Clinical trials identifier:	**NCT03128658**
Principal Investigator:	**SIMS, CARRIE**
Protocol Title:	**Trauma Induced Coagulopathy and Inflammation**
Date:	**August 2, 2018**
Protocol Description:	**This is a prospective observational trial designed to evaluate the factors that contribute to the development of trauma induced coagulopathy, post injury inflammation and the development of organ dysfunction in adult trauma patients. Demographic data, physiologic data, blood samples and clinical variables will be collected over the 5 days following traumatic injury.**

Protocol

Abstract
While a number of factors are known to be associated with the development of trauma induced coagulopathy (TIC), inflammation, and multi-organ failure, we currently cannot predict which patients are at risk for developing these life-threatening conditions with any certainty. In this prospective observational study, we will investigate the many factors that contribute to the development of trauma induced coagulopathy, post injury inflammation and the development of organ dysfunction in order to develop a multi scale computational algorhythm and ex vivo models capable of clinical prediction. Using a convenience sample technique, demographic data, physiologic data, fresh and residual blood samples, urine samples, and clinical variables will be collected over 5 days following traumatic injury. In addition to a computational model, ex vivo models using microfluidic devices and high resolution cellular respirometry, and nucleic acid analysis will be used to predict the development of TIC and multi-organ failure.

Objectives

Overall objectives
1) Develop a computational algorithm to predict the development of trauma induced coaguloapthy (TIC) 2) Validate ex-vivo microfluidic TIC models 3) Develop ex-vivo assays to predict the development of trauma-induced inflammation and the development of multi-organ failure

Primary outcome variable(s)
Coagulation parameters including thromboelastrography and mirocofluidic assessment on admission, 3 hours, 6 hours, 12 hours, 24 hours, 48 hours, and 5 days post admission.

Secondary outcome variable(s)
Respirometry of platelets, peripheral blood mononuclear cells, and neutrophils on admission, 3 hours, 6 hours, 12 hours, 24 hours, 48 hours, and 5 days post admission; Development of multiorgan failure within 30 days of admission; Level of free serum free nucleic acids; Expression of pro and anti- inflammatory proteins and genes and genetic variants in serum, platelets, and white blood cells.

Background
Traumatic injury results in 5-6 million deaths per year worldwide with $518 billion global cost with about half of trauma deaths due to acute blood loss. Acute blood loss and standard resuscitation with crystalloids and stored blood products causes hypothermia, acidosis, tissue hypoxia, hypotension, inflammation, the activation and consumption of coagulation factors including platelets, the release of free nucleic acids, the development of mitochondrial dysfunction and eventually organ failure. Importantly, about a quarter of trauma patients display a coagulopathy, (trauma induced coagulopathy, TIC) which greatly increases the risk of death and/or the development of multigrain failure. We currently, however, cannot predict who will develop TIC or its associated complications. In fact, two patients who have the same clinical presentation may have very different outcomes. Developing a multi scale computational model and ex-vivo point of care assays would allow us to efficiently identify and effectively treat at risk patients and potentially improve outcomes.

Study Design

Phase*
Not applicable

Design
Prospective, observational, convenience sampling of trauma patients 18 yrs old or older who present to the trauma bay will be included. Minimally injured patients will be compared to those with a systolic blood pressure of 90 mmHg or less, the need for blood product transfusion within 1 hour of admission, and/or an ISS of greater than or equal to 15. Demographic data including past medical/medication history as well as clinical data including continuous vital signs (when available) will be recorded. Blood samples (approximately 15 ml) and urine samples (approximately 10 ml) will be taken on admission, 3hr, 6hrs, 12hrs, 24 hrs, 48 hrs, and 5 days post admission. Residual blood samples (which would otherwise be discarded) will be obtained from the PPMC clinical laboratory on 0 and 2 days post admission. Blood samples may be analyzed for coagulation parameters included ex vivo microfluidic

assays, blood gas analysis, cellular respirometry, inflammatory mediators, free nucleic acids, DNA polymorphisms, and pro/anti-inflammatory protein and gene expression. Residual samples will be collected for protein biomarker measurements and DNA analyses. Urine samples will be analyzed for biomarkers of organ injury and dysfunction. When the patient is capable of consenting, or the patient's power of attorney is identified, they will be approached for consent and for continued participation. If consent is denied, all collected data/samples will be discarded and the subject will not be enrolled.

Study duration
We anticipate enrolling and completing this study within 3 years. Each subject's maximum participation will be 30 days. Blood and urine samples will be taken over 5 days and clinical data will be collected until the subject is discharged. Residual samples will be collected on day 0 and day 2. If patients are discharged from the hospital before 30 days, the study will end on the date of discharge. We anticipate starting this study February 1, 2017 and ending February 28, 2022.

Resources necessary for human research protection
Describe research staff and justify that the staff are adequate in number and qualifications to conduct the research. Describe how you will ensure that all staff assisting with the research are adequately informed about the protocol and their research related duties. Please allow adequate time for the researchers to conduct and complete the research. Please confirm that there are adequate facilities for the research.
In addition to the PI's (Sims and Diamond), this research will be conducted by the Penn Acute Research Collaboration (PARC) research coordinators and assistants. PARC provides 24 hour translational research services to the Penn Presbyterian community. All PARC research staff are CITI trained and will be familiar with the study protocol and execution prior to its initiation. The PI is a qualified trauma surgeon with clinical trial experience and training. The PARC research coordinators have clinical research experience and will directly oversee the training of research assistants in order to coordinate the study and ensure compliance. After each enrollment, the study coordinator will evaluate for study compliance. The entire research staff will conduct monthly meetings and the PI and research coordinator will meet at least every 2 weeks. All patients, including enrolled subjects, will be admitted to the trauma and surgical critical care service. They will be managed according to generally accepted medical standards for traumatic injury, which includes surgical interventions, damage control maneuvers, and sub-specialty consultation as needed and at the discretion of the treating trauma surgeon/surgical intensivist. Blood and urine samples will be processed and analyzed in the trauma at PPMC as well as at the PARC facility on 3 Mutch, PPMC. Blood and urine samples and case report forms will be stored at the PARC facility on 3 Mutch, PPMC.

Characteristics of the Study Population

Target population
trauma patients 18 years or older who present to the trauma bay

Subjects enrolled by Penn Researchers
300

Subjects enrolled by Collaborating Researchers
0

Accrual
This will be prospective observational study using convenience enrollment. Injured patients who present to the trauma bay will be evaluated by the on call trauma surgeon and as well as the PARC research assistant . If eligibility criteria are met, the research blood samples will be drawn at the same time as routine clinical samples. Depending on the research expertise available (e.g. microfluidic assessments or cellular respiration experiments), eligible patients may not have all the research variables investigated at each time point. Given that we will be recruiting a number of minimally injured patients, as well as injured patients with significant variability (eg severity of injury, age, gender, race, and past medical history), a large accrual number is required in order to develop a computational model that can accurately determine which factors predict the development of TIC, inflammation and

multiorgan failure.

Key inclusion criteria
In order to develop a robust predictive model, we will need to include a variety of injured patients ranging from minimally injured to severely injured. Inclusion criteria, therefore, will include any trauma alert activation. This highest level of activation is reserved for patients who meet either physiologic parameters (e.g. hypotension) or who have a mechanism of injury that would suggest significant injury (e.g. high speed motor vehicle crash). that being said roughly 30% of trauma alerts are not found to have significant injury. Only patient's whose age is equal to or greater than 18 years old will be included.

Key exclusion criteria
Transfer to trauma service of greater than 6 hours Known pregnancy - these patients are excluded because drawing multiple blood samples has an unknown risk to the fetus. Women of child bearing age, however, will be eligible. If they are found to be pregnant before enrollment, they will be excluded (eg. obvious gravid uterus, + fetus seen on trauma ultrasound, or + pregnancy test, which is routinely done on all female trauma patients) . If they are found to be pregnant after the initial blood draw, this sample will be processed, but no additional blood samples will be taken. The patient, or next of kin if appropriate, will be asked to consent for analysis of the processed sample and for continued clinical data collection.

Vulnerable Populations

Children Form

x **Pregnant women (if the study procedures may affect the condition of the pregnant woman or fetus) Form**

Fetuses and/or Neonates Form

Prisoners Form

Other

x ~~**None of the above populations are included in the research study**~~

The following documents are currently attached to this item:

There are no documents attached for this item.

Populations vulnerable to undue influence or coercion
Given the nature of trauma and the physiologic consequences associated with hemorrhagic shock, many of the eligible trauma patients in this study would be considered cognitively or decisionally impaired. Obtaining informed consent from the patient or their surrogate at the time of the initial blood draw may not be practicable in many circumstances. As such, we will be seeking delay in obtaining informed consent under these circumstances. HIPAA authorization and consent to continued participation will be obtained from the patient's next of kin or surrogate when available. If and when the subject becomes capable of consenting during their hospitalization, he/she will informed of the study including the risks and benefits and HIPAA authorization/consent will be obtained from the patient. If he/she declines, he/she will be de-enrolled. All data and blood samples will be purged. On occasion, enrolled patients may become arrested while in hospital. If consent for enrollment has been obtained prior to the arrest, the IRB will be consulted to determine if subjects can continue in the study. If the arrest (and not merely detainment or police presence) occurs prior to obtaining consent, the patient will be de-enrolled given the risk of undue influence or coercion. On occasion, people who work at or attend school at the University of Pennsylvania will be trauma victims and therefore eligible for enrollment. These patients and/or their next of kin will be consented as in private and data will be de-identified as previously described. Subjects will be informed in person and in the consent form that their standing with the University will not in any way be affected by their decision to participate.

Subject recruitment
Given the unexpected nature of trauma, subjects will not be recruited for this study a priori of their injury.

Will the recruitment plan propose to use any Penn media services (communications, marketing, etc.) for outreach via social media avenues (examples include: Facebook, Twitter, blogging, texting, etc.) or does the study team plan to directly use social media to recruit for the research?
No

The following documents are currently attached to this item:

There are no documents attached for this item.

Subject compensation*
Will subjects be financially compensated for their participation?
No

The following documents are currently attached to this item:

There are no documents attached for this item.

If there is subject compensation, provide the schedule for compensation per study visit or session and total amount for entire participation, either as text or separate document

Study Procedures

Suicidal Ideation and Behavior
Does this research qualify as a clinical investigation that will utilize a test article (ie- drug or biological) which may carry a potential for central nervous system (CNS) effect(s)?
No

Procedures
During the initial trauma evaluation, 15 ml of blood will be collected for research purposes during the routine trauma blood draw. Additionally, 10 ml of urine will be collected directly from a Foley catheter, or if a catheter is not in place as part of standard care, from a spontaneous void. Additional 15ml samples of blood and 10 ml samples of urine will be collected at 3 hours, 6 hours, 12 hours, 24 hours,
48 hours and 5 days post admission. Blood and urine sample collection in unstable patients will be deferred or delayed if it is determined by the clinical team that taking the sample would interfere with clinical care. Smaller blood and urine volume samples maybe taken at each time point (eg 10 ml rather than 15 ml of blood) if research expertise is not available for sample analysis (e.g microfluidic or high resolution respirometry) at that time point. Residual plasma and whole blood samples will be collected from the PPMC clinical laboratory on day 0 and day 2 from trauma bay admission. Blood samples will be analyzed for coagulation and microfluidic flow parameters, proteins involved in inflammation and coagulation, mitochondrial function and respiration of white blood cells and platelets, DNA sequencing of specific genes involved in organ failure, and gene expression of proteins of interest. Residual samples will be further studied for protein biomarker measurements and DNA analyses. Urine samples will be analyzed for biomarkers of organ injury and dysfunction. Vital signs, number of blood transfusions, volume of crystalloid, administration of medications, and the values of routine laboratories will be monitored continuously for 24 hours, and then cumulatively for up to 5 days. This data will be collected by reviewing the electronic medical record via EPIC. Discrete data will be recorded on case report forms and then entered into REDCap - an institutionally approved and managed secure network that is also password protected. Continuous data will be deidentified and maintained on REDCap. The development of multiorgan failure will be monitored for up to 30 days post enrollment. If patients are discharged or die prior to completing the 5 days of blood samples, additional samples and/or clinic appointments for the purpose of research will not be obtained. After the last blood draw, we will be following the patient's outcome until discharge. This data is routinely extracted as part of the Pennsylvania Trauma Outcomes Study - a state trauma center requirement - and will not require additional contact with the patient. We will not personally follow up patients if they are discharged prior to 30 days.

The following documents are currently attached to this item:

There are no documents attached for this item.

Deception
Does your project use deception?
No

Analysis Plan
Patients who develop coagulopathy, altered cellular respiration, or multi-organ failure will be compared using T-tests or Mann-Whitney tests for continuous variables and Chi-squared or Fischers exact tests for dichotomous variables. Spearmans rank correlation will be used to assess associations between continuous variables. Logistic regression analysis will be used to identify risk factors for the development of trauma induced coagulopathy or multiorgan failure.. Receiver operating characteristic curves will be used to assess accuracy of microfluidic measurements compared to standard measures of coagulation . Continuous deidentified data including vital signs, laboratory values, and medications will be shared with collaborators at Princeton University in order to create a mathematical model. The computational whole-patient systems model is a multiscale, multi-compartment model whose state-space is defined by a very large and heterogeneous set of variables as well as a large number of input parameters. It is straightforward to make direct contact with the clinical trauma blood profiles because the measured variables in these profiles are also included in the model state space. This comparison first will be used to establish the validity of the model. Here, the model will simply be integrated in time for various initial trauma conditions in an attempt to determine whether the model can be predictive. In particular, we will determine whether it is possible to reproduce the variation between the various time states at admission,3, 6, 12, 24, 48 hours and 5 days post admission. A more challenging data mining application is to discover new variables that are more predictive of clinical outcomes than those employed in current clinical protocols. The workhorse data mining technique we plan to explore, extend, and use to establish links between our multiscale model and clinical data is known as Diffusion Maps. This is a framework based upon diffusion processes for finding meaningful geometric descriptions of data sets, even when the underlying geometry of the data is complex, nonlinear and corrupted by noise. The method is based on the construction of a Markov transition probability matrix corresponding to a random walk on a graph whose vertices are the data points with transition probabilities being the local similarities between pairs of data points. The framework relates the spectral properties of Markov processes to their geometric counterparts and it unifies ideas arising in a variety of contexts such as nonlinear dimensionality reduction methods, machine learning, and harmonic analysis. The first few eigenvectors of the sparse Markov matrix are then used to generate a new set of intelligent coordinates that embody the intrinsic geometry of the data set. These are the diffusion map coordinates. Most importantly, these eigenvectors integrate the local similarities into a globally efficient low-dimensional representation of the complex geometric structure. The usage of eigenvectors of similarity matrices for dimensionality reduction is not new. In fact, the classical method of principal component analysis (PCA) computes principal components as eigenvectors of the covariance matrix of the data set and find a low dimensional representation of the data by projecting it onto the subspace spanned by the first few principal components that capture the most variability (or energy) of the data. Diffusion Maps is a successful generalization of PCA to complex nonlinear data sets whose structure is unknown in advance: unlike PCA, the diffusion map coordinates are nonlinear projections of the data; moreover, the nonlinear embedding is based only upon local similarities of neighboring data points. Diffusion Maps first will be used on the multiscale simulation data sets. This will establish macroscopic observables that define the trajectory of the overall patient-scale model. This is crucial because it is much simpler to establish a connection to patient outcome when only a few variables are being tracked (instead of the large variable space that defines the full multiscale model). However, these variables are generally not obviously connected to clinical variables and we will use the simulation data to establish relationships between the Diffusion Maps variables and actual measureable quantities. The result of this work will be to isolate variables that are highly predictive of patient outcome and allow assessment of different interventions.

The following documents are currently attached to this item:

There are no documents attached for this item.

Are you conducting research outside of the United States?
No

Data confidentiality

- x **Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.**
- x **Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.**
- x **Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.**
- x **Wherever feasible, identifiers will be removed from study-related information.**

A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.

A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)

Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.

Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.

Subject Confidentiality
Each patient will be assigned a study number. A protected REDCap database,an institutionally maintained and protected data network, will be used to link each patient to their assigned study number. Only the assigned study number will be directly connected to patient data and only Dr. Sims will have access to this link. The database linking each patient to their assigned study number will be destroyed five years after the conclusion of the study. The data collected will only be used for the proposed IRB study. Only de-identified patient data will be shared with Dr. Diamond and our Princeton collaborators using DataLocker, an encrypted portable data device. Samples (without patient identifiers) will be labeled with the study number. Samples will be stored in a locked laboratory facility on Mutch 3. Samples will be stored for 5 years and then will be destroyed. Laboratory reports, medication reports, and vital signs will be downloaded via EPIC. Each continuous file will be de-identified and labeled only with the study number, these will then be stored on a password protected REDCap database. This de- identified file will be given to Dr. Diamond and Dr. Sinno for mathematical modeling. Laboratory results, specific medications, fluid balance and vital signs will be recorded at specific time points on a case report form with only the study ID number and recorded into a secure, password protected REDCap database. Consent, patient data and case report forms will be collected and stored in a locked cabinet on Mutch 3. As mentioned data will be entered and stored using REDCap. Only Dr. Sims, Dr. Diamond and PARC research team will have access to the RedCAP file. Only Dr. Sims will have access to both the patients name and their research number. The PARC office and lab space on Mutch 3 are locked with front door security code. Computers and REDCap files are password protected.

Sensitive Research Information*
Does this research involve collection of sensitive information about the subjects that should be excluded from the electronic medical record?
No

Subject Privacy
Privacy refers to the person's desire to control access of others to themselves. Privacy concerns people, whereas confidentiality concerns data. Describe the strategies to protect privacy giving consideration to the following: The degree to which privacy can be expected in the proposed research and the safeguards that will be put into place to respect those boundaries. The methods used to identify and contact potential participants. The settings in which an individual will be interacting with an investigator. The privacy guidelines developed by relevant professions, professional associations and scholarly

disciplines (e.g., psychiatry, genetic counseling, oral history, anthropology, psychology).
Consent will only be obtained in a private setting (private family or consultation room, private ICU room, etc. Consent will only be obtained with the next of kin or patient. Additional family members/ friends will not be part of the discussion. Consents, patient notes, CRF's will be stored in a locked facility immediately accessible only to the research staff (PARC research space, Mutch 3). Each patient will be assigned a study number. A REDCap database will be used to link each patient to their assigned study number. Only the assigned study number will be directly connected to patient data and only Dr. Sims will have access to this link. The database linking each patient to their assigned study number will be destroyed at the conclusion of the study. Only de-identified and encrypted data will be shared with Dr. Diamond and our Princeton collaborators. Data will be entered and stored using a password- protected RedCAP file. Only Dr. Sims, Dr. Diamond and the PARC research team will have access to this RedCAP file.

Data Disclosure
Will the data be disclosed to anyone who is not listed under Personnel?
Data will disclosed to members of the research team, Office of Regulatory Affairs, Office of Human Research, the FDA and NIH as needed.

Data Protection*

- x **Name**
- **Street address, city, county, precinct, zip code, and equivalent geocodes**
- x **All elements of dates (except year) for dates directly related to an individual and all ages over 89**
- **Telephone and fax number**
- **Electronic mail addresses**
- **Social security numbers**
- x **Medical record numbers**
- **Health plan ID numbers**
- **Account numbers**
- **Certificate/license numbers**
- **Vehicle identifiers and serial numbers, including license plate numbers**
- **Device identifiers/serial numbers**
- **Web addresses (URLs)**
- **Internet IP addresses**
- **Biometric identifiers, incl. finger and voice prints**
- **Full face photographic images and any comparable images**
- **Any other unique identifying number, characteristic, or code**
- **None**

Does your research request both a waiver of HIPAA authorization for collection of patient information and involve providing Protected Health Information ("PHI") that is classified as a "limited data set" (city/town/state/zip code, dates except year, ages less than 90 or aggregate report for over 90) to a recipient outside of the University of Pennsylvania covered entity?
No

Tissue Specimens Obtained as Part of Research*
Are Tissue Specimens being obtained for research?
Yes

Tissue Specimens - Collected during regular care*
Will tissue specimens be collected during regulator clinical care (for treatment or diagnosis)?
Yes

Tissue Specimens - otherwise discarded*
Would specimens otherwise be discarded?
No

Tissue Specimens - publicly available*
Will tissue specimens be publicly available?
No

Tissue Specimens - Collected as part of research protocol*
Will tissue specimens be collected as part of the research protocol?
Yes

Tissue Specimens - Banking of blood, tissue etc. for future use*
Does research involve banking of blood, tissue, etc. for future use?
Yes

Genetic testing
If genetic testing is involved, describe the nature of the tests, including if the testing is predicative or exploratory in nature. If predictive, please describe plan for disclosing results to subjects and provision of genetic counseling. Describe how subject confidentiality will be protected Note: If no genetic testing is to be obtained, write: "Not applicable."
The concentration of free nucleic acids in the serum will be measured. We will measure the expression of pro- and anti-inflammatory genes by extracting RNA from white blood cell populations and platelets and creating a cDNA library for the gene expression of proteins of interest that will be studied. Further, the DNA sequences of these proteins will be analyzed to look for polymorphisms associated with organ failure. The results of these investigations will only be linked to the patient's study number and not their name.

Consent

1. Consent Process

Overview
Given the unpredictability and emergent nature of trauma, we will not be able to identify potentially eligible patients until they arrive to the trauma bay. All patients will have suffered an unexpected traumatic event, they will be in pain, and the trauma service will be assessing them rapidly in order to identify potentially life-threatening injuries. In the majority of these cases, the patients will be severely injured, hemodynamically unstable and unable to consent for themselves. Given the urgent and timesensitive nature of the proposed research, we will be seeking a delay in obtaining informed consent. Specifically, we will be requesting that the initial 15 ml of blood sample for research be collected at the same time that other blood samples for clinical care are drawn on admission to the trauma bay. Patients who have a Glasgow Coma Score of 15 and do not appear to be clinically intoxicated will be considered able to consent and approached after the initial trauma evaluation. In circumstances where the patient is unable to consent, we will approach the patient's next of kin or power of attorney after the trauma team has had the opportunity to update them regarding the patient's clinical condition. The next of kin will be informed that the initial blood sample has been drawn. After explaining the study, including its risks and benefits, we will ask for HIPAA authorization and consent. The next of kin will be able to withhold consent, in which case we will cease collecting data and samples. They may also consent to the initial blood draw and data collection, but decline further sample and data collection, or they may consent to full enrollment. When the patient is consentable, and after the trauma team has had the opportunity to inform the patient of his/her clinical situation, the research team will inform the patient of any blood draws that have occurred. At this time, the patient can consent to enrollment (and any further sample collection) or withhold consent (even if the next of kin had already authorized). If HIPAA authorization or consent is withheld, all data and samples will be destroyed. The discussion of the study as well as the consent will be conducted at the level of a 5th or 6th grade reading comprehension. Consent will only be obtained in a private setting with the patient and/or his/her next of kin. Additionally, in the event that the patient expires prior to consent, we will approach the family only after the clinicians have explained

to the family the clinical course and outcome. We will explain the purpose of the study and explain that samples were collected. We will then attempt to consent the family. If the family is in distress and cannot be consented prior to leaving the hospital, we will obtain the family's contact information. The PI will then contact the family member at least two weeks after the patients passing to discuss the study and attempt verbal consent in the presence of a witness. If the family member does not consent to the patient participating in the study, all samples and clinical data will then be destroyed. Theoretically, enrolled subjects could represent as a trauma alert again. If they are 30 days out from their initial enrollment, they would be eligible to participate again. However, this is very, very rare.

Children and Adolescents
We do not routinely treat children or adolescents at the Penn Presbyterian Trauma Center. Patients under the age of 18 will not be included in this study.

Adult Subjects Not Competent to Give Consent
see above

2. Waiver of Consent

Waiver or Alteration of Informed Consent*
Waiver or alteration of required elements of consent

Minimal Risk*
This research involves minimal risk. The initial blood sample (15 ml) will be drawn at the time other blood samples are taken for standard clinical care. As such, it does not require an additional venipuncture. In total, 7 blood samples (a max of 15 ml per sample) will be taken over the course of 5 days. When research expertise is not available for specific assays (e.g microfluidics or respirometry) this blood volume will be decreased to 10 ml. Additionally, collections of research samples will be deferred or delayed if the clinical team feels that collection would interfere with the clinical care of an unstable patient. Moreover, a volume of 15 ml X 7 times over 5 days is the maximum amount of blood that will be collected. Many of these patients will be bleeding and will require a number of blood transfusions because of their injuries. Each blood transfusion is 300 ml. We do not feel that a maximum of 105 ml of blood over 5 days will pose a higher risk to our patients. Residual blood collection (which would otherwise be discarded) involves obtaining samples from the clinical lab on day 0 and day 2 and does not confer risk above loss of confidentiality. Lastly, sample collection of 10 ml of urine totaling 70 ml over 5 days imposes only minimal risk to the patient as it is a prospective collection via noninvasive means. The urine specimen will be obtained at the time staff is performing a clinical draw and collected directly from a Foley catheter or, if a catheter is not in place as part of standard care, from a spontaneous void.

Impact on Subject Rights and Welfare*
This study will attempt to protect the patient's rights by (1) informing and consenting the patient or surrogate prior to the initial blood draw and urine collection whenever practicable (2) informing and obtaining consent for continued participation when a surrogate is identified and (3) informing and consenting the patient when he/she regains capacity to make an informed choice. If consent is not obtained, the subject will be un-enrolled and the data and biological samples will be discarded.

Waiver Essential to Research*
Trauma remains the leading cause of death for those under the age of 40 in the United States, with a large percentage of patients dying from hemorrhagic shock within the initial post-injury hours. Potential therapeutic interventions will have the most impact if we can identify which patients are at risk for developing trauma induced coagulopathy, exuberant inflammation, and multi-organ failure. In order to develop a robust model, data and biologic samples will need to be collected BEFORE interventions in order to determine which interventions either positively or negatively influence outcomes. Given the unpredictability and emergent nature of trauma, potentially eligible patients cannot be identified prior to their arrival to the trauma bay. Moreover, patients who are severely injured and/or hemodynamically unstable are unable to consent for themselves. Frequently, these patients are rapidly intubated, aggressively resuscitated with blood products and brought to the operating room or IR suite for hemorrhage control within minutes of initial arrival. In general, the resuscitative effort is well on the way by the time the patient's family is located - a process that typically takes hours to days.

Additional Information to Subjects
Contact information from the patient and/or the surrogate will be kept in a separate file that is not associated with any HIPPA or study data. Participants will have the option of receiving a copy of the study results or manuscript at the conclusion of the study either by email or standard post.

Written Statement of Research*
No

If no written statement will be provided, please provide justificiation

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit

Potential Study Risks
This study has minimal risk. Seven blood and urine samples with a maximum cumulative total volume of 105 ml and 70 ml, respectively, over 5 days is well tolerated. Every attempt to will be made to collect research samples during routine clinical phlebotomy or from existing lines. Blood samples will be collected only by nursing/medical/phlebotomy staff in order to minimize the minimal risk of pain and infection associated with routine phlebotomy.

Potential Study Benefits
There are no direct benefits to study participants. The benefit will be toward advancing our knowledge of how severely injured patients develop complications such as coagulopathy and organ failure. This study will hopefully help us develop better assays to identify and treat patients at risk.

Alternatives to Participation (optional)
None. If a subject chooses not to participate he/she will receive standard care.

Data and Safety Monitoring
After each enrollment, the PARC research coordinator will audit the case report form in order to ensure proper consent procedures were performed, that data collection and entry are accurate and that personal data is stored properly. Data analysis will be performed after every 50th subject enrolled.

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit Assessment
This study presents minimal risk to patients.