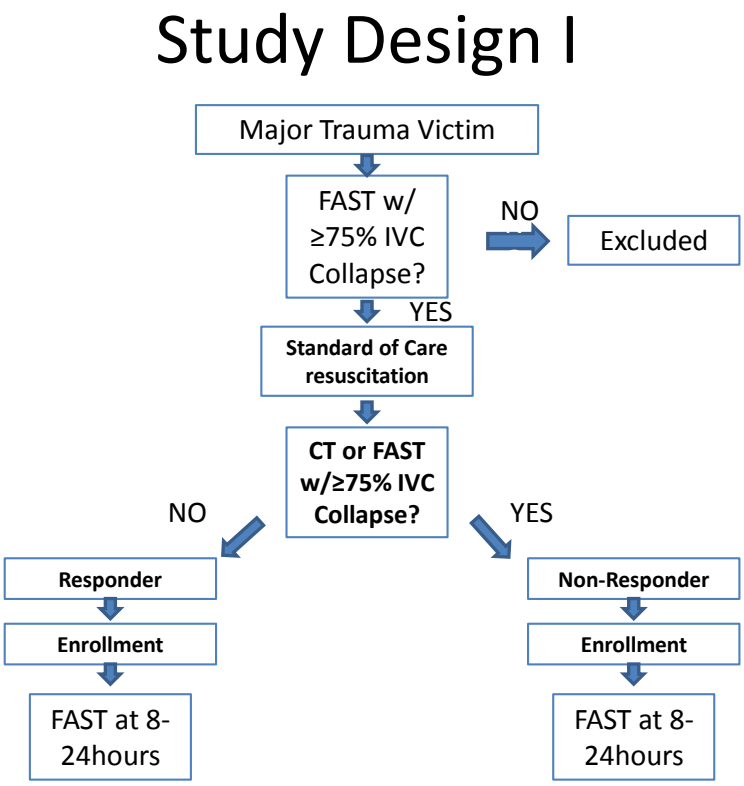
Figure 2.


Study Design I
Major Trauma Victim
FAST w/ ≥75% IVC Collapse?
NO
Excluded
YES
Standard of Care resuscitation
CT or FAST w/≥75% IVC Collapse?
NO
YES
Responder
Enrollment
FAST at 8-24hours
Non-Responder
Enrollment
FAST at 8-24hours

AAST Website Datasheet

Datapoint	Desc
Facility ID	ID of Facility, i.e. 1,2,3
Patient Serial	Serial of patient for facility
UID	Unique identifier
Age	years
Gender	M/F
Race	White, Black Am Indian, Alaskan Native, Pacific Islander, Asian, Hispanic, Not Documented, Unknown
Weight	kg
Height	cm
Injury Date	Date of Injury (or estimate)
Injury Time	Time of injury (or estimate)
Admit Date	Date of admission
Admit time	Time of Admission
Transfer from other facilty	No - if yes, excluded
Transport	Air –ALS, Air –BLS, Ground –ALS, Ground –BLS, Law Enforcement, POV/Ground, Walk-in, Other
EMS scene arrival time	Time EMS arrived on scene
Prehospital IV fluid	ml (optional)
Mechanism of injury 1	ICD-9 Ecode 1
Mechanism of injury 2 (optional)	ICD-9 Ecode 2
Blunt / Penetrating	Blunt, Penetrating Injury
Prehospital Systolic BP	Lowest recorded
Prehospital Diastolic BP	Lowest recorded
Prehospital Heart rate	Highest recorded
Prehospital Respiratory Rate	Highest recorded
Admission Systolic BP	First recorded
Admission Diastolic BP	First recorded
Admission Heart rate	First recorded
Admission Respiratory rate	First recorded
Post-resus Systolic BP	Diastolic BP on leaving resus bay
Post-resus Diastolic BP	Systolic BP on leaving resus bay
Post-resus Heart Rate	HR on leaving resus bay
Post-resus Respiratory Rate	RR on leaving resus bay
ABG Time	Time of first ABG
ABG pH	First blood gas pH
ABG pCO2	First blood gas pCO2
ABG pO2	First blood gas pO2
ABG B/E	First blood gas Base Excess
Lactate	First blood gas lactate
ISS	Injury Severity Score 3-75
GCS - Eyes Score	1, 2, 3 or 4

GCS - Verbal Score	1, 2, 3, 4 or 5
GCS - Motor Score	1, 2, 3, 4, 5 or 6
Airway interventions	Intubated when Respiratory Rate Taken, Chemically Paralyzed, Chemically Sedated, Intubated and Chemically Paralyzed, Intubated and Chemically Sedated, Intubated, Chemically Paralyzed and Sedated, No Intervention
Intubated at time of FAST	Yes/No
Time of 1st fast	Date/Time if not embedded/correct in images
1st FAST result	Positive, Negative, Equivocal for intrabdominal, intrapericardial fluid
1st FAST report	Text of report
Time of 2nd fast	Date/Time if not embedded/correct in images
2nd FAST result	Positive, Negative, Equivocal for intrabdominal, intrapericardial fluid
2nd FAST report	Text of report
Time of 3nd fast	Date/Time if not embedded/correct in images
3rd FAST result	Positive, Negative, Equivocal for intrabdominal, intrapericardial fluid
3rd FAST report	Text of report
DPL result	None, Positive, Negative, Equivocal (optional)
Time of 1st Abd CT	Date/Time if not embedded/correct in images
1st Abd CT result	Positive, Negative, Equivocal for intrabdominal injury
Text of 1st Abd CT result	Text of report
Vena cava horizontal diameter on 1st Abd Ct	Widest diameter in mm of vena cava at hepatic veins on axial CT
Vena cava vertical diameter on 1st Abd Ct	Widest diameter in mm of vena cava at hepatic veins on axial CT
Date/Time Video clip FAST ultrasound vena cava #1	Date/ time IVC 1 video
Video clip FAST ultrasound vena cava #1	video image file - AVI, WMV, MOV
Date/Time Video clip FAST ultrasound vena cava #2	Date/ time IVC 2 video
Video clip FAST ultrasound vena cava #2	video image file - AVI, WMV, MOV
Date/Time Video clip FAST ultrasound vena cava #3	Date/ time IVC 3 video
Video clip FAST ultrasound vena cava #3	video image file - AVI, WMV, MOV
ICU LOS	days
Ventilator Days	days
Hospital LOS	days
Crystalloid volume from admit to IVC video 1	ml
Crystalloid volume from IVC video 1 to IVC video 2	ml
Crystalloid volume from IVC video 2 to IVC video 3	ml
pRBCs volume from admit to IVC video 1	ml
pRBCs volume from IVC video 1 to IVC video 2	ml
pRBCs volume from IVC	ml

video 2 to IVC video 3		
Total packed red cells for admisssion or 30 days	units	
Plasma volume from admit to IVC video 1	ml	
Plasma volume from IVC video 1 to IVC video 2	ml	
Plasma volume from IVC video 2 to IVC video 3	ml	
Total plasma units for admission or 30 days	units	
Platelet volume from admit to IVC video 1	ml	
Platelet volume from IVC video 1 to IVC video 2	ml	
Platelet volume from IVC video 2 to IVC video 3	ml	
Total Platelets for admission or 30 days	units	
First Bladder Pressure	cm H2O	First bladder pressure, if recorded
Highest Bladder Pressure	cm H2O	Highest bladder pressure in first 24 hours, if recorded
Compartment syndrome during stay	Y/N	
Compartment syndrome during stay	If Yes to above then Date-time of diagnosis	
Compartment syndrome at admission	Yes/No	Request from MD
Laparotomy	Time/Date	For first procedure
Thoractomy	Time/Date	For first procedure
Craniotomy	Time/Date	For first procedure
Angiographic Embolization	Time/Date	For first angiographic intervention (not CT angio)
ARDS	Yes/No	Registry Definition
Renal Failure	Yes/No	Registry Definition
Abd compartment syndrome	Yes/No	Registry Definition
Abd fascia left open	Yes/No	Registry Definition
Intracranial pressure monitor	Yes/No	ICP monitor placed during stay
Other complications	Text	Registry Definition
Death	Yes/No	
Date/Time of Discharge/Death	Date/Time	
Discharge Disposition (if not dead)	Home, Rehab, SNF, Long term care facility, Hospice	
Comment	Text	