The National Trauma Institute: Lessons learned in the funding and conduct of sixteen trauma research studies

Short Title: National Trauma Institute: Lessons Learned

Authors Byline: National Trauma Institute Research Group; Michelle A. Price, Ph.D.; Gregory J. Beilman, M.D.; Timothy C. Fabian, M.D.; David B. Hoyt, M.D.; Gregory J. Jurkovich, M.D.; M. Margaret Knudson, M.D.; Ellen J. MacKenzie, Ph.D.; Vivienne S. Marshall, Ph.D.; Kimberly E. Overton, R.N.; Andrew B. Peitzman, M.D.; Monica J. Phillips, M.S.N., M.B.A.; Basil A. Pruitt, Jr., M.D.; Sharon L. Smith, M.S.; Ronald M. Stewart, M.D.; and Donald H. Jenkins, M.D.

Authors' Institutional Affiliations:

National Trauma Institute Research Group, San Antonio, TX, USA,
communications@nationaltraumainstitute.org

Michelle A. Price, Ph.D., University of Texas Health Science Center at San Antonio, Texas, USA, pricema@uthscsa.edu

Gregory J. Beilman, M.D., University of Minnesota, North Memorial Medical Center, Robbinsdale, MN, beilm001@umn.edu

Timothy C. Fabian, M.D., University of Tennessee Health Science Center, Memphis, TN, USA, tfabian@uthsc.edu

David B. Hoyt, M.D., American College of Surgeons, Chicago, IL, USA, dhoyt@facs.org

Gregory J. Jurkovich, M.D., University of California - Davis, CA, USA, gjjurkovich@ucdavis.edu

M. Margaret Knudson, M.D., University of California – San Francisco, CA, USA, Peggy.Knudson@ucsf.edu

Ellen J. MacKenzie, Ph.D., Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, emacken1@jhu.edu

Vivienne S. Marshall, Ph.D., Children's Hospital of San Antonio, San Antonio, TX, USA, vivienne.marshall@christushealth.org

Kimberly E. Overton, R.N., National Trauma Institute, San Antonio, TX, USA,
khicks89@hotmail.com

Andrew B. Peitzman, M.D., University of Pittsburgh, Pittsburgh, PA, USA,
peitzmanab@upmc.edu

Monica J. Phillips, M.S.N., M.B.A., National Trauma Institute, San Antonio, TX USA,
Monica.Phillips@NationalTraumaInstitute.org

Basil A. Pruitt, Jr., M.D., University of Texas Health Science Center at San Antonio, Texas, USA, pruitt@uthscsa.edu

Sharon L. Smith, M.S., National Trauma Institute, San Antonio, TX USA,
Sharon.Smith@NationalTraumaInstitute.org

Ronald M. Stewart, M.D., University of Texas Health Science Center at San Antonio, Texas, USA, stewartr@uthscsa.edu

Donald H. Jenkins, M.D., Mayo Clinic, Rochester, MN, USA, Jenkins.Donald@Mayo.edu

Corresponding Author: Donald H. Jenkins, M.D.
Mayo Clinic
200 First Street SW
Rochester, MN 55905
Phone: (507)255-2923
Fax: (507)2559872
Jenkins.Donald@Mayo.edu

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BACKGROUND

Trauma is the leading cause of death among individuals 46 years and younger, and the single largest cause for years of life lost in the United States (1). In the United States (U.S.), 199,756 persons suffered fatal injury in 2014, and 30,888,063 were treated in emergency departments for non-fatal injuries in 2013 (2). Medical treatment and work loss costs for civilian fatal and non-fatal injuries in the U.S. totaled more than \$586 billion in 2010 (2). In the conflicts in Iraq and Afghanistan, there have been 52,407 injured U.S. military and DoD civilians and 6,881 deaths from trauma (3). These statistics point to the dramatic burden of injuries on the health of this country in both civilian and military sectors.

Military medicine has been a rich source of information and experience that fosters investigation and advances trauma patient care (4). The United States' investment in combat casualty care research since 2001 has contributed to the lowest case fatality rate ever recorded in war, and subsequent translation of life-saving interventions to civilian trauma care (5). Similarly, advances in civilian trauma care transformed the military's joint trauma system (6). Experiences with mass casualty events during conflicts have also been instructive during civilian disasters (7). Therefore, properly conducted, well-funded trauma research directly benefits combat casualty care and has the potential to impact the primary public health problem in the U.S.

Despite the impact of trauma deaths, years of potential life lost, and treatment costs, there is no federally funded national institute or dedicated funding mechanism for the systematic study of trauma care. Currently, trauma receives a small fraction of the funding awarded to cancer and heart disease research. National Institutes of Health (NIH) funding of clinical trauma research is disproportionate to the burden of the disease and by that metric ranks last among 27 disease categories (8). The DoD funds research that is relevant to the military but cannot address or fund

all research needs. The National Trauma Institute (NTI) was founded in 2006 to secure and manage funding for trauma research and to be a national coordinating center for such research. Civilian and military collaboration has always been an integral part of the NTI's vision, as is cross-discipline research. Active and retired members of the Army, Air Force and Navy are included on its Board of Directors, along with senior civilian leaders from the American Association for the Surgery of Trauma (AAST), American College of Surgeons Committee on Trauma (ACS-COT), Eastern Association for the Surgery of Trauma (EAST), Western Trauma Association (WTA), the American College of Emergency Physicians (ACEP), the Shock Society, the Orthopedic Trauma Association (OTA) and the American Association of Neurological Surgeons (AANS).

NTI receives and distributes research funding to clinical investigators across the U.S. through a rigorous peer review process led by its Science Committee and Board of Directors. NTI received congressional funding in federal FY2008, FY2009 and FY2010 (executed by the DoD) to issue and coordinate awards for trauma research projects (Contract #W81XWH-08-1-0758, #W81XWH-10-1-0924 and #W81XWH-11-1-0841). NTI issued calls for proposals in 2009 and 2010. The 2009 announcement solicited pre-proposals for multi-center translational or clinical research with special interest in hemorrhage/shock/coagulopathy, hospital-acquired infection, technology development, airway and ventilation, disaster preparedness and burns. In response, investigators submitted 85 pre-proposals from which 15 full proposals were invited. Seven proposals were funded. The 2010 announcement solicited pre-proposals for translational or clinical trauma research with priority areas of hemorrhage, intensive care, trauma systems and pre-hospital care. Seventy-two pre-proposals were submitted, and 22 full proposals were invited. Nine applications were funded.

NTI's Science Committee, comprising senior trauma researchers, reviewed the pre-proposals, invited full proposals and selected awards on the basis of: military and NTI relevance of research objectives, scientific merit, clinical relevance and potential impact, multicenter collaboration, innovation, potential for follow-on studies and feasibility. The goals of the Science Committee were to fund as many feasible studies as possible with geographic dispersion as well as to fund both established and developing investigators. The committee met to review the applications, assigning primary and secondary reviewers to each application. Each proposal was discussed, scored and ranked. The Science Committee made recommendations on study design modifications and budget adjustments. The budget and scope of activity for ten proposals were reduced. The top proposals were recommended for funding to the full NTI Board of Directors, which subsequently approved the selected studies.

NTI funded 16 applications totaling \$3,889,938. The funding awards ranged from \$125,000 to \$675,761 and averaged \$243,341. Due to the novel nature of this funding mechanism, the studies had to be selected and submitted as part of the full National Trauma Institute's prime application to the DoD before the award to NTI and the subawards to the selected sites were issued. This requirement delayed the first contracts by five months and the second group by nearly ten months.

Over the past five years, 16 studies in 35 cities and 22 states involving 59 investigators were initiated. Ten of the studies were multi-institutional. The funded studies were comprised of seven randomized clinical trials, seven prospective observational or cohort studies, one study utilizing healthy volunteers and one retrospective review study (Table 1). Twelve studies have been completed, three were closed without completion due to slow enrollment or failure to

initiate, and one continues to enroll (80% success rate) (Table 1). Nine clinical trials were registered on www.clinicaltrials.gov (Table 2).

In January 2014, the principal investigators (PIs) presented study updates at the annual NTI Board of Directors meeting. At that meeting, the Science Committee decided to seek investigators' input regarding their experiences conducting the studies to identify barriers and facilitators to the research process. This manuscript presents the investigators' responses along with study management data and provides "lessons learned" for trauma investigators planning single or multi-site research protocols. It also offers guidance for grant reviewers and funders on selection of proposals and investigators that are likely to succeed.

METHODS

Members of the NTI Science Committee and executive board identified key topics pertaining to study management. A semi-structured interview was developed that consisted of 30 open-ended questions addressing: study management, regulatory review, financial management, investigator development and scientific productivity. Phone interviews were conducted between March and September 2014. Of the 16 PIs, 15 participated and one declined (93% participation). Interview responses were de-identified and analyzed in aggregate. NTI Science Committee meeting minutes were reviewed regarding study selection criteria and study oversight. NTI study management data were also analyzed. Data were entered into a Microsoft Excel workbook (Microsoft Excel 2013, Microsoft Corp., Redmond, WA). Descriptive statistics were calculated. Qualitative analysis focused on identifying common themes.

RESULTS

Study Management

All PI's submitted quarterly progress reports that were reviewed by NTI staff and the Science Committee. The Science Committee met regularly to discuss study progress. When there were concerns regarding protection of human subjects, accrual or other issues, a member of the Science Committee met with the PI via telephone and reported back to the committee. The Science Committee decided if the correction plan was appropriate or if the study should be closed. Three studies were closed due to low enrollment or start-up delays.

Institutional approval and delays of study initiation

The DoD Human Subjects Protection Regulatory Requirements stipulate specific language in contracts that involve human subjects (9). The DoD Human Research Protection Office (HRPO) must approve any research involving human subjects prior to the implementation of the DoD-funded research. Therefore, contracts were not issued to the recipient institutions until Institutional Review Board (IRB) and DoD HRPO approval of the protocols was secured. There was wide variability among the sites in the time required to obtain approval (Table 3). Six studies had secured IRB approval by the date they received notification of NTI funding selection. Among the remaining 10 studies, the mean number of days from funding selection to IRB approval was 210 days (minimum = 51, maximum = 537, standard deviation [SD] = 142). The randomized clinical trials (RCT) had the highest mean days from funding selection to IRB approval (mean = 262 days; SD = 140 days) and the highest mean days from IRB to DoD HRPO approval (mean = 239 days; SD = 93 days) compared to prospective observational or cohort

studies, with a mean of 131 days from selection to IRB approval (standard deviation = 103 days) and a mean of 126 days from IRB to DoD HRPO approval (SD = 64 days), respectively. The mean total number of days from notice of selection to HRPO approval for all studies was 401 days (SD = 245 days). One RCT study and three prospective cohort studies secured approval for a waiver or delay of informed consent provision. Three of the RCTs also required an Investigational New Drug approval from the Food and Drug Administration.

Forty percent of the investigators reported challenges in obtaining regulatory approval at one or more institutional levels. Several investigators reported challenges in navigating the requirements for the DoD HRPO approval processes. Multi-site studies had additional delays due to multiple IRB reviews with conflicting revisions and subcontracting processes. One PI relocated to another institution during the review process and had to start over at the new institution. During the one-year approval process for one of the studies, another research group published a study that obviated the study design. As a result of the published study, the proposed experimental treatment became standard of care in most hospitals, so the NTI study design had to be revised. The time required to obtain approvals delayed the funding awards considerably and resulted in the loss of study sites, turnover in research trainees, and the need to use alternate sources of funds for research staff salaries, protocol review, and community consultation costs. PIs reported that turnover in research trainees and other research staff while securing approvals further delayed the onset of some of the studies because of replacement and retraining. The mean time from HRPO approval to initiation of enrollment was 99 days (minimum = 0; maximum = 280; standard deviation = 91) (Table 3).

Screening and enrollment

Active enrollment periods for the completed studies ranged from 104 to 943 calendar days (mean = 551; SD = 280 calendar days). The enrollment periods were substantially longer than originally estimated on the applications. As of January 2016, 28,725 patients were screened, and 5,579 participants were enrolled. Among the RCTs and prospective studies (n=12), screening and enrollment varied widely. Four investigators (33%) reported that screening and enrollment were at or above initial targets, and eight (67%) reported that rates had been below initial estimates. Factors associated with lower screening and/or enrollment were lower incidence of disease, sicker patients, early mortality, shorter lengths of stay in the intensive care unit, inconsistent or lower screening/enrollment at multiple sites, patient or family refusal, lack of off-hour staffing for screening/enrollment, insufficient funding for staffing and shortened enrollment period due to delays in institutional approval. The definition of a screen varied as well. Half of the RCTs or prospective protocols defined a screen as any high-level trauma activation attended by study personnel or admission of a trauma patient to the intensive care unit, whereas the other half used more specific screen criteria (e.g., specific medical condition or intervention). Therefore, screening to enrollment rates varied greatly, with from 3% to 100% of screened patients being enrolled into the prospective observational or cohort studies and from 1% to 29% in the RCTs.

Obtaining participant or legally authorized representative consent

Previous trauma research has shown severely injured trauma patients can seldom provide consent, and legally authorized representatives (LARs) are often unavailable, suggesting the Exception from Informed Consent (EFIC) is necessary to recruit a representative sample (10). Under the Federal Drug Administration's policy for EFIC, emergency research EFIC may only

be conducted when: 1) the human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory and collection of valid scientific evidence is necessary to determine the safety and effectiveness of particular interventions; 2) obtaining informed consent is not feasible; 3) research participation may provide direct benefit to the subject; 4) clinical investigation could not practicably be conducted without the waiver; 5) the investigational plan specifies the potential therapeutic window, and the investigator attempts to contact an LAR within that period; 6) the IRB has approved the informed consent procedure that will be used when feasible; and 7) additional protections of the rights of the subjects will be provided including community consultation (11). A waiver of consent in the PROspective Observational Multi-center Major Trauma Transfusion (PROMMTT) study was invaluable in enrolling sufficient numbers of participants and avoiding consent bias (12). Three of the NTI prospective (cohort or observational) studies and one of the RCTs received approval for EFIC. Of the 13 protocols using informed consent, 10 (77%) had consent documents and interpreters for languages other than English (e.g., Spanish, Chinese or other language) and eight (61.5%) reported encountering potential participants with a primary language other than English.

Multi-site study coordination

Ten of the studies were multi-site (ranging from two to 11 participating sites). Of these, four had one or more sites withdraw from the study prior to enrolling participants (three RCTs and one retrospective review study). Some sites withdrew because they were unable to obtain IRB approval or due to delays in IRB and/or HRPO approvals. Others withdrew due to changes in the protocol that were required by the IRB or HRPO. One military site was unable to participate due to site PI's deployment. One site withdrew because the funding was insufficient.

Several PIs discussed challenges in coordinating across multiple sites. Strategies used to manage multiple sites were funding additional research nurse/coordinator effort and holding regular teleconferences to monitor progress at all sites.

Study Financial Management

Nine of the PIs (60%) reported that the study budget was inadequate, particularly for research staffing and coverage. Six of these study budgets were reduced by the Science Committee during the review process. Budgeted full-time equivalents (FTEs) for the studies ranged from 0.6 or 60% of one research staff member to 2.4 FTEs (mean = 0.85 FTE). Nine PIs reported augmenting the study funding with other sources of funds (either departmental/institutional start-up or bridge funds). Seven investigators reported that they were able to achieve 24-hour/seven days per week research staffing through leveraged funds from other sources. Budgeted effort for PIs ranged from 0.0 to 0.25 FTE, with a mean of 0.09 or 9% effort. Other areas of insufficient funding cited were diagnostic or laboratory testing, IRB approval and community consultation costs, statistical analysis, travel to satellite sites for study coordination and indirect costs (which was set at 10% of direct costs).

Initial Scientific Contributions

As of January 2016, 10 NTI-funded studies completed initial data analysis, two were analyzing data, one was enrolling participants and three had closed due to low enrollment or start-up issues. In total, the studies have generated 16 publications (13-29), two manuscripts under review, and 15 presentations at national meetings, two presentations at regional meetings and six presentations at state or local trauma meetings. Ten of the 13 studies (76%) produced one

or more peer-reviewed publication(s) or manuscripts under review. This level of productivity compares favorably to a recent study that found only 29% of completed clinical trials conducted at academic medical centers were published within two years of study completion (30). Four investigators have submitted or are in the process of submitting funding applications for additional investigation of their NTI-funded research questions. Two PIs have received \$500,000 each for further investigation through the Congressionally Directed Medical Research Program's (CDMRP) Joint Warfighter Medical Research Program. Twelve of the PIs (80%) reported training junior researchers, residents, fellows or students in the conduct of their study. Moreover, the completed and ongoing studies have been productive with respect to scholarly contribution, obtaining additional research funding and training investigators.

DISCUSSION

This manuscript describes the first two funding cycles of DoD funded trauma studies coordinated by the National Trauma Institute. Study management data and NTI Science Committee minutes were combined with PI interviews regarding regulatory review, accrual, multi-site and financial management, and productivity to date. Lessons learned in the conduct of these 16 studies are instructive to trauma researchers in four key areas: regulatory processes, multi-site coordination, adequate funding and the importance of an established research infrastructure to ensure study success.

First, investigators should anticipate an extended lead-time for institutional approval, particularly for studies with multiple local IRBs and/or external review by entities such as HRPO or with exemption from informed consent (EFIC). The IRB submission and review process took an average of 210 days, or roughly seven months (for the studies that didn't have approval at the

time of selection). This is similar to the time to IRB approval reported by the Resuscitation Outcomes Consortium (ROC) (median of 10.5 months), which had similar regulatory challenges with informed consent and EFIC in the emergency setting (31). Other multi-site studies have reported timelines of up to a year to obtain approval (32-34). Due to the novel funding mechanisms of these studies, there were significant delays between the date the proposals were selected for funding and the issuance of the prime funding contract to NTI (232 days and 321 days). This contracting process resulted in some studies going back to their local IRBs with revisions required by HRPO, which added to the overall lead time. To minimize further amendments at the local IRB level, consent language and protocol stipulations required by the funding source should be incorporated into the initial IRB submission. Funding sites, program officers or coordinating centers may provide toolkits or other guides (e.g.,

https://mrmc.amedd.army.mil/index.cfm?pageid=Research_Protections.orpToolkit.getTools).

For multi-site emergency research studies with more than minimal risk, development of a centralized IRB may be more efficient than managing approval from multiple IRBs. Although not a panacea for all regulatory challenges, they may improve review processes for emergency care research by providing expertise, reducing variability inherent in multi-site review and reducing redundancy (35). Additional new approaches with collaborative efforts from investigators, IRBs and funding sources are needed to overcome the regulatory challenges (35). The newly formed Coalition for National Trauma Research (CNTR) could encourage the use of centralized IRB models or other novel approaches within clinical trial networks (at

<http://coalitionntr.org>).

Second, managing multi-site protocols requires a high level of PI diligence during site selection, institutional approval and contracting processes and participant accrual. Lead PIs of

the multi-center studies stressed the need to assess whether the supporting sites have adequate eligible patient populations, research infrastructure and an understanding of what resources will be required to meet study enrollment goals at the outset. The observed site attrition supports the need for thorough discussion with investigators at each site regarding requirements and commitment at the time of application; review of study budget, funding and infrastructure at each site; and ongoing site visits or teleconferences to monitor study progress. Lead PIs can use a web-based questionnaire in the pre-trial phase to assess prospective sites' patient populations, research team expertise and barriers and facilitators of accrual (36). Another strategy is to establish a study coordinating center that oversees and assists with administrative and research processes across all sites.

Third, successful study management is highly dependent on adequate study budgeting for staff efforts. Alternatively, sites may leverage institutional funding (e.g., departmental start-up or hospital funding) to achieve required staffing levels. This is an important consideration for the staff costs involved in securing IRB approval, particularly when community consultation is required for a waiver of informed consent, if these costs will be incurred as a pre-condition for funding. Given the amount of PI attention required, it is also imperative that PIs'/Co-Is' effort is included in the budget. Otherwise, clinical productivity or other revenue generating expectations may not be adjusted to allow for research time. Most studies will require at least 10% of a full-time equivalent or 4 hours/week of a PI's time. Clearly, adequate budgeting must be supported by sustained federal funding for a national trauma clinical research program.

Finally, studies were most successful in institutions with an established research infrastructure. Research resources should be assessed as part of the review process for funding selection. Components of a well-developed infrastructure include experienced research

coordinators or nurses, ability to staff 24 hours per day or at least during key recruitment times, an electronic data collection system, biostatistical collaboration, and a research administrator (37). Support of research residents or fellows to assist with subject enrollment, study management and manuscript preparation is also important. At the academic department level, there should be alignment between the investigators' research objectives and department management regarding signature research areas and expectations for protected time. At the institutional level, IRBs, Hospital Research Management and Offices of Sponsored Programs that are supportive of research and provide timely responses to investigators are also critical. Research resources and infrastructure will be a selection criterion for future NTI funded projects.

In summary, the challenges encountered on the NTI studies can be categorized as either institutional/process-related or investigator-related. Institution-related challenges include human subjects review, funding for pre-award activities such as community consultation, data sharing restrictions and availability of translation services for non-English speaking participants and family members, and adequate funding at a national level to conduct several high impact, well-powered clinical trials at multiple trauma centers. Investigator-related challenges include inaccurate estimates of numbers of eligible patients, underestimation of staffing requirements in the study budget and site attrition among multi-site studies. Table 4 presents challenges along with recommendations for proactively managing them.

Limitations

The experiences drawn from this group of 16 studies and the NTI Science Committee and may not be representative of study management in all settings. Therefore, the generalizability of

these observations is somewhat limited. Additionally, the PIs were interviewed during a seven-month period when they were at varying stages in the research process. Their perspectives on the barriers and facilitators may have been affected by where they were in the research process. Also, the study management data were reviewed retrospectively, and some data points were equivocal or missing. Finally, there may be other variables that impact the research process that were not considered or were overlooked by the PIs.

Next steps

Advances in trauma care have markedly reduced trauma-related deaths and complications (38). The initial NTI experience demonstrates the existence of a large number of potential investigators, and that investment in these investigators' projects leads to productive scholarly output. Investigators should plan for institutional hurdles, judiciously select and actively manage multi-site studies and ensure that studies are adequately funded to achieve recruitment targets. DoD may wish to evaluate current practices and timeliness as well. In the amount of time it takes for a research idea to produce a study finding, many individuals will suffer morbidity and mortality; thus, any processes that can be streamlined stand to benefit those citizens and soldiers most in need of this research information. As available research funding shrinks and federal budget pressure increases, it is essential that the return from dollars invested in research be maximized by the timely initiation of well-planned and productive research protocols.

Nationally, a unified, stronger voice to advocate for additional trauma research funding and supporting infrastructure is required. The Coalition for National Trauma Research (CNTR) was formed in 2015 with member organizations of the AAST, EAST, WTA, the ACS COT and NTI to advocate for a national trauma research agenda, a robust infrastructure to support a Trauma

Clinical Trials Network, and additional, sustained federal funding for clinical trials (39). In 2015 CNTR held its first Trauma Research Advocacy Day in Washington, D. C., with 40 trauma surgeons visiting key Congressional offices. This resulted in the addition of \$10 million to the FY 2016 DoD budget, specifically for a National Trauma Clinical Trials Network. CNTR returned to Washington D. C. in 2016 to request additional funding for the research network in the 2017 federal budget. Reducing the burden of injury through clinical trials will require sustained federal funding at a level commensurate with the problem.

AUTHORS CONTRIBUTION

T.C.F., D.H.J., G.J.J, M.M.K., M.A.P., B.A.P., S.L.S. and R.M.S. designed this study. M.A.P. conducted the literature search. K.E.O. and M.A.P. contributed to data collection and performed statistical analyses. M.A.P., K.E.O. and S.L.S. analyzed and interpreted the data. M.A.P. and S.L.S. wrote the manuscript. All authors participated in critical revision.

DISCLOSURE

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TABLES

Table 1: Summary of Studies Funded through the National Trauma Institute

Study	Study Type	Award	# of sites
1	Randomized Clinical Trial	\$125,000	1
2	Prospective Observational	\$190,000	6
3	Prospective Observational	\$230,000	4
4	Healthy Volunteer	\$200,000	1
5	Randomized Clinical Trial	\$180,000	2
6	Prospective Observational	\$225,000	6
7	Prospective Cohort	\$224,950	3
8	Prospective Observational	\$299,422	11
9	Randomized Clinical Trial	\$295,172	6
10	Prospective Observational	\$235,000	1
11	Randomized Clinical Trial	\$188,541	4
12	Prospective Cohort	\$154,109	1
13	Retrospective Review	\$225,000	4
14	Randomized Clinical Trial	\$130,500	1
15	Randomized Clinical Trial	\$675,761	3
16	Randomized Clinical Trial	\$300,000	1

Table 2: Clinical Trials Registered on Clinicaltrials.gov

Identifier	Protocol Title
NCT00990236	Thrombelastography based dosing of enoxaparin for thromboprophylaxis: A prospective randomized trial
NCT01180894	A multi-center, randomized, double-blind comparison of intravenous iron supplementation to placebo for anemia of traumatic critical illness
NCT01580267	Hepcidin and anemia in trauma
NCT01611935	Arginine vasopressin during the early resuscitation of traumatic shock
NCT01810276	The safety and efficacy of platelet transfusion in patients receiving antiplatelet therapy that sustain intracranial hemorrhage
NCT01820455	Methicillin-resistant staphylococcus aureus in a trauma population: Does decolonization prevent infection?
NCT01897792	Effects of antioxidant vitamins on coagulopathy and nosocomial pneumonia after severe trauma
NCT01901354	Acute lung injury ventilation (ALIVE) trial
NCT01989273	Detection and management of non-compressible hemorrhage by vena cava ultrasonography

Table 3: Study Progression – measured in calendar days

Study	Study Type	Selection to IRB Approval	IRB Approval to DoD HRPO Approval	DoD HRPO Approval to Enrollment	NTI Prime Contract to Site Enrollment	Enrollment & Data Collection
1	RCT	537	424	133	950	Ongoing
2	PO	*	**	0	125	693
3	PO	*	**	194	242	751
4	HV	*	**	280	437	105
5	RCT	128	220	115	226	673
6	PO	76	92	8	29	686
7	PC	51	234	0	138	943
8	PO	*	**	88	40	382
9	RCT	155	779	7	704	140
10	PO	88	67	116	128	794
11	RCT	248	115	30	246	829
12	PO	307	111	30	211	688
13	RR	*	**	NA	NA	NA
14	RCT	173	249	68	253	381
15	RCT	*	**	141	482	828
16	RCT	332	222	276	593	104
	Mean Days	210	251	99	320	571
	Minimum	51	67	0	29	104
	Maximum	537	779	280	950	943
	Standard Deviation	142	221	91	254	280

IRB: Institutional Review Board; DoD HRPO: Department of Defense Human Research Protection Office; HV: Healthy Volunteer; PC: Prospective Cohort; PO: Prospective Observational; RCT: Randomized Clinical Trial; RR: Retrospective Review; NA: Not Applicable; *Denotes studies that had IRB approval at the time of selection notification; **Unknown

Table 4: Summary of Institution- and Investigator-Related Challenges and Recommendations

Institution- or Process-Related Challenges	Recommendations
1. Multiple human subject review processes at two or more levels (IRB & HRPO)	Incorporate required IRB and HRPO language in protocol and consent documents in first submission to IRB; Academic departments should facilitate IRB application submissions. IRB approval should be obtained prior to submission of the funding application.
2. Completing community consultation process prior to the grant award	Identify funding from alternate source (e.g., departmental start-up or bridge funds) if funding is not provided by granting institution. Community consultation should be completed prior to submission of funding application.
3. Data sharing restrictions between trauma centers	Determine the potential for data sharing prior to including investigative sites in proposal
4. Adequacy of translation services for non-English speaking patients	Explore using translation services available through hospital when research staff are not able to translate
Investigator-Related Challenges	Recommendations
1. Inadequate assessment of eligible patient density	Require that the PI document study patient accessibility and report recruitment success in clinical studies completed at the hospital over the past three years.
2. Underestimation of PI effort, personnel and other study costs	Application budgets should accurately include PI effort, staff and other costs at all sites. PIs should also document adequate research infrastructure and institutional support.
3. Site attrition among multi-site studies	Thorough assessment of site capacity and study requirements (by each site PI) should be completed at the time of site enrollment during the application process. PIs and funding organizations should establish quarterly progress goals and require explanation of failure to meet goals in quarterly progress reports.

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ACCEPTED