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14. ABSTRACT
The purpose of this project is to focus DoD high priority research in: vascular injury, pain, and airway management. These studies will extend evidenced-based pre-hospital interventions as well as populate the National Trauma Research Repository (NTRR). During the second year, IRB and HRPO approval for the ketamine pain study were secured. The vascular injury study (PROOVIT) continued to accrue participants and preliminary results were presented at the AAST conference. The trauma research repository and airway simulator projects proceeded on schedule. A request for proposals was issued for a vendor to build and host the research repository was issued and a vendor was selected. There are no major finding/results at this time.

15. SUBJECT TERMS Vascular injury, airway management, pain management, Ketamine, National Trauma Research Repository

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INTRODUCTION:

Advances in trauma care in both pre-hospital and hospital settings have reduced trauma-related deaths and morbidities markedly; however, there is a substantial opportunity to further reduce deaths in the pre-hospital setting. Gaps in civilian and military pre-hospital care must be closed to reduce the number of potentially preventable deaths among wounded warriors and civilian trauma patients. The purpose of this project is to focus on three specific areas of research identified high priority by the DoD: better solutions for vascular injuries, improved pain management, and better approaches for airway management. These studies will extend evidenced-based hospital interventions as well as populate the National Trauma Research Repository (NTRR) that will allow for data sharing, secondary analysis and greater power to detect statistical significance. As available research funding shrinks and federal budget pressure increases, it is essential that the return from dollars invested in research be maximized by replacing the expensive and repetitive assembly and disassembly of short-lived clinical investigator networks with a stable and enduring operational infrastructure for clinical trauma research.

KEYWORDS:

Vascular injury, airway management, pain management, Ketamine, National Trauma Research Repository, research dissemination

ACCOMPLISHMENTS:

Major Objectives of the Project:

Objective: To conduct research projects addressing military research gaps in pain management, vascular injury, and airway management; and to develop tools to allow for the collection and dissemination of results and data from studies

Technical Objective 1: To conduct research projects addressing military research gaps in pain management, vascular injury and airway management**;** the contractor (NTI) will perform award management and compliance to include subcontracts, contract compliance, and all appropriate USAMRMC HRPO requirements.

Technical Objective 2: To develop tools to allow for the collection and dissemination of results and data from studies, including:

1) Develop a scalable repository of translational research data.
   a) Determination of common data element based on previously NTI funded project and other database sources.
   b) Creation of the data dictionary
   c) Development of policies for utilization guidance which includes repository requirement documents and website development.
   d) Conduct vendor solicitation and vendor selection process based upon requirements and capabilities identified.
   e) Build a scalable repository
   f) Alpha and beta testing with previous NTI funded studies and studies funded through this grant.

2) Provide a forum for the dissemination of research outcomes to the trauma community.

Accomplishments under these Goals:

Major activities of this grant are organized and reported under the major Technical Objectives 1 and 2.

Technical Objective 1: To conduct research projects addressing military research gaps in pain management, vascular injury, and airway management, the contractor (NTI) will perform award management and compliance to include subcontracts, contract compliance, and all appropriate USAMRMC HRPO requirements.

STUDY 1:

Protocol Title: Determining the Efficacy and Safety of Ketamine as a Battlefield Analgesic
Principal Investigator: John Fauerbach, PhD
Participating Site: Johns Hopkins University School of Medicine
HRPO Assigned A-number: A-19299.2
Abstract: Background: Early, effective pain control for acute traumatic injury is important for successful outcomes. Despite the known importance of pre-hospital pain management, few studies have reported the use of analgesics and the type of analgesics used in combat. Ketamine has emerged recently as a potentially effective analgesic alternative to narcotics for use in combat-associated casualties. While early case reports attest to its effectiveness, these reports are anecdotal. Ketamine is the only single-agent anesthetic capable of producing a "dissociative" anesthesia, which has been useful for a variety of outpatient and inpatient surgical procedures. More than 50,000 service members have been injured in OIF, OEF, and OND and experience varying degrees of pain throughout their care. Of these injured service members, 31.8% are also diagnosed with PTSD.
Hypothesis: The addition of ketamine to narcotic analgesics will reduce significantly self-rated pain during dressing change/debridement on the Visual Analogue Scale for Pain (VAS-Pain):
Methods: Persons enrolled in the study through the informed consent process will be patients admitted to the Johns Hopkins Burn Center after sustaining burns less than 25% total burn surface area and not requiring initial endotracheal intubation. This would enable them to participate in structured interviews conducted by a psychologist assigned to the Burn Unit. These interviews would evaluate:

- The effectiveness of sub-anesthetic doses of ketamine as a sole analgesic vs. as a narcotic sparing drug for the treatment of acute post-traumatic pain
- The side effect profile of ketamine when administered in sub-anesthetic doses
- Whether the early administration of ketamine during the first three days following injury has a sustained effect on reducing the incidence or severity of Acute Stress Disorder/Post-Traumatic Stress Disorder (PTSD)
- Whether the early administration of ketamine during the first three days following injury has a sustained effect on reducing the incidence or severity of clinical depression

Once IRB and HRPO approval is secured, patients will be randomized to a trial comparing a usual pain regimen, typically narcotics and benzodiazepines (UR-N) against a low dose ketamine regimen supplemented with usual pain medications (K+UR) on the effect of self-reported pain severity at the start of the procedure, every 5 minutes during the procedure and 5 minutes after the procedure ending, as well as the incidence and severity of PTSD and Depression at 24 hours, one week, and one month.

Military Significance: The DOD has identified capability gaps in combat casualty care. Several of the high priority gaps are well-suited for research in the civilian setting including en route care. A specific gap in these capabilities that the DoD has identified as high risk to the military and amenable to study in the civilian setting is: Ability to provide 100% acute and chronic pain management for wounded and injured soldiers, starting at the point of injury and continuing across the spectrum of care.

Progress Reported:

Year 1

Refinement of eligibility criteria and exclusion criteria as well as drafting of the screening protocol, enrollment protocol and final consent form was accomplished as stated in the Scope of Work.

The human subjects documentation (study protocol, consent form, etc.) was submitted to the local IRB and was pending approval by the High Risk Review Committee. That committee requested minor clarification regarding the role of nurses on the protocol. This study sought authorization to screen 300 for 100 completers. The PI, Dr. Fauerbach, worked with the John Hopkins Bayview Medical Center pharmacy to finalize drug handling procedures such as clarify procedures for sub-anesthetic, low-dose, slow infusion of ketamine for pain management during wound care sessions. The participant recruitment folder was completed and the protocol Manual of Operations was in final stages of preparation. Study clinical report forms are in the final stage of completion. The Study 1 team presented a poster depicting the protocol for the "Ketamine for Acute Burn Pain" project at a local Behavioral Pharmacology Research Unit conference.

Study 1: Participant Accrual in Year 1

Site	Recruited	Screened	Enrolled	Completed
Johns Hopkins University	0	0	0	0

Number of subjects recruited/original planned target: **0/300**
Number of subjects screened/original planned target: **0/300**
Number of patients enrolled/original planned target: **0/100**
Number of patients completed/original planned target: **0/100**

Year 2

The original period of performance for this project was from January 1, 2016 through December 31, 2016. Due to delays in study initiation, PI requested and was granted a no cost extension on the sub-contract to Johns Hopkins (the clinical site). The period of performance was extended to June 30, 2018. The study team worked with the hospital pharmacy to update the hospital's ketamine administration policy (to modify processes for sub-anesthetic dose administration). HRPO approval was received in June 2017. A study amendment was approved by the IRB on 9/28/17 and was submitted to HRPO on 10/18/2017. Dr. Fauerbach presented study progress to the NTI board of directors on September 30, 2017 (see appendices). The NTI board concluded that monthly monitoring was necessary to ensure that the study is completed during the remaining period of performance. Once approved, the study will begin to enroll patients (screening 300 patients for 100 completers).

Study 1: Participant Accrual in Year 2

Site	Recruited	Screened	Enrolled	Completed
Johns Hopkins University	0	0	0	0

Number of subjects recruited/original planned target: **0/300**
Number of subjects screened/original planned target: **0/300**
Number of patients enrolled/original planned target: **0/100**
Number of patients completed/original planned target: **0/100**

STUDY 2

Protocol Title: The PROspective Observational Vascular Injury Trial (PROOVIT)
Principal Investigator: Joseph DuBose, MD (Travis Air Force Base)
Lead Site: University of California at Davis
Participating Sites: Baylor College of Medicine/Ben Taub Hospital, Emory University, Loma Linda Medical Center, University of Southern California, Scripps Health, University of Maryland/R. Adams Cowley Shock Trauma, University of Tennessee – Memphis, University of Texas Health Science Center at Houston, University of Wisconsin School of Medicine and Public Health, Wright State University, East Carolina University
HRPO Assigned A-number: A-19299.1a-1m

Abstract: Background: Few, if any, decisions throughout the phases of vascular trauma management are guided by strong evidence. This fact is unfortunate, as many new diagnostic, therapeutic and surveillance strategies have the potential to improve morbidity and mortality following this vexing injury pattern. The lack of evidence-based practice is even more concerning given the devastating consequences associated with mismanaged vascular trauma. To date, no studies exist that allow for the prospective aggregation of larger amounts of data pertaining to all phases of vascular trauma management.
Hypothesis: This prospective, multi-center, observational study will provide the necessary data to develop best practices and optimize the care of this unique population of patients.
Specific Aims: 1. To determine the impact of tourniquet utilization after extremity vascular injury on limb-specific complications and limb salvage; 2. To determine the optimal utilization of endovascular versus open repair modalities after vascular injury; 3. To determine the role of early anticoagulation in mitigating complications after vascular injury repair.
Study Design: This study is a prospective multi-center observational trial on the management of vascular trauma. Data and endpoints will be observational and involve no proscribed therapeutic interventions or alterations in patient care. Waiver of informed consent has been received. Institutions and providers are conducting normal diagnosis, management and surveillance procedures without interference by this study. The location and type of endovascular therapy for vascular trauma is tracked including comparison of outcomes to those following open operative repair of similar injury patterns. Finally, data elements are gathered in a wide range of age groups with vascular trauma including the challenging scenarios of pediatric and geriatric vascular injury.
Military Benefit: Hemorrhage from vascular injury, at both Non-Compressible Vascular Injury (NCVI) and Compressible Vascular Injury (CVI) sites, remains a primary cause of mortality and morbidity on modern battlefields. This study will provide linkage to crucial elements of subsequent limb salvage and long-term outcomes – data that are presently not available on any significant scale in the military realm.

Progress Reported:

Year 1

In the first year of this project, the PROOVIT study was adapted to meet DoD funding requirements. All sub-awards were executed. All sites had IRB approval. All clinical sites received HRPO approval and were screening and enrolling. (UTHSCSA is providing statistical analysis only.) PROOVIT enrolled 573 participants in Year 1. Preliminary data analyses were conducted and results were presented to the American Association for the Surgery of Trauma (AAST) 2016 annual meeting (see Products).

Study 2: Participant Accrual in Year 1

Site	Recruited	Screened	Enrolled	Completed
Baylor	85	85	85	14
Emory	50	50	30	20
HSC-Tennessee	121	121	40	40
Loma Linda	157	157	90	90
Scripps	55	55	6	0
UC Davis	32	32	22	10
University of MD	4,055	4,055	84	16
USC	21	21	21	0
UT Houston	194	194	87	0
Wisconsin	0	0	0	0
Wright State	141	141	108	108
Total	**4,911**	**4,911**	**573**	**298**

Note: The new format breaking down the information by quarter is not available.

Year 2

In Year 2, East Carolina University was added as a clinical site. The sub-contract was issued and HRPO approval was received. Subjects were actively enrolled at 12 clinical sites. Interim data analyses were conducted and abstracts were submitted/presented to the American Association for the Surgery of Trauma (AAST) 2017 annual meeting (see Appendices). Dr. Dubose presented study progress to the NTI board of directors on September 30, 2017 (see Appendices). The NTI board had no concerns regarding study progress.

Study 2: Participant Accrual in Year 2 Quarter 1

Site	Recruited	Screened	Enrolled	Completed
Baylor	17	17	17	
East Carolina U	0	0	0	
Emory	30	30	24	
HSC-Tennessee	163	163	99	99
Loma Linda	43	43	14	
Scripps	0	0	0	
UC Davis	12	12	5	
University of MD	23	23	12	
USC	45	45	26	
UT Houston	36	36	53	
Wisconsin	25	25	6	
Wright State	19	19	13	
Total	**413**	**413**	**269**	**99**

Note: The only site to have reported completed in Year 2 Quarter 1 was Tennessee.

Study 2: Participant Accrual in Year 2 Quarter 2

Site	Recruited	Screened	Enrolled	Completed
Baylor	15	15	15	12
East Carolina U	0	0	0	0
Emory	14	14	12	12
HSC-Tennessee	24	24	24	24
Loma Linda	32	32	18	0
Scripps	0	0	0	0
UC Davis	7	7	3	0
University of MD	7680	7680	33	0
USC	16	16	16	0
UT Houston	35	35	35	19
Wisconsin	100	100	7	7
Wright State	4	4	6	0
Total	7927	7927	169	74

Study 2: Participant Accrual in Year 2 Quarter 3

Site	Recruited	Screened	Enrolled	Completed
Baylor	11	11	11	9
East Carolina U	0	0	0	0
Emory	0	0	0	12
HSC-Tennessee	40	40	40	40
Loma Linda	50	50	17	0
Scripps	20	20	6	0
UC Davis	10	10	10	5
University of MD	1531	1531	27	0
USC	53	53	53	0
UT Houston	31	31	31	51
Wisconsin	275	275	7	7
Wright State	36	36	9	13
Total	**2,057**	**2,057**	**211**	**137**

Study 2: Participant Accrual in Year 2 Quarter 4

Site	Recruited	Screened	Enrolled	Completed
Baylor	10	10	10	10
East Carolina U	18	18	18	16
Emory	38	38	34	6
HSC-Tennessee	39	39	13	0
Loma Linda	20	20	2	0
Scripps	31	31	31	31
UC Davis	8	8	8	14
University of MD	1547	1547	58	0
USC	29	29	29	37
UT Houston	35	35	35	26
Wisconsin	300	300	10	10
Wright State	18	18	6	9
Total	**2,093**	**2,093**	**254**	**159**

Study 2: Participant Accrual - Cumulative Year 2

Site	Recruited	Screened	Enrolled	Completed
Baylor	53	53	53	31
East Carolina U	18	18	18	16
Emory	82	82	70	30
HSC-Tennessee	258	258	194	194
Loma Linda	164	164	62	0
Scripps	40	40	8	0
UC Davis	37	37	26	19
University of MD	10781	10781	130	0
USC	143	143	124	37
UT Houston	137	137	154	96
Wisconsin	700	700	30	24
Wright State	65	77	34	22
Total	**12,490**	**12,490**	**903**	**469**

Study 2: Participant Accrual - Cumulative Years 1 and 2

Site	Recruited	Screened	Enrolled	Completed
Baylor	138	138	138	45
East Carolina U	68	68	48	36
Emory	203	203	110	70
HSC-Tennessee	415	415	284	284
Loma Linda	219	219	68	0
Scripps	72	72	30	10
UC Davis	4092	4092	110	35
University of MD	10802	10802	151	0
USC	337	337	211	37
UT Houston	137	137	154	96
Wisconsin	841	841	138	132
Wright State	77	77	34	22
Total	**17,401**	**17,401**	**1,476**	**767**

Number of subjects recruited/original planned target: **17,401/5,000**
Number of subjects screened/original planned target: **17,401/5,000**
Number of patients enrolled/original planned target: **1,476/5,000**
Number of patients completed/original planned target: **767/5,000**

PROJECT 1

Project Title: High Anatomic Fidelity Surgical Airway Training System
Principal Investigator: Robert Buckman, MD
Lead Site: Operative Experience, Inc.
HRPO Assigned A-number: Not applicable
Abstract: Background: Airway obstruction is the third most common cause of potentially preventable combat death. Because of this, surgical management of the threatened or obstructed airway is an essential skill for special operations medics and combat surgeons. Cricothyroidostomy and tracheostomy are infrequently performed, life-saving surgical procedures required when a casualty's airway cannot be maintained by other means. Surgical airway management procedures may be required at any level along the continuum of care/evacuation. Published data from recent theaters of war indicate that these emergency procedures are often performed incorrectly. Due to the limitations of existing methods of training, surgical airway management procedures are not currently taught to all combat medics. Improved, simulation-based methods of training will not only improve the training and enhance the capability of special operations forces (SOF) medics and surgeons, but also will allow additional military healthcare providers and combat lifesavers to be trained in this critical skill. The Defense Health Board recommended optimized airway devices and training as a research priority for the Combat Casualty Care Research Program, contributing to the identification of a Combat Casualty Care Capability Gap.
Methods: Develop a prototype surgical airway simulator that provides high anatomical and surgical fidelity and challenges trainees with increasing degrees of clinical difficulty. This project will develop an airway simulator that is capable of accurate anatomic representation of the airway from the mouth to the lungs, simulates a variety of traumatic tissue disruption with the face and neck, bleeds realistically, and supports training in tracheostomy and cricothyroidotomy. Development includes anatomic design, engineering design, medical modeling, physical modeling, engineering and system integration.

Progress Reported:

Year 1

The sub-award was fully executed on 05/12/2016. The PI and Operative Experiences, Inc. (OEI) developed the model base and integrated electro-mechanical systems of the simulators. Programmable logic controllers (PLC) were developed, but not yet been fully integrated. OEI substituted a microcontroller to support more hardware at lower cost.

Year 2

In Year 2, OEI continued development of a table-top simulator that can be integrated into a full-sized manikin. This involved adaptation of the head and neck model to the thorax of an existing OEI prototype Tactical Combat Casualty Care (TC3) manikin. Completed activities included:

1) Integrated the major vascular structures of the neck, including the carotid arteries and internal jugular veins
2) Designed methods to enhance the elasticity of the facial skin and mucosa
3) Finalized the design for the principal module of the simulator, which will extend from the in for orbital region of the face to the thoracic inlet. This module will be exchangeable and is being engineered to incorporate submodules simulating a variety of combat-relevant wounding patterns, including those that directly injure the airway and others that cause deformation or deviation of the airway by tissue injury or hematomas.
4) Developed a method for creating multi-laminar models of the soft tissue structures of the face and neck which will incorporate potential spaces for fluid. This capability will permit the reversible deformation of head and neck soft tissue structures to simulate the effects of hematomas and/or edema. It will also allow the deviation of the airway by surrounding soft tissue injuries to be simulated.
5) Designed asymmetric submodules that can be exchanged within the modular face and neck structures to simulate varying combat-relevant wound patterns that are exchangeable
6) Re-sculpted the facial features of the simulator and deconstructed the revised sculpture of the superficial and deep anatomy to incorporate the maxilla and mandible
7) Invented a mechanism to create separate mucosal planes over a simulated cartilage laryngotracheal skeleton. This mechanism permits the incorporation of potential submucosal spaces, which can be reversibly and controllably infused with fluids to simulate intrinsic airway edema. The mechanism is similar to the recently-engineered method for creating simulated potential spaces in the soft tissues of the muscular and fascial layers of the face and neck

Dr. Buckman, principal investigator at Operative Experiences, Inc (OEI) presented project progress via videoconference to Dr. Jenkins and NTI staff on May 19, 2017. There were no concerns regarding project progress.

In response to the Year 2 Quarter 3 technical report, Florence D'Orazi, Ph.D., the study's Science Officer, requested information on the plans for intellectual property and commercialization. The following images are excerpts from the Research Subcontract between the National Trauma Institute and Operative Experience, Inc. of the clauses governing intellectual property and patents and invention reporting requirements.

Research Subcontract

No. NTI-NTRR15-14-OEI ("Subcontract")
Under DOD/Army Medical Research Acquisition Activity ("Prime Sponsor") Prime Contract No. W81XWH-15-2-0089 ("Prime Contract")

This Subcontract is entered into between the Prime Contractor and Subcontractor named below for the performance of a portion of the Scope of Work originally awarded to the Prime Contractor. The parties agree to the following terms and conditions:

Prime Contractor ("Contractor") Name: National Trauma Institute Address: 9901 IH 10 West, Suite 720 DUNS: 800219185	**Subcontractor** ("Subcontractor") Name: Operative Experience, Inc. Address: 500 Principio Parkway West, Suite 900 North East, MD 21901 DUNS: 827977435
Prime Contractor PI Name: Donald Jenkins, MD	Subcontractor PI Name:

5. Intellectual Property. The determination of rights in ownership and disposition of inventions resulting from the performance of the Statement of Work ("Subject Inventions") and the administration of patents will be in accordance with 37 CFR 401 and the terms of this Subcontract. Subcontractor agrees to comply with regulations regarding inventions pursuant to 37 CFR Part 401. Disposition of any copyrights or any copyrightable material created by Subcontractor in performance of the Statement of Work will be determined by the policy of the Subcontractor. Any copyrighted materials are subject to a royalty-free non-exclusive and irrevocable license to the Contractor and U.S. Government to reproduce, publish or otherwise use the copyrighted material for noncommercial purposes and to authorize others to do so for federal purposes. Subcontractor shall own the data it generates under this Subcontract. Subcontractor hereby grants to Contractor the right to receive copies of such data and to use data created as provided in the Statement of Work for the purpose of education and research or to the extent required to meet Contractor's obligations under its Prime Contract. Subcontractor acknowledges the rights of the U.S. Government to use such data. Notwithstanding the foregoing, Subcontractor shall retain ownership of any and all intellectual property rights owned by or licensed to Subcontractor in existence as of the date of this Agreement or developed independently of this Subcontract, and Subcontractor shall own all inventions, innovations, new uses, processes, copyrights, trade secrets, techniques and discoveries developed or conceived by Subcontractor in connection with the performance of its obligations in this Subcontract, including all methods and procedures, and all related technology, information, techniques, instruments, methods, procedures and materials, and all intellectual property rights relating to arising from the foregoing, regardless of whether Contractor or any other party, person or entity, or their personnel, participated in or were otherwise involved in the development of such intellectual property.

6. Patents and Inventions Reporting Requirements.

- iEdison and annual reporting. The subcontractor shall electronically file Invention Disclosures and Patent Applications using the Interagecy Edison (iEdison) system through the National Instiututes of Health (https://s-edison.info.nigh.gov/iEdison) within the times specified for reporting. In addition, inventions made during the year shall also be reported annually (within 30 days of the anniversary date of the award) on a DD Form 882, "Report of Inventions and Subcontracts." If there are no inventions during the year, no annual DD Form 882 is required. The DD Form 882 can be accessed at https://www.usamraa.army.mil.

Technical Objective 2: To develop tools to allow for the collection and dissemination of results and data from studies, including:

1) **Develop a scalable repository of translational research data.**
   a) Determination of common data element based on previously NTI funded project and other database sources.
   b) Creation of the data dictionary
   c) Development of policies for utilization guidance which includes repository requirement documents and website development.

d) Conduct vendor solicitation and vendor selection process based upon requirements and capabilities identified.
e) Build a scalable repository
f) Alpha and beta testing with previous NTI funded studies and studies funded through this grant.

2) Provide a forum for the dissemination of research outcomes to the trauma community.

PROJECT 2

Project Title: National Trauma Research Repository
Principal Investigator: Donald Jenkins, MD
Lead Site: The National Trauma Institute
HRPO Assigned A-number: Not applicable

Abstract: There is a critical need for a national trauma research repository to make research study data available for maximum use. Advances due to clinical trauma research have been accomplished primarily through separate and disconnected efforts. Even when funding has derived from federal entities, individual projects have been somewhat dispersed and uncoordinated. This situation leads to research delays, duplications, inefficiencies and increased costs. To date, relatively little attention has focused on data sharing in trauma research. While clinical researchers in different locations may pursue similar lines of investigation, the computer systems do not, and for the most part cannot, transmit, receive, combine, analyze and use shared data. Therefore, clinical research data are fragmented, sometimes within one facility, and can rarely be repurposed to answer additional research questions. Sharing data maximizes its value, promotes follow-up studies and minimizes duplicative data collection. Universal developments in information technology, like the creation of distributed data networks and virtual data access, provide ways to address clinical research needs that did not exist before. It is time use these technologies to support clinical trauma research.

The consolidation and linkage of datasets in a shared data repository would greatly expand their use and provide a robust scientific platform. Pooled datasets (from multiple studies using common data elements) can provide the additional statistical power necessary to demonstrate clinical and statistical significance. This clinical research repository will be particularly beneficial in maximizing trauma study data. It is often difficult to obtain informed consent from trauma patients or their legally authorised representative (due to the patient's level of consciousness and that family are often unavailable in the early stages of treatment after trauma). This results in small samples with limited statistical power to evaluate interventions. The ability to make aggregated research data widely available to clinical investigators is critical to advance trauma research and care with larger samples. The formation of a national trauma research repository will facilitate maximal utilization of trauma data for translation into evidence-based practice.

The NTRR will be a scalable, customizable repository capable of curating and sharing data from multiple studies across the continuum of trauma research. The NTRR will be structured such that any study can contribute any or all of its data. It will also allow investigators to make study manuals, data dictionaries, publications and study metadata available to other investigators for secondary or aggregate analyses. It will link to study data on www.clinicaltrials.gov and import protocol registration elements, registration for expanded access, and results data. The NTRR will be a resource to investigators who need a data sharing plan and repository when the International Committee of Medical Journal Editors requirements for data sharing take effect in 2018-2019.

Progress Reported:

Year 1

National Trauma Research Repository (NTRR)

The National Trauma Research Repository (NTRR) Steering Committee, consisting of stakeholder organizations and the DoD, provided oversight and governance of the project. Individuals were chosen

based on national leadership positions, experience with database development, and other subject matter expertise. An Executive Committee of the larger body established four subcommittees of injury researchers and technical experts: Architecture, Regulatory/Human Subjects Protection, Data Definitions and Policies and Procedures.

National Trauma Research Repository Steering Committee

Organization Represented	Name	Home Institution
Coalition for National Trauma Research (CNTR), Clinician Scientists and Other Stakeholders	Don Jenkins, MD—Chair	Mayo Clinic
	Eileen Bulger, MD—Vice-chair	University of Washington
	Peggy Knudson, MD	UC-San Francisco
	Jerry Jurkovich, MD	UC-DS
	Greg Beilman, MD	University of Minnesota
	Joe DuBose, MD	Travis AFB
	Alex Valadka, MD	Virginia Commonwealth University
	Jason Sperry, MD	University of Pittsburgh
	Ellen MacKenzie, PhD	Johns Hopkins University
	Avery Nathens, MD	Sunnybrook HSC, Toronto
	Jim Ficke, MD	Johns Hopkins University
American College of Surgeons/Committee on Trauma	Ronny Stewart, MD	UTHSC—San Antonio
	Len Weireter, MD	Eastern Virginia Med. School
Department of Defense	LTC Kyle Remick, MD	CCRP, Military Deputy
	Jose Salinas, PhD	USAISR, San Antonio
	Mary Ann Spott, PhD	Dir. Joint Trauma System
	Tammy Crowder, PhD	CCCRP, Trauma Portfolio
	Frank Lebeda, PhD	MRMC, Dir. System Biology
National Institutes of Health	Matt McAuliffe, PhD	NIH, CIT, Bethesda MD

Note: Grayed background denotes members of Executive Group of the Steering Committee

NTRR Subcommittees

Architecture	Human Research Protections/Regul.	Data Definitions	Policies & Procedures
Jose Salinas	Len Weireter	Greg Beilman	TBN
Matt McAuliff	Peggy Knudson	Alex Valadka	Joe DuBose
Avery Nathens	Eileen Bulger	Jim Ficke	Ellen MacKenzie
Ronny Stewart	Mary Ann Spott	Jerry Jurkovich	
	Laura Brosch	Mary Ann Spott	

Note: Grayed background denotes subcommittee chair.

The subcommittees were established and charged as follow:

1. Architecture—Determine functional requirements of the physical product, reviewing how other clinical research databases are built and desired level of compatibility with related products such as the FITBIR informatics system; consider how to build the back end and front end of the database, including a plan for data quality and validation, report writing, and the user help desk.
2. Regulatory/Human Protections—Develop complete understanding of factors including protections/use of military data; established regulations in other research databases; how to meet or exceed requirements for human subject research protections; recommendations for future hosting of NTRR based on regulatory or human research protection requirements. Develop guiding policies and procedures on Data Sharing, Data Submission Requests.
3. Defining Data—Identify Common Data Elements and a well-defined data dictionary, following review of assembled elements from other trauma research databases (GLUE grant, ROC, etc.)

4. Policies & Procedures—Develop standards operating procedures and management policies for launching and maintain the NTRR.

The Architecture Subcommittee developed user requirements for NTRR which became a formal Requirements document. NTI/NTRR project staff identified and reviewed the top 10 programming languages for front-end and back-end (database) websites and presented this information to the Architecture subcommittee. Several existing platforms were reviewed (e.g., Research Electronic Data Capture (REDCap), FITBIR, and Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC)). This committee also developed Use Case Scenarios for the various users of the repository. NTI project staff developed a request for proposal (RFP) and statement of work (SOW).

Human Subject Protection/Regulatory Subcommittee drafted several policy documents adapted from FITBIR policies for data sharing, data contribution, data requesting, and the use of de-identified data. A Policy on Policies detailing all applicable regulatory references was written. The subcommittee also developed a Data Storage and Sharing Policy, a Data Access Request and Data Use Certification Policy.

The Data Definitions Subcommittee and NTI/NTRR staff reviewed more than 30 existing research databases, registries, and repositories with over 1,000 common data elements. Trauma specific registries/repositories included in this review were the Glue Grant, FITBIR, The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) Study, The Resuscitation Outcomes Consortium (ROC), National Trauma Data Standards (NTDB), National Burn Data Standards (NBDS), and the National Emergency Medicine Information System (NEMSIS). Common data elements were ranked in order of frequency across datasets and then evaluated by the Data Definitions Subcommittee. The subcommittee recommended an initial 18 clinical CDEs and 45 study attributes or meta-study data elements. Additional CDEs and unique data elements (UDEs) will be drawn from the PROOVIT and Ketamine studies funded by this award. Using the CDEs selected by the Data Definition Subcommittee, NTI project staff created the NTRR data dictionary with 31 standardized data attributes for each element. The dictionary uses widely accepted data definitions/parameters from existing trauma and related research registries, and data from previous and ongoing studies.

Providing a forum for the dissemination of research outcomes to the trauma community

Dissemination of trauma research was diverse and multipronged in Year 1. NTI supported the study PIs development of presentations and preparation of manuscripts and magnified those efforts through a comprehensive communications strategy. This strategy to amplify published work includes NTI website announcements and content, blog posts, electronic communications and newsletters, white papers for external audiences, social networking, and distribution of reprints at professional conferences. In Year 1, the NTI website had an average of 1,109 users per month. NTI communicated with the trauma stakeholder community regarding research findings via 10 communiques to 4,625 subscribers. NTI also tweeted 75 trauma research-related messages to 641 followers. Additionally, 26 blog posts regarding trauma research advances were posted on the NTI website (www.nationaltraumainstitute.org). The goal was to comprehensively disseminate published works to the wider trauma network through a Knowledge Translation Plan thereby accelerating the adoption of research findings to improve civilian trauma and combat casualty care and outcomes.

Year 2

National Trauma Research Repository (NTRR)

In Year 2, the NTRR Steering Committee continued to provide oversight and governance of the NTRR development. The NTI project staff continued to compile data on related registries, commercial vendors, and data elements. Additionally, NTI staff met with Dr. Mary Ann Spott, Director of the DoD Trauma Registry (DoDTR), and Melanie Neal, with American College of Surgeons Trauma Quality Improvement Program (TQIP) to discuss compatibility of data definitions across military trauma registries, civilian trauma registries and the NTRR. Potential CDEs were presented to the NTRR Data

Definition Subcommittee. The NTRR Data Definitions Subcommittee finalized proposed clinical data and study meta-data elements for the initial repository. They reported their work to the NTRR Steering Committee Meeting on 10/28/2016.

NTI project staff continued to identify existing research and clinical repositories to review and compare and compiled a list of the top 10 programming languages for front-end and back-end (database) websites, which was presented to the NTRR Architecture subcommittee. With the committee's oversight, NTI staff developed NTRR requirements and use cases. These documents were presented to and approved by the NTRR Steering Committee on 10/28/2016. NTI project staff developed a formal request for proposals (RFP) including the repository requirements and use cases.

The NTRR RFP was released February 1, 2017. Responding vendors were instructed to submit a proposal to build a repository within six months (roughly July – December 2017) followed by 12 months of hosting and technical support. The RFP was distributed to 3,411 recipients via Constant Contact. The announcement had 29% (989) open rate and 13% (443) click-through rate. The RFP was posted on the NTI website and on the Small Business Association call for proposals website. An extensive internet search was performed to identify vendors that perform similar work. Thirteen potential vendors were identified and solicited. Interested vendors were required to submit a letter of intent by February 24, 2017. NTI received letters of intent (7) from: Healytics, ImageTrend, Med Star Health, National Institutes of Health Center for Information Technology (NIH CIT) with Sapient Government Services, QuesGen Systems, Quintiles, and Webhead. Vendors submitted questions about the proposal to NTI by March 1, 2017 and questions/answers document was provided by NTI on March 9, 2017. Proposals were due March 31, 2017. Four vendors submitted proposals (table below).

NTRR Vendor Proposals Submitted

Vendor	Development Cost	Hosting Cost	Total Cost
ImageTrend	$545,610	$88,660	$634,270
NIH CIT/Sapient	$576,064	$215,204	$791,268
QuesGen	$610,856	$524,520	$1,135,376
WebHead	$165,642	$37,706	$203,348

The NTRR Architecture Sub-committee (four reviewers) scored proposals on the strength of each vendor's technical approach/responsiveness to the RFP, relevant experience and past performance evaluations (see NTRR Review Form). The aggregated scores are in the table below (maximum possible score was 440). For detailed reviewer scores, please see NTRR Technical & Prior Performance Matrix in the Appendices.

NTRR Vendor Proposals Scores

Vendor	Technical Approach	Vendor Previous Experience	Total Scores*
ImageTrend	122	122	244
NIH CIT/Sapient	229	136	365
QuesGen	128	116	244
WebHead	119	76	195

NIH CIT/Sapient was the unanimous choice of the review committee. NIH CIT/Sapient proposed to customize the Biomedical Research Informatics Computation System (BRICS) to meet the functional needs of the NTRR. BRICS is a NIH-developed, disease agnostic, web-based research data repository system currently used by seven research communities including Federal Interagency Traumatic Brain Injury Research (FITBIR), Clinical Informatics for Trials and Research (CiSTAR), and the Center for Neuroscience and Regenerative Medicine (CNRM). This system meets 80% of the NTRR requirements and can be customized to meet the remaining 20% (see NIH CIT proposal in the appendices for details). The proposal included maintenance and hosting on the BRICS servers, which sit in "NIH's demilitarized zone" at the Center for Technology in Bethesda, MD. The BRICS team will ensure that all

software/data developed for the NTRR are in accordance with the rules of the Federal Information Security Management Act (FISMA) and all Health and Human Services information security policies.

NTI requested additional information on the NIH CIT/Sapient proposal regarding the scope of work and costs (via a written request and a teleconference with a product demonstration). NIH CIT/Sapient submitted a written response and a revised budget that was reviewed with Dr. Jose Salinas (chair of the NTRR Architecture Subcommittee). The vendor recommendation, vendor proposal and budget were sent to the NTRR Executive Committee for review on 06/23/2017. The NTRR Executive Committee and the NTI Executive Committee approved the selection of NIH CIT/Sapient on 7/19/2017.

In the fourth quarter of Year 2, we learned that NIH would not be able to host the NTRR. Therefore, we have been working with NIH and Sapient to identify commercial hosting options. The selected commercial option will meet or exceed all of the security standards described in the request for proposal. We discussed this with COL Mike Davis in September 2017 and he did not express any concerns about hosting via a commercial solution as opposed to NIH. We also discussed this with Jose Salinas, PhD, chair of the Architecture subcommittee. He was not concerned about using a commercial hosting vendor. Sapient is pricing commercial options and working with NIH to execute a technology transfer agreement.

Dr. Jenkins presented the NTRR project to the NTI board of directors on September 30, 2017. There were no concerns regarding project progress.

Providing a forum for dissemination of research outcomes to the trauma community

In year 2, NTI's knowledge translation and awareness-raising activities included robust social media outreach through Facebook, Twitter, and website blog posts. Our 36 posts to Facebook had a total reach of 5,595 people; while our 96 tweets and retweets on Twitter garnered more than 117,000 impressions. Over the period, NTI's Twitter follower base saw a 30% increase. In addition, we posted 26 times to NTI's website blog in the course of the year. We sent seven communications directly to our stakeholder community of roughly 4,500 people, including general news about NTI and CNTR, announcements about grants and meetings, and an opportunity to participate in a research project. NTI's messages average an open rate of 29%, above the industry standard of 25% for nonprofit email campaigns.

With the launch of a new, more agile NTI website (www.NatTrauma.org) in July 2017 after nearly four months under construction, we began increasing output of original trauma research content: creating new infographics and posting a different trauma survivor story each month. We also published an exclusive interview with incoming Director of the Combat Casualty Care Research Program, COL Michael Davis in August, 2017. The site improvements aim to engage more stakeholders with compelling and accessible content on trauma research outcomes and raise awareness both about NTI and the toll of trauma in the United States. In addition, the new site provides improved insight into the diffusion of NTI-sponsored research by linking to Altmetric scores for each resulting research publication. The new site has information about the coming National Trauma Research Repository and will have a portal to that site. Since the launch of the new site, the number of unique visitors has held steady around 1,300 per month.

Also during Year 2, the NTI Board of Directors launched two new committees in an effort to increase its profile and outreach: the Communications Committee and the Advocacy and Patient Engagement Committee. These committees will support this study's objective to provide forum to disseminate research outcomes to the trauma community. The mission of the Communications Committee is to assist communications planning by engaging stakeholder groups in developing compelling messages regarding DoD funded trauma research. Chaired by NTI Board member Dr. Steven Venticinque, the Communications Committee is currently in the formation stage as staff and board members prioritize audiences. Once established, the committee will serve as generator of and sounding board for molding the messages and visuals that connect dots between research and outcomes, tie trauma treatment research to relevant news stories (unfolding natural disasters, mass casualty events, public health and safety, national security, the national healthcare conversation, aging, etc.) and resonate with policy makers and funders. Committee members will facilitate connections with

the health and healthcare policy press that result in published articles, op-eds, and quotes from our experts in related stories.

The mission of the Advocacy and Patient Engagement Committee is to widen the perspective of NTI to include those personally affected by trauma (military and civilian) and professionals along the continuum of trauma care. Through this committee, NTI seeks to craft more compelling messages and to make broader and more connections between DoD funded research and patient outcomes. It will also be a vehicle to involve patients and family members in the development of new research programs (e.g., including patient-centered outcomes in research designs and including patients on study steering committees). This committee has launched with NTI Board member Dr. Martin Croce as chair, and five members: Dr. Anna Newcomb, a new NTI Board member and Trauma Research Manager at Inova Trauma Center in Fairfax, Virginia; Peter Thomas, principal with the law firm Powers Pyles Sutter & Verville with a practice in healthcare and disability policy and a trauma survivor, himself; Patrick Downes, a survivor of the 2013 Boston Marathon Bombing and an amputee who advocates for tighter collaboration between civilian and military resources in the treatment of trauma patients; Ian Weston, executive director of the American Trauma Society; and Terrie Stewart, a trauma nurse and Trauma Program Director at Blake Medical Center in Bradenton, Florida. The committee will engage with NTI's government relations team and participate in strategy discussions; attend congressional and agency meetings and planned advocacy days on Capitol Hill; contact fellow stakeholders; and contribute ideas and content for policy-related materials and research advocacy communications. Additionally, committee members will be tapped to weigh in on NTI's research agenda, helping to advance NTI's patient-centered approach.

Study/Projects Major Tasks and Accomplishments to Date (Years 1 and 2)

STUDY 1: KETAMINE STUDY	**Timeline in Months**	**Actual completion date**	**% of completion**
Major Task 1: Prepare and adapt Research Protocol for DoD Funded Status for Study 1			
Subtask 1: Refine research protocol	1-3	06/28/2016	100%
Refine eligibility criteria, exclusion criteria, screening protocol, enrollment protocol	1-3	06/28/2016	100%
Finalize consent form and human subjects protocol	1-3	06/28/2016	100%
Coordinate IRB protocol submission	1-3	06/28/2016	100%
Submit for Military 2nd level IRB review (ORP/HRPO)	3-6	05/30/2017	100%
Submit amendments, adverse events and protocol deviations as needed	6-18	Ongoing	N/A
Milestone Achieved: Protocol for Study 1 developed	3	06/28/2016	100%
Milestone Achieved: Local IRB approval	4-5	03/20/2017	100%
Milestone Achieved: HRPO approval	8	06/21/2017	100%
Major Task 2: Data Analysis for Study 1			
Subtask 1: Monitor data collection and data quality	8-20	Ongoing	50%
STUDY 2: PROOVIT STUDY			

Major Task 3: Adapt PROOVIT Protocol for DoD Funded Status for Study 2			
If applicable, coordinate with sites for IRB protocol submission	1-6	01/05/2016	100%
Coordinate with sites for Military 2nd level IRB review (ORP/HRPO)	1-6	03/31/2016	100%
Submit amendments, adverse events and protocol deviations as needed	As needed	Ongoing	N/A
Coordinate with sites for annual IRB report for continuing review	Annual	06/28/2017	100%
Prepare and submit quarterly progress report to DoD	Qrtly	06/28/2017	100%
Milestone Achieved: Local IRB approval at all sites	3	03/29/2016	100%
Milestone Achieved: HRPO approval for all protocols	6	04/22/2016	100%
Major Task 4: Subcontract with all Study Sites for Study 2			
Verify sub-award documents: budget, budget justification, salary verification	1-3	03/22/2016	100%
Issue and execute sub-award document	1-3	04/13/2017	100%
Receive quarterly progress reports	Qtrly	03/15/2017	100%
Review quarterly progress reports	Qtrly	04/11/2017	100%
Milestone Achieved: Subawards issued for all sites	3	04/13/2017	100%
Major Task 5: Data Analysis for Study 2			
Subtask 1: Coordinate with sites and NTI for monitoring data collection rates and data quality	4-6	Ongoing	75%
Perform all analyses according to specifications, share output and findings with all investigators	Ongoing	Ongoing	75%
PROJECT 1: SURGICAL AIRWAY SIMULATOR			
Major Task 6: Develop High Fidelity Airway Simulator			
Execute Subaward	1	05/12/2016	100%
Develop a model base	1-4	07/01/2016	100%
Engineer hydraulic, mechanical and pneumatic systems for head movement, airway lubrication, respiration and circulation	1-4	07/01/2016	100%
Develop and integrate a programmable logic controller	1-4	07/06/2016	100%
Integrate subsystems into the infrastructure built upon the base	5-9	03/31/2017	100%
Develop a layered, high-fidelity anatomical model for face, neck and upper thorax	5-9	02/24/2017	100%
Separate the components of high-fidelity anatomical model for molding	5-9		80%
Create molds of the anatomical components including bones, selected individual muscles,	10-12		60%

fascia, larynx, trachea, thyroid gland, major arteries and veins			
Create serial iterations of the models and molds to complete engineering	10-12		60%
Research materials for high anatomical and surgical fidelity laryngo-tracheal complex	10-12	08/31/2017	100%
PROJECT 2: NATIONAL TRAUMA RESEARCH REPOSITORY			
Major Task 8: Determine Data Dictionary and Vendor Requirements			
Coordinate with Steering Committee to determine Common Data Element Workgroup	1-3	03/29/2016	100%
Common Data Element Determinations	1-6		98%
Develop Data Dictionary	6-9		98%
Milestone Achieved: Data dictionary			
Major Task 9: Vendor solicitation and selection			
Determine repository requirements	1-6	08/11/2016	100%
Vendor solicitation and selection process	6-9		100%
Milestone Achieved: Repository requirements document		08/11/2016	100%
Milestone Achieved: Vendor Selected		07/19/2017	100%
Major Task 10: Repository build and testing			
Repository build (back and front end)	9-12		0%
Major Task 11: Website development and policy			
Develop management policies	3-9		95%
Develop website and interfaces	6-15		25%
Milestone Achieved: Policies available on functional website			

Training and Professional Development

Training of research staff at all sites including research ethics and privacy and confidentiality has been completed. On Study 1 (ketamine), an educational PowerPoint was developed for burn wound care (see appendices).

Dissemination of Results to Communities of Interest

Year 1

Although we did not have study findings or completed projects, there were three opportunities for disseminating information to communities of interest in Year 1.

Study 1: Determining the Efficacy and Safety of Ketamine as a Battlefield Analgesic

The Study 1 team presented a poster depicting the protocol for the "Ketamine for Acute Burn Pain" project at a local Behavioral Pharmacology Research Unit conference.

Study 2: PROOVIT Study

The PROOVIT Study team gave two research presentations with data from this study at the 2016 the American Association of Surgery for Trauma (see products).

Project 1: Airway Management Simulator

No dissemination of results to report.

Project 2: National Trauma Research Repository

The project PI (Dr. Donald Jenkins) and the NTI study team were invited to submit a manuscript detailing the work underway for this contract for the 2016 Shock Military Supplement. The team prepared a manuscript detailing the development of the National Trauma Research Repository and submitted it in May 2016. It was accepted and published in the Military in August 2016. Additionally, the project PI (Dr. Donald Jenkins) and the NTI study team were invited to present at the 2016 Military Health System Research Symposium during the Surgical Critical Care and Burn Session moderated by Dr. Jose Salinas. The presentation detailed work completed previous DoD funded projects with the National Trauma Institute and introduced the National Trauma Research Repository under for this grant.

Year 2

Study 1: Determining the Efficacy and Safety of Ketamine as a Battlefield Analgesic

No dissemination of results to report.

Study 2: PROOVIT Study

The PROOVIT Study team published two articles on this study in trauma journals. They gave two podium presentations and two poster presentations from this study at the 2017 American Association of Surgery for Trauma annual conference (see products).

Project 1: Airway Management Simulator

No dissemination of results to report.

Project 2: National Trauma Research Repository

Information regarding the National Trauma Research Repository was disseminated via the call for proposals, the NTI website and other social media (see products)

Plans for the Next Quarterly Reporting Period

Study 1: Determining the Efficacy and Safety of Ketamine as a Battlefield Analgesic

Once HRPO approval for amendments and continuing review are received, the study will be initiated. NTI staff will hold monthly meetings for the study team to monitor progress.

Study 2: PROOVIT Study

PROOVIT sites will continue to enroll subjects.

Project 1: Airway Management Simulator

Simulator development will continue.

Project 2: National Trauma Research Repository

A subcontract will be issued to Sapient Governmental and a technology transfer agreement with NIH will be executed. Sapient will begin to build the application in close collaboration with NTI staff. Data elements (common data elements and unique data elements) will be finalized. Unique data elements from the ongoing studies under this project (Ketamine and PROOVIT) will be identified and defined. The Policies and Procedures subcommittee will develop additional standards, policies and operating procedures. Data sharing, data submission and data sharing policies will continue to be refined.

NTI staff will continue to implement the Knowledge Translation Plan and provide a forum for disseminating research outcomes to the trauma community in the next quarter.

IMPACT:

As we have just completed Year 2 of a three-year period of performance, there are no major developments in the principal discipline, other disciplines, technology transfer or to society beyond science and technology to report at this time.

CHANGES/PROBLEMS:

There are no changes in the approach for this work. Study initiation for the Study 1 (ketamine for pain management) has taken much longer than planned for various reasons. Therefore, NTI granted an 18-month no cost extension and took a more active monitoring role. Currently, we are holding monthly reporting meetings to closely monitor progress. The NTI Science Committee is monitoring this study.

The NTRR development funded through this Agreement is intended to be the initial product development and maintenance. Further development and sustainment funding will be required.

PRODUCTS:

Year 1

Year 1 products were included in the appendices of the Year 1 Annual Report.

1. Song, A., Gerold, K., McCann, U.D., Caffrey, J., Latif, A., Milner, S.M., Fauerbach, J.A. Safety and Efficacy of Ketamine as a Battlefield Analgesic for Acute Burn Pain. Poster presentation at the Asthma and Allergy Center of Johns Hopkins Bayview Medical Center in Baltimore, MD, July 27, 2016.
2. Smith SL, Price MA, Fabian TC, Jurkovich GJ, Pruitt BA, Jr., Stewart RM, et al. The National Trauma Research Repository: Ushering in a new era of trauma research (Commentary). Shock. 2016;46(3 Suppl 1):37-41.
3. Jenkins, DH. Impact of Department of Defense Research to the National Trauma Institute. Presented at the Military Health System Research Symposium, Orlando FL, August 17, 2016.

4. Loja MN, Wishy A, Humphries M, Savage S, Fabian T, Scalea TM, Holcomb JB, Poulin N, Galante JM, Rasmussen TE, AAST PROOVIT Study Group. Systemic anticoagulation in the setting of vascular extremity trauma. Podium Presentation, American Association for the Surgery of Trauma Annual Meeting, Maui, Hawaii, 2016.
5. Loja MN, DuBose J, Saummann A, Li CS, Savage S, Scalea T, Holcomb JB, Rasmussen TE, Knudson MM, AAST PROOVIT Study Group. The Mangled Extremity Score and Amputation: Time for a Revision. Quickshot Podium Presentation, American Association for the Surgery of Trauma Annual Meeting, Maui, Hawaii, 2016.
6. Human Subjects Policies/procedures from NTRR
7. NTRR Requirements Document
8. NTRR Use Case Document
9. Knowledge Translation Plan

Year 2

Products completed in Year 2 are included in the appendices of this report.

1. Coimbra R, Kozar RA, Smith JW, Zarzaur BL, Hauser CJ, Moore FA, Bailey JA, Valadka A., Jurkovich GJ, Jenkins DH, Davis KA, Price MA, Maier RV. The Coalition for National Trauma Research supports the call for a national trauma research action plan. J Trauma Acute Care Surg. 2017 Mar;82(3):637-645.
2. Clinical report forms, staff training and other materials for the ketamine study
3. Loja MN, DuBose J, Sammam A, Li CS, Liu Y, Savage S, Scalea TM, Holcomb JB, Rasmussen TE, Knudson MM, AAST PROOVIT Study Group. The Mangled extremity score and amputation: Time for a revision. J Trauma Acute Care Surg. 2017 Mar;82(3):518-523.
4. Faulconer ER, Branco B, Loja M, Grayson K, Sampson J, Fabian T, Bee T, Holcomb JB, Brenner M, Scalea TM, Skarupa D, Inaba K, Poulin N, Rasmussen TE, DuBose JJ, AAST PROOVIT Study Group. Use of open and endovascular surgical techniques to manage vascular injuries in the trauma setting: A review of the AAST PROOVIT Registry. Podium presentation - American Association for the Surgery of Trauma Annual Meeting, Baltimore, MD, 2017.
5. Ferencz SA, DuBose JJ, Hennigan J, Nolan K, Sampson JB, Rasmussen TE, Galante JM, Bee T, Fabian TC, Menaker JA, Scalea TM, Holcomb JB, Skarupa DJ, Inaba K, Bini JK, AAST PROOVIT Study Group. Contemporary tourniquet use in extremity vascular trauma: The AAST prospective observational injury treatment (PROOVIT) registry. Quick shot presentation - American Association for the Surgery of Trauma Annual Meeting, Baltimore, MD, 2017.
6. Loja MN, DuBose JJ, Stephenson J, Kessel B, Bee T, Fabian T, Menaker J, Scalea TM, Holcomb JB, Skarupa D, Inaba K, Catalano R, Poulin N, Bini JK, Rasmussen TE, AAST PROOVIT Study Group. Pediatric vascular trauma: Current management and early outcomes. Poster presentation - American Association for the Surgery of Trauma Annual Meeting, Baltimore, MD, 2017.
7. Russo R, Galante J, DuBose JJ, Bee T, Fabian T, Holcomb JB, Brenner M, Scalea TM, Skarupa D, Inaba K, Poulin N, Turay D, Bini J. Rasmussen TE, AAST PROOVIT Study Group. Contemporary outcomes and management of blunt cerebrovascular injuries: Results from the AAST PROOVIT multicenter registry. Poster presentation - American Association for the Surgery of Trauma Annual Meeting, Baltimore, MD, 2017.
8. Loja MN, Galante JM, Humphries M, Savage S, Fabian T, Scalea T, Holcomb JB, Poulin N, DuBose J, Rasmussen TE; AAST PROOVIT Study Group. Systemic anticoagulation in the setting of vascular extremity trauma. Injury. 2017 Sep;48(9):1911-1916.
9. 3 PowerPoint Protocol/project presentations to the National Trauma Institute Board of Directors
10. New NTI website www.NatTrauma.org, social media materials, communications

Submitted manuscripts (under review as of the end of Year 2):

1. Faulconer ER, Branco B, Loja M, Grayson K, Sampson J, Fabian T, Bee T, Holcomb JB, Brenner M, Scalea TM, Skarupa D, Inaba K, Poulin N, Rasmussen TE, DuBose JJ, AAST

PROOVIT Study Group. Use of open and endovascular surgical techniques to manage vascular injuries in the trauma setting: A review of the AAST PROOVIT Registry. – Submitted J Trauma Acute Care Surg
2. Ferencz SA, DuBose JJ, Hennigan J, Nolan K, Sampson JB, Rasmussen TE, Galante JM, Bee T, Fabian TC, Menaker JA, Scalea TM, Holcomb JB, Skarupa DJ, Inaba K, Bini JK, AAST PROOVIT Study Group. Contemporary tourniquet use in extremity vascular trauma: The AAST prospective observational injury treatment (PROOVIT) registry. – Submitted J Trauma Acute Care Surg.
3. Russo R, Galante J, DuBose JJ, Bee T, Fabian T, Holcomb JB, Brenner M, Scalea TM, Skarupa D, Inaba K, Poulin N, Turay D, Bini J. Rasmussen TE, AAST PROOVIT Study Group. Contemporary outcomes and management of blunt cerebrovascular injuries: Results from the AAST PROOVIT multicenter registry. – Submitted J Trauma Acute Care Surg.
4. Loja MN, DuBose JJ, Stephenson J, Kessel B, Bee T, Fabian T, Menaker J, Scalea TM, Holcomb JB, Skarupa D, Inaba K, Catalano R, Poulin N, Bini JK, Rasmussen TE, AAST PROOVIT Study Group. Pediatric vascular trauma: Current management and early outcomes. – Submitted J Trauma Acute Care Surg.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Name	Project Role	Nearest person month worked	% Effort	Contribution to the project
Donald Jenkins	Principal Investigator	0.6	5%	Oversight of entire project
Amy Flores	Controller	3.45	25% (Oct-Dec) 30% (Jan-Sept)	Managed subawards
Monica Phillips	Research Operations Director	4.8	70% (Sept-Oct) 80% (Nov-Dec) 20% (Jan-Sept)	Subaward document preparation, negotiation, and execution for 12 subawards. Assist in data element review. Attends all committee meetings.
Ana Guerrero	Admin Support	2.95	50% (Sept-Oct) 60% (Nov-Dec) 30% (Jan-May)	Coordinating Steering Committee meetings, drafting minutes, planning face to face steering committee meeting.
Pam Bixby	Communications	3.68	25% (Sept-Dec) 32.5% (Jan-Sept)	Responsible for the communication and dissemination tasks of the projects and for broader trauma research dissemination according to the Knowledge Translation Plan
Sharon Smith	Project Administrator	6.2	60% (Sept-Oct) 50% (Nov-Dec) 45% (Jan-Sept)	Managing Steering Committee meetings, agenda, process. Establishment of working groups.
Michelle Price	Co-Investigator/ Program Manager	9.65	100% (Sept-Oct) 90% (Nov-Dec) 65% (Jan-Sept)	Conducting repository research, managing the RFP and vendor selection processes. Communicating with stakeholders and potential

				collaborators at DoD, NIH, academic trauma centers and trauma professional organizations. Regulatory oversight and coordination of regulatory reviews and reporting for the 13 research subawards. Data element review.

The current support information has changed for PI, Donald Jenkins, MD. The projects previously listed under current that were titled "A National Coordinating Center for Trauma Research Funding" (W81XWH-11-1-0841) and "Micro vesicle Production After Trauma and its Clinical Impact on Venothromboembolism" have ended. Dr. Jenkins currently has effort on three projects. In addition to this project, he now has effort on: "A National Coordinating Center for Prehospital Trauma Research Funding Transfusion Using Stored Fresh Whole Blood" (W81XWH-15-2-0039) and "Management of Noncompressible Hemorrhage Using Vena Cava Ultrasound" (W81XSH-15-1-0709). These projects were previously listed as pending and are now funded projects. Dr. Jenkins support document is included in the appendices. There is no overlap between funded support and dates.

Current support has also changed for Michelle Price, PhD., co-investigator. The project previously listed under current that was titled "A National Coordinating Center for Trauma Research Funding" (W81XWH-11-1-0841) has ended. Dr. Price currently has effort on three funded projects and three projects are pending. Dr. Price's support document is included in the appendices. There is no overlap between funded support and dates.

Other Collaborating Organizations

Organization	Location	Contribution to Project
Baylor College of Medicine/Ben Taub General Hospital	1504 Taub Loop, Houston, TX 77030	PROOVIT Clinical Site (PI: Dr. Ramyar Gilani)
Emory University	201 Dowman Drive, Atlanta, GA 30322	PROOVIT Clinical Site (PI: Dr. Ravi Rajani)
Loma Linda Medical Center	11234 Anderson Street, Loma Linda, CA 92354	PROOVIT Clinical Site (PI: Dr. Richard Catalano)
University of Southern California	1983 Marengo Street, Los Angeles, CA 90033	PROOVIT Clinical Site (PI: Dr. Kenji Inaba)
Scripps Health	4077 Fifth Avenue, San Diego, CA 92103	PROOVIT Clinical Site (PI: Dr. Michael Sise)
University of California, Davis	2315 Stockton Boulevard, Sacramento, CA 95817	PROOVIT Clinical Site (PI: Dr. Joseph Galante)
University of Maryland/R. Adams Cowley Shock Trauma	22 S. Greene Street, Baltimore, MD 21201	PROOVIT Clinical Site (PI: Dr. Thomas Scalea)
University of Tennessee – Memphis	920 Court Street, Memphis, TN 38163	PROOVIT Clinical Site (PI: Dr. Timothy Fabian)
University of Texas Health Science Center at Houston	6410 Fannin Street, Houston, TX 77030	PROOVIT Clinical Site (PI: Dr. Laura Moore)
University of Wisconsin School of Medicine and Public Health	750 Highland Avenue, Madison, WI 53276	PROOVIT Clinical Site (PI: Dr. Suresh Agarwal)
Wright State University	1 Wyoming Street, Dayton, OH 45409	PROOVIT Clinical Site (PI: Dr. John Bini)
University of Texas Health Science Center at San Antonio	7703 Floyd Curl Drive, San Antonio, TX 79230	PROOVIT Statistical Analysis (PI: Dr. Joel Michalek)

Johns Hopkins University	600 North Wolfe Street, Blalock 1415, Baltimore, MD 21287	Ketamine Clinical Site (PI: Dr. John Fauerbach)
Operative Experience, Inc.	500 Principio Parkway West, Suite 300, North East, MD 21901	Airway Management Simulator Development (PI: Dr. Robert Buckman)

SPECIAL REPORTING REQUIREMENTS

The Quad chart for this project follows.

APPENDICES:

1. Previous, Current and Pending Support – Donald Jenkins, MD
2. Previous, Current and Pending Support – Michelle Price, PhD
3. Coimbra R, Kozar RA, Smith JW, Zarzaur BL, Hauser CJ, Moore FA, Bailey JA, Valadka A., Jurkovich GJ, Jenkins DH, Davis KA, Price MA, Maier RV. The Coalition for National Trauma Research supports the call for a national trauma research action plan. J Trauma Acute Care Surg. 2017 Mar;82(3):637-645.
4. Clinical report forms, staff training and other materials for the ketamine study
5. Loja MN, DuBose J, Sammam A, Li CS, Liu Y, Savage S, Scalea TM, Holcomb JB, Rasmussen TE, Knudson MM, AAST PROOVIT Study Group. The Mangled extremity score and amputation: Time for a revision. J Trauma Acute Care Surg. 2017 Mar;82(3):518-523.
6. Faulconer ER, Branco B, Loja M, Grayson K, Sampson J, Fabian T, Bee T, Holcomb JB, Brenner M, Scalea TM, Skarupa D, Inaba K, Poulin N, Rasmussen TE, DuBose JJ, AAST PROOVIT Study Group. Use of open and endovascular surgical techniques to manage vascular injuries in the trauma setting: A review of the AAST PROOVIT Registry. Podium presentation - American Association for the Surgery of Trauma Annual Meeting, Baltimore, MD, 2017.
7. Ferencz SA, DuBose JJ, Hennigan J, Nolan K, Sampson JB, Rasmussen TE, Galante JM, Bee T, Fabian TC, Menaker JA, Scalea TM, Holcomb JB, Skarupa DJ, Inaba K, Bini JK, AAST PROOVIT Study Group. Contemporary tourniquet use in extremity vascular trauma: The AAST prospective observational injury treatment (PROOVIT) registry. Quick shot presentation - American Association for the Surgery of Trauma Annual Meeting, Baltimore, MD, 2017.
8. Loja MN, DuBose JJ, Stephenson J, Kessel B, Bee T, Fabian T, Menaker J, Scalea TM, Holcomb JB, Skarupa D, Inaba K, Catalano R, Poulin N, Bini JK, Rasmussen TE, AAST PROOVIT Study Group. Pediatric vascular trauma: Current management and early outcomes. Poster presentation - American Association for the Surgery of Trauma Annual Meeting, Baltimore, MD, 2017.
9. Russo R, Galante J, DuBose JJ, Bee T, Fabian T, Holcomb JB, Brenner M, Scalea TM, Skarupa D, Inaba K, Poulin N, Turay D, Bini J. Rasmussen TE, AAST PROOVIT Study Group. Contemporary outcomes and management of blunt cerebrovascular injuries: Results from the AAST PROOVIT multicenter registry. Poster presentation - American Association for the Surgery of Trauma Annual Meeting, Baltimore, MD, 2017.
10. Loja MN, Galante JM, Humphries M, Savage S, Fabian T, Scalea T, Holcomb JB, Poulin N, DuBose J, Rasmussen TE; AAST PROOVIT Study Group. Systemic anticoagulation in the setting of vascular extremity trauma. Injury. 2017 Sep;48(9):1911-1916.
11. 3 PowerPoint Protocol/project presentations to the National Trauma Institute Board of Directors
12. New NTI website www.NatTrauma.org, social media materials, communications

A National Coordinating Center for Trauma Research

Veterans Health Administration R&D www.research.va.gov

Defense Health Agency

PI: Donald Jenkins, MD **Org:** National Trauma Institute

Study/Product Aim(s)

Hypothesis: The civilian trauma research community can be used as a surrogate for military combat casualty care research, maximizing the return from dollars invested by replacing the expensive and repetitive assembly and disassembly of short-lived clinical investigator networks with a stable and enduring operational infrastructure for clinical trauma research.

- Technical Objective 1: To manage specific research projects addressing military research gaps in airway management, pain management and vascular injury.
- Project 1: Determining the Efficacy and Safety of Ketamine as a Battlefield Analgesic;
- Project 2: High Anatomic Fidelity Surgical Airway Training system;
- Project 3: The PROspective Observational Vascular Injury Trial (PROOVIT);
- Technical Objective 2: Develop tools to allow or the collection and dissemination of results and data from studies.

Airway management simulator under development

Timeline and Cost (direct + indirect)

Activities	FY16	FY17	FY18
Ketamine Study			
Airway Simulator Development			
PROOVIT			
NTRR Development			
Total Budget ($M)	$2.1M	$1.4M	$1.1M

Goals and Milestones

CY16 Goal –
- ☑ HRPO approval for studies
- ☑ Subcontracting complete
- ❑ Studies commence (Ketamine study pending initiation)
- ☑ Common Data Elements and NTRDB functional requirements

CY17 Goals
- ❑ Airway simulator developed (ongoing)
- ☑ PROOVIT study continues
- ☑ NTRR developer solicited and chosen

CY 18 Goals
- ❑ NTRRR development and testing
- ❑ Ketamine study concludes

Comments/Challenges/Issues/Concerns: Delays on ketamine study

Florence D'Orazi ((301) 619-7035/Florence.d.dorazi.ctr@mail.mil)

Previous, Current and Pending Support

Donald Jenkins, MD

Previous

Title: National Trauma Institute: A National Coordinating Center for Trauma Research Funding
Funded by Department of Army. (W81XWH-11-1-0841). Contracting Officer: Elena Howell, 301-619-6871
Period of Performance: 9/29/11-9/28/16
Role: Principal Investigator, 5% (no salary report received)
Amount: $3,845,000.00
Brief Description: NTI will manage multiple studies of scientific merit in trauma and emergency or critical care medicine selected by peer-review. The clinical data resulting from these studies becomes a fundamental piece of infrastructure and a vehicle to knowledge. Both the initial set of studies funded through this contract, as well as potential new studies, will be used to establish a set of common data elements. Initially this would be a small but scalable data repository for both animal and human study data, giving trauma investigators access to more data than they are able to collect on their own, and providing a much faster route to the large datasets required to draw conclusions to improve trauma care.

Title: Microvesicle production after trauma & its Clinical Impact on Venothromboembolism.
Funded by Department of Army. (W81XWH-10-2-0110).
Period of Performance: 10/2010-12/2015
Role: Co-Investigator, 5%
Amount: $1.5million
Brief Description: The major goals of this project are to fund the proposed prospective case-cohort study examining the role of microvesicle production and thrombin generation in those trauma patients who develop venothromboembolism.

Current:

Title: A National Coordinating Center for Trauma Research
Funded by: Department of Defense W81XWH-15-2-0089
Role: Principal Investigator, 5% effort
Amount: $199,997
Period of Performance: September 30, 2015 – September 29, 2018
Brief Description: The civilian trauma research community can be used as a surrogate for military combat casualty care research, maximizing the return from dollars invested by replacing the expensive and repetitive assembly and disassembly of short-lived clinical investigator networks with a stable and enduring operational infrastructure for clinical trauma research. As available research funding shrinks and federal budget pressure increases, we must replace the expensive and repetitive assembly and disassembly of short-lived clinical investigator networks with a stable and enduring operational infrastructure for clinical trauma research. This research effort funds two clinical studies, one simulation development, and the development of tools for the collection and dissemination of results and data from studies – the National Trauma Research Repository.
Specific Aims: 1. To manage specific research projects to address military research gaps; 2. To develop tools to allow for the collection and dissemination of results and data from studies.
No overlap

Title: A National Coordinating Center for Prehospital Trauma Research Funding Transfusion Using Stored Fresh Whole Blood
Funded by: Department of Defense. W81XWH-15-2-0039
Role: PI
Effort: 5%, no support
Amount: $499,995
Period of Performance: August 25, 2015 – August 24, 2018
Brief Description: This research effort funds a feasibility study examining a system for collection, banking, and delivery of FWB in a civilian trauma center and comparing the use of FWB leukocyte reduced with a platelet sparing filter to component therapy for trauma patients with hemorrhagic shock.
Specific Aims: (1) Determine the shelf life of whole blood units leukocyte reduced with a platelet sparing filter stored at 4 degrees. (2) Prospectively determine the effectiveness of whole blood leukocyte reduced with a platelet sparing filter compared to component therapy as measured by coagulation capacity after transfusion and clinical outcomes. (3) Determine the feasibility of providing an inventory of whole blood leukoreduced with a platelet sparing filter for resuscitation of trauma patients in hemorrhagic shock.
Overlap?: No

Title: Management of Noncompressible Hemorrhage Using Vena Cava Ultrasound
Funded by: Department of Defense. W81XSH-15-1-0709
Role: PI
Effort: 5%, no support
Amount: $498,269
Period of Performance: September 15, 2015 – September 14, 2018
Brief Description: The hypothesis of this research effort is that an ultrasonic assessment (USA) protocol of inferior vena cava (IVC) or internal jugular vein diameter and collapsibility can detect and aid management of non-compressible hemorrhage in major trauma victims.
Specific Aims: 1) Determine the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of ultrasonic assessment (USA) of inferior vena cava expiration (IVCe), inferior vena cava inspiration (IVCi) and inferior vena cava collapsibility index (IVC-CI) or internal jugular expiration and inspiration (IJe, IJi) and internal jugular vein collapsibility index (IJ-CI) to predict the need for blood transfusion or hemostatic interventions such as surgery or angioembolization. 2) Determine the sensitivity, specificity and accuracy of USA of IVCe, IVCi and IVC-CI or IJe, IJi and IJ-CI with the classic clinical parameters for hypotension (SBP<90), indicative of hemorrhagic shock.
Overlap?: No

Pending:

Title: Development and Implementation of viable cold stored blood products on the Prehospital Resuscitation in severely injured patients in South Texas
Funds: South Texas Regional Advisory Committee/ San Antonio Area Medical Foundation
Project Rol: Co-PI
Effort: 1%, no salary support
Amount: $200,000
Period of performance: Pending
Brief Description: This award primary goal is to develop a functional cold stored whole blood product and implement a sustainable prehospital transfusion program for trauma patients in South Texas.

Title: Predictors of Venous Thromboembolism: A Multicenter Prospective Cohort Study
Funds: DOD/Mayo Clinic
Project Role: Co-PI
Effort: 5%
Amount: $303,317
Period of performance: Pending
Brief Description: To assess an individual patient's coagulation phenotype, using the Calibrated Automated Thrombinogram (**CAT**) to quantify the kinetics of plasma thrombin generation. In addition to testing the plasma coagulome by CAT, study directly address the Surgeon General's charge to "*conduct research into when genetic testing is appropriate*," by testing prothrombotic single nucleotide polymorphisms (**SNP**s) as risk factors for VTE among trauma patients. Study propose to validate a personalized and individualized VTE risk score for acutely injured patients and to address the NIH initiative of defining the *"role of laboratory monitoring… to help better define those at risk of bleeding and thrombosis*."

Title: Precision Medicine-based hemorrhage resuscitation utilizing individualized measurements of Anemia and Hypovolemia
Funds: NIH/Mayo Clinic
Project Role: PI
Effort: 5%
Amount: $61,020
Period of performance: Pending
Brief Description: To determine the ability for compensatory reserve index (CRM) to provide early and accurate resuscitation volume estimates in individual patients with varying compensatory responses compared to traditional vital sign measurements in hemorrhaging trauma patients. To develop and validate a clinically useful interface device (PROTOTYPE) that aggregates the CRM output and the modified-SpHb (percutaneous continuous hemoglobin monitor) mathematical model and directs blood product and fluid resuscitation in hemorrhaging trauma patients.

Previous, Current and Pending Support

Michelle Price

Previous (5 years)

Title: National Trauma Institute: A National Coordinating Center for Trauma Research Funding
Funded by: Department of Defense. W81XWH-11-1-0841
Role: Consultant
Effort: 20%
Amount: $92,986
Period of Performance: December 1 2013 – April 30, 2016
Brief Description: The purpose of this award was to distribute and manage funding for peer-reviewed research projects for areas of greatest impact in trauma, in order to change practice to save lives affected by trauma, and to disseminate research findings to the trauma community.
Specific Aims:

1. The contract will support a national coordinating center for trauma research funding.
   a) Requests for proposals (RFP) based on areas of scientific merit in trauma and emergency or critical care will be prepared and issued.
   b) NTI Board Science Committee will score proposals according to scientific merit, clinical impact, ability to perform the research, innovation, and military relevance.
   c) NTI Board will update trauma research subject areas based upon the impact on survival or care of patients, existing funding, and funding availability annually.
   d) Perform Award management and compliance to include all appropriate USAMRMC HRPO requirements.
   e) Provide research funding for proposals that seek to address areas of urgent need in the treatment of trauma.
      i. *The Safety and Efficacy of Platelet Transfusion in Patients Receiving Antiplatelet Therapy that Sustain Intracranial Hemorrhage.* PI - Mark Cipolle, MD, PhD, Christiana Health Care System, Newark, DE.
      ii. *Effect of Antioxidant Vitamins on Coagulopathy and Nosocomial Pneumonia after Severe Trauma.* PI – Jean-Francois Pittet, MD, University of Alabama at Birmingham, AL.
      iii. *Detection and Management of Non-Compressible Hemorrhage by Vena Cava Ultrasonography.* PI - Jay J Doucet, MD, University of California - San Diego, CA.
      iv. *Splenic Injury Prospective Outcomes Trial.* PI – Ben Zarzaur, MD, MPH, University of Tennessee health Science Center, Memphis, TN and AAST.
      v. *Transfusion of Stored Fresh Whole Blood in a Civilian Trauma Center: A Prospective Evaluation of Feasibility and Outcomes.* PI – Henry Cryer, MD, UCLA Dept of Surgery, Los Angeles, CA.
      vi. *Acute Lung Injury Ventilation Evaluation (ALIVE) Trial.* PI – Suresh Agarwal, MD, Boston Medical Center, Boston, MA.
      vii. *Methicillin-Resistant Staphylococcus aureus in a Trauma Population: Does Decolonization Prevent Infection?* PI – Robert Maxwell, MD, University of Tennessee Health Science Center, Chattanooga, TN.
      viii. *Hepcidin and Anemia in Trauma*. PI – Lena Napolitano, MD, University of Michigan Health System, Ann Arbor, MI.

ix. *Thrombelastography (TEG®) based dosing of enoxaparin for thromboprophylaxis: a prospective randomized trial.* PI – Martin Schreiber, MD, Oregon Health and Science University, Portland, OR.

x. Establish a multi-disciplinary national Steering Committee that will guide the planning, development and implementation of National Trauma Research Repository to achieve the highest level of acceptance, involvement and utilization

xi. Review/evaluate existing trauma data sources and platforms to understand the current landscape of registries and research repositories, and achieve any efficiencies from working in collaboration with others

xii. Initiate identification of existing Common Data Elements and Data Dictionary, beginning with existing NTI funded studies

f) Establish a multi-disciplinary national Steering Committee that will guide the planning, development and implementation of National Trauma Research Repository to achieve the highest level of acceptance, involvement and utilization

g) Review/evaluate existing trauma data sources and platforms to understand the current landscape of registries and research repositories, and achieve any efficiencies from working in collaboration with others.

h) Initiate identification of existing Common Data Elements and Data Dictionary, beginning with existing NTI funded studies

The subaward with UTHSCSA for Dr. Price was terminated when she became a full-time staff member of NTI in February of 2016.

Title: National Trauma Institute: A National Coordinating Center for Trauma Research Funding
Funded by: Department of Defense. W81XWH-11-1-0841
Role: Research Director
Effort: 20%
Amount: $4,145,000
Period of Performance: September 29, 2011 – September 28, 2015
Brief Description: The purpose of this award was to distribute and manage funding for peer-reviewed research projects for areas of greatest impact in trauma, in order to change practice to save lives affected by trauma, and to disseminate research findings to the trauma community.
Specific Aims:

1. The contract will support a national coordinating center for trauma research funding.
   i) Requests for proposals (RFP) based on areas of scientific merit in trauma and emergency or critical care will be prepared and issued.
   j) NTI Board Science Committee will score proposals according to scientific merit, clinical impact, ability to perform the research, innovation, and military relevance.
   k) NTI Board will update trauma research subject areas based upon the impact on survival or care of patients, existing funding, and funding availability annually.
   l) Perform Award management and compliance to include all appropriate USAMRMC HRPO requirements.
   m) Provide research funding for proposals that seek to address areas of urgent need in the treatment of trauma.

xiii. *The Safety and Efficacy of Platelet Transfusion in Patients Receiving Antiplatelet Therapy that Sustain Intracranial Hemorrhage.* PI - Mark Cipolle, MD, PhD, Christiana Health Care System, Newark, DE.

xiv. *Effect of Antioxidant Vitamins on Coagulopathy and Nosocomial Pneumonia after Severe Trauma.* PI – Jean-Francois Pittet, MD, University of Alabama at Birmingham, AL.

xv. *Detection and Management of Non-Compressible Hemorrhage by Vena Cava Ultrasonography.* PI - Jay J Doucet, MD, University of California - San Diego, CA.

xvi. *Splenic Injury Prospective Outcomes Trial.* PI – Ben Zarzaur, MD, MPH, University of Tennessee health Science Center, Memphis, TN and AAST.

xvii. *Transfusion of Stored Fresh Whole Blood in a Civilian Trauma Center: A Prospective Evaluation of Feasibility and Outcomes.* PI – Henry Cryer, MD, UCLA Dept of Surgery, Los Angeles, CA.

xviii. *Acute Lung Injury Ventilation Evaluation (ALIVE) Trial.* PI – Suresh Agarwal, MD, Boston Medical Center, Boston, MA.

xix. *Methicillin-Resistant Staphylococcus aureus in a Trauma Population: Does Decolonization Prevent Infection?* PI – Robert Maxwell, MD, University of Tennessee Health Science Center, Chattanooga, TN.

xx. *Hepcidin and Anemia in Trauma*. PI – Lena Napolitano, MD, University of Michigan Health System, Ann Arbor, MI.

xxi. *Thrombelastography (TEG®) based dosing of enoxaparin for thromboprophylaxis: a prospective randomized trial.* PI – Martin Schreiber, MD, Oregon Health and Science University, Portland, OR.

xxii. Establish a multi-disciplinary national Steering Committee that will guide the planning, development and implementation of National Trauma Research Repository to achieve the highest level of acceptance, involvement and utilization

xxiii. Review/evaluate existing trauma data sources and platforms to understand the current landscape of registries and research repositories, and achieve any efficiencies from working in collaboration with others

xxiv. Initiate identification of existing Common Data Elements and Data Dictionary, beginning with existing NTI funded studies

n) Establish a multi-disciplinary national Steering Committee that will guide the planning, development and implementation of National Trauma Research Repository to achieve the highest level of acceptance, involvement and utilization

o) Review/evaluate existing trauma data sources and platforms to understand the current landscape of registries and research repositories, and achieve any efficiencies from working in collaboration with others.

p) Initiate identification of existing Common Data Elements and Data Dictionary, beginning with existing NTI funded studies

Current

Title: A National Coordinating Center for Trauma Research
Funded by: Department of Defense W81XWH-15-2-0089
Role: Research Director
Effort: 65%
Amount: $4,642,860
Period of Performance: September 30, 2015 – September 29, 2018
Brief Description: The civilian trauma research community can be used as a surrogate for military combat casualty care research, maximizing the return from dollars invested by replacing the expensive and repetitive assembly and disassembly of short-lived clinical investigator

networks with a stable and enduring operational infrastructure for clinical trauma research. As available research funding shrinks and federal budget pressure increases, we must replace the expensive and repetitive assembly and disassembly of short-lived clinical investigator networks with a stable and enduring operational infrastructure for clinical trauma research. This research effort funds two clinical studies, one simulation development, and the development of tools for the collection and dissemination of results and data from studies – the National Trauma Research Repository.
Specific Aims: 1. To manage specific research projects to address military research gaps; 2. To develop tools to allow for the collection and dissemination of results and data from studies.
Overlap?:No

Title: Multinstitutional Multidisciplinary Injury Mortality Investigation in the Civilian Pre-Hospital Environment (MIMIC)
Funded by: Department of Defense. W81XWH-17-2-0010
Role: Research Director
Effort: 20%
Amount: $3,979,380
Period of Performance: March 20, 2017 – March 19, 2021
Brief Description: This study will create a collaborative multi-disciplinary, multi-institutional panel of subject matter experts in the fields of trauma surgery, emergency medicine / pre-hospital / emergency medical services, neurosurgery, radiology and forensic pathology. This Study Group will develop metrics for the injury survival potential in the pre-hospital environment. Teams of Study Group members will conduct record reviews of 3,000 pre-hospital trauma deaths at 6 selected medical examiner offices across the US. These reviews will produce a robust data repository supporting the study of potential mitigation strategies to improve pre-hospital injury outcomes. The central hypothesis for this research effort is that 25% of civilian pre- hospital injury deaths are potentially survivable.
Specific Aims: 1. Develop a framework and methodology for evaluating the causes and pathophysiologic mechanisms of pre-hospital deaths, in order to determine survivability; the appropriateness of EMS response and the care delivered; and the potential for survivability. 2. Organize a multidisciplinary Study Group to apply the methodology to identify causes of pre- hospital deaths due to trauma and estimate the potential for survivability. 3. Define the causes and mechanisms of 3,000 hospital deaths occurring in 6 regions of the country, and estimate the potential for survivability by mechanism of injury, the maturity of the local trauma system, and age of the decedent. 4. Describe the epidemiology of pre-hospital mortality in the context of trauma system development, and estimate impact on society. 5. Develop a blueprint for a sustained effort at public health injury mitigation strategies in the pre-hospital environment, identifying high priority areas for injury prevention, trauma systems performance improvement, and opportunities for advancements in research and development.
Overlap?: No

Title: The Pathogenesis of Post-Traumatic Pulmonary Embolism: A Prospective Mutli-center Investigation by the CLOTT Study Group
Funded: DoD, BA160400
Project Role: Co-I
Effort: 5%
Amount: $4,262,853
Period of Performance: 30 September 2017 – 29 September 2019
Brief Description: This research effort is a multi-center prospective observational study to characterize the risk factors for those with symptomatic, central Pulmonary Embolism (PE) versus those with asymptomatic, peripheral thrombi. Additionally, a subset of five centers will analyze thromboelastography (TEG) results to identify patients with failure of clot lysis (fibrinolytic shutdown). The association between fibrinolytic shutdown and the subsequent development of PE will be explored.

Specific Aims: 1) Explore the hypothesis that small, peripheral, asymptomatic clots seen on computed tomography scans of the chest are not embolic events (PE) from DVT but are instead thrombi associated with inflammation and can be safely observed without specific treatment. 2) Identify patients with fibrinolytic shutdown/failure of clot lysis and to test the hypothesis that these patients are at increased risk for post-traumatic PE.
Overlap?: No scientific overlap. Upon contracting Dr. Price's effort on W81XWH-15-2-0089 will be decreased

Pending

Title: National Coordinating Center for Trauma Research: Damage Control Resuscitation and Remote Damage Control Resuscitation using Cold Whole Blood
Funded by: DoD
Role: Principal Investigator
Effort: 10%
Period of Performance: pending
Brief Description: This research effort is a multi-center prospective observational study to investigate the outcomes of cold whole blood administration in Damage Control Resuscitation and Remote Damage Control Resuscitation patients versus component therapy.
Specific Aims: 1) To examine in a prospective, observational fashion the effects of a pre-hospital RDCR protocol using CWB in the treatment of trauma and burn patients when compared to historic control patients who received RDCR using plasma and pRBC. These data will expand the NTRR with a pre-hospital module facilitating data sharing for resuscitation research in the pre-hospital setting by multiple investigators. 2) To examine in a prospective, observational fashion the effects of an in-hospital DCR protocol using CWB in the treatment of trauma and burn patients when compared to historic control patients who received DCR using plasma and pRBCs. These data will expand the NTRR in-patient module facilitating data sharing for resuscitation research in the hospital setting by multiple investigators.
Overlap?: No scientific overlap. Upon contracting Dr. Price's effort on W81XWH-15-2-0089 will be decreased

Title: Developing a National Trauma Research Action Plan for the United States
Funded by: DoD
Role: Co-Principal Investigator
Effort: 30%
Period of Performance: pending
Brief Description: This research effort will develop a National Trauma Research Action Plan that: 1) unifies the entire U.S. trauma medical community around a prioritized, comprehensive research agenda; 2) develops the optimal tools for long-term functional outcome assessment for injured patients; 3) identifies gaps in current federal funding for trauma research, defines the burden of injury, and recommends increased research funding to address critical gaps; and 4) identifies regulatory barriers to conducting trauma research and develops recommendations for best practices including optimal clinical endpoints.
Overlap?: No scientific overlap. Upon contracting Dr. Price's effort on W81XWH-15-2-0089 will be decreased.

The Coalition for National Trauma Research supports the call for a national trauma research action plan

Raul Coimbra, MD, PhD, Rosemary A. Kozar, MD, PhD, Jason W. Smith, MD, PhD, Ben L. Zarzaur, MD, MPH, Carl J. Hauser, MD, Frederick A. Moore, MD, Jeffrey A. Bailey, MD, Alex Valadka, MD, Gregory J. Jurkovich, MD, Donald H. Jenkins, MD, Kimberly A. Davis, MD, MBA, Michelle A. Price, PhD, *and* **Ronald V. Maier, MD**, *San Diego, California*

Several forums have been convened in the last two decades regarding civilian research priorities in trauma, including but not limited to National Institutes of Health (NIH) roundtables, Centers for Disease Control meetings, and others.[1–3] In 2015, the NIH and American College of Surgeons (ACS) convened a group of 60 leading researchers and clinicians to develop a national surgical disparities research agenda.[4] Most recently, the National Academies of Sciences, Engineering and Medicine (NASEM) released a report calling for a national, integrated, military-civilian plan to achieve zero preventable deaths after injury.[5] This aim (zero preventable deaths) is similar to other national goals to spur progress in treatment research for challenging health conditions such as infectious disease (i.e., "the countdown to the cure" for HIV) and cancer (i.e., the "moonshot" to end cancer).[6,7] Among the recommendations in that report was the formation of a National Trauma Research Action Plan requiring a resourced, coordinated, joint approach to trauma care research.[5] With the emergence of new scientific and clinical paradigms, the need for an updated research agenda is evident. As new knowledge is incorporated into clinical practice and new challenges in clinical care are identified in both civilian and military environments, research remains the driving force behind advances in the care of injured patients. Overlapping priorities among the military casualty care and civilian trauma care communities mandate the formulation of a new combined research agenda.

The current ongoing military conflicts in Iraq and Afghanistan and the global war on terror have brought to light the need for strong collaboration between civilian and military sectors in clinical care, training, education, and particularly in research. The NASEM report examined how the US military's use of focused empiricism to reduce morbidity and mortality after injury might have implications for improving care in civilian settings.[8] Research manpower and capacity are clearly abundant in the civilian sector, and the US Department of Defense (DoD) is of utmost importance in research funding and priorities (Fig. 1). Currently, DoD funding represents more than 80% of the United States federal government's annual investment in trauma care research.[8]

In 2014, the American Association for the Surgery of Trauma (AAST) and National Trauma Institute (NTI) began discussing the need for a unified, stronger voice to advocate for additional trauma research funding, as well as a mechanism to conduct large multi-institutional clinical trials. This discussion, initially held at the headquarters of the ACS, escalated rapidly. Several months later, the Coalition for National Trauma Research (CNTR) was formed to include not only the AAST and NTI, but also the ACS Committee on Trauma, Eastern Association for Surgery of Trauma (EAST), and Western Trauma Association (WTA).[10] CNTR is focused on developing a centralized national trauma research agenda that establishes priorities and eliminates redundancies in both civilian and military injury treatment, building a robust trauma research infrastructure that includes a Trauma Clinical Trials Network, and securing consistent and significant federal funding for research that increases the understanding of injury and informs clinical practice.[11,12]

CNTR's Executive Committee established three working committees: the Clinical Trials Network Committee (CTN), the National Trauma Research Repository Committee, and the Research Agenda (RA) Committee. The CTN Committee is charged with developing a national clinical trials network, comprising trauma research centers of various sizes and capabilities, using a fair and publicly available process with representative geographic distribution. This committee collaborates and coordinates activities with the AAST Multi-Institutional Trials Committee as well as the CNTR RA Committee. The National Trauma

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1. Unit-based prehospital trauma registries
2. Food and Drug Administration (FDA)-approved freeze-dried blood products (such as plasma and platelets)
3. Clinicopathological review of every U.S. Combat fatality, including preventable death analyses from combat units
4. Development and testing of non-compressible torso and junctional hemorrhage control devices
5. Optimized airway devices and training
6. Optimized fluid resuscitation for casualties with TBI and shock
7. Training and evaluation methods for Traumatic Combat Casualty Care (TCCC) skills
8. Impact of TCCC interventions in preventing Post Traumatic Stress Disorder (PTSD) and TBI, including the role of analgesia in preventing PTSD
9. Combat casualty care monitoring devices
10. Impact of Tactical Evacuation (TACEVAC) provider level and skill sets on survival

Figure 1. Defense Health Board research, development, training, and evaluation high priorities.[9]

Research Repository Committee is charged with establishing a multidisciplinary steering committee that will guide the planning, development, and implementation of an electronic database that combines civilian trauma registries, such as the National Trauma Data Bank of the ACS, and—as permissible—military trauma data repositories to create the "big data" necessary to define and explore critical issues. Additionally, the trauma research repository is envisioned to contain the data elements of all studies funded and implemented through CNTR activities. The RA Committee is charged with developing a national trauma research agenda that reflects scientific questions and research gaps, both civilian and military, based on a review of relevant and recent work groups or publications by other trauma organizations or entities. The committee's charge also includes prioritizing the agenda so that resources will be directed toward the questions needing answers first, and clinical trials related to these questions will evolve over the next five to 10 years.

METHODS

The CNTR RA Committee is comprised of 10 expert scientist-practitioners in the care of injured patients. AAST, WTA, EAST, and NTI each nominated surgeons and/or injury researchers to serve on the committee (Table 1). A member of the CNTR Executive committee served as an ex officio member of the committee. Using conference call technology, the RA Committee met three times during January and February 2015. Each member was asked to review DoD documents and literature provided,[1,2,9,13] and to list research topics/priorities and gaps in three domains: clinical, translational, and mechanistic trauma research. A modified Delphi process was used for the collection of research priorities.[1] Topics were compiled after three rounds of analysis and comments by the committee members. There was a high level of concurrence among committee members in identifying the research topics and gaps (80%). The committee members determined that the "Clinical" and "Translational" domains should be combined, and hence, the final product is organized into two domains, clinical/translational and mechanistic. The lists were reviewed by the RA Committee members and approved for discussion with the CNTR Executive Committee.

In addition to a list of priorities, the RA Committee was asked to provide a condensed prioritized document, which would be aligned with the gap analysis already performed by the DoD for military casualty care research. The priority areas are, therefore, those that are intended to be relevant for both the civilian and military sectors. Specifically, the RA Committee was asked to provide three major focus areas with described goals and specific projects suggested. The final work condensed the lists of research topics. The research priorities were presented to the CNTR leadership. The Executive Committee of CNTR reviewed the RA Committee's work and considered it a comprehensive template to guide future funding and research programs.

RESULTS

There are three major focus areas in which there is considerable overlap between military casualty care research and civilian trauma care research needs. These are acute resuscitation topics, central nervous system trauma, and transfer to definitive care (Table 2). Under the clinical/translational domain, the research priorities focus on three areas. The first large area focuses globally on resuscitation, including optimal timing for and type of resuscitation fluids, endpoints for resuscitation, methods of hemorrhage control, and the identification and management

TABLE 1. CNTR Research Agenda Committee

Member	Representation/Affiliation
Raul Coimbra, MD (Chair)	AAST
Ronald V. Maier, MD (Co-Chair)	AAST
Alex Valadka, MD	AAST
Jason W. Smith, MD, PhD	EAST
Ben L. Zarzaur, MD	EAST
Jeff A. Bailey, MD	NTI
Frederick A. Moore, MD	NTI
Carl J. Hauser, MD	WTA
Rosemary A. Kozar, MD, PhD	WTA
Gregory J. Jurkovich, MD	CNTR Executive Committee—Ex officio member

of coagulopathies and their contribution to posttraumatic thromboembolic disorders. Sequelae of massive resuscitation, including the development of multisystem organ dysfunction and wound healing dyscrasias, were included in this topic area. The second large area under the clinical/translational domain is specific patient populations, with a focus on patients with central nervous system injury. Optimal management strategies in these two disparate populations and outcomes are included. The final large category under the clinical/translational domain focuses on the prehospital environment and the development of trauma systems of care. Specific to this area is the development of registries to facilitate data capture. Details of the clinical/translational domain are illustrated in Figure 2.

The second major domain for trauma research priorities is mechanistic. Topics for study in this domain include mechanisms of immune modulation, the impact of genomics on the response to trauma and outcome trajectories, and the identification of novel targets for therapy (Fig. 3). Although mechanistic research is not the focus of CNTR, it is important for the advancement of trauma research as a whole.

DISCUSSION

In examining the multitude of priorities and needs for trauma research, the RA Committee was particularly interested in examining scientific questions that would address both civilian and military trauma surgeon needs. To that end, the three major topics (Table 2) of acute resuscitation, central nervous system injury, and the interface between field (prehospital) care and definitive (hospital) care rose to the top.

In the area of acute resuscitation, it was determined that focused research efforts yielding the greatest benefit to injured patients (and soldiers) would be clinical trials on novel fluid resuscitation strategies that could potentially minimize ischemia and reperfusion injury, and prevent or treat the development of coagulopathy. It was theorized that a combination of new or developing pharmacologic agents, blood substitutes, or more durable forms of blood and plasma storage (lyophilized or dried formulations) could address these needs. It was determined that prospective, randomized trials comparing different treatment strategies including, but not limited to, forms of inflow occlusion (resuscitative endovascular balloon occlusion of the aorta), aortic cross-clamping, direct hemorrhage control and novel packing agents, etc., in severe traumatic shock are also needed to refine the indications and results of each method. Studies are also needed to determine the safety, efficacy, and effectiveness of modulators of inflammation and coagulation, specifically blood component therapy, procoagulation complexes, fibrinogen, and other procoagulant agents. This would include the specific role of modulators on perception and treatment of pain. Additionally, the effect of resuscitation strategies on the development of heterotopic ossification and functional limb outcomes should be prioritized.

Central nervous system injury, a second major area of interest that crosses multiple disciplines, encompasses both direct impact and blast injury. The committee selected three specific goals of research: better methods of diagnosing and characterizing brain injury; better methods of preventing brain injury and its sequelae, and better methods of predicting outcome of brain injuries to provide the resources needed for recovery. Multimodal imaging and biomarkers can be used for diagnosis, follow-up, and determination of outcomes following TBI. Multiwell plates to measure biomarkers known to be related to TBI-could be used to create a risk index to predict intracranial hemorrhage in mild to moderate injury patients, and to predict progression of injury in moderate to severely injured patients. The correlation of clinical data, biomarkers, and imaging could lead to the development of more timely and specific treatment strategies. In addition, the biomarker levels could be used to improve selectivity of patients who require cerebral computed tomography following mild to moderate injury to reduce overall radiation exposure and to improve prediction/detection of progression of brain injury, as well as identification of patients who require earlier or more frequent re-imaging or surgical intervention. TBI studies should have long-term follow-up to estimate and measure quality of life; to validate CDE, Patient Reported Outcomes Measurement Information System (PROMIS), Quality of Life in Neurological Disorders, and NIH Toolbox initiatives; and to utilize neurocognitive testing. This would include impact on recovery from concomitant extremity injury, especially when blast is the mechanism.

The third overlapping area of civilian and military trauma care is the interface between field care and hospital care. This area includes the most time-sensitive injuries, and the research agenda suggests that focus areas that might lead to improved outcomes by the most rapid interventions include physiologic derangements, improved communication strategies and tools between these areas of care, and finally, novel management strategies for the prehospital/field arena. The study of the interface between the prehospital system and the definitive care

TABLE 2. Overlapping Trauma Research Priorities in Military and Civilian Settings

Major Areas	Goals	Specific Projects
Acute resuscitation	Hemorrhage control and resuscitation	Novel fluids, components or transfusion, modulation of coagulation, and inflammation
Central nervous system injury	Diagnosis, brain protection, outcomes	Multimodal imaging, biomarkers of injury, prevention/limitation of secondary brain injury, outcome predictions by multimodal monitoring, maxillofacial trauma related to TBI
Scene to definitive care interface	Improve physiology, communication, and management interface	Advanced monitoring, automated decision support technology, wireless data and image transmission, interface hospital-based physicians with prehospital nonphysicians, prehospital hemorrhage control strategies

Clinical/Translational

RESUSCITATION

- Optimal resuscitation strategies
- Shock resuscitation
  - Fluids
    - Freeze-dried plasma
    - Blood products
      - Whole blood
      - 1:1:1 component therapy
      - 1:1 component therapy
      - Plasma alone
      - Cold-stored platelets
  - Genomics/Proteomics – defining trends in inflammatory response to blunt trauma and identifying possible biomarkers to guide resuscitation and predict outcome trajectories
  - Novel adjuncts to resuscitation: Modulation of coagulation/inflammation
    - Drugs
    - Fibrinogen
  - End points
    - Cardiovascular Reserve Monitor-Driven Resuscitation from Hemorrhagic Shock
    - Tissue oxygenation monitoring
    - Use of transesophageal echocardiography and/or transthoracic ultrasonography in optimizing shock resuscitation
    - Develop novel technology to assist clinicians in shock resuscitation (computer software guided resuscitation, new technologies to monitor patients, etc.)
  - Attenuation of metabolic demand and extension of viability (suspended animation)
  - Extremity injury management effects of resuscitation, including the development of heterotopic ossification

HEMORRHAGE CONTROL

- Novel means of hemorrhage control
- Endovascular hemorrhage control
- Development of innovative technologies to be used in pre-hospital management of hemorrhaging patient
- REBOA- identify optimal patients, device, technique +/- imaging
- Prospective trial on the utilization of REBOA in trauma patients with hemorrhagic shock. Comparison of REBOA to resuscitative thoracotomy.
- Determine effect of REBOA on mortality, identify ideal time and patient population to utilize REBOA.
- Determine institutional characteristics hospital type, trauma level, location of resuscitation bay, presence/absence of in house trauma attending, vascular attending, interventional radiology attending, hybrid operating room, etc. for evaluation of extremity salvage and functional outcome in those with extremity injury.

COAGULATION/COAGULOPATHY

- Development of strategies to utilize thromboelastography (TEG) to control traumatic coagulopathy
- Effect of new class of anticoagulants (e.g., rivaroxaban) on bleeding risk in elderly
- Acute coagulopathy of trauma
  - Identification
  - Prevention
  - Correction
    - Procoagulant concentrates
    - Tranexamic Acid (TXA)
- The role of TEG in the management of coagulopathy after trauma, focused on the impact of patient co-morbidities and medication use.
- Optimal platelet storage and preservation

Figure 2. Clinical/translational trauma research priorities.

- Understanding the interplay between coagulation and inflammation after trauma
- Approaches to correct acute coagulopathy during massive transfusion.

BIOMARKERS/GENETIC PROFILING/POCT/RISK MODELING

1. Biomarkers to predict:
   - Injury severity
   - Injury severity response – time
   - Shock and shock response
   - Inflammation following severe injury and shock
   - TBI (GFA, NSE, S100 and ceruloplasmin)
   - Polytrauma
   - Early biomarkers of severe injury (predict transfusion, need for surgery)
   - Early biomarker of increased venous thromboembolism (VTE) risk
   - Early biomarker of increased heterotopic ossification risk
   - Early biomarker of increased pain and long term pain syndromes

2. Therapeutic targets
   - Human specific genes or gene pathways
   - Signaling

3. Development of applications for risk prediction
   - Creation of an application that incorporates complex risk models including Trauma and Injury Severity Score (TRISS), Revised Injury Severity Classification (RISC/RISCII) as well as injury specific risk adjustors (like out unplanned intubation risk calculator) that can be used to rapidly predict risk at time of patient admission. +/- incorporation of technology into an electronic medical record (EMR). May include continuous updates with information that is gathered over time such as Acute Physiology and Chronic Health Evaluation (APACHE), Sequential Organ Failure Assessment (SOFA) etc., that can be used to give a daily "overall risk" for mortality like a "5th" vital sign that will be displayed to physicians whenever vital signs are checked and may prompt an upgrade or downgrade in level of care based on risk. This may also be used to predict functional extremity outcome and development of pain syndromes.

VENOUS THROMBOEMBOLISM (VTE)/DEEP VEIN THROMBOSIS (DVT)

- Optimal strategy for VTE prophylaxis (dosing interval, algorithm, dose adjustments)
- Oral anti-Xa inhibitor for inpatient VTE prophylaxis
- Duration of VTE prophylaxis post-discharge
- Long term morbidity for patients with VTE after trauma
- DVT Prophylaxis
  - Continuation and duration of Lovenox after discharge, and the immobility factor?
  - Prolonged VTE prophylaxis after spine injury: quadrapalegic vs paraplegic?
  - When is it safe to start prophylaxis after spine surgery?
- Trial to determine the safety and efficacy of early pharmacologic VTE prophylaxis in trauma patients with spinal fractures with and without spinal cord injury. Variables of interest include type of fracture, patient demographics, surgical intervention. Outcomes include bleeding, progression of neurological injury, need for surgery, epidural hematoma, VTE, mortality.

TRAUMATIC BRAIN INJURY (TBI)

- Optimal resuscitation strategies after TBI
- Intracranial pressure (ICP) monitors and outcome
- Interstitial oxygenation monitoring and optimization
- Hypernatremia in TBI: bolus vs. infusion, dose, sodium target, and duration
- Comparative efficacy of reversal strategies for patients on anticoagulants and anti-platelet agents. Examine effects, if any, of prothrombin complex concentrate (PCC), plasma, platelet transfusion, desmopressin (DDAVP), dialysis, or other reversal agents on progression of brain injury, need for surgical intervention in TBI, mortality, complications, and neurological outcome.
- Impact of New Technologies and Assays:
  - TEG
  - Thrombogram
  - "Plavix" assay

Figure 2. Continued

facility is important to allow for the development of better care at the scene and during transport in civilian as well as in military austere settings.

In most urban systems, transport time is short, and there is very little time for interpretation of data prior to implementing life-saving interventions. In the battlefield, this time from injury

ORGAN FAILURE/SEPSIS/Multiple Organ Failure (MOF)/Intensive Care Unit (ICU) Care

- Organ insufficiency and failure
  - Risk stratification and early identification
  - Organ replacement therapy
    - Cardiopulmonary
    - Hepatic
    - Renal based on AKIN classification
    - Pulmonary – extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS)
- Modern classification and assessment of post traumatic sepsis and MOF
- Impact of nutrition and mobility on outcomes after ICU admission
- ECLS after trauma
- Study feasibility of developing regional centers of excellence in resource intense therapies – i.e., – ECMO / ECLS
- Computer based algorithm to detect risk of clinical deterioration/transfer to ICU for patients on floor/Intensive Medicine Unit (IMU)
- The timing of an optimal method of tracheostomy: examining the possible benefits of early tracheostomy in specific patient populations and outcomes relative to the technique used.
- Sedation and analgesia regimen to limit delirium after traumatic and septic shock
- Closed loop clinical decision support to provide basic ICU care (e.g. ICP management, ventilator management, resuscitation)
- Early exercise and physical therapy in the ICU
- Optimize perioperative care to limit acute kidney injury
- Optimal antibiotics in treating nosocomial infections
- Strategies to limit nosocomial infections
- Polymerase chain reaction (PCR) based early detection of bacterial pneumonia
- Effect of prolonged shock on organ injury and recovery
- Effect of aortic occlusion on organ injury and MOF
- Effect of aortic occlusion on functional extremity salvage

ELDERLY

- Long term outcomes after trauma in the elderly – functional recovery and mortality
- Quality improvement for geriatric trauma
- Elderly TBI - Effectiveness of pathways and bundles
  - Cohort elderly patients in a unit
  - Establishing sleep/wake immediately
    - Dim the lights at 9pm on at 7am
    - Soothing music
  - Swallow evaluation and timing
  - The role of early enteral tube feeding in patients with altered levels of consciousness in the prevention of aspiration
  - Mobility
- Elderly rib fractures
  - Mobility
  - Respiratory therapy
  - Pain control algorithm
- Performance improvement and outcomes assessment of the geriatric trauma patient, with a focus on the identification of appropriate metrics
- Ethical decision making in Elderly trauma patients

TRAUMA SYSTEM/TRAUMA CENTERS/REGISTRIES

- Development of formula/paradigm for optimal placement of trauma centers (Can we develop an echelon system within the US?)
- Study feasibility of developing surgical strike teams for rapid deployment to rural hospitals or disaster areas for management of (multiple?) bleeding patients
- Develop technology to automate population of registries with data
- EHR and Registry Interaction
  - Data acquisition
    - Epidemiology
    - Mechanism

Figure 2. Continued

        - Physiology
        - Injury Severity
        - Biomarkers
        - Interventions
        - Co-morbidity
        - Morbidity
        - Autopsy
        - Pre-hospital data management
            - Registries
            - Automated data collection
            - Remote virtual management augmentation
    - Analytics
        - Performance metrics and outcomes
        - Risk identification and adjusted benchmarks
    - Enhanced interoperability and data sharing

- Preventable causes of mortality
- Evaluation of impact of hybrid OR's. Outcomes of interest mortality/morbidity following orthopedic injuries, vascular injuries, time to definitive control of hemorrhage, need for repeat surgical/interventional procedures, transfusion requirements, cost/charges. Variables to study, presence/absence of hybrid OR, location of hybrid OR, service primarily involved (vascular, IR, trauma surgery), teaching facility, trauma level, hospital size, trauma volume, percent penetrating injuries.

PREHOSPITAL

- Novel pre-hospital diagnostics and therapeutics
- Optimal use of blood products in the pre-hospital setting
- Optimal use of military CCCT techniques in the civilian pre-hospital environment (Tourniquets, Combat Gauze, Celox, etc.)
- Pre-hospital (pre-surgical) hemorrhage control
    - Truncal (thoracic, abdominal, pelvic)
    - Junctional
    - Extremity (including analysis of salvage and function)
- Advanced pre-hospital resuscitation during prolonged transportation times
- Video streaming to trauma centers from pre-hospital (scene and ambulance)
- Real time data streaming of physiologic data from pre-hospital to trauma centers
- Pre-injury environment/transportation and relationship to post-injury recovery and outcome following major trauma

WOUND HEALING AND PAIN CONTROL

- Novel methods of optimizing wound healing, especially in craniomaxillofacial injury as well as prevention of heterotopic ossification in extremity injury
    - New Drugs
    - Gene Therapy
    - Others
- Novel use of current pain agents, continuous versus bolus and utilization of novel pain control agents to optimize recovery and long term functional outcomes

Figure 2. Continued

to definitive care may be longer, as it would be in many rural or austere environments. The development and testing of miniaturized biomonitoring systems that allow advanced assessment and interpretation of the physiologic response to injury, linked to automated decision support systems that inform medics about interventions needed in a timely fashion, may improve prehospital trauma care. These data points, as well as real-time video streaming at the scene and during transport, could be transmitted wirelessly to definitive care facilities (trauma centers, forward surgical hospitals) for resource mobilization and team preparation. Studies could be designed to measure the impact of data and image transmission from the prehospital to the hospital setting in terms of resource utilization, timing of interventions (e.g., intubation, chest tube placement, diagnostic peritoneal aspiration, etc.), improved resuscitation (e.g., early use of blood or novel agents), and cost. Ultimately, the data transmitted from the prehospital phase of care should be incorporated into trauma registries.

In selected groups of bleeding patients, the development and application in the prehospital phase of novel techniques and/or drugs to achieve bleeding control should be performed. Studies on the effectiveness of prehospital administration of blood, blood components, and procoagulant factors should be performed. Techniques (devices or substances) used to temporarily control junctional or cavitary hemorrhage should be tested. Time to definitive care and monitoring of physiologic

- Mechanisms contributing to age-related outcomes after trauma
- Genomics of trauma to predict outcomes
- Mechanisms of coagulopathy of trauma and TBI
- Identify novel methods/compounds for restoring hemostasis following hemorrhagic shock induced coagulopathy
- Influence of microbiota of outcomes after trauma
- Mechanism of immune suppression/alteration following severe TBI
- Molecules as therapeutic targets after hemorrhage
- Identify alternative resuscitation strategies/methods for correcting shock and its underlying physiologic derangements.
- Acute Coagulopathy of Trauma (ACOT)
- Ischemia reperfusion identification and prevention/treatment
- Attenuation of metabolic demand and extension of viability (suspended animation)
- Biomarkers and genetic profiling
    - Injury Severity
    - Injury severity response – time
    - Shock
    - TBI
    - Polytrauma including extremity salvage and function
- Therapeutic targets
    - Human specific genes
    - Signaling
- Improved animal models of injury (polytrauma models, humanized mice)
- Human specific genes
- Mechanism of trauma induced coagulopathy
- Gut and lung microbiome (effect on SIRS, effect on nosocomial infection)
- Exosomes as mediator of SIRS
- Regenerate or reverse extremity dysfunction with stem cell therapy
- Extend survival and limit organ failure after hypotensive resuscitation
- Regenerate or reverse TBI and SCI with stem cell therapy
- Optimal fluid resuscitation for shock resuscitation
- Regenerate or reverse craniomaxillofacial injury with stem cell therapy
- Early genomic and proteomics responses to trauma and septic shock
- Tracking and treatment of late inflammation and immunosuppression after trauma and septic shock
- Mechanisms of diminished resistance to infection after injury
- Mechanisms of the perpetuation of inflammation (and thus organ failure) after injury
- Non-antibiotic means of diminishing infection and the emergence of resistant organisms.

Figure 3. Mechanistic trauma research priorities.

response to resuscitation may impact type and degree of options for extremity injury reconstruction and will be subject to thorough investigation, especially in the multiple injuries patient.

In conclusion, research in the areas of acute resuscitation, central nervous system injury, and the interface between field (pre-hospital) care and definitive (hospital) care addresses gaps in knowledge that impact the care of both civilian and military critically injured patients. The DoD's Combat Casualty Care Research Program and the military's learning health system have already resulted in knowledge or materiel solutions in these areas.[8] Successful execution of the research agenda proposed herein would go a long way to address the NASEM report goal of achieving zero preventable deaths after injury.[5] CNTR views the NASEM report to be in complete alignment with its mission and will continue to advocate for the development of a National Trauma Research Action Plan.[14]

AUTHORSHIP

R.C., R.V.M., G.J.J., and M.A.P. conducted the literature search. R.C., R.V.M., A.V., J.W.S., B.L.Z., J.A.B., F.A.M., C.J.H., R.A.K., G.J.J. served on the CNTR Research Agenda Committee. R.C., R.V.M., and G.J.J. conducted data analysis. R.C., R.V.M., G.J.J., D.H.J., K.A.D., and M.A.P. wrote the article. R.C., R.A.K., A.V., J.A.B., G.J.J., D.H.J., K.A.D., M.A.P., R.V.M. assisted with critical revisions.

DISCLOSURE

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The authors declare no conflicts of interest.

REFERENCES

1. Nathens AB, Rivara FP, Jurkovich GJ, Maier RV, Johansen JM, Thompson DC. Management of the injured patient: identification of research topics for systematic review using the delphi technique. *J Trauma*. 2003;54(3):595–601.
2. Cairns CB, Maier RV, Adeoye O, Baptiste D, Barsan WG, Blackbourne L, Burd R, Carpenter C, Chang D, Cioffi W, et al. NIH Roundtable on Emergency Trauma Research. *Ann Emerg Med*. 2010;56(5):538–550.

3. Kaji AH, Lewis RJ, Beavers-May T, Berg R, Bulger E, Cairns C, Callaway C, Camargo CA Jr, Carcillo J, DeBiasi R, et al. Summary of NIH Medical-Surgical Emergency Research Roundtable held on April 30 to May 1, 2009. *Ann Emerg Med*. 2010;56(5):522–537.
4. Haider AH, Dankwa-Mullan I, Maragh-Bass AC, Torain M, Zogg CK, Lilley EJ, Kodadek LM, Changoor NR, Najjar P, Rose JA, et al. Setting a national agenda for surgical disparities research: recommendations from the National Institutes of Health and American College of Surgeons Summit. *JAMA Surg*. 2016;151(6):554–563.
5. National Academies of Sciences E, and Medicine. A national trauma care system: Integrating military and civilian trauma systems to achieve zero preventable deaths after injury. Washington, DC: The National Academies Press, 2016.
6. Holcomb JB, Hoyt DB. Comprehensive injury research. *JAMA*. 2015;313 (14):1463–1464.
7. Rasmussen TE. A national trauma care system: from call to action. *J Trauma Acute Care Surg*. 2016;81(5):813–815.
8. Rasmussen TE, Kellermann AL. Wartime lessons—shaping a national trauma action plan. *N Engl J Med*. 2016;375(17):1612–1615.
9. Defense Health Board. Battlefield Medical Research, Development, Training and Evaluation Priorities, 2012-08. Defense Health Headquarters, 7700 Arlington Boulevard, Suite 5101, Falls Church, VA 22014-5101: 2012.
10. Cioffi WG. American Association for the Surgery of Trauma Presidential Address. *Seventy-third Annual Meeting of the American Association for the Surgery of Trauma and Clinical Congress of Acute Care Surgery*. September 11, 2014; Philadelphia, PA.
11. Cioffi WG. Responsibility. *J Trauma Acute Care Surg*. 2015;78(4):661–70.
12. Price MA, Beilman GJ, Fabian TC, Hoyt DB, Jurkovich GJ, Knudson MM, MacKenzie EJ, Marshall VS, Overton KE, Peitzman AB, et al. The National Trauma Institute: lessons learned in the funding and conduct of 16 trauma research studies. *J Trauma Acute Care Surg*. 2016; 81(3):548–554.
13. Defense Health Board. Battlefield Trauma Care Research, Development, Test and Evauation Priorities 2011–01. 2011.
14. Jenkins DH, Cioffi WG, Cocanour CS, Davis KA, Fabian TC, Jurkovich GJ, Rozycki GS, Scalea TM, Stassen NA, Stewart RM Coalition for National Trauma Research (CNTR). Position statement of the Coalition for National Trauma Research on the National Academies of Sciences, Engineering and Medicine report, A National Trauma Care System: Integrating Military and Civilian Trauma Systems to Achieve Zero Preventable Deaths After Injury. *J Trauma Acute Care Surg*. 2016;81(5):816–818.

Safety and Efficacy of Ketamine for Acute Burn Pain in Austere Conditions

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- Department of Psychiatry & Behavioral Sciences
- Department of Neuroscience

Johns Hopkins Institute For Clinical and Translational Research

Johns Hopkins Bayview Medical Center

- Johns Hopkins Burn Center
- Nursing
- Research Pharmacy

NATIONAL TRAUMA INSTITUTE

Background/Scientific Rationale

The Problem: Acute Burn Pain Management in Austere Conditions

Standard of Care for Acute Burn Wounds

- Wound Care Sessions: Twice daily for adults with acute intermediate and/or deep partial thickness burns.
- Pain During Each Sessions: Severe pain during dressing removal, debridement, wound cleansing, re-application of topical ointment, and dressing replacement. Especially during the first week.
- Standard Pain Management: intravenous opiate medications (i.e., fentanyl).

Military & Civilian:

- Urgent need: for a well-controlled and rigorously designed study with sufficient power to test definitively the hypothesis that fentanyl when augmented with low-dose, slow-infusion ketamine provides superior analgesia in the acute burn setting.
- Findings from acute burn centers are likely to generalize to a number of austere trauma settings, including injuries sustained in a battlefield setting.

NATIONAL TRAUMA INSTITUTE

Background/Scientific Rationale

Opiates as Mainstay for Acute Burn Pain Management

Opioid Treatments:

- Opiate Side Effects:
  - Diminished cognitive & physical function
  - Suppression: Respiratory, Cardiac & Digestion/Excretion
- Comorbidities & Outcomes
  - Impaired cognitive and physical function on core military tasks
  - Downward Spiral: Tolerance-Dependence-Addiction
  - Under-treated Acute Pain-Central Sensitization-Chronic Pain
  - Chronic Pain associated with higher rates of Opiate Dependence, PTSD, Depression

NATIONAL TRAUMA INSTITUTE

Background/Scientific Rationale:
Ketamine Augmentation of Opiate Medications for Acute Burn Pain Management

Ketamine: Opioid Augmentation, Sub-anesthetic, low-dose, slow infusion

- Ketamine Side Effects:
  - **Diminished response time** but not precision on key military tasks
  - **Dissociation, confusion** – less severe, less frequent, briefer duration with low-dose, slow infusion
- **Comorbidities & Outcomes:** Abuse potential, Possible neurotoxicity (high doses, administered quickly via IV, in chronic abusers)

NATIONAL TRAUMA INSTITUTE

Low Dose Ketamine for Analgesia in Acute Pain

The evidence base is solid and expanding for the safety and efficacy of ketamine either alone or as adjuvant analgesia in:

Emergency Department

- Multiple systematic reviews/meta-analyses
- Safe, Effective, across diverse severe pain populations

Pre-hospital Transport

- Multiple publications, consistent pain reduction findings
- *Safe, Effective, in transport, EMTs*

Ketamine Analgesia: Mechanism & Relation to Opioid Effect

NMDA Receptor function – Potentiates painful stimuli (hyperalgesia, central sensitization);

KETAMINE – NMDA Receptor Antagonist with “slow off rate”

Also, in combination with Opiates:

- Augments opioid mu-receptor function by potentiating “downstream” opioid-induced phosphorylation and thus requiring lower opioid doses for equal phosphorylation.
- Delays opioid receptor desensitization, improves resensitization, thus prolonging opiate effect

Ketamine for Mood Disorder and Posttraumatic Stress Disorder

The evidence base is also solid and expanding for the safety and efficacy of ketamine for PTSD and Major Depressive Disorder:

Ketamine: Low dose, slow infusion - Rapid relief for 1-2 weeks

Chronic PTSD:

- Accruing military & civilian samples, diverse trauma

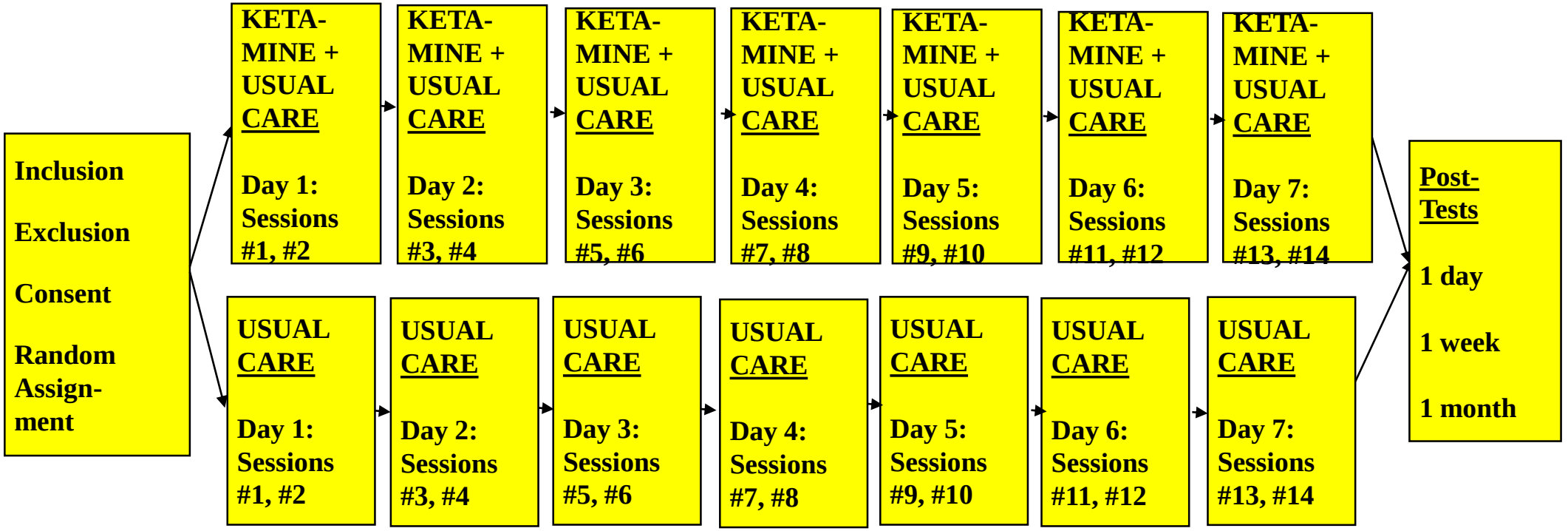
Treatment Resistant MDD:

- Years of failed drug trials

Suicidal Ideation / Imminent Risk of Suicide

- Possible Treatment Component: Cognitive Impairment

KETAMINE FOR ACUTE BURN PAIN
Study Design & Flow Diagram



DESIGN: This is a randomized, controlled, parallel group trial, utilizing repeated treatments, Triple-blinding

Study Hypotheses/Aims

Specific Aim #1: To test the safety and effectiveness of ketamine augmentation to usual care relative to Usual Care alone in reducing the severity of acute nociceptive pain during burn wound care.

a. *Mean Pain; *mean Pain Unpleasantness
b. *Time to Maximal Pain Relief
c. *Recall Effect on Pain
d. *Sympathetic Arousal (HR, HRV, BP, RR)
e. *Satisfaction with Pain Management
f. Central Sensitization: Secondary Hyperalgesia; Allodynia.

*Average of 14 sessions, and, Trajectory across sessions 1-14 and follow-up.

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Study Hypotheses/Aims

Specific Aim #2: To determine whether adjunctive ketamine is associated with opiate sparing.

Opiate Sparing Effect: Significant mean group difference across treatment arms in the request for supplemental analgesic medications.

Prior Findings: Ketamine in one study were reported to be equally effective as opiates but much more rapid in achieving maximum pain relief in burn wound care

Measure: Requests for Additional Analgesic Medications (i.e., RAAMs) for acute nociceptive pain during each wound care sessions (7 Days, 14 Sessions).

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Study Hypotheses/Aims

There are Two Secondary Outcomes:
Rates and symptom severity of:
1) Posttraumatic Stress Disorder (i.e., ASD and PTSD), and
2) Major Depressive Disorder (MDD):

Prior Findings:
Pain and PTSD are highly correlated, and, are reciprocally related over time (Mutual Maintenance Theory).

Ketamine drastically reduces chronic PTSD and chronic Treatment Resistant Depression for up to 2 weeks.

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Study Hypotheses/Aims

There are 12 mediators of outcome:

RISK FACTORS

Preburn:

- Pain History
- Drug/Alcohol History
- Psychiatric History
- Trauma History

Sympathetic Arousal

Pain-related Anxiety

Pain Catastrophizing

PROTECTIVE FACTORS

Sleep (quality, duration)

Emotion Regulation

Pain Coping

Optimism

Trauma Resilience

Benefit Finding

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Study Sample & Methods

SAMPLE: 94-104 acute adult burn patients hospitalized in the Johns Hopkins Bayview Medical Center's Johns Hopkins Burn Center (Burn Intensive Care Unit) who have sustained burns ≥2% and ≤40% total body surface area (TBSA ≥2% & ≤40%).

ASSIGNMENT: Subjects will be randomly assigned to either a fentanyl ("usual care") + saline (UC) condition, or to fentanyl (usual care) plus ketamine (K + UC) condition.

STUDY DRUG ARM: Subjects in the K + UC condition will receive low-dose, slow-infusion ketamine (see information below on medications, dosing, timing etc.).

USUAL CARE ARM: Subjects in the UC condition will receive fentanyl plus normal saline instead of fentanyl plus ketamine.

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KETAMINE STUDY ARM (Fentanyl PLUS Ketamine)

i. Ketamine Loading Dose (Study Drug, slow infusion) = 0.3 mg/kg

Initiated 10-minutes prior to wound care and infused over 3 minutes.

THEN, …

ii. Fentanyl Loading Dose = 1 mcg / kg

This is given to participants in both Group 1 and Group 2 starting at <1 minute before wound care is initiated.

THEN, …

iii. Ketamine (Study Drug, Infusion): 2.5 mcg/kg/min

Initiated immediately following the Loading Dose and continued for the duration of the session.

USUAL CARE STUDY ARM (Fentanyl PLUS Saline)

i. Saline Loading Dose (Placebo, slow infusion) = An identical volume of saline as that in 0.3 mg/kg of ketamine.

Initiated 10-minutes prior to wound care and infused over 3 minutes.

THEN, …

ii. Fentanyl Loading Dose (Usual Care, Injection) = 1 mcg / kg

This is given to participants in both Group 1 and Group 2 starting at <1 minute before wound care is initiated.

THEN, …

iii. Saline (Placebo, Infusion): 2.5 mcg/kg/min

An identical volume of saline as that in 2.5 mcg/mg/min of ketamine.

Initiated immediately following the Loading Dose and continued for the duration of the session.

*PRN: Provided to participants when additional pain relief is requested.

- PRN Fentanyl (injection) :

  PRN = 1 mcg / kg based on Pain NAS score >3.

- Criteria for providing PRN fentanyl are based on customary nursing practices, including a self-reported NAS pain >3/10 but also involves nursing judgment, observation of patients, vitals, etc.

- ***Request*** not Delivery: Request for Additional Analgesic Medication (RAAM), and, Reported Present Pain Intensity >3/10.

KETAMINE FOR ACUTE BURN PAIN
Assessment Diagram

PRE-RANDOM-IZATION:

Inclusion
TBSA: ≥2% & ≤40%

Exclusion
Pain: 1st NAS in ER AND BICU <6/10; Insensate, Lacks Capacity; Intubated; LOS<~4 days

Allocation Strategy:
Group Allocation, in random blocks of 2, 4, 6

BASELINE: PREBURN MO

Pain – (Month)
Average, Type, Location
Pain Medications
Brief Pain Inventory (BPI)
Pain Anxiety (PASS)
Pain Coping Q.
Catastrophizing Q
Med Side Effects (SEM-O.K.™)

PTSD Hx (LETE)
Depression (BDI-II)
Suicide Risk Scale

Post-Trauma Resilience Scale
Emotion Regulation Scale

SF-12
DSM V Adult Psycho-pathology Screen (lifetime, 12 months)

Days: 1 – 7 Sessions #1 - #14

Pre—Session (~1-hr)
Burn Pain: Mean pain since last Session
Pre-procedure:
Wound
Proximal to wound
Distal to wound
- **Pain Medications**

Sleep-Pain Diary

Intra-Session
Burn Pain: Mean pain every 10 minutes during session:
- **Mean pain since last NAS**
- **Locations (above)**

Additional Pain Meds

Post-Session
Burn Pain Recall:
NAS @ 1 hr (AM, PM)
NAS @ 6 hrs (AM only)
- **Mean Dsg Change**

Pain & Unpleasantness
Pain Mgmt Satisfaction

Days: 3, 5, 7: Sessions: #6, #10, #14 .

Pre—Session
Pain Anxiety (PASS)
Pain Coping
Pain Catastrophizing
PTSD (Davidson Trauma Scale)
Depression (BDI-II)
**All other pre-session measures as shown in prior box for Sessions 1-14.

Intra-Session
*All intra-session measures as shown in prior box for Sessions 1-14.

***Post-Session**
*All post-session measures as shown in prior box for Sessions 1-14.

POST-TESTS

1 Day
Burn Pain (Mean 24-hr NAS) at Locations:
Wound
Proximal to wound
Distal to wound
Pain Medications
Pain Management Satisfaction
PTSD (Davidson Trauma Scale)
Depression (BDI-II)
Benefit Finding (BF)
Emotion Regulation Scale (ERS)

1 Week:
*All post-session measures as shown above for 24-hour follow-up.

1 Month:
*All post-session measures as shown for 1- & 7-Day follow-ups.
Burn Specific Health Scale (BSHS),
SF-12

Ketamine RCT: Staff, Coverage

Wound Care & Outcome Coverage

- Enrollment Rate:
  - 12 Participants/Month, 3 Participants/week
- Staff Coverage:
  - SESSIONS: 14 Total Shifts/week, 4 hours/Shift, 3 Part/shift
  - OUTCOME: 3 follow-ups/Participant (1 Day, 1 week, 1 month)

Shift (AM/PM)	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
AM (9a-1p)	Rayyan	Emily	Amanda	Emily	Amberly	Emily	Rayyan
PM (9p-1a)	Shanna	Rayyan	Emily	Shanna	Emily	Amberly	Amberly

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Ketamine Sample: Target & Actual

Target Accrual Rate:

- 100 Participants in 8 Months (Nov ‘17–June ‘18)
- 12 Participants/Month, 3 Participants/week

Actual Eligible Admission Rate (5-year mean):

- 350 annual mean admission rate
- Adjusted for 8 months: 233 admits, 30/month (7/week)
- 2-4 eligible/week, 3 enrolled/week = 96 total

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Challenges/Lessons Learned

- DoD Grants:
  - Steep Learning Curve
    - Several Stages of Approval
    - Ambiguous Expectations, Time Frames & Funding Release
- Funding Release
  - Prolonged Delay “Post-Award“
    - Study Staff – could not be hired
    - Faculty Time – protected time not available
- Hospital Policy Changes
  - Ketamine – Clinical Application vs IRB-Approved
- Team Turnover:
  - JHBC Director Retired
  - Nurse Manager: 1 Resigned, 1 Interim Manager, 1 New Manager
  - Nursing Turnover (new training required)

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NEW KNOWLEDGE FROM TRIAL / DESIGN

Dose Response to Ketamine:

- Does impact improve with repeated sessions?
- This has vast implications for combat casualties in austere conditions with delayed evacuation, as well as for their ongoing analgesia once they have been moved to a field hospital.

Dual Target Variables:

- Pain and PTSD have never been targeted by ketamine in the same trial, using repeated treatments, in humans, and only a few times in preclinical studies.

Ketamine as Prevention:

- Treating acute pain to prevent central sensitization and chronic pain - Likely to have implications for opiate dependence and disability.
- Reducing symptoms of acute stress disorder and depression to prevent syndromal PTSD and depression

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Related Research Presentations/Publications

Posters

Annual JHU Undergraduate Competition: DREAM

- Ketamine for Acute Burn Pain

Annual Post Doctoral Research Pot Pouri; NIDA & the JHU Behavioral Biology Research Unit

- Ketamine for Acute Burn Pain, Opiate Sparing, Acute Stress Symptoms

Paper Presentations

American Burn Association – Spring, 2018

1. Pain and PTSD: A Test of the Mutual Maintenance Model
2. Acute Pain: Does PTSD Mediate Transition to Chronic Pain?
3. Acute PTSD: Does Pain Mediate Transition to Chronic PTSD?

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IRB Approved: Change in Research (09/28/2017)
Remaining Steps:

- ICU RNs, Fellows, PA providers
  - Training in specifics of the study (Yvette Wilson, Emily Werthman)
  - IRB – Change in Research: Study Staff, (Fauerbach)
- HRPO Review
- Drug Order Set Build –
  - Takes ~1-week after IRB approval. Tad Edwards
- Screen, Recruit, Enroll, …

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Future Directions

1. **Multicenter RCT Replication and Extension:** Refine methods, procedures, measures from knowledge gained here. Focus Aims & Hypotheses on direct relevance to military & civilian contexts of most austere conditions.

2. **Next-Generation War Plans:** Prolonged time lapse before extrication – repeated, effective wound care, acute pain and distress management.

3. **Deployment-Ready Ketamine Delivery Device:** low dose, slow-infusion ketamine in austere conditions, multiple sessions and days, tamper proof, lightweight

4. **Zero Preventable Deaths and Disability:** Integrate acute pain and psychological distress management with the DOD's initiative.

5. **Cornerstone for the Military-Civilian Program:** integrate acute care into prevention of chronic disability in the cross-fertilization and continuous training of military and civilian.

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Can Burn Wound Care Pain Management be Improved?

An RCT Comparing Fentanyl Versus Fentanyl Plus Ketamine

JOHNS HOPKINS NURSING

October 27, 2017

Understanding the Goals of the Study and Our Role in its Success

Goals

At the completion of this presentation you will be able to demonstrate:

- Ketamine's unique qualities and why it may reduce pain when used with opioids
- The Study Protocol and Your Role and Activities for Consenting Patients
- Problem Solving Team Members: Contact info you have any questions or concerns.

Overview of study

The Johns Hopkins Burn Center team is leading a Triple-Blind, RCT to test the hypotheses that fentanyl supplemented by ketamine reduces:

- Burn Wound Care Pain
- The amount of PRN opioid needed in Wound Care

Overview of study, cont.

Inclusion / Exclusion Criteria:

Study team will approach burn admits to determine eligibility, recruit, enroll:

Inclusion: 18-70 yo; 2-40% TBSA, estimated LOS at least 3 days

Exclusion: Intubated, Impaired MS

Consenting Patients: Study team will notify the primary RN

Overview of study, cont.

During dressing changes, a research assistant (RA) will be in the room. The RA will ask the patient questions related to their pain throughout the procedure.

Just as with a typical dressing change, the RN will be able to administer PRN medication to address pain.

Ketamine review

- Ketamine is a medication used for sedation and analgesia. For the purposes of this study, the patient will receive a loading dose and a low dose infusion of the medication. The RN will be responsible for administering both the loading dose and the infusion.

Expected outcomes

Before we discuss the RARE, but serious adverse reactions to ketamine a reminder:

IN THE LOW DOSES USED FOR THIS STUDY WE DO NOT ANTICIPATE SEEING ADVERSE EVENTS LIKE THOSE ABOUT TO BE DETAILED.

Expected outcomes, cont.

The most common side effect we anticipate in this low dose study is a dissociative state, marked by a change in mental status.

Ketamine adverse effects

These are rare and most commonly accompany higher dose

Cardiovascular: Hypertension, Tachycardia

Neurologic: Psychiatric sign or symptom

Cardiovascular: Bradyarrhythmia, Cardiac dysrhythmia, Hypotension

Respiratory: Apnea, Laryngeal spasm, Pulmonary edema, Respiratory depression

Study specifics

The study has 2 groups: study and placebo.

Both groups will receive fentanyl loading doses *prior to wound care.*

Both groups will also receive PRN fentanyl *during wound care.*

Both groups will receive an infusion during wound care, either ketamine or saline.

Study specifics

Treatment Conditions

- Fentanyl + Ketamine (Study Drug Group)
- Fentanyl + saline (Usual Care group)

Triple Blind: **Nurse & Tech, Participant** & RA/Assessor - won't know if patient is on fentanyl alone or with Ketamine.

Provider & Pharmacist: Will always know participant group and medications

Study specifics

Fentanyl plus ketamine **(study group)**

1. Ketamine loading dose, 0.3 mg/kg prior to wound care, infused over 5 min
2. Fentanyl loading dose, 1mcg/kg <1 min prior to wound care
3. Ketamine infusion, 2.5 mcg/kg/min

PRN medication, as requested by patient

Study specifics

- Fentanyl plus saline (usual care group)
    1. Saline loading dose, 0.3 mg/kg
    2. Fentanyl loading dose, 1 mcg/kg
    3. Saline infusion, 2.5 mcg/kg/min

PRN medication, as requested by patient

Study specifics

An order set will be entered by the physician.

An IV bag will be sent from pharmacy. As the study is blinded, the name of the medication will not be on the label. The medication will still be scanned in Epic.

Study specifics, cont.

KEY POINT

As the medication could be either placebo or ketamine, the RN must monitor and recover ALL study participants

Nursing responsibilities

Administration of loading doses, infusions of ketamine or placebo.

VS q15m, including mental status changes, during procedure

Recovery for up to 1 hour following procedure, using previously approved recovery flowsheets. This recovery period is until the patient returns to baseline.

Study staff

- Dr. Julie Caffrey, Interim Director, Johns Hopkins Burn Center
- Dr. Jim Fauerbach & Dr. Kevin Gerold, Co-Principle Investigators
- Lisa Ruppel, Research Pharmacist
- Emily Werthman, Study Coordinator
- Research Assistants: Rayyan, Shanna, Amanda, Emily, Amberly

Staff roles, Dr. Gerold

Dr. Gerold's role is to participate in developing and designing the protocol as an authority on medications and resource on issues related to comorbid pre-injury and burn-related factors that may affect enrollment and continuation.

Staff roles, Dr. Caffrey

Dr. Caffrey's role is as the Executive-in-Chief, the – project manager providing:

project go-ahead

"top-of-the-line" decision-making &

problem solving

Questions?

- Please contact Emily Werthman
- Study Coordinator
- Ketamine For Acute Burn Wound Care Pain RCT
- (410) 550-0890
- ewerthmi@jhmi.edu

Ketamine Administration for Treatment of Pain During Burn Wound Care

Drug Review for Nurses

History:

- Ketamine was originally approved for induction and maintenance of general anesthesia on February 19, 1970.
- Was given CIII controlled substance status in 1999.
- Also used for: analgesia, treatment of refractory major depressive disorder, procedural sedation and refractory status epilepticus. These are all unlabeled uses.

Mechanism of Action:

- Non-competitive NDMA receptor antagonist.
- Other NDMA receptor antagonists include: dextromethorphan, phencyclidine (PCP), methadone, tramadol
- Anesthetic doses produce a dissociative state.
- Sub-anesthetic doses produce analgesia, modulate central sensitization and reduce post-synaptic spinal reflexes.

Research protocol: Evaluating the Safety, Efficacy and Opiate Sparing Effects of Ketamine in a Setting Analogous to Austere Battlefield Conditions (IRB00089761)

- **Objectives:** (1) To test the effectiveness of ketamine augmentation to usual opiate care (K+UC) relative to Usual Care (UC) in reducing the severity of acute nociceptive pain in response to pressure at: a) the burn wound (primary hyperalgesia); b) in body areas adjacent to the burn (secondary hyperalgesia) and; c) body areas distal to the burn (allodynia).

  (2) To determine whether adjunctive ketamine is associated with opiate sparing.

- **Study Design:** A double-blind, placebo controlled clinical trial to evaluate the safety and efficacy of low-dose, slowly infused ketamine for the treatment of pain during acute burn wound care
- **Treatment Plan:** Patients will be recruited through the population of adults 18-65 years of age admitted with acute burn injuries to the Johns Hopkins Burn Center. Patients will be randomized to receive usual care (fentanyl) or ketamine + usual care for analgesia during daily burn dressing changes (up to 3x daily) for seven (7) days.

How the Study Process Works:

- Eligible patients will be identified and consented by the study team.
- Once informed consent is obtained, the study team will enter the order set into EPIC.

- The research pharmacy will randomize the patient into one of two blinded treatment arms:
    - Usual Care (fentanyl) + placebo (saline)
    - Usual Care (fentanyl) + ketamine
- The research pharmacy will prepare a blinded 50ml bag containing either NSS or Ketamine 50mg in NSS 50ml and delivery it prior to each dressing change.
- **All patients will receive** fentanyl loading dose < 1-minute prior to wound care. Nurses will obtain fentanyl from the pyxis medstation per usual routine.
- **All patients will receive** fentanyl as needed for NAS pain score ≥7/10 or a persisting rise in NAS of ≥2/10.
- **All patients will receive** a blinded bag labeled Ketamine 50mg/placebo in NSS 50ml.
- Loading Dose of ketamine: is 0.3mg/kg over 5 minutes. The onset of action of IV ketamine is under a minute.
    - The rate of administration will be set so that the volume of ketamine solution delivered or the volume of placebo delivered will be the same.
    - For example: For a 70kg patient, the dose of ketamine is 0.3mg/kg x 70kg = 21mcg = 21ml. Regardless of the contents of the bag, 21ml will be delivered to provide the loading dose.
- Ketamine maintenance infusion: will run at 2.5mcg/kg/min for the duration of the wound care.
    - As with the loading dose, the placebo rate will be calculated to be equal to the ketamine infusion rate.
    - For example: For a 70kg patient, 2.5mcg/kg/min = 10.5mg/hr = 10.5ml/hr regardless of the contents of the bag.

Adverse Reactions:

- **Emergence reactions –** vivid dreams, hallucinations, delirium, confusion
- **Respiratory depression –** most likely to occur with rapid administration (IV push)
- **Cardiovascular –** hypo- OR hypertension, brady- OR tachycardia, arrhythmia
- **CNS –** tonic-clonic movements

Cautions: Use with extreme caution in these patient populations

- **Schizophrenia –** may have an exacerbation of symptoms even if previously controlled by medications.
- **CNS masses/structural abnormalities/hydrocephalus –** may increase ICP
- **Thyroid disorder or medications –** may have an increased sympathomimetic effect (increased BP & HR)
- **Cardiovascular disease –** may have increases in BP, HR & CO
- **Active pulmonary infection or airway disease (asthma, COPD) –** increased risk of laryngospasm
- **Seizure disorder –** may lower the seizure threshold.

Drug Interactions – The following drugs can enhance the effect of ketamine:

- **CNS depressants, including SSRI antidepressants**
- **Antiepileptics**
- **Rifampin & rifabutin**
- **Dexamethasone**
- **Magnesium Sulfate**

	Baseline	Day 1, Session 1	Day 1, Session 2	Day 2, Session 1	Day 2, Session 2	Day 3, Session 1	Day 3, Session 2	Day 4, Session 1	Day 4, Session 2	Day 5, Session 1	Day 5, Session 2	Day 6, Session 1	Day 6, Session 2	Day 7, Session 1	Day 7, Session 2	Follow-Up Day 1	Follow-Up Day 7	Follow-Up Day 30
Ketamine Demographics and Injury Descriptors																		
CAGE																		
Screening Form																		
ED Vitals and Pain																		
MMSE																		
LOT-R																		
Emotion Regulation Questionnaire																		
Connor Davidson Resilience Scale																		
DSM-5 Screening Form																		
LEC																		
Beck Depression Inventory + CSSRS																		
Brief Pain Inventory																		
Wake Diary																		
NAS + Vitals																		
NAS + Central Sensitization																		

Davidson Trauma Scale																		
Pain: Coping, Anxiety, and Catastrophizing																		
Acute Stress Disorder Scale																		
Sleep Diary																		
NAS (Avg. 24-hour Pain)																		
5D Itch Scale																		
Pain Treatment Satisfaction																		
Burn-Specific Health Scale-Brief																		
Return to Usual Major Activity Survey																		
SWAP																		
Posttraumatic Growth Inventory																		
Insomnia Severity Index																		
SF-12 Health Survey																		
SEM-OK																		
Study Progress Form																		

= Instrument = Event

= Pain = Psychiatric Symptoms = Miscellaneous Measures

Instrument	Baseline	Day 1, Session 1	Day 1, Session 2	Day 2, Session 1	Day 2, Session 2	Day 3, Session 1	Day 3, Session 2	Day 4, Session 1	Day 4, Session 2	Day 5, Session 1	Day 5, Session 2	Day 6, Session 1	Day 6, Session 2	Day 7, Session 1	Day 7, Session 2	Follow-Up Day 1	Follow-Up Day 7	Follow-Up Day 30
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SWAP																		
Posttraumatic Growth Inventory																		
Insomnia Severity Index																		
SF-12 Health Survey																		
SEM-OK																		
Study Progress Form																		

= Pain

= Psychiatric Symptoms

= Miscellaneous Measures

PROspective Observational Vascular Injury Treatment (PROOVIT) Registry

PRINCIPAL INVESTIGATOR(S):

JOE DUBOSE, MD FACS, FCCM

TODD E. RASMUSSSEN, MD FACS

R ADAMS COWLEY SHOCK TRAUMA CENTER

UNIVERSITY OF MARYLAND MEDICAL SYSTEM

Participating Sites – 25 enrolling centers

- U Texas - Houston
- U Tennessee - Memphis
- U Maryland - R Adams Shock Trauma
- University of Florida - Jacksonville
- Los Angeles County + USC
- Loma Linda University
- East Carolina University
- University of Texas - San Antonio
- Miami Valley Medical Center
- Ben Taub / Baylor College of Medicine
- Indiana University School of Medicine
- San Antonio Military Medical Center
- Ryder Trauma Center (Jackson Memorial Miami)
- University of California - Davis
- Emory University at Grady Memorial
- Creighton University Medical Center
- University of Wisconsin
- Chandler Regional Medical Center
- Baylor University Medical Center
- Peace Health Southwest Washington Medical Center
- Massachusetts General Hospital
- Scripps Mercy Hospital
- Lutheran Medical Center, Brooklyn
- St. Luke's Hospital
- Brigham and Women's Hospital

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Background/Scientific Rationale – Evolutions in Vascular Trauma Management

- **Pre-hospital**
  - Tourniquet utilization
- **Resuscitation practices**
  - Balanced resuscitation
- **Diagnostic modalities**
  - CTA
- **Damage control tools**
  - Shunts
- **Endovascular modalities**
  - Hybrid utilizatons
  - Definitive management
- **Antiplatelet / Anticoagulation utilization**

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Prior sources of data on vascular injury outcomes / treatment

- **Single center retrospective series**
- **National Trauma Data Bank**
  - Lacks key detail
  - No follow-up
- **Society of Vascular Surgery Vascular Quality Initiative**
  - One year follow-up
  - Designed for peripheral vascular disease

The Model: Balad Vascular Registry / GWOT

- Balad Vascular Registry / Global War on Terror Vascular Initiative
  - Linked pre-hospital intervention, in-hospital treatments and outcomes
  - Specific population
  - Limited long-term outcome data

Study Design

- Prospective multi-center observational registry
- Patients age > 2 yo with CTA, duplex, angiographic or clinical / operative diagnosis of vascular injury
- Linked follow-up module

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Primary Registry Aim

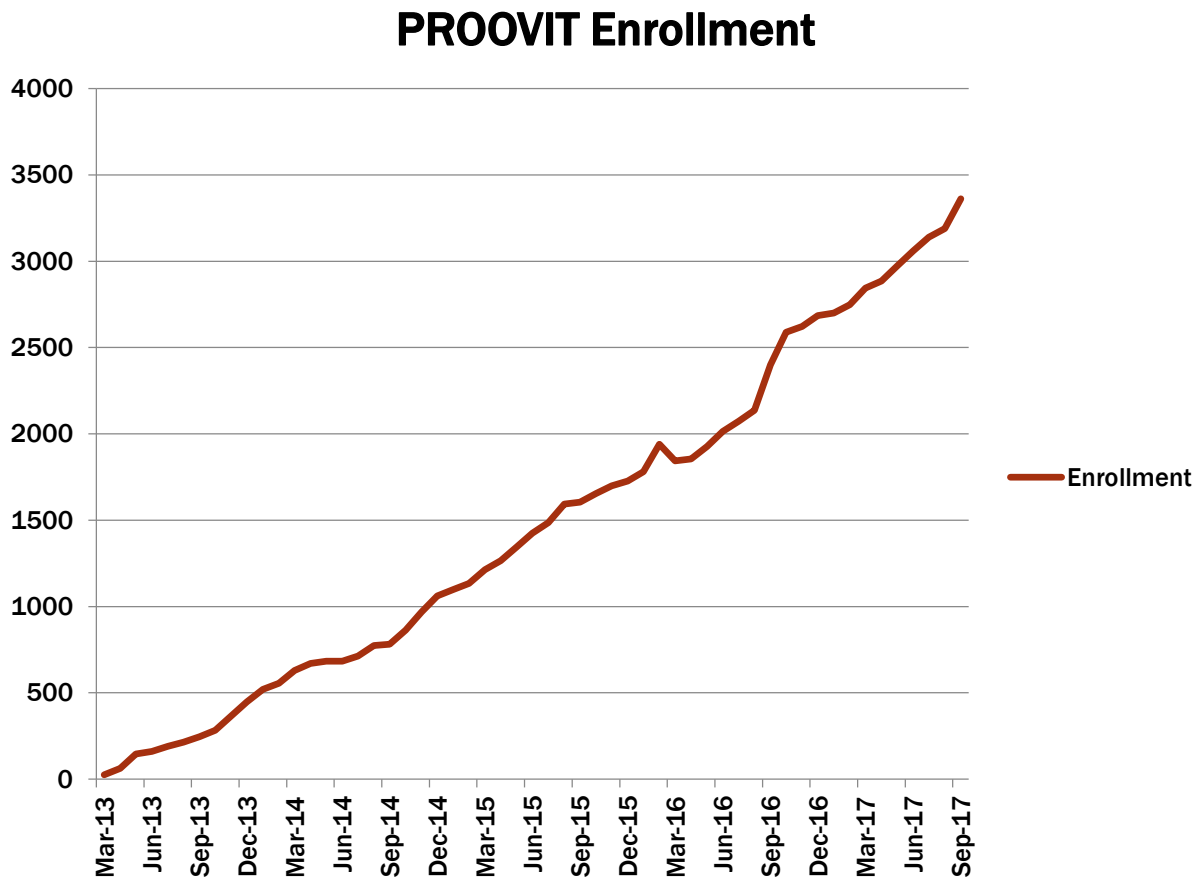
- **Primary Aim:** To establish an aggregate database of information on the presentation, diagnosis, management (acute and definitive), surveillance and outcomes following vascular trauma

Secondary Registry Aims

- To subcategorize data from the overall repository into three anatomic patterns of injury, extremity, torso and cervical to allow for a focused analysis of specific vessel injuries.
- To analyze the type and manner of catheter-based, endovascular therapies by subcategorizing and analyzing these methods of management.
- To compare short and long term feasibility and ultimate effectiveness of open operative to endovascular approaches to specific patterns of vascular trauma.
- To assess the frequency and modality utilized for surveillance after the occurrence of and treatment for vascular injury.
- To analyze vascular trauma management and outcomes in the extremes of age including pediatric and geriatric patients.
- To address specific questions related to patient and therapy-centered outcomes including type and duration of antithrombotic therapy, repair patency and durability and need for after vascular trauma.

Current Status

- AAST MCT approval 2012
- Launched data entry March 2013
- 3,361 injuries
  - 25 centers
- 1053 follow visits
  - 15 centers
  - Out to 3 years



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Challenges/Lessons Learned

- Follow up for vascular injured patients remains a challenge
  - Solutions institution specific
- Long delays in achieving “complete” status for data entry
  - Awaiting ISS / AIS scoring
- Communication, communication, communication
  - Separate email
  - Monthly updates
- Evolving as a resource for the trauma community

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Research Findings - Myriad

- Endovascular utilization continues to grow
  - Axillosubclavian in particular
- Cerebrovascular injuries
  - NOM predominates
  - Endovascular / operative interventions associated with appreciable stroke rates
- Pediatric vascular injuries are rare
  - Primarily penetrating, primarily treated open with good outcomes
- Temporary vascular shunts utilized in damage control scenarios decrease amputation rates for extremity injuries
- Adoption of pre-hospital tourniquet use appears to have stalled despite good outcomes

Oral presentations

- ***DuBose JJ***, Savage SA, Fabian T, Menaker J, Scalea T, Holcomb JH, Poulin N, Konstantinos C, Inaba K, Luo-Owen X, O'Callaghan TA, Larentzakis A, Velmahos G, Culabon G, Rasmussen T. The AAST prospective observational vascular injury treatment (PROOVIT) registry: Multicenter data on modern vascular injury diagnosis, management and outcomes. American Association for the Surgery of Trauma 73rd Annual meeting. Philadelphia, PA. 10 Sept 2014
- Loja MN, Wishy A, Humphries M, Savage S, Fabian T, Scalea TM, Holcomb JB, Poulin N, Galante JM, Rasmussen TE, *AAST PROOVIT Study Group*. Systemic anticoagulation in the setting of vascular extremity trauma. Podium Presentation, American Association for the Surgery of Trauma Annual Meeting, Maui, Hawaii, 2016.
- Loja MN, ***DuBose J***, Saummann A, Li CS, Savage S, Scalea T, Holcomb JB, Rasmussen TE, Knudson MM, AAST PROOVIT Study Group. The Mangled Extremity Score and Amputation: Time for a Revision. Quickshot Podium Presentation, American Association for the Surgery of Trauma Annual Meeting, Maui, Hawaii, 2016.

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Oral presentations

- Faulconer ER, Branco B, Loja M, Grayson K, Sampson J, Fabian T, Bee T, Holcomb JB, Brenner M, Scalea TM, Skarupa D, Inaba K, Poulin N, Rasmussen TE, ***DuBose JJ,*** *AAST PROOVIT Study Group.* Use of open and endovascular surgical techniques to manage vascular injuries in the trauma setting: A review of the AAST PROOVIT Registry. Podium presentation - American Association for the Surgery of Trauma Annual Meeting, Baltimore, MD, 2017.
- Ferencz SA, ***DuBose JJ,*** Hennigan J, Nolan K, Sampson JB, Rasmussen TE, Galante JM, Bee T, Fabian TC, Menaker JA, Scalea TM, Holcomb JB, Skarupa DJ, Inaba K, Bini JK, *AAST PROOVIT Study Group.* Contemporary tourniquet use in extremity vascular trauma: The AAST prospective observational injury treatment (PROOVIT) registry. Quick shot presentation - American Association for the Surgery of Trauma Annual Meeting, Baltimore, MD, 2017.

Posters

- Loja MN, ***DuBose JJ,*** Stephenson J, Kessel B, Bee T, Fabian T, Menaker J, Scalea TM, Holcomb JB, Skarupa D, Inaba K, Catalano R, Poulin N, Bini JK, Rasmussen TE, *AAST PROOVIT Study Group*. Pediatric vascular trauma: Current management and early outcomes. Poster presentation - American Association for the Surgery of Trauma Annual Meeting, Baltimore, MD, 2017.
- Russo R, Galante J, ***DuBose JJ,*** Bee T, Fabian T, Holcomb JB, Brenner M, Scalea TM, Skarupa D, Inaba K, Poulin N, Turay D, Bini J. Rasmussen TE, *AAST PROOVIT Study Group*. Contemporary outcomes and management of blunt cerebrovascular injuries: Results from the *AAST PROOVIT* multicenter registry. Poster presentation - American Association for the Surgery of Trauma Annual Meeting, Baltimore, MD, 2017.

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Manuscripts published

- ***DuBose JJ***, Savage SA, Fabian T, Menaker J, Scalea T, Holcomb JH, Poulin N, Konstantinos C, Inaba K, Luo-Owen X, O'Callaghan TA, Larentzakis A, Velmahos G, Culabon G, Rasmussen T. The AAST prospective observational vascular injury treatment (PROOVIT) registry: Multicenter data on modern vascular injury diagnosis, management and outcomes. *J Trauma Acute Care Surgery.* 2015 Feb;78(2):215-223.

- Loja MN, ***DuBose J***, Sammam A, Li CS, Liu Y, Savage S, Scalea TM, Holcomb JB, Rasmussen TE, Knudson MM, AAST PROOVIT Study Group. The Mangled extremity score and amputation: Time for a revision. *J Trauma Acute Care Surg.* 2017 Mar;82(3):518-523.

- Loja MN, Galante JM, Humphries M, Savage S, Fabian T, Scalea T, Holcomb JB, Poulin N, ***DuBose J***, Rasmussen TE; *AAST PROOVIT Study Group.* Systemic anticoagulation in the setting of vascular extremity trauma. *Injury.* 2017 Sep;48(9):1911-1916.

Manuscripts submitted

- Faulconer ER, Branco B, Loja M, Grayson K, Sampson J, Fabian T, Bee T, Holcomb JB, Brenner M, Scalea TM, Skarupa D, Inaba K, Poulin N, Rasmussen TE, ***DuBose JJ, AAST PROOVIT Study Group.*** Use of open and endovascular surgical techniques to manage vascular injuries in the trauma setting: A review of the AAST PROOVIT Registry. – *Submitted J Trauma Acute Care Surg*

- Ferencz SA, ***DuBose JJ,*** Hennigan J, Nolan K, Sampson JB, Rasmussen TE, Galante JM, Bee T, Fabian TC, Menaker JA, Scalea TM, Holcomb JB, Skarupa DJ, Inaba K, Bini JK, *AAST PROOVIT Study Group.* Contemporary tourniquet use in extremity vascular trauma: The AAST prospective observational injury treatment (PROOVIT) registry. – *Submitted J Trauma Acute Care Surg.*

- Russo R, Galante J, ***DuBose JJ,*** Bee T, Fabian T, Holcomb JB, Brenner M, Scalea TM, Skarupa D, Inaba K, Poulin N, Turay D, Bini J. Rasmussen TE, *AAST PROOVIT Study Group*. Contemporary outcomes and management of blunt cerebrovascular injuries: Results from the *AAST PROOVIT* multicenter registry. – *Submitted J Trauma Acute Care Surg.*

- Loja MN, ***DuBose JJ,*** Stephenson J, Kessel B, Bee T, Fabian T, Menaker J, Scalea TM, Holcomb JB, Skarupa D, Inaba K, Catalano R, Poulin N, Bini JK, Rasmussen TE, *AAST PROOVIT Study Group*. Pediatric vascular trauma: Current management and early outcomes. – *Submitted J Trauma Acute Care Surg.*

Next Steps/Future Direction

- Continue to grow recruitment
  - Several centers added following recent AAST meeting
  - International growth opportunities
- Support data utilization by any and all submitting appropriate proposals for use
- Additional funding to support improved follow-up data collection
  - Think outside the box

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The mangled extremity score and amputation: Time for a revision

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BACKGROUND: The Mangled Extremity Severity Score (MESS) was developed 25 years ago in an attempt to use the extent of skeletal and soft tissue injury, limb ischemia, shock, and age to predict the need for amputation after extremity injury. Subsequently, there have been mixed reviews as to the use of this score. We hypothesized that the MESS, when applied to a data set collected prospectively in modern times, would not correlate with the need for amputation.

METHODS: We applied the MESS to patient data collected in the American Association for the Surgery of Trauma PROspective Vascular Injury Treatment registry. This registry contains prospectively collected demographic, diagnostic, treatment, and outcome data.

RESULTS: Between 2013 and 2015, 230 patients with lower extremity arterial injuries were entered into the PROspective Vascular Injury Treatment registry. Most were male with a mean age of 34 years (range, 4–92 years) and a blunt mechanism of injury at a rate of 47.4%. A MESS of 8 or greater was associated with a longer stay in the hospital (median, 22.5 (15, 29) vs 12 (6, 21); $p = 0.006$) and intensive care unit (median, 6 (2, 13) vs 3 (1, 6); $p = 0.03$). Of the patients' limbs, 81.3% were ultimately salvaged (median MESS, 4 (3, 5)), and 18.7% required primary or secondary amputation (median MESS, 6 (4, 8); $p < 0.001$). However, after controlling for confounding variables including mechanism of injury, degree of arterial injury, injury severity score, arterial location, and concomitant injuries, the MESS between salvaged and amputated limbs was no longer significantly different. Importantly, a MESS of 8 predicted in-hospital amputation in only 43.2% of patients.

CONCLUSION: Therapeutic advances in the treatment of vascular, orthopedic, neurologic, and soft tissue injuries have reduced the diagnostic accuracy of the MESS in predicting the need for amputation. There remains a significant need to examine additional predictors of amputation following severe extremity injury. (*J Trauma Acute Care Surg.* 2017;82: 518–523. Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Prospective, prognostic study, level III.

KEY WORDS: Mangled; trauma; vascular; extremity; amputation.

The decision on whether to proceed with amputation or reconstruction of a mangled extremity is perhaps one of the most difficult for civilian trauma surgeons, as these types of injuries are seen relatively infrequently. Factors considered in the decision-making process include patient's age, physiologic condition at presentation, associated injuries, soft tissue factors, and the potential for salvaging a useful limb.[1] The Mangled Extremity Severity Score (MESS) was developed 25 years ago at Harborview Medical Center in Seattle by Johansen et al.[2] in an attempt to create a tool that accurately predicted the need for amputation. The MESS takes into consideration the degree of skeletal and soft tissue injury, limb ischemia, the presence of shock, patient's age, and ischemia time. It has been widely used since its inception despite continued questions over its prognostic accuracy. The use of this scoring system, or any other such scoring system, is further questioned given the major advances that have been made in the management of severely mangled extremities, including increased use of tourniquets in both civilian and military settings, numerous new hemostatic agents, advanced tissue transfer techniques, and novel vascular interventions.

In 2013, the AAST Multicenter Trials Committee initiated a prospective registry designed to collect data specific to vascular injuries. The PROspective Observational Vascular Injury Treatment (PROOVIT) registry includes extensive treatment and outcome data from multiple major trauma centers with the aim of informing practice and protocols to improve outcomes.[3] The purpose of our study was to use the PROOVIT database to re-evaluate the MESS on data collected prospectively in modern times. The hypothesis was that MESS would be predictive of the need for amputation.

METHODS

Patient data were collected from the AAST Multicenter PROspective Observational Vascular Injury Treatment (PROOVIT) registry. The details describing this large database have been previously described. In brief, it is a prospectively collected

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This study was presented as a quick shot at the 75th annual meeting of the American Association for the Surgery of Trauma, September 14–17, 2016, in Waikoloa, HI.

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TABLE 1. Mangled Extremity Severity Score (MESS) Components Prospectively Collected in the PROOVIT Registry

A. Skeletal/Soft tissue injury
1. Low energy (stab wound, simple fracture, low-energy gunshot wound)
2. Medium energy (open or multiple fractures, dislocation)
3. High energy (high-speed motor vehicle collision or rifle gunshot wound)
4. Very high energy (above plus gross contamination)
B. Limb ischemia*
1. Pulse reduced or absent but perfusion normal
2. Pulseless; paresthesia, diminished capillary refill
3. Cool, paralyzed, insensate, numb
C. Shock
0. Systolic blood pressure always > 90 mm Hg
1. Systolic blood pressure transiently < 90 mm Hg
2. Systolic blood pressure persistently < 90 mm Hg
D. Age (years)
0. <30
1. 30–50
2. >50

*Score doubled for ischemia time > 6 hours.

database of injuries to named arterial and venous structures from 14 Level I trauma centers across the country.[3] The database includes patients' demographics, mechanism of injury, concomitant injuries, and intraoperative and postoperative variables for patients entered during the index hospital stay only. The database is actively accruing data from follow-up clinic visits and readmissions, and these data were not included in this study.

Lower extremity named arterial injuries were identified between February 2013 and August 2015. Each component of the MESS was obtained prospectively during data collection using the scoring system shown in Table 1. The MESS was calculated for each patient by adding the numerical scores of the skeletal/soft tissue injury, limb ischemia, shock, and age scores. If there were greater than 6 hours of ischemia time, the ischemia score was doubled. There were 57 patients in which one component of the MESS (skeletal/soft tissue injury, shock, or ischemia) was missing. The missing data were found to be missing at random with $p = 0.59$ compared to the nonmissing variable of age. The missing data were then treated using multiple imputation with 20 imputations. There was no difference in the correlation of MESS or its components before or after use of multiple imputation, suggesting that the bias imposed by the missing data is minimal. The percentage increase in standard error due to the missing values was 6.9% for MESS, 0.03% for shock, 0.02% for skeletal score, and 0.6% for ischemia score.

A MESS of 8 was chosen based on a prior study from the original creators of the scoring system, who suggested in their 2016 publication that a threshold of 8 was more appropriate in a modern setting.[4] A receiver operating characteristic (ROC) analysis was performed, which demonstrated that a MESS of 5 was a better balance of sensitivity and specificity than a MESS of 8. The ROC curves can be found in Figure 1.

Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA). Univariable logistic regression was used to look at the correlation of the MESS, as well as each MESS component, with the risk of amputation. Odds ratios comparing amputation versus limb salvage were generated. Age, sex, injury mechanism (blunt, penetrating, or mixed blunt and penetrating), injury type (transection, flow-limiting lesion, occlusion, pseudoaneurysm, or other), arterial injury location (femoral, popliteal, below-popliteal arteries, or multilevel injury), use of shunting, prehospital tourniquet use, fasciotomy performed at any time during the admission, injury severity score (ISS), and concomitant vein, nerve, or orthopedic injury were assessed for confounding. Of note, the database did not distinguish the severity of vein, nerve, or orthopedic injury; it reports a binary value of injured or not injured. Independent predictors of amputation were identified by univariable logistic regression. Significant variables ($p \leq 0.1$) were injury mechanism, the presence of a transection, arterial injury location, ISS, concomitant nerve, or orthopedic injury. A multivariable logistic regression with these confounders was performed of the MESS, and separately of the MESS components, with the binary outcome of amputation compared to limb salvage. These were performed separately due to the confounding nature of including both MESS and its components in the same model. The area under the receiver operating characteristic (AUROC) curve for the logistic regression model including MESS was 0.86 [95% confidence interval [CI], 0.79–0.93]. The Hosmer-Lemeshow goodness-of-fit test had a $p = 0.93$. The AUROC for the model, which included the components age score, skeletal score, ischemia score, and shock score was 0.88 [95% CI, 0.82–0.94], and the

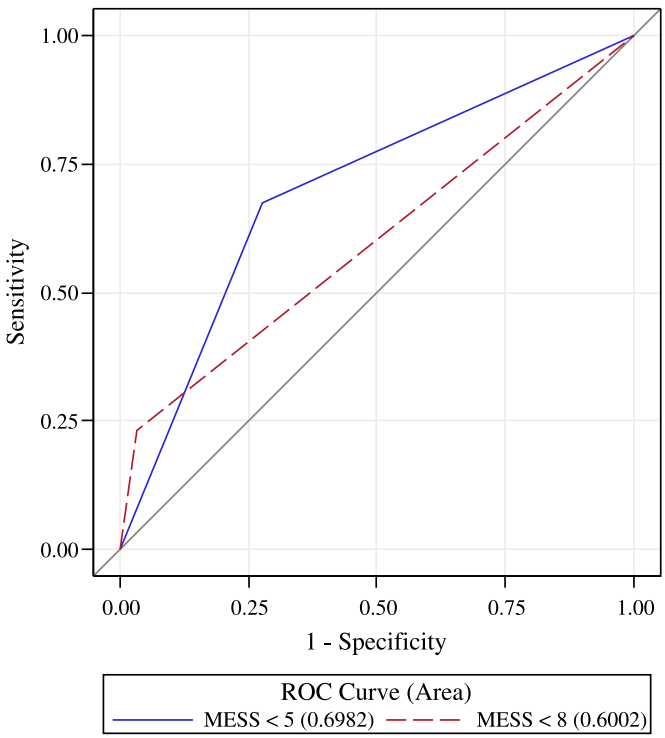

Figure 1. Receiver operator characteristic (ROC) curve for a MESS cutoff of 5 versus 8. A MESS cutoff of 5 was found to have the best balance of sensitivity and specificity, however, only was predictive of MESS in 20.2% of patients. A MESS of 8 was predictive of amputation in 43.2% of patients.

Hosmer-Lemeshow was nonsignificant with $p = 0.29$. The probability of amputation was modeled using univariable logistic regression to predict amputations with a MESS cutoff of 5 and 8. Finally, demographics of patients with the MESS cutoff of 8 were compared using Wilcoxon rank-sum test and Fisher exact test. A $p < 0.05$ was considered statistically significant.

RESULTS

Between February 2013 and August 2015, 230 patients with lower extremity arterial injuries were entered into the PROOVIT registry. The cohort consisted predominantly of men (87.8%) with an average age of 34 ± 15.3 years (range, 4–92 years). The mechanism of injury was reported as blunt in 109 patients (47.4%), penetrating in 114 patients (49.6%), and mixed blunt and penetrating in the remainder (Table 2). Isolated femoral injuries were found in 102 patients (44.3%) and isolated popliteal injuries in 60 patients (26.1%). Sixty-three injuries to arteries distal to the popliteal artery were identified (27.4%), and five injuries were to both the above- and below-knee arterial beds. The injury to the artery was most often a transection, present in 45.7% of patients. There were 50 concomitant venous injuries (21.7%). Ninety-four percent of these venous injuries were repaired at the time of initial operation and the remainder ligated. There were 94 concomitant orthopedic injuries (40.9%) and 33 nerve injuries (14.4%).

Twenty-two patients had a prehospital tourniquet applied (9.6%). Ninety-four (40.9%) fasciotomies were performed during the index hospitalization, including 40 prophylactic fasciotomies at the initial procedure, 48 therapeutic fasciotomies at the initial procedure, and 5 delayed fasciotomies (one was not categorized). A temporary shunt was used for damage control in 17 patients (7.4%).

We modeled the probability of amputations based on MESS and determined that MESS greater than or equal to 8 was predictive of in-hospital amputation in only 43.2% of patients. Receiver operating characteristic analysis (Fig. 1) showed the best balance of sensitivity and specificity was a MESS of 5 (AUROC, 0.70 [95% CI, 0.62–0.77]) compared to a MESS of 8 (AUROC, 0.60 [95% CI, 0.54–0.67]; $p = 0.02$). However, a MESS of 5 was only predictive of amputation in 20.2% of cases. Based on prior studies and this increase in ability to predict amputation, a MESS of 8 was chosen for further analysis. Sixteen patients had a MESS of greater than or equal to 8 (7.0%). The median MESS was 4 (25th percentile (Q1), 3; 75th percentile (Q3), 6). The median skeletal injury component score was 2 (1, 3), the median ischemia score was 2 (1, 2), the median shock score was 0 (0, 1), and the median age score was 1 (0, 1). Patients with a MESS of 8 or greater were on average older (48.3 years old vs 32.8, $p < 0.0003$), and were more likely to have sustained a blunt injury (81.3% vs 44.9%, $p = 0.004$). Patients with a MESS of 8 or greater had a higher median ISS (21 vs 10.5, $p = 0.0003$), although they had no difference in mean abbreviated injury score of the extremity, admission systolic blood pressure, or GCS (Table 2). There were more concomitant nerve (68.8% vs 10.3%, $p < 0.001$) and orthopedic injuries (68.8% vs 38.8%, $p = 0.02$) when MESS was greater than or equal to 8. There was no difference in concomitant venous injuries between the groups (Table 2).

Primary or secondary amputations were performed in 43 patients (18.7%, median MESS, 6 (4, 8)), including 21 primary amputations performed for damage control (9.1%). Limbs were ultimately salvaged in 187 patients (81.3%; median MESS, 4 (3, 5); $p < 0.001$; Table 3). There were 12 deaths (5.2%) in the total cohort.

Univariable logistic regression was performed, looking at age, sex, injury mechanism, injury type, arterial injury location, use of shunting, prehospital tourniquet use, fasciotomy performed at any time during the admission, ISS, and concomitant vein, nerve, or orthopedic injury for confounding. Blunt injuries were associated with amputation with an odds ratio of 6.4 [95% CI, 2.7–15.1] compared to penetrating injuries ($p < 0.0001$). Transection was associated with amputation with an odds ratio of 2.4 [95% CI, 1.2–4.7] ($p = 0.014$). Popliteal arterial injuries were associated with a 6.8-fold higher risk of amputation than femoral arterial injuries [95% CI, 2.7–17.3] ($p < 0.001$). Injury severity score

TABLE 2. Comparison of Demographics Between Patients with Mangled Extremity Severity Score (MESS) < 8 and MESS ≥ 8

		MESS Score		
	All	MESS < 8	MESS ≥ 8	
Variable	(n = 230)	(n = 214)	(n = 16)	*p*
Age, mean ± SD	34 ± 15.3	32.8 ± 14.7	48.3 ± 15.6	0.0003
Male, n (%)	202 (87.8)	187 (87.4)	15 (93.8)	0.4
Injury mechanism				0.004
Blunt, n (%)	109 (47.4)	96 (44.9)	13 (81.3)	
Penetrating, n (%)	114 (49.6)	112 (52.3)	2 (12.5)	
Mixed blunt and penetrating, n (%)	7 (3.0)	6 (2.8)	1 (6.3)	
Injured artery:				0.7
Femoral, n (%)	102 (44.3)	97 (45.3)	5 (31.3)	
Popliteal, n (%)	60 (26.1)	55 (25.7)	5 (31.3)	
Distal to popliteal artery, n (%)	63 (27.4)	57 (26.6)	6 (37.5)	
Multiple levels, n (%)	5 (2.2)	5 (2.3)	0 (0)	
Transection, n (%)	105 (45.7)	93 (43.5)	12 (75)	0.01
Flow-limiting defect, n (%)	44 (19.1)	42 (19.6)	2 (12.5)	0.4
Occlusion, n (%)	38 (16.5)	36 (16.8)	2 (12.5)	0.5
Pseudoaneurysm, n (%)	9 (3.9)	9 (4.2)	0 (0)	0.5
Other injury type, n (%)	41 (17.8)	40 (18.7)	1 (6.3)	0.2
Median ISS (Q1, Q3)	11 (9, 19)	10.5 (9, 18)	21 (17, 26)	0.0003
Median AIS-extremity (Q1, Q3)	3 (3, 4)	3 (3, 4)	3 (3, 4)	0.1
Mean admission SBP ± SD	120.9 ± 30.0	121.4 ± 29.9	115.9 ± 31.7	0.5
Median GCS (Q1, Q3)	15 (14, 15)	15 (15, 15)	15 (14, 15)	0.7
Concomitant venous injury, n (%)	50 (21.7)	46 (21.5)	4 (25)	0.5
Vein repaired, n (%)	47/50 (94.0)	43/46 (93.4)	4/4 (100%)	0.4
Concomitant nerve injury, n (%)	33 (14.4)	22 (10.3)	11 (68.8)	<0.001
Concomitant orthopedic injury, n (%)	94 (40.9)	83 (38.8)	11 (68.8)	0.02
Prehospital tourniquet, n (%)	22 (9.6)	20 (9.4)	2 (12.5)	0.5
Temporary shunt used, n (%)	17 (7.4)	17 (7.9)	0 (0)	0.3
Fasciotomy, n (%)	94 (40.9)	89 (41.6)	5 (31.3)	0.3

Q1, lower quantile (25th percentile).
Q3, upper quantile (75th percentile).
AIS, abbreviated injury score; GCS, Glasgow coma score; SBP, systolic blood pressure.

TABLE 3. Mangled Extremity Severity Score (MESS) Elements Compared Between Patients Who Underwent Amputations and Those Who Did Not; Before and After Adjustment for Significant Confounders of Injury Mechanism, Arterial Transection, Arterial Injury Location, ISS, and Concomitant Nerve and Orthopedic Injuries

MESS Elements	Amputations Median (Q1, Q3) (n = 43)	Limb Salvage Median (Q1, Q3) (n = 187)	*p* Value Unadjusted	*p* Value Adjusted
Skeletal/Soft tissue score	3 (2, 3)	1 (1, 3)	<0.001	0.50
Limb ischemia	2 (1, 3)	1 (1, 2)	<0.001	0.79
Shock	0 (0, 1)	0 (0, 1)	0.21	0.20
Age score	1 (0, 1)	1 (0, 1)	0.22	0.22
Total MESS	6 (4, 8)	4 (3, 5)	<0.001	0.18

Q1, lower quantile (25th percentile).
Q3, upper quantile (75th percentile).

was only weakly associated with amputation with an odds ratio of 1.02 [95% CI, 1.00–1.05] ($p = 0.08$). Concomitant nerve and orthopedic injuries were associated with amputation with an odds ratio of 11.6 [95% CI, 5.1–26.5] and 6.8 [95% CI, 3.2–14.7], respectively ($p < 0.0001$ for each). Age, sex, use of shunting, prehospital tourniquet use, fasciotomy performed at any time during the admission, and concomitant vein injury were not significantly associated with amputation and were not included in the final model. After controlling for confounding factors, the overall MESS and its components were no longer different between salvaged and amputated limbs (Table 3). After adjustment, concomitant nerve injury was the only factor that remained an independent predictor of amputation (odds ratio, 6.9 [95% CI, 2.3–21.2]; $p = 0.001$).

A MESS of 8 or greater was associated with a longer stay in the hospital (median, 22.5 (15, 29) vs 12 (6, 21); $p = 0.006$) and intensive care unit (6 (2, 13) vs 3 (1, 6), $p = 0.03$). There was a higher percentage of both primary traumatic amputations performed for damage control (50.0% vs 6.1%, $p < 0.001$) and overall amputations (62.5% vs 15.4%, $p < 0.001$) in the group of patients with a MESS of 8 or greater. There was no statistically significant difference in the number of re-interventions or in death between the groups (Table 4).

DISCUSSION

The original MESS was developed in 1990 by a retrospective review of 25 consecutive patients with lower extremity injuries.[2] The same authors subsequently applied the scoring system to a group of 26 comparable patients studied prospectively. In the original study, the MESS for salvaged limbs ranged from 3 to 6, whereas the MESS for the amputated limbs ranged from 7 to 12. These authors concluded that in their hands, a MESS of 7 or greater predicted amputation with 100% accuracy. Subsequent authors were unable to obtain this degree of accuracy and developed alternative scoring systems. These systems include the Limb Salvage Index; the Predictive Salvage Index; the Nerve Injury, Ischemia, Soft-tissue Injury, Skeletal Injury, Shock and Age of Patient Score (NISSA); and the Hannover Fracture Scale.[1] Each contains various elements of patients' characteristics at presentation (e.g., age, presence of shock), structural injury (e.g., concomitant bone, muscle, skin, nerve, vascular, injury, degree of contamination), and treatment factors (e.g., warm ischemia time, time to treatment).[5–8] These five scoring systems were prospectively evaluated in 2001 by Bosse et al.[9] as part of the Lower Extremity Assessment Project (LEAP) study group. A total of 556 high-energy injuries were evaluated including ischemic limbs, type III-A, III-B, and III-C tibial fractures, severe distal tibial fractures (open pilon fractures or type III-B ankle fractures), hindfoot fractures, and isolated soft tissue injuries of the lower extremities. This extensive analysis could not validate the clinical use of any of these scoring systems. The scores did have high specificity in predicting limb-salvage potential but had a low sensitivity in predicting the need for amputation. A subsequent study by the LEAP group showed that none of these scoring systems were predictive of functional recovery in patients who underwent successful limb reconstruction.[10]

Recent re-evaluations of the MESS have continued to question its validity. Menakuru et al.[11] found that of 148 patients, a MESS greater than 7 had a sensitivity of only 44% and a specificity of 70% in predicting amputation. Recent systematic reviews further confirm the unreliability of the MESS. Fodor et al.[12] concluded that MESS correctly identified the need for amputation in only 25% of cases, whereas Schiro et al.[13] found the range of reported accuracy of a MESS greater than 7 to be anywhere between zero percent and 93.4% in the literature. The MESS has also been evaluated in combat-related injuries. Sheean et al.[14] reported on 155 patients treated for type III open tibia fractures in US military service personnel, involving primarily blast injuries. One hundred ten had successful limb salvage, and 45 underwent primary amputation. The mean MESS values for amputees was 5.8 and for those that were salvaged was 5.3 ($p = 0.057$). The sensitivity and specificity of a MESS of 7 or greater in predicting the need for amputation in the combat setting were 35% and 87.8%, respectively (positive predictive value of 50%). These military surgeons concluded that the MESS was not useful in battlefield-related injuries. Additional studies on

TABLE 4. Comparison of Outcomes Between Patients with MESS < 8 and MESS ≥ 8

	All (n = 230)	MESS < 8 (n = 214)	MESS ≥ 8 (n = 16)	*p*
Total units packed red blood cells, median (Q1, Q3)	3 (0, 8)	3 (0, 8)	8 (2.5, 10)	0.07
Hospital length of stay, median (Q1, Q3)	12 (6, 22)	12 (6, 21)	22.5 (15, 29)	0.006
Days in Intensive Care Unit, median (Q1, Q3)	3 (1, 6)	3 (1, 6)	6 (2, 13)	0.03
Reintervention required, n (%)	35 (15.2)	32 (15)	3 (18.8)	0.5
Damage control primary traumatic amputation, n (%)	21 (9.1)	13 (6.1)	8 (50)	<0.001
All amputations, n (%)	43 (18.7)	33 (15.4)	10 (62.5)	<0.001
Death, n (%)	12 (5.2)	10 (4.7)	2 (12.5)	0.2

Q1, lower quantile (25th percentile).
Q3, upper quantile (75th percentile).

battlefield-related extremity vascular injuries did find that those with preserved limbs but high MESS scores (≥7) had higher levels of dysfunction as rated with the Short Musculoskeletal Function Assessment tool.[15]

In another contemporary analysis of the mangled lower extremity, de Mestral et al.[16] retrospectively examined a cohort of patients entered into the National Trauma Databank between 2007 and 2009. A total of 1354 patients were identified, with a 21% amputation rate. These authors found that the presence of a severe head injury, shock in the emergency department, and a high-energy mechanism of injury were associated with early amputation. Unfortunately, the National Trauma Databank does not contain sufficient data to accurately calculate the MESS score, which is why the PROOVIT database project is so important. A recent study from Austria looked at early failed attempts at salvage in open lower limb fractures demonstrating that in addition to MESS, other important predictors of secondary amputations included complex fractures, severe soft tissue damage, and the need for fasciotomy.[17] In 60% of these patients, failed limb salvage resulted from infectious complications and 40% from a failed vascular reconstruction.

In 2015, Aarabi et al. from Seattle presented their data on the use of MESS 25 years after its creation. In their series of 48 patients with mangled extremities complicated by acute arterial insufficiency, 81% were salvaged (MESS mean of 4.8) and 19% required amputation (MESS mean of 9.1).[4] In their series, the 77% of those who went on to secondary amputation had a popliteal artery injury. These authors also reported that MESS independently predicted the cost and length of hospitalization; on average, for every 1-point increase in MESS, the hospital cost increased by almost $6000.

Our study found blunt injuries, vessel transection, popliteal injuries, and concomitant nerve and orthopedic injuries were associated with the need for amputation, and were more predictive than an isolated MESS score. Although patients who underwent limb salvage had a lower MESS score on average, this was not significant after adjustment for confounders. Mangled Extremity Severity Score was a very poor predictor of amputation in this cohort, predicting only 43.2% of amputations.

This analysis includes 10 patients who died without receiving an amputation. The PROOVIT database does not distinguish if the limb was viable when the patient died, but these are included in the limb salvage category, representing a potential confounding variable. Mangled limbs without arterial injuries are not included in the PROOVIT database. In addition, although these data were prospectively obtained, incomplete or inaccurate data entry is an inherent flaw across all database studies. In this study, patients with missing MESS components were included as missing, meaning that some patients could have a falsely low total MESS. This was evaluated by correcting the missing values using multiple imputation, and no difference was found in the analysis. The increase in standard error was minimal for the missing component analysis and 6.9% for overall MESS. The missing data were also found to be missing at random compared to nonmissing variables; and thus, we conclude that although bias may be present, it is minimal for this study. Furthermore, this study reflects modern practice only among major Level I academic institutions across the country. Practice patterns of the larger enrolling centers may have dictated some of the trends observed.

While our data are robust, prospectively collected, and this series is relatively large, we do acknowledge that future investigations will need to examine the long-term outcomes of the patients with salvaged limbs. Late amputations (performed after the first hospitalization) may be required for limb dysfunction, persistent infections/open wounds, or in patients with chronic pain, as these problems can contribute to significant physical, psychological, financial, and social distress for these patients.[18] As the LEAP study group has demonstrated, in selected patients, the long-term quality of life may be the same in those with amputations and successful prosthetics, as it is in patients with limb salvage.[19]

Prehospital use of a tourniquet, damage control, balanced resuscitation, use of vascular shunts to reduce ischemia time, early fasciotomy, aggressive wound care, microsurgical abilities, and advanced tissue coverage techniques have all contributed to our increased ability to care for patients with mangled extremities. At this juncture, we advocate for the use of a team approach to decision making regarding limb salvage rather than the use of a score. Experienced surgeons from vascular, trauma, orthopedic, and plastic surgical disciplines evaluating the patient at the bedside and the patient's limb collaboratively ultimately contributes to the best outcome for the patient and for the extremity. Additionally, continued re-evaluation in the hospital and after discharge with long-term functional outcome data is needed to inform practice decisions and to assure the best quality of life for individual patients with limb-threatening mangled extremities.

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M.N.L., A.S., J.D., M.M.K. contributed to study design, literature search, data analysis, data interpretation, manuscript writing, and critical revision of the manuscript. C.-S.L., Y.L., contributed to study design, data analysis, and critical revision of the manuscript. S.S., T.S., J.B.H., T.E.R. contributed to study design, data collection, data interpretation, and critical revision of the manuscript. AAST PROOVIT Study Group contributed to data collection and critical revision of the manuscript.

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DISCLOSURE

The authors declare no conflicts of interest.

REFERENCES

1. Scalea TM, DuBose J, Moore EE, West M, Moore FA, McIntyre R, Cocanour C, Davis J, Ochsner MG, Feliciano D. Western Trauma Association critical decisions in trauma: management of the mangled extremity. *J Trauma Acute Care Surg*. 2012;72(1):86–93.
2. Johansen K, Daines M, Howey T, Helfet D, Hansen ST Jr. Objective criteria accurately predict amputation following lower extremity trauma. *J Trauma*. 1990;30(5):568–572; discussion 72–3.
3. DuBose JJ, Savage SA, Fabian TC, Menaker J, Scalea T, Holcomb JB, Skarupa D, Poulin N, Chourliaras K, Inaba K, et al. The American Association for the Surgery of Trauma PROspective Observational Vascular Injury Treatment (PROOVIT) registry: multicenter data on modern vascular injury diagnosis, management, and outcomes. *J Trauma Acute Care Surg*. 2015;78(2): 215–222; discussion 22–3.
4. Aarabi S, Kavousi Y, Friedrich J, Singh N, Bulger E. Severe lower extremity injury: MESS (Mangled Extremity Severity Score) twenty-five years later. *J Trauma Acute Care Surg*. 2016 (In press).
5. Howe HR Jr, Poole GV Jr, Hansen KJ, Clark T, Plonk GW, Koman LA, Pennell TC. Salvage of lower extremities following combined orthopedic and vascular trauma. A predictive salvage index. *Am Surg*. 1987;53(4):205–208.
6. McNamara MG, Heckman JD, Corley FG. Severe open fractures of the lower extremity: a retrospective evaluation of the Mangled Extremity Severity Score (MESS). *J Orthop Trauma*. 1994;8(2):81–87.
7. Russell WL, Sailors DM, Whittle TB, Fisher DF Jr, Burns RP. Limb salvage versus traumatic amputation. A decision based on a seven-part predictive index. *Ann Surg*. 1991;213(5):473–480; discussion 80–81.
8. Tscherne H, Oestern HJ. A new classification of soft-tissue damage in open and closed fractures (author's transl). *Unfallheilkunde*. 1982;85(3):111–115.
9. Bosse MJ, MacKenzie EJ, Kellam JF, Burgess AR, Webb LX, Swiontkowski MF, Sanders RW, Jones AL, McAndrew MP, Patterson BM, et al. A prospective evaluation of the clinical utility of the lower-extremity injury-severity scores. *J Bone Joint Surg Am*. 2001;83-A(1):3–14.
10. Ly TV, Travison TG, Castillo RC, Bosse MJ, MacKenzie EJ; LEAP Study Group. Ability of lower-extremity injury severity scores to predict functional outcome after limb salvage. *J Bone Joint Surg Am*. 2008;90(8):1738–1743.
11. Menakuru SR, Behera A, Jindal R, Kaman L, Doley R, Venkatesan R. Extremity vascular trauma in civilian population: a seven-year review from North India. *Injury*. 2005;36(3):400–406.
12. Fodor L, Sobec R, Sita-Alb L, Fodor M, Ciuce C. Mangled lower extremity: can we trust the amputation scores? *Int J Burns Trauma*. 2012;2(1):51–58.
13. Schirò GR, Sessa S, Piccioli A, Maccauro G. Primary amputation vs limb salvage in mangled extremity: a systematic review of the current scoring system. *BMC Musculoskelet Disord*. 2015;16:372.
14. Sheean AJ, Krueger CA, Napierala MA, Stinner DJ, Hsu JR; Skeletal Trauma and Research Consortium (STReC). Evaluation of the mangled extremity severity score in combat-related type III open tibia fracture. *J Orthop Trauma*. 2014;28(9):523–526.
15. Scott DJ, Watson JD, Heafner TA, Clemens MS, Propper BW, Arthurs ZM. Validation of the Short Musculoskeletal Function Assessment in patients with battlefield-related extremity vascular injuries. *J Vasc Surg*. 2014;60 (6):1620–1626.
16. de Mestral C, Sharma S, Haas B, Gomez D, Nathens AB. A contemporary analysis of the management of the mangled lower extremity. *J Trauma Acute Care Surg*. 2013;74(2):597–603.
17. Fochtmann A, Mittlböck M, Binder H, Köttstorfer J, Hajdu S. Potential prognostic factors predicting secondary amputation in third-degree open lower limb fractures. *J Trauma Acute Care Surg*. 2014;76(4):1076–1081.
18. Prasarn ML, Helfet DL, Kloen P. Management of the mangled extremity. *Strategies Trauma Limb Reconstr*. 2012;7(2):57–66.
19. MacKenzie EJ, Bosse MJ, Pollak AN, Webb LX, Swiontkowski MF, Kellam JF, Smith DG, Sanders RW, Jones AL, Starr AJ, et al. Long-term persistence of disability following severe lower-limb trauma. Results of a seven-year follow-up. *J Bone Joint Surg Am*. 2005;87(8):1801–1809.

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Systemic anticoagulation in the setting of vascular extremity trauma

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ABSTRACT

Introduction: There is conflicting data regarding if patients with vascular extremity trauma who undergo surgical treatment need to be systematically anticoagulated. We hypothesized that intraoperative systemic anticoagulation (ISA) decreased the risk of repair thrombosis or limb amputation after traumatic vascular injury of the extremities.

Methods: We analyzed a composite risk of repair thrombosis and/or limb amputation (RTLA) between patients who did and did not undergo ISA during arterial injury repair. Patient data was collected in the American Association for the Surgery of Trauma PROspective Vascular Injury Treatment (PROOVIT) registry. This registry contains demographic, diagnostic, treatment, and outcome data.

Results: Between February 2013 and August 2015, 193 patients with upper or lower extremity arterial injuries who underwent open operative repair were entered into the PROOVIT registry. The majority were male (87%) with a mean age of 32.6 years (range 4–91) and 74% injured by penetrating mechanism. 63% of the injuries were described as arterial transection and 37% had concomitant venous injury. 62% of patients underwent ISA. RTLA occurred in 22 patients (11%) overall, with no significant difference in these outcomes between patients who received ISA and those that did not (10% vs. 14%, $p = 0.6$). There was, however, significantly higher total blood product use noted among patients treated with ISA versus those that did not receive ISA (median 3 units vs. 1 unit, $p = 0.002$). Patients treated with ISA also stayed longer in the ICU (median 3 days vs. 1 day, $p = 0.001$) and hospital (median 9.5 days vs. 6 days, $p = 0.01$).

Discussion: In this multicenter prospective cohort, intraoperative systemic anticoagulation was not associated with a difference in rate of repair thrombosis or limb loss; but was associated with an increase in blood product requirements and prolonged hospital stay. Our data suggest there is no significant difference in outcome to support use of ISA for repair of traumatic arterial injuries.

Background

Routine intraoperative systemic anticoagulation (ISA) is a mainstay of therapy in elective arterial reconstruction and treatment of acute limb ischemia [1]. In the setting of trauma, surgeons have been reluctant or unable to systemically anticoagulate patients when performing arterial repair due to concern for potential local and systemic bleeding [2]. It is unclear if the improved patency seen with elective vascular repair can be generalized to traumatic arterial repair, particularly in patients

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with acute traumatic coagulopathy or resuscitation-associated coagulopathy. There is limited and conflicting retrospective data in the literature correlating improved patency or limb salvage with use of ISA during traumatic arterial injury repair [3–9]. Retrospective reviews of patients who received ISA during lower extremity arterial injury repair report a limb salvage rate of 85–91% [2,5,7,8]. Other reviews, however, report lower limb salvage rates of 83–84% with similar injuries, despite routinely not giving ISA [4,10]. Comparative studies have shown no statistically significant difference in outcome between patients who are given ISA and those who are not [6,7]. Proponents, however, argue that the risks of ISA are minimal, and may decrease the risk of distal in situ thrombus or microvascular thrombosis [5,9]. We hypothesized that intraoperative systemic anticoagulation (ISA) decreased the risk of repair thrombosis or limb amputation (RTLA) after traumatic vascular injury of the extremities.

Methods

Patient data was collected from the American Association for the Surgery of Trauma (AAST) Multicenter PROspective Observational Vascular Injury Treatment (PROOVIT) registry. The details of this registry have been previously described [11]. This is a prospectively-collected database of injuries to named arterial and venous structures from fourteen Level I trauma centers across the United States. The database includes demographic, diagnostic, treatment, and outcome data for the index hospital stay. The registry is accruing data from clinic and readmission follow up.

Patients with upper or lower extremity arterial injuries who underwent open arterial revascularization between February 2013 and August 2015 were identified. Patients treated with arterial ligation, primary traumatic amputation, endovascular repair or embolization were excluded. Arterial injuries to the upper extremity utilized for analysis included individual injuries to the brachial or distal forearm arteries. The rare combined brachial and radial artery injuries were categorized as brachial artery injuries. Arterial injuries to the lower extremity included individual injuries to the femoral, popliteal or distal to the popliteal artery. Method of repair included autologous conduit, synthetic interposition or bypass graft and primary repair. Patients treated with vein interposition or bypass, vein patch or autologous artery as a conduit were included in the autologous category. ISA was defined as systemic anticoagulation with unfractionated heparin (UFH) utilized during the initial operation or vascular repair. Intraoperative regional anticoagulation was not included in this study. The total mangled extremity severity score (MESS) was calculated

Table 1
Demographics of included patients, analyzed by intraoperative anticoagulation status.

		Intraoperative Systemic Anticoagulation		
Factor	All	Received	Not Received	p-value
Mean age (SD)	32.6 (15.3)	32.2 (15.1)	33.4 (15.7)	0.6*
Male, n (%)	167/193 (87)	109/119 (92)	58/74 (78)	0.02†
Injury mechanism				0.5†
Blunt, n (%)	47/193 (24)	32/119 (27)	15/74 (20)	
Penetrating, n (%)	142/193 (74)	85/119 (71)	57/74 (77)	
Mixed blunt and penetrating, n (%)	4/193 (2)	2/119 (2)	2/74 (3)	
Specific mechanism				0.5†
Gunshot, n (%)	80/193 (42)	53/119 (45)	27/74 (37)	
Stabbing, n (%)	29/193 (15)	16/119 (13)	13/74 (18)	
Motor Vehicle Collision, n (%)	25/193 (13)	17/119 (14)	8/74 (11)	
Other, n (%)	59/193 (31)	33/119 (28)	26/74 (35)	
Injury description				0.5†
Flow limiting defect, n (%)	33/193 (17)	22/119 (19)	11/74 (15)	
Occlusion, n (%)	24/193 (12)	18/119 (15)	6/74 (8)	
Pseudoaneurysm, n (%)	6/193 (3)	3/119 (3)	3/74 (4)	
Transection, n (%)	121/193 (63)	71/119 (60)	50/74 (68)	
Other injury type, n (%)	9/193 (5)	5/119 (4)	4/74 (5)	
Median ISS (Q1, Q3)	9 (9, 16)	10 (9, 16)	9 (5, 16)	0.1§
Mean admission SBP (SD)	120.9 (28.5)	120.5 (29.8)	121.6 (26.6)	0.8*
Median GCS (Q1, Q3)	15 (15, 15)	15 (15, 15)	15 (15, 15)	0.7§
Median AIS-extremity (Q1, Q3)	3 (3, 3)	3 (3, 3)	3 (2, 3)	0.06§
Median MESS (Q1, Q3)	4 (3, 6)	4 (3, 6)	4 (3, 5)	0.08§
Median Skeletal/Soft tissue Score (Q1, Q3)	1 (1, 2)	1 (1, 2)	1 (1, 1)	0.1§
Median Limb Ischemia Score (Q1, Q3)	1 (1, 2)	2 (1, 2)	1 (1, 1)	<0.001§
Median Shock Score (Q1, Q3)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0.9§
Median Age Score (Q1, Q3)	0 (0, 1)	0 (0, 1)	1 (0, 1)	0.3§
Concomitant vein injury, n (%)	71/193 (37)	44/119 (37)	27/74 (37)	0.9†
Vein repaired, n (%)	63/71 (89)	40/44 (91)	23/27 (85)	0.7†
Concomitant nerve injury, n (%)	63/193 (33)	31/119 (26)	32/74 (43)	0.02‡
Concomitant orthopedic injury, n (%)	66/193 (34)	43/119 (36)	23/74 (31)	0.6†

ISS = Injury severity score.
AIS = Abbreviated injury score.
SBP = Systolic blood pressure.
GCS = Glasgow coma score.
MESS = Mangled extremity severity score.
SD = standard deviation.
Q1 = Lower quantile (25th percentile).
Q3 = Upper quantile (75th percentile).
* Two-tailed *t*-test.
† Pearson's Chi-square.
‡ Chi-square with Yates' continuity correction.
§ Wilcoxon Rank-Sum.

as originally described by Johansen et al., from the prospectively obtained components described in Appendix B in the Supplementary material [12].

The primary endpoint was a composite risk of RTLA during the index admission, between patients who did and did not undergo ISA during arterial injury repair. Secondary endpoints included need for reintervention after initial operation for any reason, total units of packed red blood cells (PRBC) required in the first 24 h, length of intensive care unit (ICU) stay and length of total hospital stay.

Statistical analysis was performed using Stata Version 14.1 (StataCorp, College Station, TX, USA). Differences in demographics for patients who received ISA and were compared using the Wilcoxon rank-sum test for ordinal variables and two-sample *t*-test for continuous variables. The Fisher's exact test was used for 2×2 contingency tables with 20 or less patients in any category. P-values are reported as double the 1-sided exact probability. Pearson's chi-squared test with Yates' correction for continuity was used for 2×2 contingency tables when there were between 21 and 40 patients in a given category. Pearson's chi-squared test was used for all larger contingency tables. A p-value < 0.05 was considered statistically significant.

Results

Between February 2013 and August 2015, 193 patients with upper or lower extremity arterial injuries who underwent open arterial repair were entered into the PROOVIT registry from 14 Level-1 trauma centers. The 14 centers contributed between 1 and 52 patients each (mean 13.8, median 4), with five centers being the largest contributors with over 25 patients each. ISA was given to 119 patients in total (62%). The patients were predominantly male, with a mean age of 32.6 years (range 4–91, Table 1). Men were more likely to receive ISA than women (92% ISA were male vs. 78% without ISA were male, p = 0.02). Most injuries were penetrating in nature (74%), and were most often caused by gunshot wounds (42%). The injury identified was most often a transection (63%). There were no differences in ISS, admission systolic blood pressure, or Glasgow coma score (GCS) between patients who received ISA and those who did not. There was a trend towards higher AIS-extremity in patients who received ISA compared to those who did not, but it did not reach statistical significance (median of 3 (25th percentile (Q1) – 75th percentile (Q3) 3–3) vs. 3 (Q1–Q3 2–3), p = 0.06). MESS did not differ between patients who received ISA than those who did not (median of 4 (Q1–Q3 3–6) vs. 4 (Q1–Q3 3–5), p = 0.08). When each component was analyzed individually, however, patients who received ISA had a higher limb ischemia score compared to those who did not (median of 2 (Q1–Q3 1–2) vs. 1 (Q1–Q3 1-1), $p < 0.001$).

In total, there were 71 concomitant venous injuries (37%), of which 63 were repaired (89%). The remaining 8 injured veins were ligated. Sixty-three patients had concomitant nerve injuries (33%), and 66 patients had associated orthopedic injury (34%). There were no significant differences in concomitant venous or orthopedic injuries between patients who received ISA and those who did not. Patients with concomitant nerve injuries were less likely to receive ISA (26% with ISA vs. 43% without, p = 0.02).

Forty-three patients had a pre-hospital tourniquet placed (22%). Most patients had an ischemia time (from time of injury to time of definitive repair) between 3 and 6 h (54%, Table 2). Damage-control temporary shunt placement was used in 9 patients (5%), 8 of whom received ISA. Arterial repair with autologous conduit was performed in 103 patients (53%), including 100 vein interposition or bypass grafts, 2 vein patches and one autologous artery used as conduit. The artery was repaired primarily in 81 patients (42%), and with synthetic graft in 8 patients (4%). Patients who underwent a repair with any autologous conduit were more likely to receive ISA than not (62% vs. 39%, p = 0.001). Twenty-eight patients (15%) required a revision of the arterial repair during the initial operation (Table 2). There was no difference in administration of ISA in patients who required immediate revision (17% with ISA vs 11% without, p = 0.3). Extremity fasciotomies were performed in 78 patients, including 13 involving the upper extremity. Patients who underwent fasciotomy at any time during the initial hospitalization were more likely to have received ISA than not (48% vs. 28%, p = 0.01). Patients who had an operative time of greater than 6 h were more likely to receive ISA than not (10% vs. 5%, p = 0.04).

There were 96 and 97 injuries to the upper and lower extremity, respectively. There were no combined upper and lower extremity injuries, and no combined above- and below-knee arterial injuries. There were two combined brachial and radial injuries. ISA was given for popliteal arterial injuries in 84% (26/31) of cases, in 67% (39/58) of femoral and in only 38% (3/8) of below-popliteal injuries

Table 2
Management of injuries, analyzed by intraoperative anticoagulation status.

Factor	All	Intraoperative Systemic Anticoagulation		p-value
		Received	Not Received	
Pre-hospital Tourniquet, n (%)	43/193 (22)	24/119 (20)	19/74 (26)	0.4‖
Time from Injury to Repair				0.4†
Less than 3 h, n (%)	41/193 (21)	23/119 (19)	18/74 (24)	
3–6 h, n (%)	104/193 (54)	71/119 (60)	33/74 (45)	
Greater than 6 h, n (%)	33/193 (17)	20/119 (17)	13/74 (18)	
Temporary shunt utilized, n (%)	9/193 (5)	8/119 (7)	1/74 (1)	0.2‖
Repair Method				0.001†
Autologous repair, n (%)	103/193 (53)	74/119 (62)	29/74 (39)	
Primary repair, n (%)	81/193 (42)	38/119 (32)	43/74 (58)	
Synthetic graft utilization, n (%)	8/193 (4)	7/119 (6)	1/74 (1)	
Immediate revision required intraoperatively, n (%)	28/193 (15)	20/119 (17)	8/74 (11)	0.3‖
Fasciotomy, n (%)	78/193 (40)	57/119 (48)	21/74 (28)	0.01‡
Intraoperative time				0.04†
Less than 3 h, n (%)	78/193 (40)	42/119 (35)	36/74 (49)	
3–6 h, n (%)	84/193 (44)	60/119 (50)	24/74 (32)	
Greater than 6 h, n (%)	16/193 (8)	12/119 (10)	4/74 (5)	

† Pearson's Chi-square.
‡ Chi-square with Yates' continuity correction.
‖ 1-tailed Fisher's exact test, doubled.

Table 3
Analysis of intraoperative anticoagulation status and outcome, by artery injured.

			Amputations		RTLA	
Artery Injured	Total Injuries	ISA Received	ISA Received	ISA Not Received	ISA Received	ISA Not Received
Brachial artery, n (%)	47/193 (24)	32/47 (68)	0/32 (0)	0/15 (0)	3/32 (9)	2/15 (13)
Forearm arteries, n (%)	49/193 (25)	19/49 (39)	1/19 (5)	0/30 (0)	1/19 (5)	1/30 (3)
Femoral artery, n (%)	58/193 (30)	39/58 (67)	2/39 (5)	2/19 (11)	4/39 (10)	3/19 (16)
Popliteal artery, n (%)	31/193 (16)	26/31 (84)	4/26 (15)	1/5 (20)	4/26 (15)	3/5 (60)
Distal to popliteal, n (%)	8/193 (4)	3/8 (38)	0/3 (0)	1/5 (20)	0/3 (0)	1/5 (20)

RTLA = Repair thrombosis and/or amputation.
ISA = intraoperative systemic anticoagulation.

($p < 0.001$, Table 3). The total limb salvage rate was 94% (182/193). Popliteal artery injuries had the lowest rate of limb salvage (84%, 26/31). Lower extremity amputations were more frequent than upper extremity amputations (10% of lower extremity injuries (10/97) vs. 1.0% of upper (1/96), $p = 0.005$). Rates of amputation and RTLA by artery injured and ISA status can be found in Table 3. Results were not analyzed for statistical significance given small numbers per group.

RTLA occurred in 22 patients (11%), including 11 amputations and 13 instances of graft thrombosis (Table 4). There was no significant difference in RTLA between patients who received ISA and those that did not (12/119 (10%) vs. 10/74 (14%), $p = 0.6$).

There was significantly higher total blood product use among patients treated with ISA versus those that did not receive ISA (median 3 units (Q1–Q3 0–8)) vs. 1 unit (Q1–Q3 0–4, $p = 0.002$). There was a longer length of ICU (median 3 days (Q1–Q3 1–6) vs. 1 day (Q1–Q3 0–3), $p = 0.001$) and hospital length of stay (median 9.5 days (Q1–Q3 4–18.5) vs. 6 days (Q1–Q3 2–13), $p = 0.01$) in patients treated with ISA compared to those who were not. Nineteen patients required return to the operating room for reintervention during the index hospitalization (10%), including the 13 with repair thrombosis, one with hematoma, three with flow-limiting stenosis, one with a pseduoaneurysm and one with an infection. There was no difference in need for reintervention between patients who underwent ISA and those who did not (9/119 (8%) vs. 10/74 (14%), $p = 0.2$). There were no deaths or hemorrhagic strokes in the total cohort.

Discussion

Anticoagulation has been investigated as a modifiable risk factor to improve outcomes for patients with extremity arterial injuries. Early use of anticoagulation has been argued to minimize distal and small vessel thrombosis and therefore improve outflow patency [5,9]. Despite the dogma for using anticoagulation in vascular repair, in patients undergoing repair of traumatic vascular injuries there is minimal and conflicting data in the literature correlating the use of ISA with improved outcomes. Routine anticoagulation in the absence of contraindications has been recommended by multiple groups [5,8,9,13], but has been found to have no difference by other groups [4,6,7,10]. Wagner et al. found a significantly lower amputation rate when ISA was used, in a review of 99 traumatic popliteal artery injuries (8% vs. 31%, $p < 0.01$) [8]. They did not, however, account for other confounding patient characteristics like degree of limb ischemia at presentation. Daugherty et al. compared patients with popliteal injuries who received ISA over two sequential five-year periods. Between 1967–1972, 13 patients received ISA with a limb salvage rate of 46%; in contrast to 7 patients who did not receive ISA and had a limb salvage rate of 43%. Between 1972–1977, 11 patients received ISA and the total limb salvage improved to 91% [5]. They also report using improved operative techniques including extra-anatomic bypass in the latter time period, which could account for the difference in outcome. Melton et al. looked at 102 patients with popliteal artery injuries, 79% of whom were given ISA with or without thrombolysis [7]. While there was a trend towards improved limb salvage in patients treated with anticoagulation and/or thrombolysis compared to no treatment ($p = 0.05$), there was no significant difference in limb salvage in subgroup of 46 patients who were given ISA alone ($p = 0.19$) [7]. Humphries et al. performed a modern retrospective review of 123 patients with extremity injuries, in which 56% of patients received ISA [6]. They found no difference in RTLA with use of ISA (OR 0.74, $p = 0.6$) [6]. Similarly, we found no significant association between ISA and amputation and/or repair thrombosis.

Table 4
Outcomes after repair, analyzed by intraoperative anticoagulation status.

		Intraoperative systemic anticoagulation		
Outcome	Total	Received	Not received	p-value
Median total units PRBC (Q1, Q3)	2 (0, 6)	3 (0, 8)	1 (0, 4)	0.002[§]
Median days of ICU stay (Q1, Q3)	2 (0, 5)	3 (1, 6)	1 (0, 3)	0.001[§]
Median days of total hospital stay (Q1, Q3)	8 (3, 17)	9.5 (4, 18.5)	6 (2, 13)	0.01[§]
Re-intervention required after repair, n (%)	19/193 (10)	9/119 (8)	10/74 (14)	0.2[‖]
Composite endpoint RTLA, n (%)	22/193 (11)	12/119 (10)	10/74 (14)	0.6[‖]
Amputation, n (%)	11/193 (6)	7/119 (6)	4/74 (5)	1.0[‖]
Thrombosis, n (%)	13/193 (7)	6/119 (5)	7/74 (10)	0.4[‖]

RTLA = Repair thrombosis and/or amputation.
PRBC = Packed red blood cells.
ICU = intensive care unit.
Q1 = Lower quantile (25th percentile).
Q3 = Upper quantile (75th percentile).
[§] Wilcoxon Rank-Sum.
[‖] 1-tailed Fisher's exact test, doubled.

The limb salvage rate observed in this study is consistent with modern studies [9], with 94% limb salvage. Popliteal artery injuries continue to have the poorest limb salvage rates. There is no appreciable improvement in the overall limb salvage rate of popliteal arteries since the 1980s; 84% in this modern study compared to historically reported rates of 83–100% [3–5,7,8,13] despite improvements in hospital and pre-hospital care.

The biggest limitation of any database is the detailed information that are not collected. Specifically, data regarding other adjuvant anticoagulation strategies including use of local heparinized-containing irrigation intraoperatively, transexemic acid, dextran, anticoagulation or antiplatelet agents given postoperatively, use of thrombectomy catheters, and details regarding specific ISA dose, pre- or post-administration activated clotting time levels were not collected in the PROOVIT database. These factors could be significant cofounding variables and warrant further investigation.

One main reason anticoagulation is withheld during arterial repair for a trauma patient is the concern for bleeding complications due to concomitant injuries. Anticoagulation given to patients with traumatic arterial injuries without absolute contraindications has been reported to have no increase in the rate of bleeding complications [5,6,9,10,14]. Wagner et al. found no hemorrhagic complications in the 71 patients given intraoperative systemic anticoagulation [8]. Humphries et al. found that use of ISA did not significantly change intraoperative blood loss (637 mL vs 926 mL, $p = 0.23$) or overall bleeding complications (42% vs 45%, $p = 0.95$) [6]. Golob et al. found a total complication (major and minor) rate of 21% in 114 patients given anticoagulation after traumatic injury [15]. Our study found significantly higher total PRBC use in patients receiving ISA, as well as longer hospital and ICU stays despite similar ISS, MESS and GCS between the groups. However, the outcomes of thrombosis, amputation, stroke or death were unchanged between the groups. The PROOVIT database does not currently include data regarding specific bleeding complications or strict contraindications for anticoagulation (i.e. intracavitary hemorrhage, need for multiple operations), and therefore these potential confounders will be missed.

Though prospectively obtained, this database reflects modern practice only among major Level I academic institutions across the country. Practice patterns of the 5 centers with higher enrollment may dictate some of the trends observed. The database did not collect information on the level of training or specialty of the operating surgeon. This study focused on open arterial repairs, as there were only two identified endovascular repairs undertaken for extremity arterial trauma recorded in the PROOVIT database for this time period. Use and outcomes of endovascular techniques for extremity trauma is being actively explored [16,17], but outcomes associated with these technologies will require additional investigation as experience matures. This preliminary report focuses on in-hospital outcomes following traumatic arterial injury repair, and does not include delayed amputations that may be required long term for limb dysfunction, delayed repair thrombosis or infection. A power calculation determined that to detect a 3% difference in rate of amputation, 1496 total patients should be analyzed. A more robust data set with information on outcomes will be obtained as the PROOVIT database continues to mature.

In this study, anticoagulation given during an operation was not associated with improved graft patency or limb salvage. Furthermore, ISA use was associated with prolonged hospital stay and increased blood product use. Our data suggest that for traumatic arterial injuries, there is no significant difference in outcome to support use of ISA. Further investigation regarding the risks of ISA for traumatic vascular injuries is needed.

Authorship

This work represents the original efforts of the investigators. All listed authors contributed to study design, data collection, data interpretation, and manuscript development.

Disclosure

The authors declare no conflicts of interest.

Acknowledgements

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Appendix A.

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Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.injury.2017.03.020.

References

[1] G.P. Casale, I.I. Pipinos. Ischemia-reperfusion. In: Cronenwett, J, Johnston, K, (Eds.). Rutherford's Vascular Surgery. 8th ed. Philadelphia, PA 2014. Chapter 7.
[2] Snyder 3rd. WH. Vascular injuries near the knee: an updated series and overview of the problem. Surgery 1982;91(5):502–6.
[3] Fabian TC, Turkleson ML, Connelly TL, Stone HH. Injury to the popliteal artery. Am J Surg 1982;143(2):225–8.
[4] Hafez HM, Woolgar J, Robbs JV. Lower extremity arterial injury: results of 550 cases and review of risk factors associated with limb loss. J Vasc Surg 2001;33(6):1212–9.
[5] Daugherty ME, Sachatello CR, Ernst CB. Improved treatment of popliteal arterial injuries using anticoagulation and extra-anatomic reconstruction. Arch Surg 1978;113(11):1317–21.
[6] Humphries M, Blume MK, Rodriguez MC, DuBose JJ, Galante JM. Outcomes after anticoagulation for traumatic arterial injuries of the extremity. JAMA Surg 2016;151(Oct. (10)):986–7.
[7] Melton SM, Croce MA, Patton Jr. JH, Pritchard FE, Minard G, Kudsk KA, et al. Popliteal artery trauma. Systemic anticoagulation and intraoperative thrombolysis improves limb salvage. Ann Surg 1997;225(5):518–27.
[8] Wagner WH, Calkins ER, Weaver FA, Goodwin JA, Myles RA, Yellin AE. Blunt popliteal artery trauma: one hundred consecutive injuries. J Vasc Surg 1988;7(5):736–43.
[9] Guerrero A, Gibson K, Kralovich KA, Pipinos I, Agnostopolous P, Carter Y, et al. Limb loss following lower extremity arterial trauma: what can be done proactively? Injury 2002;33(9):765–9.
[10] Fabian TC, Patton Jr. JH, Croce MA, Minard G, Kudsk KA, Pritchard FE. Blunt carotid injury. Importance of early diagnosis and anticoagulant therapy. Ann Surg 1996;223(5)513–22 Discussion 22–5.
[11] DuBose JJ, Savage SA, Fabian TC, Menaker J, Scalea T, Holcomb JB, et al. The American Association for the Surgery of Trauma PROspective Observational Vascular Injury Treatment (PROOVIT) registry: multicenter data on modern vascular injury diagnosis, management, and outcomes. J Trauma Acute Care Surg 2015;78(2)215–22 Discussion 22–3.
[12] Johansen K, Daines M, Howey T, Helfet D, Hansen Jr. ST. Objective criteria accurately predict amputation following lower extremity trauma. J Trauma 1990;30(5)568–72 Discussion 72–3.
[13] Lim LT, Michuda MS, Flanigan DP, Pankovich A. Popliteal artery trauma: 31 consecutive cases without amputation. Arch Surg 1980;115(11):1307–13.
[14] Cothren CC, Moore EE, Biffl WL, Ciesla DJ, Ray Jr. CE, Johnson JL, et al. Anticoagulation is the gold standard therapy for blunt carotid injuries to reduce stroke rate. Arch Surg 2004;139(5)540–5 Discussion 5–6.
[15] Golob Jr. JF, Sando MJ, Kan JC, Yowler CJ, Malangoni MA, Claridge JA. Therapeutic anticoagulation in the trauma patient: is it safe? Surgery 2008;144(4)591–6 Discussion 6–7.
[16] Desai SS, DuBose JJ, Parham CS, Charlton-Ouw KM, Valdes J, Estrera AL, et al. Outcomes after endovascular repair of arterial trauma. J Vasc Surg 2014;60(5):1309–14.
[17] Kufner S, Cassese S, Groha P, Byrne RA, Schunkert H, Kastrati A, et al. Covered stents for endovascular repair of iatrogenic injuries of iliac and femoral arteries. Cardiovasc Revasc Med 2015;16(3):156–62.

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USE OF OPEN AND ENDOVASCULAR SURGICAL TECHNIQUES TO MANAGE VASCULAR INJURIES IN THE TRAUMA SETTING: A REVIEW OF THE AAST PROOVIT REGISTRY

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Invited Discussant: [discussant]

Introduction: Vascular trauma data have been submitted to the American Association for the Surgery of Trauma PROspective Observational Vascular Injury Trial (PROOVIT) database since 2013 from multiple level I and II trauma centers throughout the United States. To date over 2,500 records have been submitted. We present preliminary data from the registry to describe the current use of endovascular surgery in vascular trauma.

Methods: We reviewed registry data from March 2013 to December 2016 with permission from the PROOVIT review panel. All patients who had an injury to a named artery, excepting forearm and lower leg, were included. Arteries were grouped into anatomical regions (neck, thoracic outlet, thorax, upper limb, major abdominal, abdominal branches and lower limb) and regions (compressible and non-compressible) for analysis. This review was limited to patients with non-compressible transection, partial transection, or flow limiting defect injuries. In addition to descriptive statistics, we developed multivariate linear models to assess the relationships between study variables.

Results: 1143 patients from 22 institutions had 1 or more arterial injuries in the regions defined. Median age was 32 years (interquartile range [IQR] 23-48) and 76% were male. Mechanisms of injury were 49% blunt, 41% penetrating, and 1.8% of mixed aetiology. Gunshot wounds accounted for 73% of all penetrating injuries. Endovascular techniques were used least often in limb trauma (upper limb 3% (n=7/203), lower limb 5% (n=18/381)) and most commonly in patients with blunt injuries to more than one region (50%, n=116/231). Penetrating wounds to any region were preferentially treated with open surgery (74%, n=341/459) with endovascular and combined approaches only accounting for 34 cases (7%). The most common indication for endovascular treatment was blunt non-compressible truncal injuries (NCTI). Patients with transection, partial transection or flow limiting NCTI treated with endovascular surgery had higher overall injury burden as reflected by injury severity scores and longer associated hospital stays, but required less packed red blood cells (PRC), and had lower in hospital mortality than those treated with open surgery on univariate analysis. On multivariate analysis of this NCTI group, low hemoglobin and abdominal injury were independent predictors of mortality, and amongst survivors, type of injury, hemoglobin, lactate, and vasopressor use were predictors of PRC use in the first 24 hours.

Conclusion: Our review of the PROOVIT registry demonstrates that both endovascular and open surgery is being performed for vascular injuries in all regions of the body. These findings support the use of endovascular treatment of vascular injuries in the severely injured, but additional investigation is needed to define indications and optimal utilization of endovascular technologies in the setting of vascular trauma.

CONTEMPORARY TOURNIQUET USE IN EXTREMITY VASCULAR TRAUMA: THE AAST PROSPECTIVE OBSERVATIONAL VASCULAR INJURY TREATMENT (PROOVIT) REGISTRY

Sarah-Ashley E. Ferencz, MD; Joseph J. DuBose, MD; Jamie Hennigan, MD; Kailey Nolan, BS; James B. Sampson, MD; Todd E. Rasmussen, MD; Joseph Galante, MD; Tiffany Bee, MD; Timothy Fabian, MD; Jay Menaker, MD; Thomas M. Scalea, MD; John B. Holcomb, MD; David Skarupa, MD; Kenji Inaba, MD; John K. Bini MD,
and the *AAST PROOVIT Study Group*

Introduction: Correct tourniquet application can be a lifesaving technique prior to definitive surgical treatment of extremity vascular trauma. After World War II, tourniquet use had fallen out of favor due to potential complications such as nerve damage and limb loss. Current guidelines recommend tourniquet use to control hemorrhage from penetrating lower extremity trauma. There are many reports of successful tourniquet use in military conflicts; however, only a few small studies have evaluated their use in the civilian trauma population. We aimed to describe the contemporary use of tourniquets in the management of civilian extremity vascular trauma and evaluate the associated outcomes.

Methods: We reviewed data from the multicenter AAST Prospective Observational Vascular Injury Treatment (PROOVIT) registry from Feb 2013 to Dec 2016. This data included key elements of vascular trauma presentation, diagnosis, management and outcomes. Data was compared with student t-tests and propensity score matching using R software. Controls were matched using the covariates Injury Severity Score, Abbreviated Injury Score of the extremity, initial systolic blood pressure, initial Glasgow Coma Scale score, initial lactate level, and age. Patients with multiple arterial injuries were excluded from analysis.

Results: A total of 623 patients with extremity arterial injuries from 14 centers were included for analysis. Pre-hospital tourniquets were placed in 17.5% of patients with extremity arterial injury. The overall number of amputations following any arterial extremity injury was low with or without the placement of a tourniquet, and not statistically different when compared to propensity matched controls (tourniquet 0.04 vs control 0.10; p=0.12). There was no statistical difference between the in-hospital mortality rates when tourniquets were used (tourniquet 0.08 vs control 0.04; p=0.18). In patients with brachial artery injuries the use of tourniquets was associated with a reduced average hospital length of stay (11.3 days vs 17.0 days; p=0.23) and average ICU length of stay (3.5 days vs 7.0 days; p=0.04). When compared to controls, tourniquet use did not significantly affect 24-hour packed red blood cell (pRBC) transfusion requirement (tourniquet 7.98 vs control 7.12; p=0.35), need for post-operative therapeutic anticoagulation (tourniquet 0.65 vs control 0.68; p=0.36), or the rate of infection in the affected limb (tourniquet 0.01 vs control 0.02; p=0.45).

Conclusion: The PROOVIT registry shows that in contemporary civilian practice, tourniquets are used for extremity arterial injury in just 17.5% of cases, a rate much lower than previously reported for both civilian and military settings. Tourniquet use was not associated with an increased rate of amputation, in-hospital mortality, 24-hour pRBC transfusion, or subsequent infection in the affected limb when compared to matched controls. There was a statistically significant shorter ICU length of stay in patients who had tourniquets placed for brachial artery injuries. There was also a trend toward shorter overall hospital length of stay by over 5 days in

this group as well, which while not statistically significant, may have important clinical implications.

Poster # 97

PEDIATRIC VASCULAR TRAUMA: CURRENT MANAGEMENT AND EARLY OUTCOMES

Melissa N. Loja MD, MAS, Joseph Dubose* MD, Jacob Stephenson* MD, Boris Kessel* MD, Tiffany Bee* MD, Timothy Fabian* MD, Jay Menaker* MD, Thomas Scalea* MD, John B. Holcomb* MD, David Skarupa* MD, Kenji Inaba* MD, Richard Catalano MD, Nathaniel Poulin* MD, John K. Bini* MD, Todd E. Rasmussen* MD, University of California, Davis

Introduction: The hospital course and early outcome of vascular injuries in the pediatric population is not well known due to a paucity of literature, and infrequent occurrence. We sought to describe pediatric vascular injuries including hospital treatment strategies and discharge outcomes using a multicenter, prospectively collected database.

Methods: We included patients 16 years or younger from patient data collected from the American Association for the Surgery of Trauma PROspective Vascular Injury Treatment (PROOVIT) registry. This registry contains demographic, diagnostic, treatment, and in-hospital outcome data for patients with vascular injuries.

Results: Between February 2013 and December 2016, 2,673 patients were enrolled into the PROOVIT registry. 83 of these patients were aged 16 years or younger (3% incidence). The majority were male (80%) with a mean age of 13.5 years (range 3-19). 60% (50/84) were injured by penetrating mechanism including 25 gunshot wounds and 7 stabbings. 36% were injured by a blunt mechanism. Hard signs of vascular injury were present in 41 patients. 61% (51/83) of patients were taken to the operating room immediately. CT scans were performed for diagnosis in 24% (20/83) of patients, most frequently for lower extremity injuries (7/20). The median ISS was 10 (25th percentile 5 – 75th percentile 18). 72% (60/83) of the injuries were to an extremity, 11% to the neck (9/83), and 17% to the abdomen or chest (14/83). Of the extremity injuries, 20% patients (12/60) had a pre-hospital tourniquet placed. 65% of extremity injuries were treated with open repair (39/60). Neck trauma was most commonly treated with observation in 5/9 patients. Abdomen or chest trauma was treated most frequently with open operations (6/14), followed by endovascular intervention (4/14). Overall mortality was 6.4% (5/83).

Conclusions: Pediatric vascular injuries are most frequently penetrating injuries to the extremities, commonly treated with open interventions. The use of endovascular techniques is rare for vascular trauma in this population. Mortality from vascular injuries in the modern era is rare.

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CONTEMPORARY OUTCOMES AND MANAGEMENT OF BLUNT CERBROVASCULAR INJURIES: RESULTS FROM THE AAST PROOVIT MULTICENTER REGISTRY

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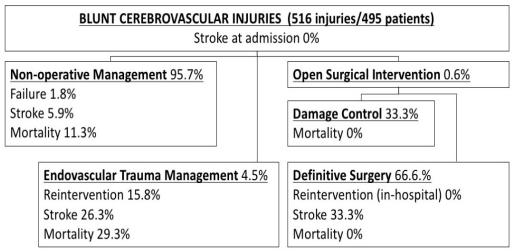
Invited Discussant: [discussant]

Introduction: In 2010 the Eastern Association for the Surgery of Trauma (EAST) published guidelines for the treatment of blunt cerebrovascular injuries. Analysis of prospectively collected data following the implementation of these guidelines can help inform future practices.

Methods: The American Association for the Surgery of Trauma PROspective Vascular Injury Treatment (PROOVIT) registry was used to collect demographic, diagnostic, treatment, and outcome data on cerebrovascular injuries.



Results: A total of 516 blunt cerebrovascular artery injuries (bCVIs) in 495 patients from 19 centers (18 ACS Level I and 1 ACS Level II) have been captured since February 2013. Most injuries occurred in males (63.4%, 327/516) with a median age of 38.0 years (IQR 28) and a documented Injury Severity Score greater than 15 in 63.2% (326/516), primarily from motor vehicle collision (67.2%, 347/516). Injuries to the common carotid (4.3%, 22/516), internal carotid (45.5%, 235/516), and vertebral (50.2%, 259/516) arteries were identified, with multiple injuries identified in 21 patients (4.2%). bCVI severity was distributed as follows: Grade I and II (intimal tear or flow limiting defects): 34.9%, III (pseudoaneurysm): 12.1%, IV and V (occlusion or transection): 24.1%. Treatment was as follows: Grades I and II: non-operative management (NOM) 96.9%, endovascular trauma management (EVTM) 2.5%, open surgical intervention (OSI) 0.3%; Grade III: NOM 96.0%, EVTM 4.0%, OSI 0%; Grade IV and V: NOM 92.8%, EVTM 5.6%, OSI 1.6%. Anti-thrombotic agents were used in 57.2% of injuries, (NOM 58.1%, EVTM 77.8%, OSI 0%; p=0.49). Failure of NOM occurred in 1.8% of injuries. EVTM required re-intervention in 15.8% with none requiring open revision. In-hospital re-intervention was not required after OSI in any patient. Stroke after initiation of management occurred in 6.8% of bCVIs (NOM 5.9%, EVTM 26.3%, OSI 33.3%; $p < 0.001$). Overall hospital mortality was 12.3% (NOM 11.3%, EVTM 29.3%, OSI 0%; p=0.11). Follow-up is available for 80 injuries (15.5%) for a median of 2.0 months (IQR 2.0 mo). During the available follow up period, out of hospital stroke rate was 0% and reintervention was necessary for only 1 injury (0.2%) after open repair due to flow-limiting stenosis.

Conclusions: Initial data suggests that management of bCVI largely follows the EAST guidelines. However, NOM predominated even in higher grade injuries. The number of bCVIs requiring intervention was small, but data suggests OSI and EVTM may be associated with a higher rate of stroke than NOM.

National Trauma Research Repository

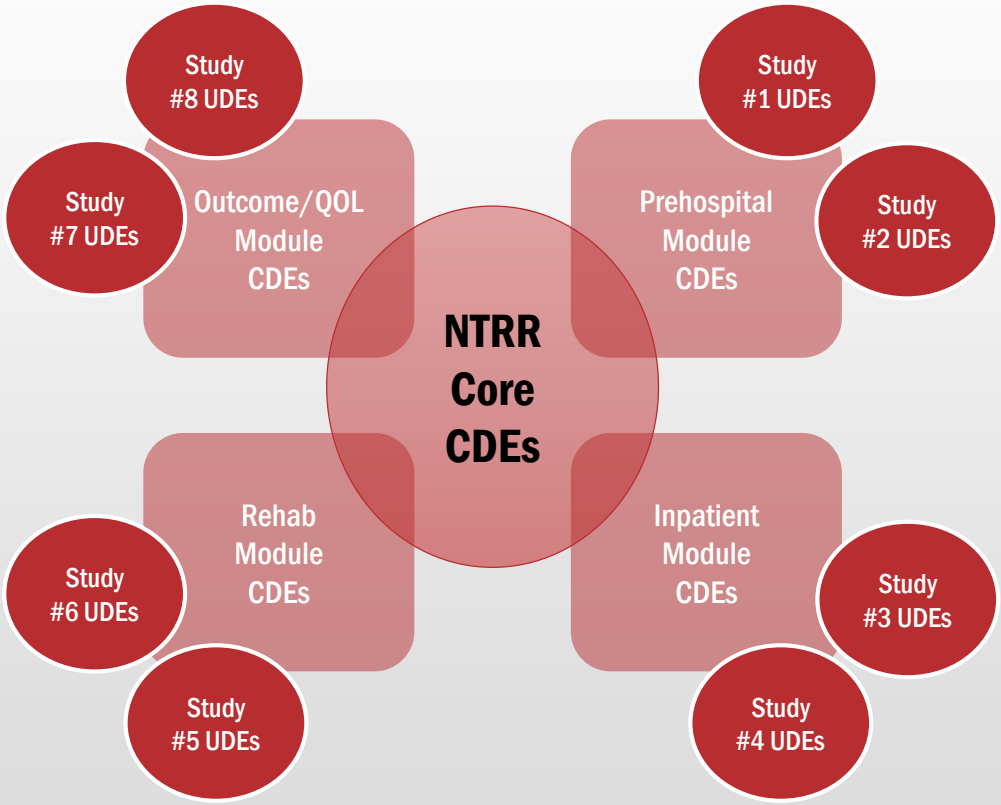
Title: National Trauma Research Repository (NTRR)

Principal Investigator: Jenkins, Donald

Total Budget: $3,089,446

Sites (n=1)	Institution	PI Last Name	PI First Name
1	University of Texas Health Science Center San Antonio	Jenkins	Donald

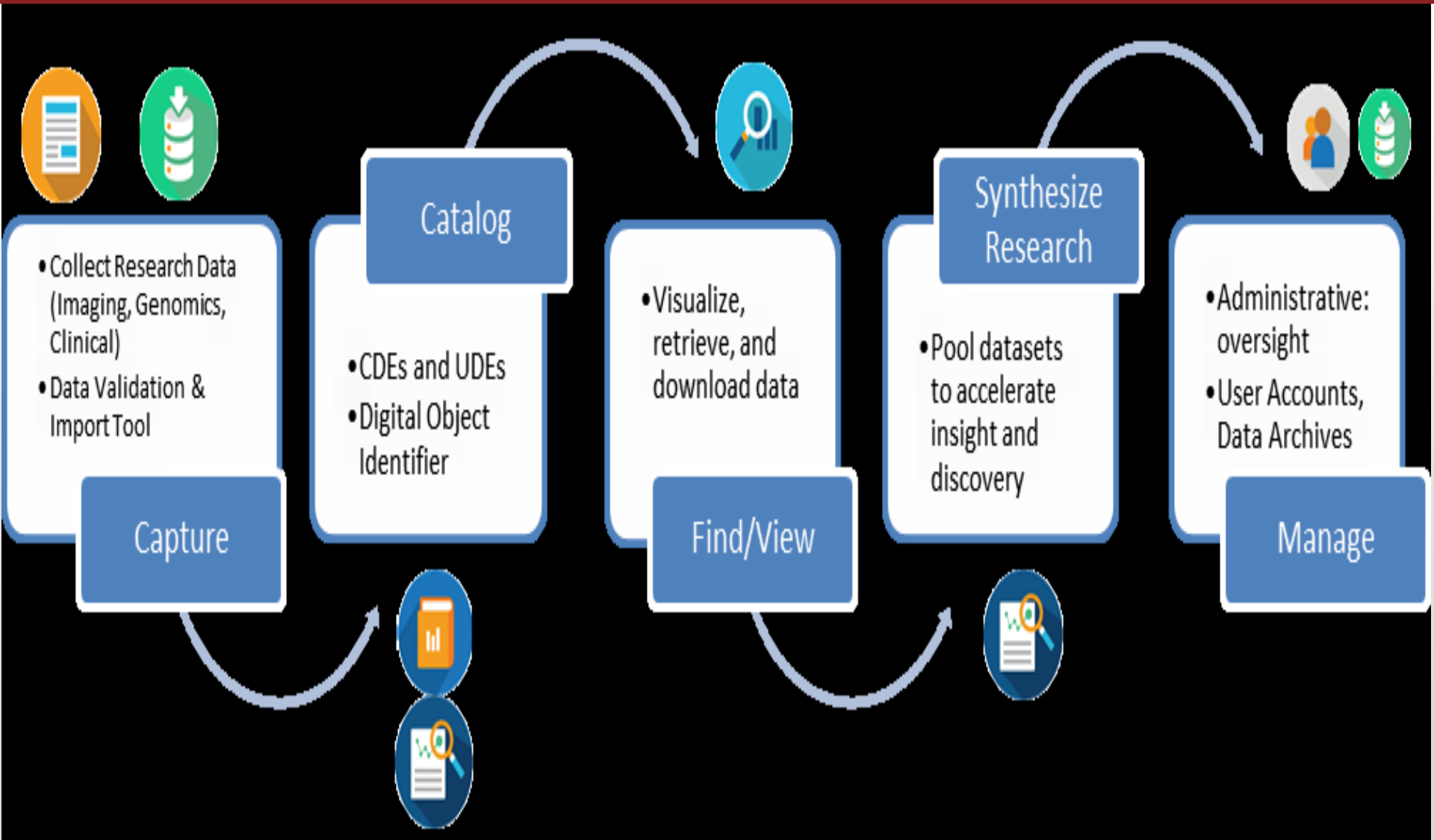
NTRR Research Data Storage Components



In this model, Study 1 would collect NTRR Core CDEs, Prehospital Module CDEs and the unique data elements (UDEs) in their study.

Note: CDEs (or required elements) will be selected judiciously to support secondary analyses across similar studies but not overly-onerous to the investigative team.

Maximizing use of Trauma Research Data

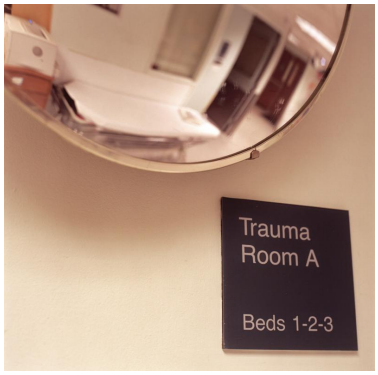


NATIONAL TRAUMA INSTITUTE

Request for Proposals

February 1, 2017

NTI REQUESTS PROPOSALS FOR THE NATIONAL TRAUMA RESEARCH REPOSITORY



The National Trauma Institute is pleased to announce its Request for Proposals to develop and host the National Trauma Research Repository (NTRR). The NTRR will be a web application for uploading and managing research datasets that supports data sharing among trauma investigators. The Request for Proposals and appendices describe the broader technical aspects of the repository, such as the infrastructure and hosting, details of its data storage model, user privileges, and protective security measures.

DOWNLOAD the RFP, cost proposal template and prior performance evaluation form **HERE**.

DUE DATES:
Letter of Intent (required): February 24, 2017
Vendor Questions: March 1, 2017
Proposal Submission: March 31, 2017

This project is funded by the Department of Defense through the National Trauma Institute (NTI). The U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick, MD 21702-5014 is the awarding and administering office. This work is supported by the Office of the Assistant Secretary of Defense for Health Affairs, through the Defense Medical Research and Development Program under Award No. W81XWH-15-2-0089.

Executive Summary of the
National Trauma Research Repository (NTRR) Request for Proposals and Evaluation Process

The NTRR request for proposals (RFP) was released February 1, 2017. The vendors were instructed to submit a plan with six months to construct the repository (roughly July – December 2017) followed by 12 months of hosting and technical support. NTI received seven letters of intent from the following organizations: Healytics, ImageTrend, Med Star Health, National Institutes of Health Center for Information Technology (NIH CIT) with Sapient Government Services, QuesGen Systems, Quintiles, and Webhead. Four vendors submitted proposals.

Vendor	Development Cost	Hosting Cost	Total Cost
ImageTrend	$545,610	$88,660	$634,270
NIH CIT	$576,064	$215,204	$791,268
QuesGen	$610,856	$524,520	$1,135,376
WebHead	$165,642	$37,706	$203,348

The NTRR Architecture Sub-committee (four reviewers) scored proposals on the strength of each vendor's technical approach/responsiveness to the RFP, relevant experience and past performance evaluations (see NTRR Review Form). The aggregated scores are in the table below. For detailed reviewer scores, please see NTRR Technical & Prior Performance Matrix.

Vendor	Technical Approach	Vendor Previous Experience	Total Scores*
ImageTrend	122	122	244
NIH CIT	229	136	365
QuesGen	128	116	244
WebHead	119	76	195

*Maximum possible score was 440.

NIH CIT was the unanimous choice of the review committee. NIH CIT proposed to customize the Biomedical Research Informatics Computation System (BRICS) to meet the functional needs of the NTRR. BRICS is a NIH-developed, disease agnostic, web-based research data repository system currently used by seven research communities including Federal Interagency Traumatic Brain Injury Research (FITBIR), Clinical Informatics for Trials and Research (CiSTAR), and the Center for Neuroscience and Regenerative Medicine (CNRM). This system already meets 80% of the NTRR requirements and can be customized to meet the remaining 20% (see NIH CIT proposal for details). The proposal includes maintenance and hosting on the BRICS servers, which sit in "NIH's demilitarized zone" at the Center for Technology in Bethesda, MD. The BRICS team will ensure that all software/data developed for the NTRR are in accordance with the rules of the Federal Information Security Management Act (FISMA) and all Health and Human Services information security policies.

NTI requested additional information on the NIH CIT proposal regarding the scope of work and costs (via a written request and a teleconference with a product demonstration). NIH CIT submitted a written response and a revised budget that was reviewed with Dr. Jose Salinas (chair of the NTRR Architecture Subcommittee).

Next steps:

1. The NTRR Executive committee will evaluate and forward a vendor recommendation to the NTI Executive Committee.
2. The NTI Executive Committee will make the final vendor selection.
3. NTI will negotiate and execute the award.

National Trauma Research Repository
Proposal Evaluation Review Form

Reviewer:

Vendor:

Proposals will be assessed on the strength of the vendor's technical approach/ responsiveness to RFP, relevant experience, past performance evaluation and cost.

A. Technical Approach: Emphasis will be on the soundness of approach and reasonableness of the time allowances proposed including methods used, and project management plan.

Rubric	Question Addressed √	Response Quality L-M-H	Comments	Score 0-10
Does the proposed solution have effective architecture, design, and technical approach(es)?				
Does the proposed solution include sufficient supporting details?				
Does the proposed solution provide reasonable assumptions?				
Is the proposed solution scalable and able to adapt to changes and growth of the NTRR, and of research data contribution volumes, in a timely, efficient, and cost effective manner?				
Does the proposed solution apply development, integration, and quality assurance, practices and approaches that demonstrate the ability of the vendor to implement a complete systems and software development lifecycle?				
Does the proposed solution have system security and business contingency plans (e.g., comprehensive disaster recovery)?				
Is the proposed solution achievable within the proposed timeframes?				

Total Technical Score: _____

Do you have any follow-up questions or concerns regarding the **proposed technical approach** that you would like the vendor to address?

B. Vendor Previous Experience: Evaluate vendor experience for its quality and relevance to the current project and to judge the ability of the vendor to meet the RFP terms.

Rubric	Question Addressed √	Response Quality L-M-H	Comments	Score 0-10
Does the vendor have the ability to deliver proven and robust solutions for maintaining data security?				
Does the vendor have experience managing medical data and/or research data repositories?				
Does the vendor have the financial strength and resources to execute its bid and access other necessary resources?				
Does the vendor has the ability to deliver proven and robust solutions for maintaining data?				

Total Vendor Previous Experience Score: _____

Do you have any follow-up questions or concerns regarding the **vendor's previous experience** that you would like the vendor to address?

Other questions/comments (if any):

Your evaluation will be combined with the other reviewers' evaluations and the cost proposal evaluation for final review/recommendation to the NTRR Executive Committee.

Please email this form to michelle.price@nationaltraumainstitute.org**.**

National Trauma Research Repository RFP Technical Evaluation Matrix

Reviewers scored each item on a scale of 1-10 with 1 being the lowest score and 10 being the highest score.

	Vendor 1 - Image Trend				Vendor 2 - NIH/Sapient				Vendor 3 - QuesGen Systems				Vendor 4 - WebHead			
A. Technical Approach:	Rev 1	Rev 2	Rev 3	Rev 4	Rev 1	Rev 2	Rev 3	Rev 4	Rev 1	Rev 2	Rev 3	Rev 4	Rev 1	Rev 2	Rev 3	Rev 4
Rubric	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score
Does the proposed solution have effective architecture, design, and technical approach(es)?	1	2	5	2	8	8	10	8	3	5	8	3	3	6	5	4
Does the proposed solution include sufficient supporting details?	1	5	4	3	7	8	9	9	3	3	6	2	2	8	5	2
Does the proposed solution provide reasonable assumptions?	1	0	4	1	8	8	8	9	5	5	7	4	2	5	4	3
Is the proposed solution scalable and able to adapt to changes and growth of the NTRR, and of research data contribution volumes, in a timely, efficient, and cost effective manner?	7	5	5	5	8	8	9	9	4	3	7	4	3	5	3	5
Does the proposed solution apply development, integration, and quality assurance, practices and approaches that demonstrate the ability of the vendor to implement a complete systems and software development lifecycle?	3	5	7	4	8	7	9	8	3	5	6	3	5	3	6	3
Does the proposed solution have system security and business contingency plans (e.g., comprehensive disaster recovery)?	8	9	6	8	6	8	8	8	2	3	5	2	3	5	5	3
Is the proposed solution achievable within the proposed timeframes?	5	5	7	4	8	9	7	9	7	7	7	6	4	5	7	5
Technical Approach Scores	**26**	**31**	**38**	**27**	**53**	**56**	**60**	**60**	**27**	**31**	**46**	**24**	**22**	**37**	**35**	**25**

	Vendor 1 - Image Trend				Vendor 2 - NIH/Sapient				Vendor 3 - QuesGen Systems				Vendor 4 - WebHead			
B. Vendor Previous Experience:	Rev 1	Rev 2	Rev 3	Rev 4	Rev 1	Rev 2	Rev 3	Rev 4	Rev 1	Rev 2	Rev 3	Rev 4	Rev 1	Rev 2	Rev 3	Rev 4
Rubric	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score
Does the vendor have the ability to deliver proven and robust solutions for maintaining data security?	8	9	8	9	8	9	9	9	2	9	7	6	2	8	5	5
Does the vendor have experience managing medical data and/or research data repositories?	9	9	8	9	9	9	10	9	7	9	9	8	2	3	5	2
Does the vendor have the ability to deliver proven and robust solutions for maintaining data?	4	5	8	6	9	5	8	8	4	8	7	8	3	8	7	4
Does the vendor have the ability to deliver proven and robust solutions for maintaining data?	7	8	8	7	7	9	9	9	6	9	9	8	4	8	5	5
Vendor Experience Scores	**28**	**31**	**32**	**31**	**33**	**32**	**36**	**35**	**19**	**35**	**32**	**30**	**11**	**27**	**22**	**16**
Total Individual Reviewer Scores	**54**	**62**	**70**	**58**	**86**	**88**	**96**	**95**	**46**	**66**	**78**	**54**	**33**	**64**	**57**	**41**
Total Combined Score	**244**				**365**				**244**				**195**			

NATIONAL TRAUMA INSTITUTE (NTI)

NATIONAL TRAUMA RESEARCH REPOSITORY (NTRR)

Response Body

DUE DATE/TIME:
March 31, 2017 / Midnight (CST)

SUBMITTED BY:
The National Institutes of Health (NIH)
Center for Information Technology (CIT)
Office of Intramural Research (OIR)
Biomedical Imaging Research Services Section (BIRSS)

EXECUTIVE SUMMARY

The Biomedical Research Informatics Computation System (BRICS) is a National Institutes of Health (NIH) developed, disease agnostic research data store and catalog that, as currently architected and built, meets 80% (see **Table 1**) of the National Trauma Research Repository (NTRR) requirements to facilitate better quality, visibility, access, and adoption within the trauma research community. The BRICS team, which comprises the NIH Center for Information Technology (CIT) Biomedical Imaging Research Services Section (BIRSS) federal team along with our long term development and services contract team from Sapient Government Services, has developed, deployed, and supported research informatics solutions for seven unique research communities over the past five years, delivering proven, robust solutions to securely manage medical and/or research data. NTI needs a team with a proven track record supporting full lifecycle development, hosting, and operations support across multiple programs, providing domain-level subject matter expertise across research areas, and collaborating effectively with NIH and Department of Defense (DoD) programs, teams, and stakeholders. The BRICS team has all of these capabilities, and a track record to demonstrate them. There are seven research communities actively collaborating with the BRICS team, to include the traumatic brain injury community (Federal Interagency Traumatic Brain Injury Research (FITBIR)), the Informatics Core of the Center for Neuroscience and Regenerative Medicine (CNRM)), the Parkinson's community (Parkinson's Disease Biomarker Program (PDBP)), the ophthalmic community (National Ophthalmic Disease Genotyping and Phenotyping Network (eyeGene)), the nursing community (National Institute of Nursing Research (NINR) Common Data Repository for Nursing Science (cdRNS)), the intramural NIH community (Clinical Informatics for Trials and Research (CiSTAR)), and the rare diseases community (National Center for Advancing Translational Sciences Global Rare Diseases Patient Registry Data Repository (GRDR)). The BRICS system offering is analogous to the software as a service (SaaS) model in that that it exists as an end-to-end hosted software solution delivered with technical and operational support. As a government developed product, a collaboration agreement (e.g. Cooperative Research and Development Agreement (CRDA)) would need to be established by NIH with the NTI to build and host the NTRR. BRICS will support all phases of NTI's research data repository lifecycle from structuring to capturing, cataloging to finding, synthesizing to visualizing, and managing to analyzing research data.

Based on requirements in the Request for Proposal (RFP) we performed a gap analysis and found that BRICS met most of the NTRR requirements except for those associated with reporting. Our approach for development is two-phased, allowing us to deliver the current architected and built BRICS solution to NTRR as quickly as possible as part of Phase 1. Many of the user, system, performance, and data and software security requirements for the Research Data Store (RDS) and the Research Data Catalogue (RDC) will be delivered with this initial deployment, enabling NTI to be trained having the ability to immediately capitalize on the existing software to import, develop, and curate Common Data Elements (CDEs) and Unique Data Elements (UDEs), and to upload and query data. Development efforts during Phase 2 will focus heavily on functionality to support NTI's reporting needs within the defined six month development period. Prior to going live with our NTRR solution at the conclusion of Phase 2, we will migrate the previously created data and deploy the new reporting capabilities for user acceptance training and ultimately a Production ready platform.

Across research communities, including trauma, there is a focus on accelerating the timeline from research and discovery to treatments that improve lives. The BRICS team is proud of the work we have accomplished to date supporting this mission. As the informatics landscape evolves and the research landscape matures, NTI needs a partner that understands the complexities of research data and can adapt to the changes and growth of the NTRR in a timely, efficient, and cost effective manner. Our team is focused on being flexible so that we can adapt to these changes. In our response, we describe our approach and methods for supporting the scope of NTI's bioinformatics needs to instantiate the NTRR.

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1. TECHNICAL APPROACH

1.1 INTRODUCTION

"We (NTI) ALREADY know that research can save lives" and through the development of the NTRR, the hope is that, by aggregating and standardizing disparate research data, it will advance and accelerate trauma research and care with the end goal of saving lives. BRICS supports all phases of the research data repository lifecycle from structuring to capturing, cataloging to finding, synthesizing to visualizing, and managing to analyzing research data. This is the lifecycle that NTI is facilitating with the NTRR and its two major components- RDS and the RDC. We understand your world- the advantages and challenges of medical research, as well as, the unwavering desire to ensure that research is used to maximize knowledge to accelerate discovery for the betterment of the community- and we see this as a mutually beneficial collaboration.

BRICS is a NIH developed, disease agnostic research data store and catalog that as currently architected meets most of the NTRR requirements, as stated in the RFP, to facilitate better quality, visibility, access, and adoption within the trauma research community. The BRICS system is presently supporting another DoD funded initiative, FITBIR, whose goal is to share data across the clinical traumatic brain injury (TBI) research field to accelerate research progress by enabling re-analysis of data, as well as re-aggregation, integration, and rigorous comparison with other data, tools, and methods. With seven BRICS instances across the NIH and DoD, to include FITBIR, PDBP, GRDR, eyeGENE, cdRNS, CiSTAR, and CNRM, we understand the importance of leveraging previous federal dollar investments in research infrastructure to support mandates for making federally funded research accessible. By using BRICS, NTRR will be able to immediately capitalize on BRICS's existing capabilities which assist with enhancing the visibility of research, increasing the efficiency of research due to reusability, and enabling researchers to ask new questions, all while promoting scientific integrity and replication. BRICS, for all of the aforementioned reasons, is a low risk, high reward solution for NTRRs needs.

BRICS Awards and Recognitions
(click here for more information)

2016 Fed Scoop Awards
2016 ACT-IAC's Igniting Innovation 2016 Showcase
2016 Bio-IT World Announces Best Practices Finalists
2015 Outstanding Information Technology Achievement in Government
2015 CIT Science Award of Merit
2015 Federal Health IT Award
2014 Excellence.gov Award for PDBP DMR
2014 NINDS Group Merit Award for Innovation

The BRICS system offering is analogous to the SaaS model in that that it exists as an end-to-end hosted software solution delivered with technical and operational support. This software provides more than 80% of the functionality required for NTRR (see **Table 1** and inset) with most of the balance possible through new development work to accomplish NTRRs requirements.

As a comprehensive bioinformatics platform, there are additional capabilities BRICS offers outside of NTIs requirements, such as:

- GUID: Global Unique Identifier which allows the ability to share a participant's data without exposing personally identifiable information (PII)
- ProFoRMS: An electronic data capture tool with reporting capabilities. It also provides the capability to schedule subjects for visits.
- Meta Study: Provides ability to save queries, aggregate datasets from different studies, and preform secondary analysis that can be referenced in future publications

BRICS offers plug-and-play modules providing a combination of web-based functionality and downloadable tools that support data definition (Data Dictionary), data contribution (ProFoRMS, Data Repository, GUID) and data access (Query Tool, Meta Study) as well as administrative oversight function (Account, Data Repository) throughout the research life cycle (see **Figure 1**).

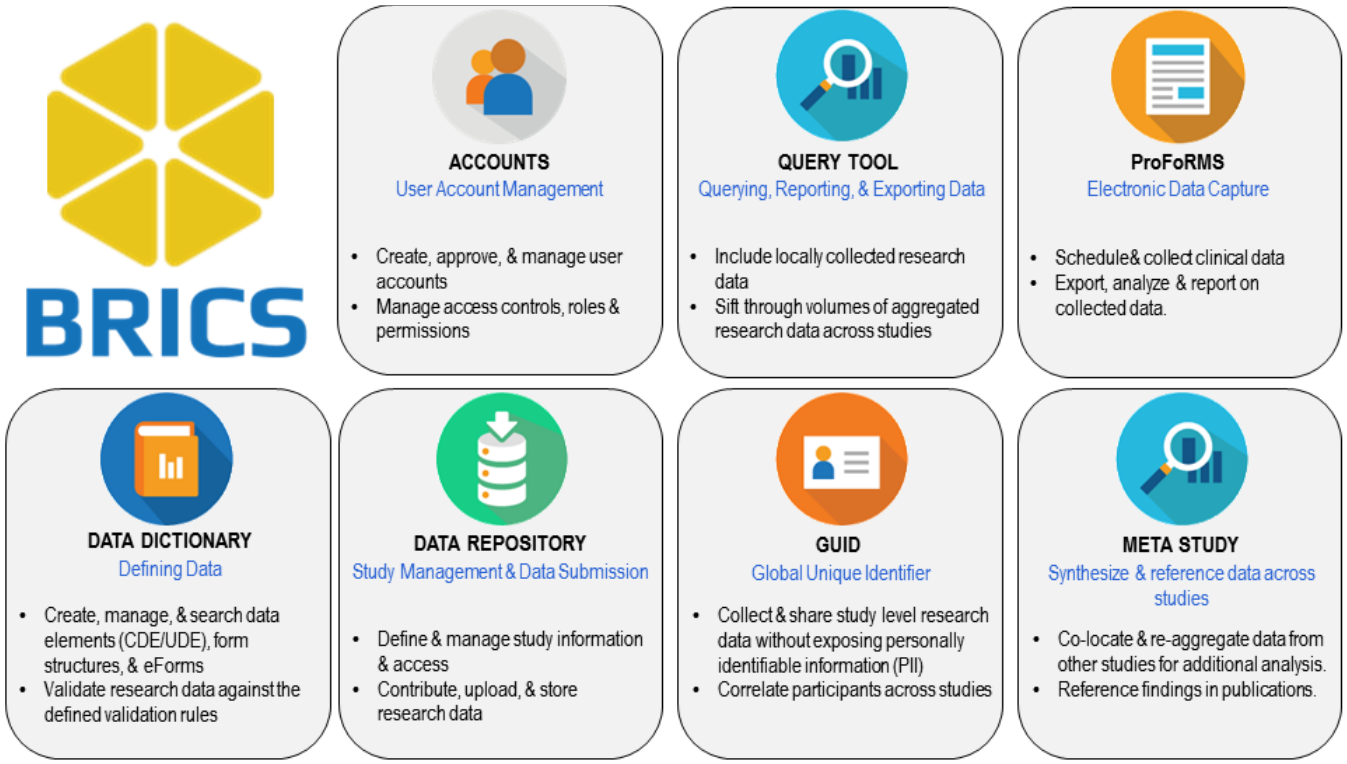


Figure 1: BRICS Functionalities

The BRICS functionalities meet the data repository needs NTI is seeking throughout the research lifecycle and will support NTI's end goal of maximizing the utility of trauma study data for translation into evidence-based clinical practice and improved patient outcomes (**Figure 2**).

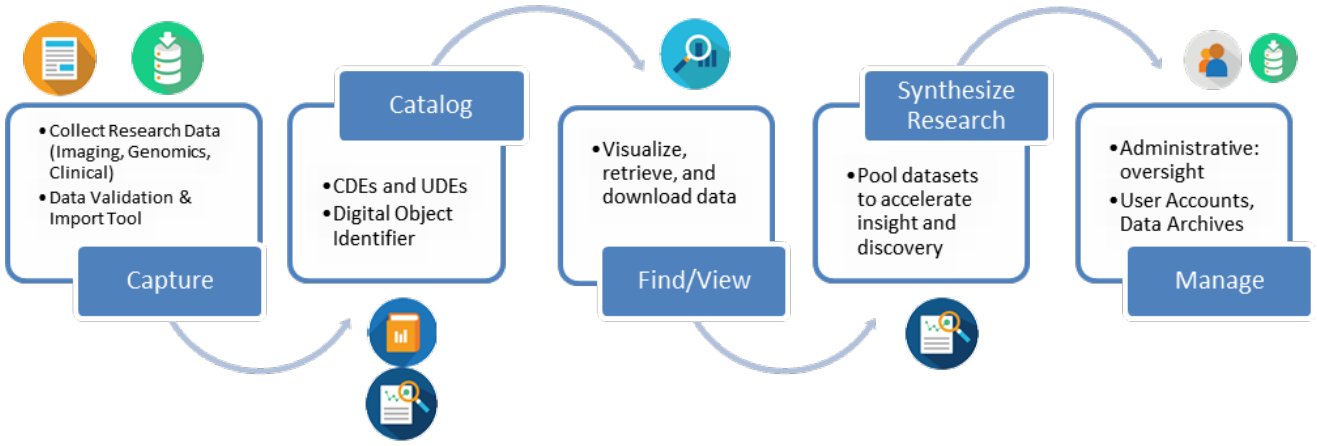


Figure 2: BRICS- A Solution for NTRRs data repository lifecycle

As part of our requirements review process, we performed a gap analysis. The outcome of this analysis found that 80% of NTRR's requirements are met with the existing BRICS platform, with an exception being reporting. Further details of the analysis can be found in **Table 1**.

Status Legend: BRICS Ready; Need to Develop; Out of Scope				
Type	**NTI Requirement**	**Related BRICS Module(s)**	**How BRICS Solution meets NTIs Requirements**	
System	Customized portal with web based modules	Infrastructure; All BRICS module	Plug-and-play modules that provide web-based functionality and downloadable tools that support data definition, data contribution, and data access throughout the research life cycle.	
	Construct RDS and RDC components	 RDS= Data Repository; RDC=Data Dictionary	Data Dictionary provides functionality for creating, managing, and searching data dictionary components (data elements and form structures), as well as services for validating research data against CDE and UDE. Data Repository provides functionality for defining and managing study information, and for contributing, uploading, and storing the research data associated with each study. Each has the ability to store relevant supporting documents.	
	Scalable for increased user activity, storage capacity, and CDE/UDEs	Infrastructure	Currently, BRICS architecture supports (7) unique BRICS instances with varying user bases, data storage and dictionary needs.	
	Provide a training system that mimics the production system	Infrastructure	Pre-production demo system.	
	Host environment proposed meets the Industry Standards and any additional needs of the NTI's proposed solution	Infrastructure	BRICS meets industry standards and can be installed client site or offsite.	
	Data interoperability options with other systems	 Data Dictionary; Data Repository	Controlled vocabularies (CDEs); Ability to ingest data from systems such as REDCap (This is accomplished through first, downloading from RedCap, second, manipulating data as needed to comply with BRICS format, and third, uploading data to BRICS.)	
User	Ability to create/upload/edit CDEs and UDEs, input forms (to RDC)	 Data Dictionary	Data Dictionary provides functionality for creating, managing, and searching data dictionary components (data elements and form structures), as well as, services for validating research data against CDEs and UDEs.	
	Ability to create/upload/edit study metadata (to RDS)	 Data Repository; ProFoRMS	Data Repository provides functionality for defining and managing study information, and for contributing, uploading, and storing the research data associated with each NTRR study.	
	Ability to upload, query, and export study data (to RDS)	 Data Repository; Query Tool	Data Repository provides functionality for defining and managing study information, and for contributing, uploading, and storing the research data associated with each NTRR study.	
	Ability to create user profiles, assign privileges, and levels of access to data	 Account	Account module supports user profile management and administrator functions, such as managing user privileges.	
	Documentation and Training Materials	Documentation; Training	Develop and maintain materials defining data architecture, system and user documentation. Train NTRR system users.	
Performance	Tolerate multiple users interacting with system at the same time searches. On the RDS there would be potentially up to 5 concurrent users.	Infrastructure	BRICS infrastructure has proven successful in (7) other instances with similar and/or greater performance needs.	

Status Legend: BRICS Ready; Need to Develop; Out of Scope				
Type	**NTI Requirement**	**Related BRICS Module(s)**	**How BRICS Solution meets NTIs Requirements**	
Reporting	Run reports on data in RDS and RDC	Data Dictionary; Data Repository	New capability for BRICS; will be developed. We currently can run a dataset 'receiver' report for a specified time period so that admins can see who has been downloading data within the repository. In the data dictionary, user can download data elements meeting certain search/filtering criteria in a csv. More reporting capabilities within the Data Dictionary and Data Repository will be developed.	
	Track embargo status and dates of RDS data	Data Repository	New capability for BRICS; will be developed.	
	Record a digital object identifier for datasets in RDS	Meta Study	Dataset is defined as a collective set of data associated with a particular study or group of studies; New Digital Object Identifier (DOI) capability is slated for next release (May/June).	
Data and Software Security	HIPAA Compliance/Security encryption (based on adherence to CFR 45 Part 160 and 164)	Infrastructure; All modules	BRICS components have been categorized as a moderate-impact information system based on acceptance of the limited data set under Health Insurance Portability and Accountability Act (HIPAA) and code of federal regulations (CFR) 45 part 160 and 164.	
	HL7 Clinical Data Architecture (CDA) or equivalent standards	Infrastructure	While the BRICS system does not yet incorporate HL7 CDA Architecture, it does leverage an equivalent Clinical Document Architecture standard which supports the exchange of clinical documents.	
	Protective security measures	Infrastructure	Certification & Accreditation (C&A); National Institute of Standards and Technology (NIST) 800-53; NIH security mandates.	

Table 1: High level assessment- How BRICS meets NTRR requirements

Based on our findings, we decided the best approach for meeting NTRR's needs would be a two phase approach to get NTRR up and running as quickly as possible while also meeting NTI's requirements within the defined six month development period. It was also decided that the NTRR will be hosted at the CIT part of the NIH in Bethesda, MD. With more than 80% of the NTRR requirements already supported in the current BRICS platform, the NTRR system will be rapidly deployed to a pre-production (Demo) environment within the first six weeks post contract commencement- this is Phase 1. The goals of Phase 1 are to setup a pre-production Demo environment of NTRR and to gather additional requirements for reporting. Requirements gathering (both functional and non-functional) will commence immediately in Phase 1 to ensure full understanding of the reporting needs of the NTRR.

In Phase 2, we will train the NTRR team about the BRICS system using the pre-production NTRR Demo environment released at the completion of Phase 1 which will allow your team to start configuring your instance with NTRR data elements and actual research data. Our approach is to hold an initial dedicated, in person, training session with key NTRR personnel at NTI with subsequent training performed via webinar. Since NTI's funded research portfolio is a mix of legacy and prospective studies, our experience tells us we should anticipate complexities (such as accurately capturing, defining, and aggregating less structured legacy data) that will need to be addressed prior to data collection and/or upload for the varied data types (such as clinical assessment and imaging) that NTRR expects to host. Therefore our initial training will go beyond just how to use the system, by partnering with NTI to leverage our lessons learned to ensure NTRR's success.

*NTI will be able to **initially use the pre-production Demo environment for training** on the BRICS system through mock data upload, data query, and data element creation. Then, after NTI staff is comfortable with BRICS system workflows, they will be able to **capitalize on the existing BRICS functionality** in the Demo environment to import, develop, and curate CDEs and UDEs, and upload and query data, which can all be **migrated to the Production environment** at the conclusion of Phase 2.*

The NTI team will have the ability to start uploading data dictionaries into the system, creating CDEs and UDEs and user import forms, uploading documentation, importing and validating data, and finally querying uploaded data in the new NTRR system. In parallel during Phase 2, we will develop the new functionalities found in our gap analysis, with a focus on delivering reporting capabilities, an interface for accessing reports, and documentation. There will be ongoing requirements clarification and support, as well as feedback elicitation from the NTI team during Phase 2 development activities. User training materials will be developed and delivered and end user training and support will commence prior to the end of Phase 2. At the completion of Phase 2, the implementation and review process (acceptance testing) will commence and during this time statistics will be gathered for a post-implementation review. Any pertinent prior work performed in the pre-production Demo environment during Phase 1 can be exported and migrated into the final Production environment. The NTRR system will then Go-Live.

A detailed project schedule is provided in **Section 2: Project Schedule.**

1.2 Repository Needs Assessment and Potential Modification of Existing Products (if applicable)

As part of this response, the BRICS team performed a preliminary needs assessment against the provided requirements to validate that BRICS is capable of supporting the NTI study lifecycle. As described in section 1.1, BRICS includes modules that work together to support de-identified data definition, collection, validation, query, sharing, and export. These modules provide a combination of web-based functionality and downloadable tools that support data definition, data contribution, and data access. Based on that analysis, BRICS can support the NTI requirements through the capabilities provided in **Figure 3**.

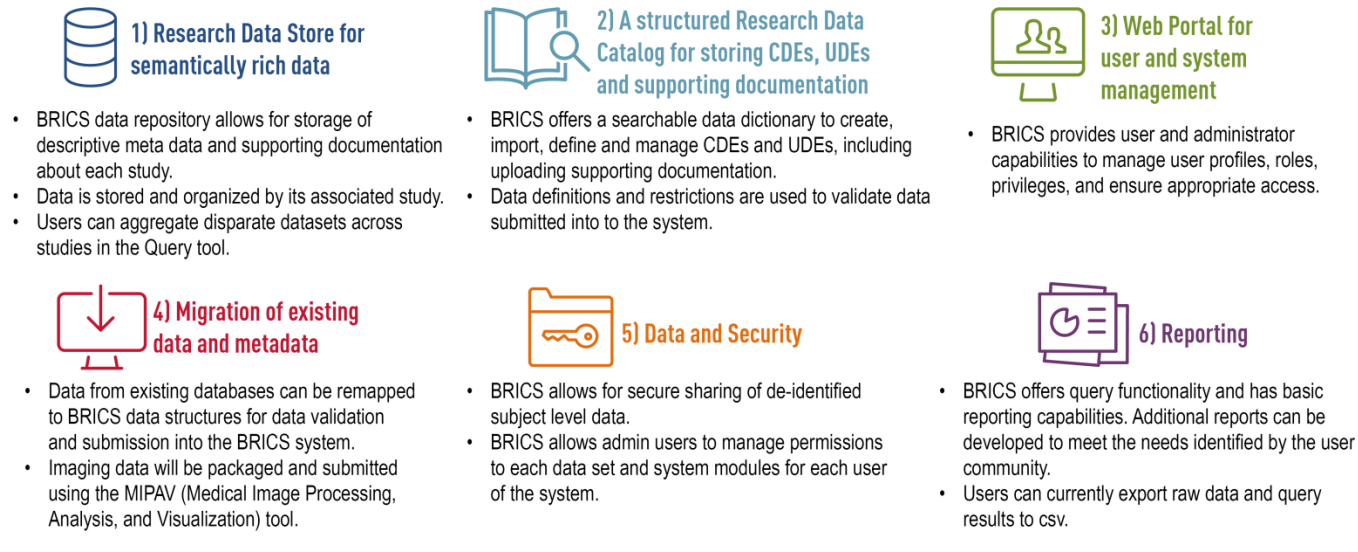


Figure 3: BRICS capabilities

In addition to the broad level requirements mapping above, BRICS also offers data query, electronic case report forms (eForms) development, and scheduling and real-time collection of clinical data based on those eForms. Legacy data (clinical, imaging, genomics) and data collected using external systems such as REDCap will be uploaded into the NTRR by Contributing Investigators (CI) and Contributing Coordinators (CC) through a validation tool that compares the data to the data elements and forms the data is being submitted against, to ensure the data complies with data definitions and constraints. BRICS offers a GUID service that allows researchers from across different studies to assign the same Identifier to common subjects without exposing PII. This means that data for a single subject can be correlated throughout the NTRR even if PII is not maintained. Once study data is submitted to the NTRR, Recipient Investigators (RI) can view and query data they have access to in the Query Tool, and then save these queries and resultant data sets for secondary analysis within a Meta Study. RIs will be able to assign a digital object identifier to their Meta Study.

Based on the gaps in functionality identified during the needs assessment, software development during the 180 days will focus mostly on developing automated reporting capabilities. Because the NTI Staff will be able to begin utilizing the system after the first release in week five, they will be able to provide feedback to the BRICS team and work together to more granularly define requirements around the reporting capabilities that have been identified for development during Phase 1. The reporting functionalities will include user, dataset, repository, data quality, and study-level reporting. We also will develop functionality to allow for a Help Desk comment and feedback page that will generate an email to the NTRR helpdesk maintained by the NTI staff. The modifications of the BRICS system proposed have been chosen in an attempt to provide the greatest additions to functionality for the NTRR within the 180 days provided.

1.3 Design & Development

The BRICS system is a modular solution that has been designed to allow for additional functionality being built in without compromising the effectiveness of the system. The primary needs of the NTI project are met by the BRICS platform, as is, and the architecture supports anticipated feature developments necessary for NTI as a long term solution.

After evaluating the needs for the NTI system from the request for proposal, we have identified the gaps between the required functionality and our software system. Based on the gap analysis, we have designed a development plan to deliver the needed capabilities within two releases. Our team will work with NTI staff to refine the requirements of the scope items outlined within this response.

While the architecture supports most of NTI's needs, we will gather requirements and develop a design for enhancements, mindful of the overall future needs of the system. Once the design is complete, it becomes translated into stories for development of modules and libraries of the system. Using the Agile approach, the development stories will be divided into logical groups/iterations called sprints. The team follows development best practices for object oriented programing standards, unit testing, and code reviews, and utilizes established tools and processes. The team will conduct reviews at the end of each iteration to provide an opportunity for NTI leadership to observe development work early in the release cycle. This Agile approach provides the flexibility to adapt to changes to system requirements and stakeholder needs during the development phase. The team supports administrative project management processes by providing regular status updates, scheduled change control meetings, and monthly/quarterly technical progress reports.

1.4 Testing/Pilot Plan

Throughout the Development during Phase 2, the BRICS team will perform system integration testing throughout each development iteration to check readiness of the system following Agile methodologies. Performance testing is conducted to understand capacity of the system to handle peak load.

Quality Assurance system testing is an invaluable component wherein the BRICS team employs scenario-based testing to determine if individual units of functionality that comprise a user scenario work together correctly to meet the defined requirements.

Based on the system's scope, our approach includes the development of manual and automated test routines. The BRICS team then prepares test cases alongside requirement definition to ensure requirements traceability and test precision. The BRICS team addresses non-functional requirements through specific performance, load, and security, testing. Once created, the BRICS team executes system test cases in every development iteration and continually collaborates with developers to log system errors and validate fixes through "Bug Review" meetings.

Within 5 weeks of initiating the project, pending coordination with CIT, we will deliver a pre-production Demo environment, designed to allow NTI staff to log in and pilot the system and create CDEs and UDEs and import study data. This phase will allow the program staff to see how the system supports the NTI use cases. Once users are familiar with the system, they can create, import, and curate NTI CDEs/UDEs and import study data. They will be able to test data upload, query, and download on a continuous basis. Any work in form structure development, data element creation, and eForm creation will be able to be migrated to a production environment delivered in the second release. A second phase of testing will be scheduled following the second release of the production environment to assure the existing and new functionalities developed work as expected. Throughout this time NTI will have continuous checkpoints with BRICS leadership to provide and capture feedback on BRICS capabilities.

At the close of development in Phase 2, the BRICS team will commence UAT. For up to two days, the BRICS team will facilitate NTRR users through an in-person series of agreed upon use cases to confirm that the NTRR system meets requirements. Should there be any issues, the BRICS team will spend the remaining eight days fixing and deploying, and we will run acceptance again. During this entire period, NTI will have access to the testing environment.

1.5 Deployment and Training

Deployment

The BRICS team follows a standardized deployment process to ensure successful environment set up and release of new functionality. This deployment process is initiated by taking production database backups and notifying users of system downtime by setting up a maintenance page. Then, release-specific database update scripts are run, and any configuration updates are made wherever applicable. The latest BRICS software version is then deployed to the pre-production Demo environment and the system is rigorously tested to ensure everything works as expected. If an issue is found, the BRICS team will determine if the issue can be fixed right away, or if the latest version of the software should be reverted while addressing the issues found. Once resolved, the BRICS team will coordinate with NTI stakeholders to receive approval before deploying to the Production environment. Upon deployment, the team will provide an email notification to NTRR users and NTI stakeholders.

After the first deployment to the pre-production Demo environment, the NTI team will have full access to BRICS and can provide the BRICS team with ongoing feedback about system functionality. During Phase 2, there will be a new deployment to the pre-production Demo environment so that NTI can perform their acceptance testing within that environment before deploying new functionality to Production for Go-Live, signaling the completion of the system development stage of the project.

System/Software Demonstrations, User Support and Training

The BRICS Team will provide system demonstrations to educate users, build their confidence, and ensure customer satisfaction. Our demonstration work will include trainings, capability presentations, and client meetings, for pre-production release and post production availability to the scientific community.

The approach to these trainings will be to facilitate the adoption of the administrator and trainer roles by NTI staff, so that NTI will feel empowered to further train the end users on the NTRR while simultaneously preforming administrator-only functions.

The BRICS Team's approach to training includes both technical and functional support to facilitate the adoption of the BRICS modules to support the relevant NTI use cases and workflows, and ensure full comprehension of how to perform tasks necessary to maintain a data repository. The first round of training will consist of demonstrations and presentations for each module to ensure a basic understanding of both the individual functionalities, and their interaction and dependencies within the system. These trainings will be mostly generic, end-user focused, and the BRICS team will deliver the relevant slide decks to the NTI staff for their utilization when training future end user and research team groups. Then, the BRICS team will train NTI staff on using the system as an administrator, and the various additional functionalities that are available to users with that role. A special emphasis will be placed on Data Dictionary and Repository maintenance, especially with regards to data import, validation, and data element curation and review. Both of these trainings will be most effective if performed in person, over a two day training session. The BRICS team is willing to provide additional webinar trainings throughout the six month period to provide onboarding support to any new NTI staff or first users of the NTRR system, with the expectation that NTI would take over training of end users with BRICS guidance and consultation as needed. The BRICS team will provide two more training sessions for new functionality, for both admin and end users, after development in Phase 2 and before NTI user acceptance training. NTI will receive relevant documents (PowerPoints, guides) after each training session as documentation and for future reference.

1.6 Implementation and Review

Implementation and review will occur in Phase 2, when a fully functional system has been deployed to the pre-production Demo environment. During the 10-day trial period, the BRICS team will facilitate a two day structured Acceptance Testing (system and user) session within the Demo environment. The testing will be based on the predetermined use cases and metrics mutually agreed upon between the team and NTI. Following Acceptance Testing, the BRICS team will gather and distribute the resulting metrics as well as lessons learned to NTI. Following the Acceptance Testing in the Demo environment, the team will migrate the data developed prior to Acceptance Testing to Production for Go-Live. This ensures that we are maintaining the quality of data developed by NTI during the entirety of Phase 2. For the production environment, a limited series of smoke tests will be implemented to validate that everything is working as expected. The BRICS team will work with system users to provide guidance on using the software and system, to make sure that the system is online and performing as expected in a Production environment.

The software maintenance team will be established upon post-implementation review (refer to **Section 1.8** for details around the proposed maintenance support).

1.7 Documentation

The BRICS team will implement a documentation process as a requirement in order to close out any development or functional tasks. The BRICS team will develop and maintain quality documentation and workflows, track nonconformance events, and track staff training.

The BRICS team will document captured requirements, as they become the foundation for conducting technical design, developing test cases, and carrying out implementation. The team uses industry standard artifacts, such as data flows, requirements traceability matrices (RTM), use cases, process flows, wireframes, screen mockups and data dictionaries. All documentation will be updated in the operations and maintenance (O&M) phase, as needed, with system and software updates. **Table 2** further describes the documentation that the BRICS team will provide by the end of the period of performance.

DOCUMENT	DEFINITION
System and Data Architecture	A logical system and data architecture for the BRICS suite of tools.
Data Dictionary	An export of the data definitions that were uploaded into NTRR.
Administrator and User Manuals	User guide for administrative functions and user functions.
User Training, Flow charts	Basic training docs and how-to infographics to assist in user training.
System configuration drawings	Part of the design documents.
Specifications (system, software)	Any requirements captured during the NTI period of performance.
Tests	Test scripts, test cases, and test results.

Table 2: List of Documentation

1.8 HOSTING AND MAINTENANCE SUPPORT

The BRICS environment consists of a custom-configured server rack. The server rack at CIT, in Building 12 of the NIH campus, includes a virtualization manager server, three virtual host servers, a shared storage server, a network storage server and an expandable set of storage arrays. The rack also contains networking equipment to provide local and remote connectivity and additional equipment necessary for the ongoing maintenance and development of the system.

The BRICS servers sit outside of the NIH's internal network in NIH's demilitarized zone (DMZ). The BRICS rack provides the underlying infrastructure of BRICS, hosting the full BRICS application suite. All standard BRICS users access the system via the BRICS portal interface, using appropriate login credentials. The portal infrastructure and supporting services provide the security to authorize and authenticate BRICS users.

The NTI NIH BRICS custom-configured system will be located at CIT in Bethesda, MD. Backups are performed nightly and there is a disaster recovery center in Sterling, Virginia.

In the System Maintenance Support phase (O&M for an additional 12 months), the BRICS team will ensure that the production system is fully functional and available for users to use. During the 12-month support phase, for the NTI system, the BRICS team will manage the operations and infrastructure in collaborations with the NTI staff. Working with NTI leadership, the BRICS team will establish a customized support model to support end users based on their functional issues and will proactively monitor the infrastructure. O&M support will include four major categories:

1. Identify, tag, debug, and deploy updated versions of the system or subsystems
2. Develop minor agreed upon enhancements to same system and subsystems
3. Provide operational support
4. Provide technical advice and support to the community

As part of the operations and maintenance work, the workstream leads will continue work with NTI staff to address any submitter or user issues that arise, technical or otherwise, as well as provide presentations, in person, or via online training, and provide any additional documentation which may be required by the NTI Network and user community. The BRICS team will perform defect fixes, data fixes, and hot fixes for any technical issues impacting users. Scheduled builds and enhancements to the BRICS system will also be deployed to the NTI system. The BRICS team will capture any issues reported by the users in JIRA where they are triaged for analysis and resolution. The issues identified as defects go through research, root cause analysis, code or data fix, testing, and deployment to production using established Software Development Lifecycle (SDLC) processes. The BRICS team will also document results and suggest ways to prevent similar cases in the future through its lessons learned and continuous improvement processes. The issues identified as changes or enhancements go through a change control board process for prioritization in future releases. The team will also support infrastructure resources, keep abreast of vulnerabilities and security patches reported by vendors, and implement resolutions to keep CIT/NTI systems secure.

1.9 DATA AND SOFTWARE SECURITY MANAGEMENT

The BRICS team ensures that all software/data it develops, accesses, and hosts/maintains as federal information system(s) are in accordance with the rules defined in Federal Information Security Management Act (FISMA) and NIST. The team will adhere to all federal and HHS information security policies that apply to this solicitation as outlined in the delivery order. NIH management recognizes the importance of contingency planning for all NIH systems, and recognizes the potential for financial and operational loss, and service interruptions which would result from the failure to maintain viable emergency response, resumption, recovery, and restoration strategies. To ensure safety and resumption of operations and services in an emergency, a contingency plan in in place in accordance with FISMA framework.

The BRICS components represent the physical and logical boundary of the security assessment and authorization (SA&A) effort and thus define the scope of data and software security. The system is characterized in detail in the risk assessment and information technology security plan for BRICS and will be provided during contract negotiation as applicable. The BRICS components have been categorized as a moderate-impact information system based on acceptance of the limited data set under HIPAA and CFR 45 part 160 and 164. Therefore, the moderate-impact recommended security baseline controls from NIST SP 800-53 have been instituted for the system. The team will need to re-evaluate these security controls to include HIPAA compliance and encryption of Protected Health Information (PHI)/PII/health data to and from vendor and NTRR, as the requirement evolves for the system. The system will collect a wide variety of clinical information including demographics, genetics information, and data from diagnostic and data after interventions specific to clinicians in the field. Currently, for all instances of BRICS, PII on research subjects (used to generate encrypted hashes that allow cross checking studies for the same individuals) is kept at the researcher's institution. Under the over-arching BRICS system de-identified data (phenotypic, clinical, genomic and imaging) is available from over 126 studies, including data for over 46,000 subjects. While the BRICS system does not yet incorporate HL7 CDA Architecture, it does leverage an equivalent Clinical Document Architecture standard which supports the exchange of clinical documents.

The BRICS team understands that data produced under this award are subject to the Federal Purpose license in accordance with the requirements of 2 CFR Part 200.315. All necessary and appropriate licenses as a condition of this award will be granted as negotiated via a CRDA or a similar agreement.

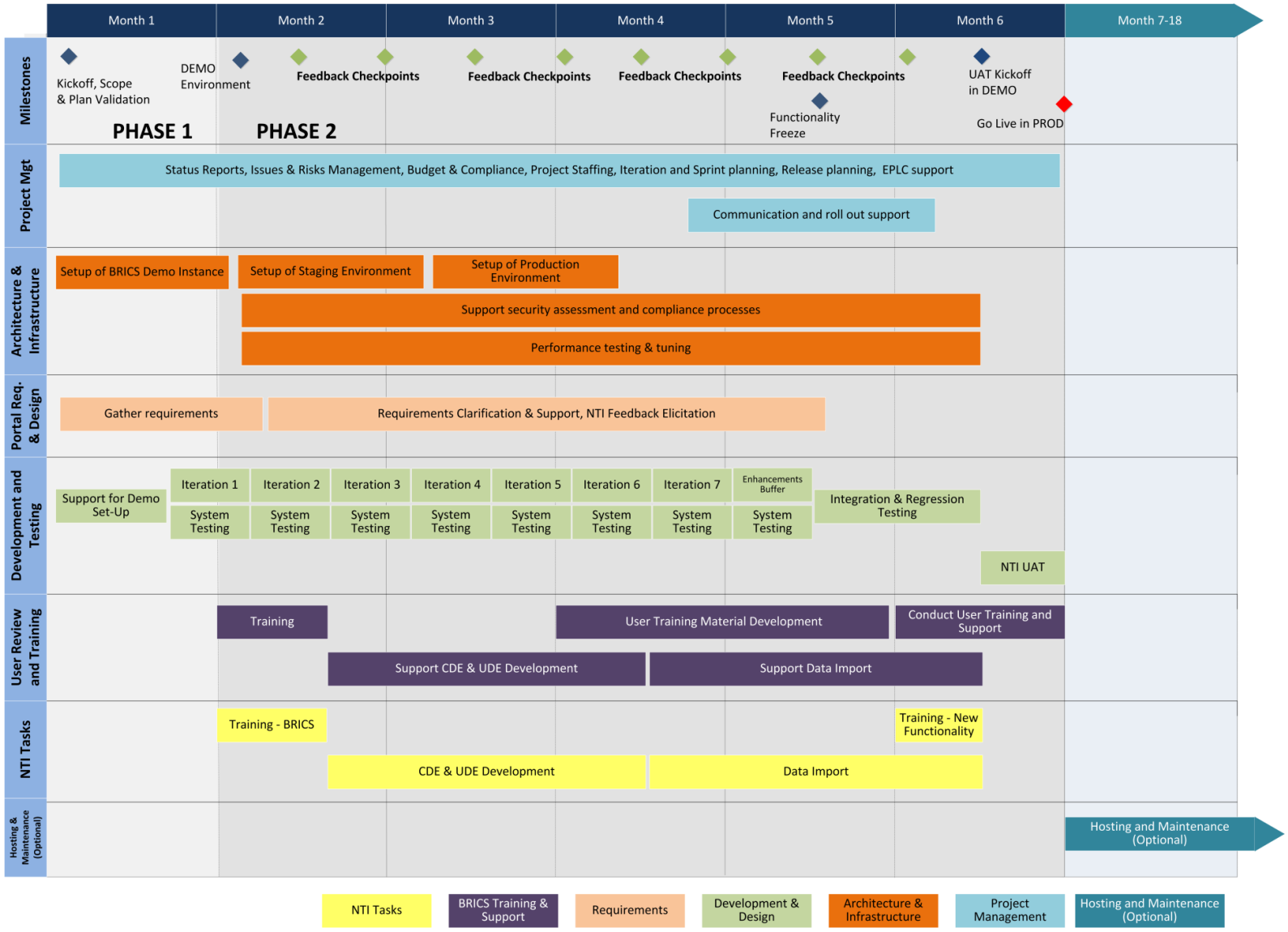
1.10 PROJECT MANAGEMENT PLAN

To establish a standard framework for project coordination and control, the Project Manager (PM) will create a Project Management Plan which will govern our overall assumptions, scope, timeline, and approach to delivering the project. As the primary point of contact for NTI, the BRICS PM will communicate project status, risks and issues frequently and consistently through recurring checkpoint meetings and reports. In addition, the BRICS team will continuously monitor the project, identifying and acting on opportunities for improvement, such as changes to team composition or reach-back to the team's subject matter experts to quickly address large or complex issues. Our management approach incorporates relevant aspects of both Agile and the Project Management Body of Knowledge (PMBoK) from the Project Management Institute (PMI). An Agile methodology reduces risk because it requires scope to be organized in manageable pieces within pre-determined, client approved time frames. Frequent, flexible checkpoints with NTI and the BRICS team, combined with iterative planning and execution will allow not only for a better final product, but for a better and more collaborative approach to the overall project. The flexibility incorporated in the project management approach is combined with project controls to manage what can be accomplished and when.

PMP COMPONENTS

1. Assumptions And Constraints
2. Scope
3. Schedule
4. Agile Development Methodology
5. Cost Management
6. Communications Management
7. Change Control Management
8. Risk And Issue Management
9. Requirements Management

2. PROJECT SCHEDULE



3. VENDOR PREVIOUS EXPERIENCE

The BRICS Team has experience managing and performing all services in this RFP. Below we have summarized our experience specific to the evaluation criteria from the RFP. In addition, we have provided detailed descriptions for five examples of our previous work and their relevancy to the NTI NTRR in **Section 3.5.**

Projects where we have supported a repository build, hosting and maintenance include:

- Biomedical Research Informatics Computing System (BRICS):
  - Federal Interagency Traumatic Brain Injury Research (FITBIR)
  - Parkinson's Disease Biomarkers Program Data Management Resource (PDBP DMR)
  - Center for Neuroscience and Regenerative Medicine (CNRM)
  - Global Rare Disease Patient Registry and Data Repository (GRDR)
  - Clinical Informatics System for Trials and Research (CiSTAR)
  - National Ophthalmic Disease Genotyping Network (eyeGENE)
  - Common Data Repository for Nursing Science (cdRNS)
- NIH, National Database for Autism Research (NDAR)

3.1 Ability to deliver proven and robust solutions for maintaining data security

Having worked extensively with NIH CIT's security office and system monitoring groups, the BRICS team understands the requirements necessary to build secure, compliant systems and to guide programs through the security accreditation process. Our system administration staff constantly monitors security developments as well as using the latest technologies to monitor system security and provide intrusion detection capabilities. The team supports infrastructure resources and keeps abreast of vulnerabilities and security patches reported by vendors and implements resolutions to keep CIT systems secure.

BRICS created private networks to facilitate upholding CIT standards for security to include firewalls, patching, and software updates. In addition, the BRICS team implements daily anti-virus scans, automated virus definition updates and email alerting across all servers. Due to ongoing threats from external sources, the team reviews logs daily and security policies to maintain consistency. Our commitment to resolving vulnerabilities in a timely manner has gained us accolades within CIT. For instance, in response to the security vulnerability, "Heartbleed," in April 2014, the BRICS team provided a rapid response where they patched over 150 servers within five days. *"[It is] your efforts in cases like this that makes the CIT ISSOs [Information Systems Security Officers] speak highly of DCB to the CIT leadership." - Dr. Anthony Fletcher, Division of Computational Bioscience (DCB) at CIT.*

3.2 Experience managing medical data and/or research data repositories

The BRICS team's experience providing bioscience, bioinformatics, and IT development support at the NIH has given us a broad understanding of how to effectively manage programs and projects within a multi- organizational collaborative research and technology environments. We have experience supporting programs and projects across the NIH which demonstrates how strategic program support, the collection and dissemination of scientific and medical information, and analysis can be combined with software development to facilitate the realization of scientific goals and to further the mission of NIH, CIT, and scientific research communities we serve within NIH. Our experience is not limited to within NIH, but rather, our footprint extends outward to the military research community including DoD, United States Army Medical Research and Materiel Command, as well as, the Henry M. Jackson Foundation for the Advancement of Military Medicine. We also have domain expertise establishing and maintaining a catalog of biosamples stored in an external biorepository that can be associated with clinical data within a BRICS instance.

The existing BRICS and Biowulf platforms have dozens of database instances, both relational and NoSQL. The BRICS team will continue to manage databases to ensure the platforms are properly functioning. The BRICS database administration team will install and configure new databases, monitor the overall health of the system using monitoring tools, work with development teams to address issues, ensure production data is synchronized for disaster recovery, performance tune queries, develop schemas for new functionality, and develop reports.

The BRICS team's technical architects and database administrators have a thorough knowledge of the database technologies critical to the projects at CIT. We also have experience and understanding of the broad range of newer technologies, including the triple-store based, Resource Description Framework (RDF) semantic web standard used in the BRICS repository and dictionary vocabularies and the Extensible Markup Language (XML) schema based data definition and storage being developed for the BRICS dictionary module. We have configured backup services within the local environment as well as externally, to offsite backup locations and cloud services, and have recovered and restored production data while minimizing impact to users.

In addition to the installation and maintenance responsibilities, database administrators (DBAs) work extensively with our software architects and development teams to optimize data models for performance and scalability. They also work extensively with development teams to create the database-specific scripts, procedures, and triggers necessary for their applications as well as implementing the supporting Extract, Transform and Load (ETL) tools and design tools that facilitate system development and integration.

3.3 Financial strength and resources to execute its bid and access other necessary resources

As a government agency, we are unable to provide a financial history however our budget and strategic plan are provided in these locations: 2017 Budget; NIH Strategic Plan.

The BRICS system has been able to scale to meet the needs of seven emerging systems, and we are confident that we will be able to scale to meet the needs of NTI.

3.4 Ability to deliver proven and robust solutions for maintaining data

Bioscience data is complex, uses disparate formats, is remotely dispersed, and based on many vocabularies. For these reasons, data modeling is critical to designing and building bioinformatics systems. The BRICS team takes a measured approach to determining the best modeling technique based on how well the structures are defined, volume and frequency of updates, and how the data will be accessed and stored. The BRICS team uses an iterative development of platform independent conceptual models to identify data relationships. These conceptual models drive the design of the data store, taking into account requirements around data analytics pipelines, storage needs, data access, and data reporting or visualization requirements. The BRICS team has experience modeling relational databases as well as non-relational stores like document databases, graph based databases, key-value stores, and multi-model stores. As part of this modeling task, we will also support load analysis and backup and recovery planning and execution.

The BRICS team's domain experts at CIT have expertise modeling complex data sets such as gene expression, ChIP-Seq, and sequence variation, and integrating them into a single model on analytics platforms like R. Our domain experts consult with technical teams to bridge the divide between CIT scientists and CIT technical teams. This work has been critical as we supported the National Institute of Neurological Disorders and Stroke (NINDS) data dictionary with CIT.

The BRICS platform, is engineered with a RDF backed Query Tool and data dictionary to enable a highly flexible query engine to facilitate discovery on large, disparate datasets. The team's experience in data modeling will enable CIT to expand modeling translations for clinical, genomics, and imaging data in a manner that facilitates discovery and data analysis.

3.5 Detailed Project Examples

NIH, Office of Intramural Research (OIR), Biomedical Research Informatics Computing System (BRICS)

The NIH OIR partnered with Sapient partnered to build BRICS, a modular, reusable, and disease agnostic bioinformatics platform. The scope of the project included architecture design, requirements gathering, development, testing, operations and user support. The BRICS team effectively launched six instances of this platform and is currently responsible for maintaining these instances. This platform is built on a foundation engineered from the NDAR platform, which the BRICS team also designed and developed. The modular and reusable architecture of the BRICS platform allows users to configure the platform any or all of the BRICS modules, allowing users to leverage exactly the functionality they need to support their research goals:

- Federal Interagency Traumatic Brain Injury Research (FITBIR)
- Parkinson's Disease Biomarkers Program Data Management Resource (PDBP DMR)
- Center for Neuroscience and Regenerative Medicine (CNRM)
- Global Rare Disease Patient Registry and Data Repository (GRDR)
- Clinical Informatics System for Trials and Research (CiSTAR)
- National Ophthalmic Disease Genotyping Network (eyeGENE)
- Common Data Repository for Nursing Science (cdRNS)

Relevancy to NTI NTRR

NTI is aiming to solve a similar problem to FITBIR, PDBP, eyeGENE, and cdRNS, in trying to increase the power of research and medical data that lead to breakthroughs in understanding through data standardization and aggregation. BRICS helps to make disparate information more accessible to these research communities and it can serve the same purpose for the trauma research community. Other groups are customizing BRICS for their research needs, which demonstrate the flexibility of BRICS for the NTI NTRR project.

The BRICS team provided architectural services throughout by designing a modular and scalable platform. The team developed the platform using open source technologies and using big data techniques like hardware virtualization, cloud integration, and harmonized data query through semantic web technologies like RDF, ontologies, and triple stores.

The BRICS platform was designed with full awareness of the sensitivity of medical research data, so all modules, both separately and in conjunction, provide for data integrity and act as a foundation for the entirety of the research lifecycle. For example, the GUID Tool is a customized software application that generates a unique ID for each study participant. This GUID is a subject ID that allows researchers to share data specific to a study participant without exposing PII. The GUID is made up of random alpha-numeric characters and is NOT generated from PII/PHI. As such, it has been approved by the NIH Office of General Counsel. Many instances use the BRICS platform to achieve broad data distribution goals while protecting the privacy of the research participants and the confidentiality of their data.

At this time, there are over 693 users representing over 134 clinical research teams across all BRICS applications, and these numbers continue to grow. The PDBP and FITBIR communities have the largest presence within the BRICS platform, each utilizing the de-identified repository to allow for longitudinal analysis across clinical sites. The PDBP community has further customized BRICS as a mechanism to share biological samples. FITBIR relies on the specialized handling of imaging data for researches to access and currently houses close to 40,000 subjects and about 1.5 million records of data. eyeGENE provides data and biospecimens for over 6,400 participants with 35 rare inherited eye conditions. cdRNS currently includes six pilot centers in Symptom Science with between two-to-four pilot projects around the nation, a centralized repository for biospecimens, and de-identified clinical databases.

The BRICS platform was developed using an Agile software development approach, as it encourages increased collaboration between various stakeholders, provides greater transparency during development, and results in higher quality products. The BRICS team's user-centric design approach has helped to develop user-friendly web interfaces and intuitive navigation for accessing a wide range of functions supported by the platform. The development was carried out using software and testing best practices and the delivery schedule was managed using Agile project management principles to meet business milestones. Dedicated functional and technical support teams were set up to support end users. The support teams provided user guides, answered helpdesk questions, curated and entered data, fixed technical issues and maintained the technical infrastructure hosting for BRICS platform programs | instances | products.

The BRICS team supports Principal Investigators (PIs) from PDBP, FITBIR, cdRNS and eyeGENE programs. The team provides research and training support to curate common data elements, develop data collection forms, submit the data to the BRICS repository, as well as provide assistance to PI's for querying and linking the data. User adoption of the bioinformatics system is extremely important for success of any research program and the user support team ensures support requests are addressed in a timely manner and any improvement suggestions are collected and fed to the technical team.

The BRICS architecture is primarily based on open source technologies such as J2EE, JBOSS application server, Virtuoso, PostgreSQL, and Mirth Connect. The infrastructure team is responsible for installation, configuration, security hardening, and maintenance of all components of BRICS architecture. The physical infrastructure is also managed by the team and consists of over 150 virtual servers, firewalls, switches, load balancers, and storage arrays. The team works with CIT infrastructure teams to ensure the environment is secure and compliant with NIH's policies.

OIR/CIT, MIPAV

The MIPAV application enables quantitative analysis and visualization of medical images of numerous modalities such as positron emission tomography (PET), magnetic resonance imaging (MRI), computed tomography (CT), or microscopy. Using MIPAV's standard user-interface and analysis tools, researchers at remote sites (via the internet) can easily share research data and analyses, thereby enhancing their ability to research, diagnose, monitor, and treat medical disorders.

Relevancy to NTI NTRR

Imaging data is a key part of trauma evaluation and subsequent research and MIPAV has been incorporated into the BRICS system as a resource. This tool assists researchers in packaging up their subject imaging files and automates the collection of some technical information captured in the headers of an imaging scan to make the submission of imaging files much easier.

NIH, National Database For Autism Research (NDAR)

NDAR is a collaborative, online research tool allowing researchers to store and share autism research data through standard, accessible and secure means. NDAR has interoperable components that integrate with local hospitals and research centers to enable the submission of data and support collaboration among dispersed scientific communities. The BRICS team members led and executed efforts in system design, requirements management, system architecture support, testing, deployment, and project management. NDAR has been able to provide researchers with the capability to create virtual electronic health records in real time based on common data standards related to the Autism Ontology to support the development of in silico autism research studies. Working in collaboration with the University of Columbia, the NDAR team developed a centralized method for generating GUIDs which allows researchers to uniquely and securely identify a subject across any study, and to aggregate

participant data across federated collections of existing and accruing research data without exposing the subject's PII. The NDAR GUID has been approved by the NIH Office of General Counsel for use both within the NDAR system and independently, and is being implemented by the Henry Jackson Foundation, and reviewed by the NCI and CDC. NDAR also uses the Autism Ontology, developed in collaboration with Stanford University, to support better queries of autism data. NDAR won an HHS Innovates Award and was recognized by the Secretary of HHS for its impacts on autism research and data sharing.

Relevancy to NTI NTRR

Our solution for NDAR created a foundation for the sharing of autism related research data to include clinical assessment and imaging data types. The NDAR solution inspired a shared vision to develop a scalable and modular disease agnostic platform to support research needs, BRICS, which is the solution that we are proposing for NTRR.

4. GLOSSARY OF ABBREVIATIONS AND ACRONYMS

ACRONYM	DEFINITION
BIRSS	Biomedical Imaging Research Services Section
BRICS	Biomedical Research Informatics Computation System
C&A	Certification and Accreditation
CC	Contributing Coordinators
CDA	Clinical Data Architecture
CDE	Common Data Elements
cdRNS	Common Data Repository for Nursing Science
CFR	Code of Federal Regulations
CI	Contributing Investigators
CiSTAR	Clinical Informatics System for Trials and Research
CIT	Center for Information Technology
CNRM	Center for Neuroscience and Regenerative Medicine
CRDA	Cooperative Research and Development Agreement
CT	Computed Tomography
DBA	Database Administrator
DCB	Division of Computational Bioscience
DMR	Data Management Resource
DMZ	Demilitarized Zone
DoD	Department of Defense
DOI	Digital Object Identifier
ETL	Extract, Transform, and Load
eyeGENE	National Ophthalmic Disease Genotyping and Phenotyping Network
FISMA	Federal Information Security Management Act
FITBIR	Federal Interagency Traumatic Brain Injury Research
GRDR	Global Rare Diseases Registry
GUID	Global Unique Subject Identifier
HIPAA	Health Insurance Portability And Accountability Act
ISSO	Information Systems Security Officer

ACRONYM	DEFINITION
MIPAV	Medical Image Processing, Analysis, and Visualization
MRI	Magnetic Resonance Imaging
NDAR	National Database for Autism Research
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
NIST	National Institute of Standards and Technology
NTI	National Trauma Institute
NTRR	National Trauma Research Repository
O&M	Operations and Maintenance
OIR	Office of Intramural Research
PDBP	Parkinson's Disease Biomarkers Program
PET	Positron Emission Tomography
PHI	Protected Health Information
PI	Principal Investigators
PII	Personally Identifiable Information
PM	Project Manager
PMBOK	Project Management Body of Knowledge
PMI	Project Management Institute
RDC	Research Data Catalogue
RDF	Resource Description Framework
RDS	Research Data Store
RFP	Request for Proposal
RI	Recipient Investigator
RTM	Requirements Traceability Matrix
SA&A	Security Assessment and Authorization
SaaS	Software as a Service
SDLC	Software Development Lifecycle
TBI	Traumatic Brain Injury
UAT	User Acceptance Training
UDE	Unique Data Elements
XML	Extensible Markup Language

Appendix 4
National Trauma Research Repository
Past Performance Evaluation

Note: This page should be completed by the vendor responding to the RFP and given to the evaluating entity (i.e., a former client).

The proposal that the **National Institutes of Health, in coordination with Sapient Government Services,** is submitting to the National Trauma Institute (NTI) requires we demonstrate past performance that is relevant to the Request for Proposal's (RFP) scope of work. This includes, but is not limited to, the vendor's record of: 1) meeting milestones; 2) timely submission of deliverables; and 3) technical competency. The vendors solicit at least two relevant past/current performance evaluations on work done within the last five years. If the offeror has been in business less than three years, relevant work conducted by the vendor's key personnel may be provided.

The National Institutes of Health, in coordination with Sapient Government Services is requesting past/current clients to complete the Past Performance Evaluation Form and email it directly to research@nationaltraumainstitute.org, prior to the closing of the solicitation on March 31, 2017.

Work performed by **The National Institutes of Health, in coordination with Sapient Government Services** upon which the performance is being evaluated:

Project or Contract Title: **Biomedical Research Informatics Computing System (BRICS), NINR cdRNS**
Contract Number: **HHSN276201500251U**
Contracting agency: **NIH, Division of Computational Bioscience (DCB)**
Type of contract: **Time and Materials**
Total contract dollars: **$7,517,552.45 (current value for entire BRICS contract)**
Contract period of performance: **08/2015 – 08/2018 (for entire BRICS contract)**
Firm or Government agency for which work was performed: **National Institute of Nursing Research**
Point of Contact (Contracting Officer or Contracting Officer's Representative): **Donna Jo McCloskey, PhD, RN, FAAN**
Name: **Donna Jo McCloskey, PhD, RN, FAAN**
Title: **Clinical Advisor**
Address: **6701 Democracy Blvd, Room 713**
Bethesda, MD 20892
Telephone number: **301-443-7835 office**

Brief description of how this work is similar to the proposed effort in this RFP:
DCB partnered with Sapient to build BRICS, a modular, reusable, and disease agnostic bioinformatics platform. The modular and reusable architecture of the BRICS platform allows users to configure the platform's modules, allowing users to leverage exactly the functionality they need to support their research goals. Together, they have executed seven instances of this platform, including the NINR cdRNS platform for the National Institute of Nursing Research. The aim of this initiative is to stimulate patient and health care provider interest in symptom science and self-management for four core symptoms of Pain, Sleep, Fatigue and Cognition. Since 2013 the NINR Centers

along with NINR, NLM and CIT have been successful in a collaborative effort in developing CDEs in symptom science and self-management and now infrastructure to support CDE metadata. The program allows approved researchers to gain access to the clinical data and samples to facilitate research to manage and eliminate symptoms caused by illness and enhance end-of-life and palliative care. cdRNS® Network currently includes 6 pilot centers in Symptom Science with between 2-4 pilot projects around the Nation, a centralized repository for biospecimens, and de-identified clinical databases. Similar to the NTI NTRR, the scope of the project included infrastructure, architecture design, requirements gathering, development, testing, operations, and user support for a repository build.

Past Performance Evaluation Form

Vendor/Contractor being evaluated: **The National Institutes of Health, in coordination with Sapient Government Services**

Evaluating Business Entity: **National Institute of Nursing Research**

The following standards shall be used in arriving at the rating:

Outstanding: Contractor's performance exceeded customer expectations and was technically excellent, providing significant features or benefits.

Satisfactory: Contractor met customer expectations or contract requirements and demonstrated an acceptable understanding of the requirements.

Unsatisfactory: Contractor's performance was either marginal or did not meet customer expectations or contract requirements.

Not applicable: If the element is not applicable, indicate with "N/A." If no data have been obtained or additional comments are provided, please note in this column.

Performance Element	***Outstanding***	***Satisfactory***	***Unsatisfactory***	***N/A***
Technical Performance (Quality of Product or Service)				
1. QUALITY OF TECHNICAL APPROACH: Were the services comprehensive, complete, and feasible? (Met the needs, performed successfully, and accommodated changing requirements)	x			
2. UNDERSTANDING OF REQUIREMENTS: Did the contractor show an understanding of the scope of the requirements and an appreciation for the complexity of the requirements? And did the contractor effectively identify flaws, inconsistencies, and other inaccuracies in your technical direction?	**x**			
Timeliness of Performance				
3. EFFECTIVE AND EFFICIENT USE OF RESOURCES: Was the contractor able to obtain in a timely manner the amount and type of personnel resources required to support the project, effectively train personnel to perform the work, and maintain the required workforce throughout the term of the contract?	x			
4. TIMELINESS OF PERFORMANCE: Was the contractor successful in planning and proposing realistic schedules, monitoring performance, completing work on time, and implementing corrections/changes in a timely manner?	x			
Performance Element	***Outstanding***	***Satisfactory***	***Unsatisfactory***	***N/A***
Quality/Customer Satisfaction				
5. QUALITY OF PERFORMANCE / CUSTOMER SATISFACTION: Was the contractor committed to customer satisfaction?	x			

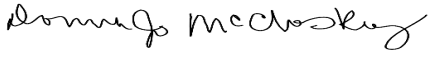
6. BUSINESS BEHAVIOR: Was the contractor reasonable and cooperative in response to changes in technical direction, correcting errors, poor performance, criticism, and other quality issues?	x			
7. COMMUNICATION: Did the contractor work and communicate well with contracting officers, technical representatives, and staff?	x			
Cost Control				
8. COST CONTROL: Was the contractor successful in planning and proposing realistic costs, monitoring performance, operating at or below budget, and implementing corrections or changes in a cost effective manner?	x			
For #9, please indicate "Yes" or "No"	**YES**		**NO**	
9. Given the choice, would you do business with this contractor again?	x			

Please provide any additional comments regarding your performance ratings in the space below. Please add additional pages as necessary.

NINR's interest in the BRICS platform centered on enabling data discovery, filtering and query across datasets using standardized dictionary Common Data Elements (CDEs) and subject identifiers as the common link across existing and ongoing clinical research data. In support of these goals, the team has provided a secure BRICS platform and for the Common Data Repository for Nursing Science (cdRNS). NINR's objectives are to have a hosted and secure infrastructure. The BRICS team including Sapient contractors have been extremely professional, supportive and competent in this effort. Currently a platform and public site has been developed

The Sapient and NIH team has been extremely responsive in developing NINR's supported CDEs and we are confident in all future efforts in related production/monitoring, including critical response, and technical support. The team has met every two weeks over the past 6-8 months for 1 hour. Currently we are on task with full deployment of the repository (April, 2017). The technical competency of the Sapient team is exceptional and come highly recommended and would not hesitate to work with them in any future efforts. Collaboration has been the hallmark of their team approach. Seamless and on time deliverables have been the norm, meeting all milestone of the project (most often earlier than expected) which included but not limited to the tasks below.

1) Setup the NINR's BRICS instance.
2) Assist and train NINR staff and configure the Data Dictionary to define and store data definitions,
3) Work with NINR to create and deploy a public facing website.
4) Perform Certification and Accreditation (C&A) of the NINR repository.
5) Provide training to NINR staff.
6) Provide operational support for the NINR BRICS-supported repository, to include user support, user administration, trouble ticket support, and system and application monitoring.

Evaluator's Signature: _  3/17/2017

Please submit this form directly to NTI at research@nationaltraumainstitute.org no later than March 31, 2017.

National Trauma Research Repository – Request for Additional Information
Vendor: The National Institutes of Health, Center for Information Technology, Office of Intramural Research, Biomedical Imaging Research Services Section

Technical Approach

As stated in the inset on page 1, GUID and ProFoRMS are capabilities beyond the NTRR requirements. However, the meta-study functionality listed in the inset is within the scope of work.

NIH Response: Yes, this was an oversight in our response. Meta Study is within the scope of work for NTRR requirements. As discussed during the 'Discussion of NIH's response to NTRR RFP & request for additional information' meeting/teleconference on June 5, 2017, the GUID module will be required in order for data to be submitted to a NTRR version of the BRICS system, however, usage of ProFoRMS is not required.

It seems that the response doesn't address the process of the Research Investigator requesting data (UR.7.), the request being sent to NTI staff for review/approval, and the NTI staff creating the dataset requested (UR.9.iv.). What is the plan for managing this process?

NIH Response: As discussed and demoed during the 'Discussion of NIH's response to NTRR RFP & request for additional information' meeting/teleconference on June 5, 2017, NTRR's workflow (in support of UR.7. and UR.9.iv) can be supported by current BRICS functionality. However, further discussion/exploration is needed to best assess how NTRR will adopt BRICS capabilities to best address NTRR's business needs.

Will the system save research investigators' searches in the Research Data Catalog (RDC) if logged in (UR.10)?

NIH Response: As discussed and demoed during the 'Discussion of NIH's response to NTRR RFP & request for additional information' meeting/teleconference on June 5, 2017, searches could be supported by current BRICS functionality via the Query Tool.

Vendor Previous Experience

No additional information requested.

Cost Proposal

As stated above, GUID and ProFoRMS are capabilities beyond the NTRR requirements and NTI's deliverables under the award statement of work. Is it possible to develop a budget for building and hosting/supporting the repository without these functions?
NIH Response: An alternative budget will not be provided as the GUID and ProFoRMS modules are part of the BRICS package. However, the ProFoRMS module could be disabled and not available to the NTRR end users at no cost.

There is $20,000 included in the development cost proposal for three virtual server environments including associated software, storage, etc. and another $42,300 included in the hosting cost proposal described using the same terms. Please clarify and/or justify the necessity of the hosting hardware/software costs.

NIH Response: In preparation for our initial response, we explored Amazon Web Services (AWS) costs, and based on our analysis recommended a co-hosted option. Hosting NTRR at CIT was more economical based on our existing capacity at CIT.

Adjustments were made to both the development & the host equipment costs. The equipment cost includes set up and maintenance of virtual servers, storage, networking and software licensing. In our proposed Product Development estimate we only provided a cost for one environment despite stating in our cost rationale that it would support 3 environments. Therefore, an adjustment to the development budget was made to account for the setup of all the 3 virtual servers. The maintenance of the 3 environments in the host budget was also incorrect related to the error in the development setup. We adjusted the host budget since the all the environments will be setup during the development phase. The cost is thereby reduced to $17,300 annually.

The hosting cost proposal includes 2,000 man hours (a FTE) to perform defect fixes and enhancements. If these defects are related to the initial build, it seems like they should be covered by some sort of warranty for the build work. While there may be minor enhancements during the year of maintenance, any further development, such as a new module, would be funded through another mechanism and should not be included in this hosting cost proposal.

NIH Response: Per our discussion during the 'Discussion of NIH's response to NTRR RFP & request for additional information' meeting/teleconference on June 5, 2017, NTI expects to only have minor enhancements and defect fixes; therefore the man hours have been adjusted to reflect that. The hours from the following labor categories were reduced: Project Manager, Business Analysts, Lead developer, and developer. Please see the "Host budget" of the cost document for details.

There are 960 man hours for the Business Analyst to liaison with NTI to troubleshoot user issues and questions as well as testing support. It seems that all testing related to the initial build would be done within the development phase of the project. What testing is covered during the maintenance and support phase? Similar question regarding the Tester and the 192 man hours. If the hosting phase doesn't include development what would be tested?

NIH Response: The Business Analyst (BA) total hours were reduced to 640 hours (0.3 FTE), however, any additional reduction is not advised. The BA can help identify a best strategy(s) to assist NTI work through complex processes like getting in legacy data. Additional activities the BA could assist with include collecting user requirements for enhancements (if needed) and assistance with Tier 1/2 support.
With regards to testing support, no additional hourly reductions were made. These hours would support testing after security patches/updates, defect fixes, as well as, testing post enhancement development. The primary focus of the testing support is to ensure that the quality of the NTRR product is maintained throughout the project lifecycle.

We would like to discuss your assumptions in terms of volume of studies, dictionaries, user support and other activities included in your labor cost proposal.

NIH Response: During the 'Discussion of NIH's response to NTRR RFP & request for additional information' meeting/teleconference on June 5, 2017, NTI shared that the number of system users would initially be low. Based on this, our assumption for the number of investigators was reduced in half from 70 to 35. Also our assumption for the number of data dictionaries was reduced to one. The NTRR data dictionary will have the capacity to encompass the NTRR Core CDES, the (4) NTRR modules (Prehospital, Inpatient, Rehab, and Outcome/QOL modules), and the individual UDEs coming from the eight NTRR studies.

Although not originally included in NIH's proposal to NTI, a budget for creating a public website was created after speaking with NTI on June 5, 2017. Details are provided below.

NTRR new public site development

All BRICS instances public websites are based on Drupal, an open source Content Management System. Assumptions made during the cost estimations include:

- NTRR website will be developed using existing BRICS templates as shown during our site demonstration
- All creative artifacts, such as logo and website imagery, will be provided by NTI
- The number of pages would be a total of 15 pages: 10 flat pages where we create the pages and put in content and 5 interactive pages, where we put in content as well as have interactive capability.
- The public site scraping functionality contains information about each study, where a listing of all of the studies as well as the detail pages for each will be displayed. This capability can be available for you at no cost; however, these pages will be enabled as-is, as customization of the pages would require additional time and effort to develop.
- The summary data charts are not included in the cost estimate; if that capability is requested, the cost estimations will be handled separately.
- All the public site development is done during the first 6 months development period; during the hosting period, there is no public site development as content can be changed and managed by NTI team.

The total cost for developing the public website is $54,248. The "Development budget" has been adjusted to reflect this new feature that was not proposed in our initial response.

National Institutes of Health (NIH)
Center for Information Technology (CIT)
Office of Intramural Research (OIR)
Biomedical Imaging Research Services Section (BIRSS)
NIH Campus/ CIT Building 12A, Room 2039
12 South Drive Bethesda, MD 20814
Matthew McAuliffe, PhD , Chief, Biomedical Imaging Research Services Section
(p) 301.594.2432

Development

Line	Product Type	Quantity	Description	Price
1	System Design & Development	1	Design and develop NTRR with all required criteria.	$ 355,444
2	Testing	1	Test all interoperability between the database and the web interface.	$ 78,994
3	Deployment & Training	1	Determine the final deployment strategy.	$ 111,113
4	Implementation & Review	1	The vendor shall demonstrate the fully functional system during a trial period of not less than 10	$ 30,513
	TOTAL			$ 576,064

Hosting

Line	Product Type	Quantity	Description	Price
1	Hosting	1	Host database and website.	$ 61,112
2	Maintenance	1	Maintain database and website.	$ 95,688
3	Support	1	Provide continued customization and maintenance of NTRR.	$ 58,404
	TOTAL			$ 215,204

Quotation shall remain valid for a period of 120 days.

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6 MONTH BUDGET

DEVELOP Web-Based National Trauma Research Repository			System Design & Development		Testing		Deployment & Training		Implementation & Review		TOTAL
	Total Hrs	Rate	Hours	Budget	Hours	Budget	Hours	Budget	Hours	Budget	
LABOR											
Program Manager	192	$ 155.00	116	$ 17,980	38	$ 5,890	19	$ 2,945	19	$ 2,945	$ 29,760
Project Manager	480	$ 133.00	288	$ 38,304	96	$ 12,768	48	$ 6,384	48	$ 6,384	$ 63,840
Business Analysts	568	$ 116.00	280	$ 32,480	-	$ -	192	$ 22,272	96	$ 11,136	$ 65,888
Technical Architect	480	$ 127.00	384	$ 48,768		$ -	48	$ 6,096	48	$ 6,096	$ 60,960
Lead developer	480	$ 112.00	384	$ 43,008	-	$ -	96	$ 10,752	-	$ -	$ 53,760
Developer	960	$ 108.00	960	$ 103,680	-	$ -	-	$ -	-	$ -	$ 103,680
Infrastructure SME	402	$ 104.00	248	$ 25,792	-	$ -	116	$ 12,064	38	$ 3,952	$ 41,808
Tester	568	$ 102.00	-	$ -	568	$ 57,936	-	$ -	-	$ -	$ 57,936
Information Architect	240	$ 102.00	240	$ 24,480	-	$ -	-	$ -	-	$ -	$ 24,480
Frontend Dev	194	$ 108.00	194	$ 20,952	-	$ -	-	$ -	-	$ -	$ 20,952
LABOR TOTAL				$ 355,444		$ 76,594		$ 60,513		$ 30,513	$ 523,064
SUBCONTRACT											
SUBCONTRACT TOTAL				$ -		$ -		$ -		$ -	$ -
CONSULTANT											
CONSULTANT TOTAL				$ -		$ -		$ -		$ -	$ -
MATERIALS & SUPPLIES											
MATERIALS & SUPPLIES TOTAL				$ -		$ -		$ -		$ -	$ -
TRAVEL											
Phase 1 Training				$ -				$ 2,400		$ -	$ 2,400
Phase 2 UAT and Training				$ -		$ 2,400		$ 2,400			$ 4,800
				$ -		$ -		$ -		$ -	$ -
TRAVEL TOTAL				$ -		$ 2,400		$ 4,800		$ -	$ 7,200
EQUIPMENT											
For 3 Environments, each environment consists of 7-8 virtual servers											
Includes virtual servers, storage, networking, software licensing, maintainance and setup				$ -		$ -		$ 45,800		$ -	$ 45,800
EQUIPMENT TOTAL				$ -		$ -		$ 45,800		$ -	$ 45,800
OTHER DIRECT COST											
OTHER DIRECT COST TOTAL				$ -		$ -		$ -		$ -	$ -
Indirect Cost Base				$ 355,444		$ 78,994		$ 111,113		$ 30,513	$ 576,064
Indirect Costs	Rate	0.00%		$ -		$ -		$ -		$ -	$ -
Budget by Task				**$ 355,444**		**$ 78,994**		**$ 111,113**		**$ 30,513**	**$ 576,064**
TOTAL PROJECT BUDGET											**$ 576,064**

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12 MONTH BUDGET

HOST & SUPPORT Web-Based National Trauma Research Repository			Hosting		Maintenance		Support		TOTAL
	Total Hrs	Rate	Hours	Budget	Hours	Budget	Hours	Budget	
LABOR									
Program Manager	-	$ 155.00	-	$ -	-	$ -	-	$ -	$ -
Project Manager	80.00	$ 133.00	-	$ -	-	$ -	80	$ 10,640	$ 10,640
Business Analysts	640.00	$ 89.00	-	$ -	204	$ 18,156	436	$ 38,804	$ 56,960
Technical Architect	-	$ 127.00	-	$ -	-	$ -	-	$ -	$ -
Lead developer	80.00	$ 112.00	-	$ -	-	$ -	80	$ 8,960	$ 8,960
Developer	480.00	$ 108.00	-	$ -	480	$ 51,840	-	$ -	$ 51,840
Infrastructure SME	480.00	$ 104.00	384	$ 39,936	96	$ 9,984	-	$ -	$ 49,920
Tester	192.00	$ 102.00	38	$ 3,876	154	$ 15,708	-	$ -	$ 19,584
Information Architect	-	$ 102.00	-	$ -	-	$ -	-	$ -	$ -
LABOR TOTAL				$ 43,812		$ 95,688		$ 58,404	$ 197,904
SUBCONTRACT									
SUBCONTRACT TOTAL				$ -		$ -		$ -	$ -
CONSULTANT									
CONSULTANT TOTAL				$ -		$ -		$ -	$ -
MATERIALS & SUPPLIES									
				$ -		$ -		$ -	$ -
MATERIALS & SUPPLIES TOTAL				$ -		$ -		$ -	$ -
TRAVEL									
TRAVEL TOTAL				$ -		$ -		$ -	$ -
EQUIPMENT									
For 3 Environments, each environment consists of 7-8 virtual servers				$ -					
Includes virtual servers, storage, networking, software licensing, maintainance and setup				$ 17,300				$ -	$ 17,300
EQUIPMENT TOTAL				$ 17,300		$ -		$ -	$ 17,300
OTHER DIRECT COST									
OTHER DIRECT COST TOTAL				$ -		$ -		$ -	$ -
Indirect Cost Base				$ 61,112		$ 95,688		$ 58,404	$ 215,204
Indirect Costs	Rate	0.00%		$ -		$ -		$ -	$ -
Budget by Task				**$ 61,112**		**$ 95,688**		**$ 58,404**	**$ 215,204**
TOTAL PROJECT BUDGET									**$ 215,204**