PROTOCOL TITLE: Clinical Assessment of Low Calcium In traUMa (CALCIUM)

SECTION A: RESEARCH TEAM AND LOCATIONS

A1. RESEARCH TEAM

Study Role	Institution/Company and Contact Information
Sponsor	*Organization/Institution/Company:* The Metis Foundation *Address:* 84 NE Loop 410, STE 325, San Antonio, TX 78216 *Point of Contact:* Noor Obaidi, MD *Name and Degree:* Noor Obaidi, MD *Title:* Vice President of Regulatory and Scientific Affairs *Phone Number:* 210-201-6001 *Email:* obaidi@metisfoundationusa.org
Principal Investigator	*Name, Rank, and Degree:* MAJ Steven G Schauer, DO, MSCR *Title:* Physician *Institution:* US Army Institute of Surgical Research *Address:* 3698 Chambers Pass, JBSA Fort Sam Houston, TX 78234 *Phone Number:* 210-771-0706 *Email:* steven.g.schauer.mil@mail.mil
Associate Investigator(s)	*Name, Rank, and Degree:* N/A *Title:* N/A *Institution/Company:* N/A *Address:* N/A *Phone Number:* N/A *Email:* N/A
Ombudsperson	*Name, Rank, and Degree:* N/A *Title:* N/A *Institution/Company:* N/A *Address:* N/A *Phone Number:* N/A *Email:* N/A

A2. ROLES AND RESPONSIBILITIES

A2.1 Principal Investigator

Name: Steven Schauer
Study Responsibilities: Responsible for the conduct of the study in accordance with the protocol. Maintenance of a list of appropriately qualified persons to whom significant study-related responsibilities have been delegated.

A2.2 Associate Investigator(s)

Name(s): N/A

Study Responsibilities: N/A

Name(s): N/A
Study Responsibilities: N/A

A2.3 Ombudsperson

Name(s): N/A
Study Responsibilities: N/A

A3. RESEARCH LOCATIONS

Data Coordinating Center (DCC): Vanderbilt University
POC: Alex Cheng, PhD
Office of Research Informatics, Department of Biomedical Informatics
Duties: The Data Coordinating Center (DCC) at Vanderbilt University provides data management, and data storage support.

***Performance Site**:* Brooke Army Medical Center
Performance Site Investigator: Steven Schauer, DO, MS

***Performance Site**:* University Hospital – University of Texas Health at San Antonio
Performance Site Investigator: Susannah Nicholson, MD

***Performance Site**:* University of Colorado – Denver
Performance Site Investigator: Franklin Wright, MD

A4. MULTISITE RESEARCH

***Lead Site**:* US Army Institute of Surgical Research
Lead Site Investigator: Steven Schauer, DO, MS
Single IRB: Headquarters, US Army Medical Research and Development Command
Function/Role of Lead Site: The USAISR will be the Lead Site with the above listed principal investigator as the overall project lead. The Lead Site is responsible for establishing and maintaining the master protocol in accordance with HQ USAMRDC IRB and USAMRDC Office of Research (ORP), Human Research Protection Office (HRPO). The Lead Site in collaboration with the sponsor (Metis Foundation) will be responsible for all HQ USAMRDC IRB and USAMRDC ORP, HRPO submissions. The Lead Site will be responsible for submitting all participating sites' HRPO submissions and maintain a record of all HRPO/IRB regulatory documents. Each site will submit all approval documents from their local regulatory office to the Lead Site and DCC for submission to the sIRB.

The Lead Site will then submit the site's protocol documents to the USAMRDC Office of Research Protections Human Research Protections Office (ORP HRPO) for the DOD-required headquarters level administrative review (HLAR). Any revisions resulting from the headquarters level review will be communicated directly from the ORP HRPO to the performance site Principal Investigator (PI), Lead Site, and the DCC. Upon completion of the HLAR, an approval memo from ORP HRPO will be sent to the site PI, Lead Site, and the DCC.

Any revisions to the master protocols or supporting documents that are requested by the local regulatory office must be reviewed and approved by the Lead Site before the site resubmits the protocols to its IRB along with the MRDC IRB. In the event that participating site IRBs require changes to the master protocols, the Lead Site will submit an amended master protocol and/or supporting document(s) to the HQ USAMRDC IRB for review and approval. Upon receipt of the HQ USAMRDC IRB amendment approval, the Lead Site will provide all approval documents for participating sites. The Lead Site will disseminate the HQ USAMRDC IRB approved documents to all participating sites for local regulatory office approval. All amendments made to the master protocols will be reported with the

Lead Site's continuing review to ORP HRPO by the Lead Site.

The DCC will be courtesy copied on electronic communications between the HQ USAMRDC IRB, ORP HRPO, and participating sites throughout the study duration.

No participating site will be able to gain DCC REDCap database access or start enrollment until all site-specific requirements (local regulatory office/HRPO approvals/protocol training/agreements). Sites will join as their documents are approved for participation. The start of each site will occur independently of the status of the other sites.

***Performance Site**:* Brooke Army Medical Center
Performance Site Investigator: Steven Schauer, DO, MS
IRB that will review for the Performance Site: Headquarters, US Army Medical Research and Development Command
Function/Role of Performance Site: Screen, enroll, data collection, and preparation of manuscripts.

***Performance Site**:* University Hospital – University of Texas Health at San Antonio
Performance Site Investigator: Susannah Nicholson, MD
IRB that will review for the Performance Site: Headquarters, US Army Medical Research and Development Command
Function/Role of Performance Site: Screen, enroll, data collection, and preparation of manuscripts.

***Performance Site**:* University of Colorado – Denver
Performance Site Investigator: Franklin Wright, MD
IRB that will review for the Performance Site: Headquarters, US Army Medical Research and Development Command
Function/Role of Performance Site: Screen, enroll, data collection, and preparation of manuscripts.

SECTION B: RESEARCH METHODOLOGY

B1. ABSTRACT

Major trauma frequently occurs in the deployed, combat setting and is especially applicable in the recent conflicts with explosives dominating the combat wounded. In future near-peer conflicts we will likely face even more profound weapons including mortars and artillery. As such, the number of severely wounded will likely increase. Hypocalcemia frequently occurs after blood transfusions secondary to the preservatives in the blood products, however, recent data suggests that major trauma in and of itself is a risk factor for hypocalcemia. Calcium is a major ion involved in heart contractility and thus hypocalcemia can lead to poor contractility. Smaller studies have linked hypocalcemia to worse outcomes, but it remains unclear what causes hypocalcemia and if intervening could potentially save lives. The objective of this study is to determine the incidence of hypocalcemia on hospital arrival and the association with survival. We are seeking to address the following scientific questions, (1) Is hypocalcemia present following traumatic injury prior to transfusion during resuscitation? (2) Does hypocalcemia influence the amount of blood products transfused? (3) To what extent is hypocalcemia further exacerbated by transfusion? (4) What is the relationship between hypocalcemia following traumatic injury and mortality? We will conduct a multicenter, prospective, observational study. We will gather ionized calcium levels at 0, 3, 6, 12, 18, and 24 hours as part of scheduled calcium measurements. This will ensure that we have accurate data to assess the early and late effects of hypocalcemia throughout the course of resuscitation and hemorrhage control. These data will be captured by a trained study team personnel at every site. Our findings will inform clinical practice guidelines and optimize the care delivered in the combat and civilian trauma setting.

B2. BACKGROUND AND SIGNIFICANCE

Hypocalcemia occurs frequently in critically ill patients including severely injured trauma patients.[1,2] Currently the Joint Trauma System guideline on Damage Control Resuscitation (Clinical practice guideline [CPG] ID:18, 12 July 2019), recommends, "Earlier calcium use recommended. One gram of calcium (30 ml of 10% calcium gluconate or 10 ml of 10% calcium chloride) IV/IO should be given to patients in hemorrhagic shock during or immediately after transfusion of the first unit of blood product and with ongoing resuscitation after every 4 units of blood products. Ideally, ionized calcium should be monitored, and calcium should be given for ionized calcium less than 1.2mmol/L." The reason for the administration of calcium after 4 units of blood has been attributed to the citrate compounds in the blood preservative that bind free calcium resulting in hypocalcemia.[3] The hypocalcemia leads to decreased heart contractility and overall hypoperfusion that can occur after massive hemorrhage.[4-6] However, new data suggests that our current paradigm with hypocalcemia in trauma maybe be inadequate. In a study by Conner et al. in Military Medicine, they prospectively collected data on casualties arriving to one forward surgical team in Afghanistan.[7] In their study, they assessed 101 patients, of which 55 (54.5%) experienced hypocalcemia on arrival to the FST with a mean ionized calcium (iCa) of 1.16 mmol/L (95% confidence interval [CI] 1.14 to 1.18) *prior to receiving any blood products*. They found that casualties injured by explosion conferred an increased risk of hypocalcemia compared to all other patterns of injury (odds ratio = 2.42, p = 0.042). Of the 101 assessed, 38 (37.6%) patients required blood product transfusion, of whom 33 (86.8%) of the patients requiring blood product transfusion were hypocalcemic on arrival. This suggests that the major trauma itself maybe a contributing factor to the hypocalcemia and it may not be attributable solely to the blood product administration. In other words, it maybe that blood product administration exacerbates a pre-existing or developing hypocalcemia.

There is currently limited clinical evidence assessing hypocalcemia in trauma patients and no outcome studies looking at the association of mortality and hypocalcemia or the association of calcium replacement with survival in trauma patients.[2] Giancarelli et al. studied the incidence of hypocalcemia during massive transfusion (MT) and found that out of 156 patients 97% experienced hypocalcemia and 71% experienced severe hypocalcemia; hypocalcemia was frequently associated with elevated lactate, other markers of coagulopathy, and *lower survival for those with severe hypocalcemia*.[8] We must note that in this study, hypocalcemia occurred during the MT which does not account for those that may have arrived already hypocalcemic.[8] Vivien et al. prospectively studied 212 patients that were given crystalloid or colloid in the prehospital setting finding that 74% became hypocalcemic after fluid infusion without blood suggesting that hemodilution itself may exacerbate this finding – before receiving blood products.[9] In a study of non-trauma, non-septic patients that were critically ill, out of 99 they found that up to 88% of them had hypocalcemia – this further suggests that critical illness in and of itself may cause hypocalcemia.[10] Webster et al. studied 55 trauma patients that were in the ED receiving blood – they found that 55% were hypocalcemic on arrival and 89% were hypocalcemia after blood product administration – however, no mortality effect was examined.[11] Ho et al., unlike in other studies, assessed mortality, finding a linear relationship between decreasing calcium and mortality among 352 patients – however, they only assessed the lowest documented value and did not trend the data over the initial 24 hours nor control for the supplementation given.[12]

We propose a study to track the ionized calcium level over 24 hours and adjusted outcomes based on supplementation provided. Magnotti et al. assessed the ionized calcium (iCa) in 591 patients finding that low calcium was associated with increased mortality, however, they assessed the iCa on admission and not based on prehospital arrival.[13] MacKay et al. assessed 77 patients noting no difference in mortality since their mortality rate was low, but they did note that hypocalcemic patients more frequently received supplementation and blood products.[14] While not assessing mortality, Cherry et al. found that hypocalcemia was associated with prehospital hypotension and a worse base deficit.[15] These findings hold the potential to change the paradigm that hypocalcemia in the setting of trauma is caused purely by transfusion during resuscitation to the concept that hypocalcemia in the trauma setting may have its origins from the injured state with exacerbation by transfusion. This parallels previously published findings that coagulopathy often exists *before* interventions are done because of the serious trauma itself.[16,17] Previously, it was proposed that coagulopathy was related to the infusion of large volumes of crystalloid – which is likely a contributing factor – however, more recent data suggests that coagulopathy is associated with traumatic injuries before dilutional effects occur.[18,19] Treatment of prehospital hypocalcemia may therefore represent an early intervention that could reduce morbidity and mortality following traumatic injury. Similar to the manner in which the exogenous and endogenous pathways impact coagulopathy, the same may be the case for hypocalcemia – our study proposes to test this hypothesis.

With the more widespread and accepted use of prehospital blood products, and the potential for prolonged casualty care scenarios, we need to further investigate this premise to determine the need for calcium supplementation closer to the point-of-injury.[20,21]

We are rapidly moving into operational planning for future conflicts in which we may not have ready access to surgical teams or locations with laboratory testing capabilities.[21,22] As such, the DoD needs to identify effective methods for early life-saving interventions, which are feasible for the prehospital combat setting. Calcium administration can be easily accomplished through an intraosseous or intravenous line.[23,24] Furthermore, ionized calcium levels may be assessed even in far-forward Role 2 environments without full laboratory capacity due to portable hand-held cartridges allowing iCa level testing. We are seeking to determine the incidence of hypocalcemia in the setting of trauma *before and during blood product administration*. If our hypothesis is supported, this potentially represents a target for a low-cost, easy-to-administer invention in the prehospital combat setting.[25] The findings of our study will potentially inform a future interventional clinical trial to study the association of early calcium replacement on survival in trauma patients.

B3. MILITARY RELEVANCE

In a recent study in Military Medicine, data was prospectively collected on casualties arriving to one forward surgical team in Afghanistan. In their study, they assessed 101 patients, of which 55 (54.5%) experienced hypocalcemia on arrival to the FST with a mean ionized calcium (iCa) of 1.16 mmol/L (95% confidence interval [CI] 1.14 to 1.18) *prior to* receiving any blood products. This study took place in Afghanistan during recent combat operations which demonstrates the significant relevance of hypocalcemia to the combat casualty care mission during the recent and ongoing conflicts in Afghanistan, Iraq, and Syria. Furthermore, these findings are likely to be more dramatic if we are to engage in a near-peer conflict in which we do not have continuous air superiority and will likely face far more dangerous weapons, such as mortar and artillery rounds. Our study will inform clinical practice guidelines that are promulgated by the Joint Trauma System to guide medical care throughout the combat theaters medical system.

B4. OBJECTIVES/SPECIFIC AIMS/RESEARCH QUESTIONS

We will determine the incidence of hypocalcemia on hospital arrival and the association with survival.

Aim 1: Overall incidence of hypocalcemia on ED arrival in major trauma patients
Aim 2: Association of hypocalcemia with severity of hemorrhage
Aim 3: Association of hypocalcemia with the number of blood products transfused and supplemental calcium administration
Aim 4: The association of hypocalcemia with early and 24-hour mortality.

B5. RESEARCH PLAN

B5.1 Research Design

We will conduct prospective, observational study.

B5.2 Research Subjects/Population(s)

B5.2.1 Subject Population(s)

All trauma patients that are admitted to the emergency department or trauma department using institutional trauma activation protocols.

B5.2.2 Number of Subjects, Records, and/or Specimens

We are seeking 391 patients with complete data that meet our a prior inclusion criteria. We are estimating that with drop out and missing data we will need 450 – 90 at BAMC, 180 at UTHSA, 180 at UCD. Since we will be

relying on trauma activation protocols at each site, the actual number with data capture will be higher. This is because our predefined inclusion criteria are more narrow than the general trauma activation protocols.

B5.2.3 Inclusion Criteria

For our primary outcome analysis, they must meet one or more of the below inclusions:

- Penetrating trauma to the head, neck, torso, or extremities (proximal to the elbow/knee)
- Traumatic arrest or CPR at any time
- Glasgow Coma Scale of 9 or less or deteriorating from initial arrival
- Systolic blood pressure <100mmHg
- Respiratory rate <10 or >29
- Intubated or requiring airway assistance (e.g. bag-valve mask, etc.)
- Any blood administered prehospital
- Vasopressors administered
- Pulseless, degloved, crushed, or mangled extremity proximal to the wrist
- Evidence of arterial bleeding with or without tourniquet application
- Amputations proximal to the wrist/ankle
- Chest needle decompression or chest thoracostomy

We will capture additional subjects that do not meet our primary inclusion analysis but may be used for secondary analyses (e.g. they had the calcium studies done, but do not meet the above listed criteria).

B5.2.4 Exclusion Criteria

We will exclude prisoners from our data analysis. While the blood draws may occur during routine clinical care, we will exclude them from any data analyses.

We will not exclude pediatric patients and pregnant women. The justification for this is that the study sites routinely provide trauma care to pregnant women and pediatric patients. As such, since we are relying on modification of standard order sets for clinical care that includes these blood draws. It would not be feasible to alter routine healthcare operations for this subset of patients. In other words, the laboratory studies will be performed regardless of whether we utilize their data. We could only exclude their data from our analysis after the fact. However, since these populations have unique physiology, data specific to these populations would greatly improve the science of trauma resuscitation within these populations. Know that we have data that could benefit these populations, exclusion of this data from analyses would be unethical.

B5.3 Research Procedures

1. Identification of Trauma Subjects
Trauma patients for enrollment in the study will be identified using site-specific trauma activation protocols in the emergency department or trauma department. The trauma activation criteria at Brooke Army Medical Center (BAMC) is provided as an example. Each site will have slight variations of this, which will be outlined in the site-specific documents. The decision to use trauma team activations will be solely at the discretion of the clinical team. All trauma patients coming in the emergency department that meet criteria for trauma activation will have routine laboratory tests done as part of the standardized order set. Of note, we will modify the existing order set to include the calcium studies as outlined in this protocol. In other words, the calcium studies will become the de facto new standard. We will enroll a continuous sample as part of routine trauma care operations via the modified order set. We will promote capture by way of staff education, staff reminders, staff-facing signage, and dissemination via routine department communications.
2. Obtaining Trauma Subject Blood Samples
All patients coming in as part of site-specific trauma activations have blood draws as part of routine clinical care. Blood draw happens as part of routine clinical care for all trauma activations. Specific to this study, we will collect samples at 0, 3, 6, 12, 18, and 24 hours after trauma center arrival. Laboratory studies are outlined in section B5.4 of the protocol. We will strive to have draws occur within +/- 1 hour of the goal times. However, given that the blood draws will be performed by way of the clinical team and the

unpredictable nature of trauma care, missed draws or draws out of the goal time frame will not be considered protocol deviations. We are estimating the total blood draw volume for the calcium studies will be <30mL with <10-15mL representing additional draws (2) beyond current clinical care standards. Only 1-2 calcium values are outside of the current clinical practices. The remainder of the draws are part of the routine clinical care.
3. Storage of the Blood Samples
The tubes of blood will be handled based on local standard operating procedures (SOP). No banking or repository of blood samples is planned for this study so all specimen storage and destruction will be based on the site laboratory SOPs.
4. Data Extraction
Data extraction will occur by local study site personnel through the electronic medical records systems and/or the local trauma registry. Of note, each site has a participating trauma registry established.
5. Data Aggregation
Data will be aggregated by a local study team member. The de-identified data will be transferred to the DCC using methods established in the site-specific documentation.

B5.4 Data Collection

Data/Element	Source	Operational Specific
Demographics	Electronic medical record system, prehospital documentation, local trauma registry	Age, sex, military status, height, weight, body mass index, mechanism of injury, admission diagnoses, discharge diagnoses, past medical history, past surgical history
Injury severity scores	Electronic medical record system, prehospital documentation, local trauma registry	Numeric
Timing of events	Electronic medical record system, prehospital documentation, local trauma registry	Date and time of injury, EMS arrival time, air transport arrival time, transferring center arrival time, trauma center arrival time, blood product infusions – type of infusion (whole blood, packed red blood cells, plasma, platelets), vital signs, labs, medications, procedures
Vital signs prehospital, first 24 hours of hospital stay	Electronic medical record system, prehospital documentation, local trauma registry	Heart rate, blood pressure, temperature, oxygen saturation, respiratory rate
Laboratory studies at (0,3,6,12,18,24	Electronic medical record system, prehospital documentation, local trauma registry	Electrolytes including magnesium, ionized calcium, serum calcium, hemoglobin, hematocrit, platelets, coagulation studies, metabolic studies, blood gas values, lactate, haptoglobin, thromboelastography, white blood cell count
Prehospital medications	Electronic medical record system, prehospital documentation, local trauma registry	Analgesics, sedatives, paralytics, vasopressors, calcium (in all medically administered forms), IV fluids, tranexamic acid, blood products

Hospital medications within the first 24 hours of admission including timing	Electronic medical record system, prehospital documentation, local trauma registry	Analgesics, sedatives, paralytics, vasopressors, calcium (in all medically administered forms), IV fluids, tranexamic acid, blood products
Major procedures within the first 24 hours of admission	Electronic medical record system, prehospital documentation, local trauma registry	Hemorrhage control interventions, chest needle decompression, chest tube, thoracotomy, intubation, REBOA, central line placement, interventional radiology procedures, exploratory laparotomy, irrigation and debridement, fracture stabilization, open vascular procedures, compressive hemorrhage procedures (e.g. liver packing, etc.)
Imaging studies within the first 24 hours	Electronic medical record system, prehospital documentation, local trauma registry	CT scans, x-ray studies, ultrasound studies
Blood products and fluids within the first 24 hours to include time of administration and volumes	Electronic medical record system, prehospital documentation, local trauma registry	Whole blood, packed red cells, plasma, platelets, cryoprecipitate
Outcome data	Electronic medical record system, prehospital documentation, local trauma registry	Discharge status, time to death (if applicable), ventilator days, intensive care unit days, hospital days, discharge location, total blood products and fluids received (first 24 hours), cardiac events (e.g. myocardial infarction, dysrhythmias, etc.); all truncated at 30 days if LOS exceeds

B5.5 Managing Data and/or Human Biological Specimens for this Research

All study data will be managed electronically. Subjects will be assigned a study identifier number by a study team member which will allow for easy removal of PHI after study completion. PHI (source documents) will be maintained at the participating sites for the purpose of data verification. De-identified data will be uploaded into the DCC REDCap with a goal of entry within 30 days of the subject hospitalization complete (truncated at 30 days if longer). The DCC utilizes the clinical research data management tool REDCap to manage clinical research studies. REDCap Data Management which is a full clinical research electronic data capture application, compliant with HIPAA and 21 CFR Part 11 regulations for data storage. Use of study data in publications, presentations, grant proposals, and other uses will require approval of the principal investigator in consultation with the site PIs. The overall de-identified data will be stored at the direction of the overall PI for data verification and/or related subanalyses indefinitely. Local site data will be stored based on institutional requirements and at the direction of the site PI. The local study keys linking the PHI to the data will be destroyed upon study closure. De-identified data may be shared with the sponsor at their request.

B5.6 Managing Data and/or Human Biological Specimens for <u>Future</u> Research

N/A – This section is not applicable as we will not be creating a data repository.

B5.7 Devices, Drugs, Dietary Supplements, Nutritional Supplements, And Biologics

B5.7.1 Devices

5.7.1.1 FDA-approved device being used in this research according to the approved labeling

N/A – This section is not applicable.

5.7.1.2 FDA-approved device being used in this research in a manner other than its approved labeling

N/A – This section is not applicable.

5.7.1.3 Any device not approved by the FDA

N/A – This section is not applicable.

B5.7.2 Drugs

B5.7.2.1 FDA-approved and used in accordance with the approved labeling

N/A – This section is not applicable.

B5.7.2.2 FDA-approved and used in a manner not in accordance with its approved labeling

N/A – This section is not applicable.

B5.7.2.3 Any drug not approved by the FDA

N/A – This section is not applicable.

B8 Statistical Analysis

B5.8.1 Sample Size Estimation

Based on prior estimates of hypocalcemia in trauma patients, the percentage of patients exposed can range between 50% to 55%.[7,11] Based on this estimate of exposure to hypocalcemia, with an alpha of 0.05, and power of 80%, we estimate a total sample size requirement of 391 trauma patients that would need to be enrolled in the study. Additional data captured as part of the routine healthcare operations that do not meet the above primary inclusion criteria will not count towards the sample size estimate of 391.

α (two-tailed) =	0.05	Threshold probability for rejecting the null hypothesis. Type I error rate.
β =	0.2	Probability of failing to reject the null hypothesis under the alternative hypothesis. Type II error rate.
q_1 =	0.5	Proportion of subjects that are in Group 1 (exposed)
q_0 =	0.5	Proportion of subjects that are in Group 0 (unexposed); 1-q_1
RH =	0.667	Relative hazard (Group 1/Group 0)

Calculate events

The standard normal deviate for α = Z_α = 1.9600
The standard normal deviate for β = Z_β = 0.8416
A = $(Z_\alpha+Z_\beta)^2$ = 7.8489
B = $(\log(RH))^2 q_0 q_1$ = 0.0410

Total events needed = A/B = **191**

q_1 =	0.5	
q_0 =	0.5	
RH =	0.667	
Total events =	191	
BER_0 =	0.35	Baseline Event Rate (events/unit time) for Group 0
ST_0 =	1.98	Median survival time in Group 0
CR =	0.3	Censoring rate - censored/unit time (assumed equal for both groups)
FU =	30	Planned average length of follow-up, in time units

Calculate group sizes

Sample size (with continuity correction)

	N	Events	Cumulative Event Rate
Group 1	196	86	0.438
Group 0	195	105	0.539
Total	391	191	0.488

B5.8.2 Data analysis

We will primarily use descriptive and inferential statistics along with regression modeling. Significance for results will be established when p-values are less than 0.05. Categorical Data will be summarized using percentages and Chi-Squared tests or Fisher's exact test where appropriate. Means and standard deviations or medians and interquartile ranges will be used as summary statistics for continuous variables, and they will be analyzed using Student's t-test and ANOVA or Wilcoxon's Test where appropriate. Data may be log-transformed for normalization. We will use Discrete-Time (eg. Complementary Log-Log) or Cox Proportional Hazards to assess associations between baseline and time-dependent covariates with time-to-hypocalcemia.

Treatment variables, such as blood product transfusion, will be measured at time-dependent covariates. Cox Proportional Hazards models will be used to assess associations between baseline covariates, time-dependent covariates (treatments and hypocalcemia), and mortality. We will analyze data using relevant statistical software including SAS (v9.4, Cary, North Carolina), JMP Statistical Discovery (v15, Cary, North Carolina), Microsoft Excel (v360, Redmond, Washington).

SECTION C: HUMAN RESEARCH PROTECTIONS

C1. RECRUITMENT AND CONSENT

C1.1 Identification and Selection of Subjects

Our study will result in minimal additional blood draw beyond the usual clinical blood draws. Subjects will be identified by the clinical staff based on the trauma activation protocols. Our primary outcome will be based on the "a priori" inclusion criteria as outlined above.

C1.2 Recruitment Process

All clinical care will remain at the direction of the attending clinician. All blood draws will occur by way of the clinical personnel.

C1.3 Eligibility

Eligibility will be determined by the clinical staff who make a decision on when a patient should be a trauma activation.

C1.4 Consent Process

We are seeking a waiver of consent as detailed below.

C1.4.1 Research involving subjects with cognitive impairment or who lack capacity to provide informed consent

N/A – This section is not applicable to our protocol. We are seeking a waiver of consent.

C1.4.2 Research involving non-English speaking subjects

N/A – This section is not applicable to our protocol. We will not be interacting with any patients that do not speak English.

C1.4.3 Research involving a waiver of the requirement to obtain informed consent OR alteration of the elements of informed consent

32 CFR 219.111(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section or waive the requirements to obtain informed consent provided the IRB finds four criteria are met as outlined below.

(1) The research involves no more than minimal risk to the subjects; and

Our research involves no more than minimal risk of the subjects. The research primarily involves 2 components. First, it involves obtaining a small amount of blood in an additional tube during their initial trauma evaluation and resuscitation. These are routine blood draws using standard clinical tubes and therefore considered no more than

minimal risk.(URL: https://www.nimh.nih.gov/funding/clinical-research/nimh-guidance-on-risk-based-monitoring.shtml, last accessed 20 March 2021) *As a point of reference, the current BAMC trauma admissions has blood draws occurring at least every 6 hours, and thus our protocol only represents a marginal increase the amount of blood drawn by <5mL total*. Other sites have protocols that generally mirror that of BAMC. Moreover, critically injured patients frequently have additional blood draws ordered beyond the current every 6 hours, and thus in the sickest of trauma patients they will almost certainly have blood draws that exceed what we are requesting as part of routine clinical care (e.g. serial lactate testing, serial coagulation studies, etc.).

Second, it involves accessing the medical records. We are seeking to perform observational data extraction from their medical records that were gathered as part of their routine healthcare operations. Extraction of the data from the medical records falls under exemption category #4 and therefore we believe it to be low risk.

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

The presence of our study will not alter their medical care in any anticipated way. The blood draws are already happening as part of their routine trauma evaluation and resuscitation. The additional tubes that we are drawing for this study are not expected to have any notable physiologic consequences given that critically injured trauma patients are subjected to blood draws every 6 hours and frequently after any major trauma for the first 24 hours post injury. All the medical care will be at the direction of the attending clinician without any involvement or interference by with the study staff. The request for a consent waiver will ensure that no delays in care occur due to the consent process.

(3) The research could not practicably be carried out without the waiver or alteration;

Trauma patients brought in by way of trauma activation are frequently critically injured and in need of immediate resuscitation. It would be impractical and unsafe to delay their medical care for the purposes of obtaining consent. Patients are not normally consented for blood draws as part of the trauma resuscitation process. Introducing a consent process as part of the study would hinder their medical care and potentially result in deleterious outcomes as a result of the delays in care. The use of a legally authorized representative would delay enrollment in the study in which the primary outcome is calcium measurement on arrival.

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

As previous stated, it is expected that many patients brought in as trauma patients may not survive. Of those that survive, many will not regain consciousness or the ability to participate in the consent process for a prolonged period. As such, it would be impractical to attempt to provide them information afterwards when they are still in critical condition. Additionally, by the time they can participate in the consent process their care will have been completed. Moreover, given that many of the blood draws represent routine clinical care, it would be inappropriate to attempt to consent them for routine clinical care that has already been delivered.

C1.4.4 Research involving a waiver of the requirement for investigator to obtain a signed consent form

Our research involves no more than minimal risk of the subjects. The research primarily involves 2 components. First, it involves obtaining a small amount of blood in additional tubes during their initial trauma evaluation and resuscitation. These are routine blood draws using standard clinical tubes and therefore considered no more than minimal risk.(URL: https://www.nimh.nih.gov/funding/clinical-research/nimh-guidance-on-risk-based-monitoring.shtml, last accessed 20 March 2021) Second, it involves accessing the medical records. We are seeking to perform observational data extraction from their medical records that were gathered as part of their routine healthcare operations. Extraction of the data from the medical records falls under 32 CFR 219 exemption category #4 and therefore we believe it to be low risk.

C1.4.5 Waivers of assent or parental permission when the research involves children

N/A – This section is not applicable.

C1.4.6 Research involving data collection for the USAMRDC Volunteer Registry Database

N/A – This section is not applicable.

C2. COMPENSATION FOR PARTICIPATION

Subjects will not be compensated.

C3. WITHDRAWAL FROM RESEARCH PARTICIPATION

We do not anticipate any subjects or withdrawal from the research participation given that the subject would likely not know about the additional blood draws since we are requesting both a waiver of consent and a HIPAA waiver. In the event a subject does request withdrawal for participation, we will not collect any additional clinical data from their medical records for this study. All data captured up until that point including their blood tests will be used for research.

C4. PRIVACY FOR SUBJECTS

We are not intending any direct interaction between study team members and subjects for the study. Clinical personnel may interact with the subjects only for routine healthcare and will not be for the purposes of this study. As we are requesting a HIPAA waiver and consent waiver, additional privacy for recruitment and such will not be required and standard measures for privacy will be maintained per usual methods for healthcare delivery. The data will be maintained and stored as outlined.

C5. CONFIDENTIALITY PROCEDURES FOR RESEARCH RECORDS, DATA, HUMAN BIOLOGICAL SPECIMENS

Data will be stored on computer systems that are approved by local site network administrators. We will collect only the minimal amount of data necessary for the conduct of the study. Data will be de-identified upon study closure. No identifiable data will be shared across the sites. Subjects will be assigned a study identifier number by a study team member which will allow for easy removal of PHI after study completion. PHI (source documents) will be maintained at the participating sites for the purpose of data verification. The DCC utilizes the clinical research data management tool REDCap to manage clinical research studies. REDCap Data Management which is a full clinical research electronic data capture application, compliant with HIPAA and 21 CFR Part 11 regulations for data storage. REDCap will serve as the primary method for sharing data across sites. Other methods will include the use of official email addresses and/or DOD SAFE. Local site data will be stored based on institutional requirements and at the direction of the site PI. The local study keys linking the PHI to the data will be destroyed upon study closure. De-identified data may be shared with the sponsor at their request. All data will be de-identified upon protocol closure. The overall de-identified data will be stored at the direction of the overall PI for data verification and/or related subanalyses indefinitely. Local datasets will be managed based on institutional policies.

C6. RISKS OF HARM, MEASURES TO REDUCE THE RISKS OF HARM, AND BENEFITS OF PARTICIPATION

C6.1 Risks of Harm

We do not anticipate any additional risks of harm associated with the study beyond that of routine clinical care and the potential risk for a data breech. The subjects of the study are already undergoing routine clinical blood draws, and we are seeking an additional tube of blood in very small amount that is unlikely to have any physiologic effect.(URL: https://www.nimh.nih.gov/funding/clinical-research/nimh-guidance-on-risk-based-monitoring.shtml, last accessed 20 March 2021) The primary risk comes in the form of data breech, which we will utilize confidentiality measures as outlined in this protocol.

C6.2 Incidental or Unexpected Findings

We do not anticipate any incidental or expected findings because of the study. We are seeking patients that are already having their blood drawn as part of routine clinical care. The only addition as part of the study is that we are drawing a small amount of blood beyond that of the usual amount drawn for routine clinical care. Blood draws are a part of routine clinical care. The data extracted from the medical records are all part of routine clinical care, and we are not getting any additional data beyond that of what is seen in the EMR system. As such, all the EMR data is available to the clinical team in real time.

C6.3 Potential Benefits

The study subjects will experience additional monitoring of their calcium as a result of the study. Moreover, their participation may optimize future clinical practice of trauma management of hemorrhage. Since trauma patients often experience future trauma (e.g. repeated visits for firearm wounds, interpersonal violence, etc.) it is plausible that they may benefit in the future from the science learned from this study.

C7. DATA AND SAFETY MONITORING

C7.1 Monitoring

Subject records may be inspected by the USAISR Quality Management and Research Regulatory Compliance Divisions, HQ USAMRDC IRB, the USAMRDC Army Human Research Protection Office and other applicable regulatory authorities responsible for human subject's protections and the integrity of the data.

C7.2 Research Monitor (as applicable)

N/A

C8. REPORTABLE EVENTS

C8.1 Expected adverse events

The only expected adverse events related to the study are related to that of the blood draw. Common adverse events include pain during the procedure which will be minor, minor bleeding at the site, or development of a hematoma. More significant risks include the possibility of a foreign body retained or infection. We do not anticipate these events would be common. Since the blood draws are occurring as part of the clinical care, the additional draws for the study is unlikely to alter that risk. Patients that are admitted to the hospital frequently have blood draws several times a day, and thus the risk associated with drawing a small amount of extra blood is negligible.

C8.2 Unexpected adverse events and unanticipated problems

We do not anticipate unexpected adverse events as blood draws are routine clinical events. Any adverse event that occurs as part of the blood draw is the same as that of routine clinical care. If an adverse event occurs specific to the research, the adverse event will be reported to the PI or a member of the study team. If the event is determined to be related to the research the PI will follow standard site-specific reporting procedures for reporting the event to the regulatory office. All unanticipated problems involving risk to subjects or others, and serious adverse events that are unexpected and determined to be at least possibly or definitely related to study participation, will be reported to the HQ USAMRDC IRB within five working days by phone (301-619-6240), or by e-mail (usarmy.detrick.medcom-usamrmc.other.irb-office@mail.mil)

C8.3 Adverse device effects

N/A – This section is not applicable.

C8.4 FDA-regulated research under IND and IDE

N/A – This section is not applicable.

SECTION D: REFERENCES

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SECTION E: ABBREVIATIONS AND ACRONYMS

BAMC = Brooke Army Medical Center
CDMRP = Congressionally Directed Medical Research Program
CPG = Clinical practice guideline
CPR = Cardiopulmonary resuscitation
CRADA = Cooperative research and development agreement
DSA = Data sharing agreement
EFIC = Exception from informed consent
iCa = ionized calcium
IO = Intraosseous
IV = Intravenous
JTS = Joint Trauma System
MT = Massive transfusion
TCCC = Tactical Combat Casualty Care
SOCOM = Special Operations Command
STaRC = Strategic Trauma Readiness Center of San Antonio

SECTION F: DoD PRIVACY RULE AND PROTECTED HEALTH INFORMATION (HIPAA)

NA – institution is not a covered entity

NA – will not use or disclose protected health information

HIPAA authorization will be obtained

X An application for waiver/alteration of HIPAA authorization will be submitted

APPENDIX – Sample trauma activation criteria from BAMC

SAN ANTONIO MILITARY MEDICAL CENTER
DEPARTMENT OF EMERGENCY MEDICINE
EMS BASE STATION RECORD V20

Report by: _____

C-Pod Staff: _____
For Priority ½ Medical, Heart Alert, Trauma Alert and Level I/II/III

Date ____/____/____ Time _____ EMS Unit _____ ETA _____
Alert Type: Trauma Heart Stroke Sepsis N/A
Age ____ Sex M F Complaint/Mechanism_____
Vitals BP_____ HR_____ SpO2_____% on _____ L NC RA NRB Intubated RR_____
GCS_____ Glucose_____ ECG/Monitor_____ if pregnant, #weeks or EDC/Due Date_____
Injuries/Findings_____
Interventions_____

M= Major Criteria
(any M criteria circled→MAJOR Activation)
Physiologic Criteria

M Traumatic arrest/CPR
M **Pediatric Trauma** patient in extremis **do NOT refuse/divert**
M Intubated
M RR <10 or >29
M Chest interventions prior to arrival (needle D, finger thoracostomy, chest tube)
M SBP <100
M HR greater than SBP (shock index >1)
M Pediatric ≤ 15yo with confirmed hypotension** (see box below)
M Transfusion prior to or upon arrival
M Vasopressors used with signs of trauma
M GCS ≤9 or worsening GCS with signs of trauma

Anatomic Criteria

M Suspected Flail Chest
M Suspected spinal injury WITH neuro deficits
M Unstable pelvic fx and/or pelvic binder use
M Pulseless, crushed, degloved, mangled, or amputated extremity proximal to ankle or wrist

Mechanism of Injury

M Penetrating injury to the head, neck, torso

R = Routine Criteria

Physiologic Criteria

R GCS 10-13 with signs of trauma

Anatomic Criteria

R ≥2 long bone fractures
R Stable pelvic fracture, no hypotension
R Pregnancy >20 weeks with blunt trauma
R Suspected spinal injury WITHOUT neuro deficits

Mechanism of Injury

R Isolated penetrating extremity injury
R Fall >3 ft with obvious injury/impairment
R Auto vs pedestrian
R >30mph MVC/MCC
R Ejection/Separation from any vehicle
R Thrown, kicked, trampled, or crushed by large animal
R Any MEDCOM transfer not meeting MAJOR (M) criteria (unless specified as internal trauma by Trauma Staff)

**Peds < 15 years of age
Existing Major/Routine Criteria apply
- SBP < 70 + (age x2) triggers Major
- Page PICU and Peds Surgery Staff for ALL Major Activations

I = Internal

Patients not otherwise meeting activation criteria:

I GCS ≥14 with Hx of trauma
I Falls <3 ft/from standing
I <30mph MVC/MCC
I Isolated burn without trauma
Page 513-BURN for all burns
I Isolated injuries to the EYE, FACE, EXTREMTIY
I MEDCOM transfers with trauma staff to ED staff discussion and approval prior to arrival

Heart Alert (STEMI)
Accept all patients

Activate code STEMI

Medical / Injury

All other categories

UPGRADE FROM ANY LEVEL ACTIVATION IS ACCEPTABLE AT ANY TIME BY THE ED/TRAUMA STAFF

Call MEDCOM 233-5815 for all trauma activations
May ask if military eligible if Priority 2/3 Medical only.
For Imminent baby delivery or Pregnant Trauma Patient ≥20 weeks gestational age:
Call 3-1111 and ask for activation of the OB-Neo Response Team!
Pregnant, significant co-morbid conditions, anticoagulation use, extremes of age (<5yo or >65yo) should be strongly considered for upgrade