

AWARD NUMBER: W81XWH-14-1-0112

TITLE: Hemorrhage control for major traumatic vascular injuries

PRINCIPAL INVESTIGATOR: Laura J. Moore, MD

CONTRACTING ORGANIZATION: The University of Texas Health Science Center at Houston
Houston, TX 77225

REPORT DATE: October 2018

TYPE OF REPORT: Annual Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

1. REPORT DATE October 2018		2. REPORT TYPE Annual		3. DATES COVERED 15 Sep 2017 – 14 Sep 2018	
4. TITLE AND SUBTITLE Hemorrhage control for major traumatic vascular injuries				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-14-1-0112	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Laura J. Moore, M.D. E-Mail: laura.j.moore@uth.tmc.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The University of Texas Health Science Center at Houston 7000 Fannin Street Houston, TX 77030-5400				8. PERFORMING ORGANIZATION REPORT	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT The objective of this proposed study is to systematically define the clinical and logistical issues surrounding traditional open vascular surgery and catheter-based hemorrhage control. The hypothesis is that minimally invasive, device-driven and expert-led NCTH control techniques improve survival compared to traditional open vascular surgery. This project will achieve the following aims: 1) Determine current practice patterns for the treatment of patients with NCTH among 4 clinical sites using a retrospective study design (Phase 1a); 2) Conduct a 2-day Delphi Panel meeting of military and civilian experts to gain consensus regarding anatomic, technology, credentialing, competency, and training issues for catheter-based hemorrhage control (Phase 1b); 3) Conduct a prospective 4-site observational study to test the hypothesis that less-invasive device-driven and expert-led hemorrhage control techniques are associated with improved survival in NCTH patients and strengthen the evidence base to inform future development of catheters, devices, and training required for surgeons for catheter-based hemorrhage control (Phase 2). At the end of Y4, enrollment and data cleaning in the prospective study has been completed, and analysis has been initiated for the 318 enrolled and eligible. We have requested an EWOFF to use remaining funds for further analysis.					
15. SUBJECT TERMS Trauma, vascular, hemorrhage, Non-compressible Torso Hemorrhage, coagulation, mortality					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Unclassified	18. NUMBER OF PAGES 29	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified			19b. TELEPHONE NUMBER (include area code)

Table of Contents

	<u>Page</u>
1. Introduction.....	4
2. Keywords.....	5
3. Accomplishments.....	6
4. Impact.....	19
5. Changes/Problems.....	20
6. Products.....	21
7. Participants & Other Collaborating Organizations.....	22
8. Special Reporting Requirements.....	27
9. Appendices.....	28

INTRODUCTION

On September 15, 2014, the U.S. Army Medical Research Acquisition Activity (USAMRAA) awarded a 2-year contract to the University of Texas Health Science Center at Houston (UTHealth). This 2-phase project will systematically define the clinical and logistical issues surrounding traditional open vascular surgery and catheter-based hemorrhage control for non-compressible torso hemorrhage (NCTH). The hypothesis is that minimally invasive, device-driven and expert-led NCTH control techniques improve survival compared to traditional open vascular surgery. In addition to UTHealth, Baylor College of Medicine, the University of Texas Health Science Center at San Antonio (UTHSCSA) and the San Antonio Military Medical Center (SAMMC)/US Army Institute of Surgical Research (USAISR) collaborated.

KEYWORDS

Trauma, Vascular, Hemorrhage, Non-compressible Torso Hemorrhage, Coagulation, Mortality

ACCOMPLISHMENTS

What were the major goals of the project?

Goals/Milestones – Phase I

1. Obtain DOD HPRO and local institutional review board (IRB) approvals
2. Conduct retrospective data collection
3. Analysis of retrospective data
4. Hold Delphi Meeting

Goals/Milestones – Phase II

5. Obtain regulatory amendment approvals for prospective study
6. Conduct prospective observational study
7. Data Analysis/Publications

What was accomplished under these goals?

Milestone 1: Obtain USAMRMC HRPO and participating sites' IRB approvals

Y1Q1 UT Houston IRB approval for the retrospective study was received 18-NOV-2014. We submitted the USAMRMC Human Research Protections Office (HRPO) application on 02-DEC-2014 for review and approval. We also sent the UTHealth IRB approval and study documents to participating sites to submit to their local IRB review and approval. Baylor College of Medicine (BCM) and the University of Texas Health Science Center at San Antonio (UTHSCSA) submitted their local IRB applications in Q1.

Y1Q2 USAMRMC HRPO approval for the retrospective study at the UTHealth site was obtained 23-JAN-2015. UTHSCSA obtained their local IRB approval on 12-MAR-2015. BCM also received local IRB approval on 10-APR-2015. San Antonio Military Medical Center (SAMMC) requested that their site be changed to the US Army Institute of Surgical Research (USAISR) because USAISR had more developed human subjects and contracting processes. USAISR submitted documents to their IRB in Q2.

Y1Q3 UTHSCSA received HRPO approval for the retrospective study on 27-MAR-2015 and BCM received HRPO approval on 20-APR-2015.

Y1Q4 USAISR received local IRB and HRPO approval on 22-JUN-2015. UTHealth received local IRB approval for their continuing review on 31-AUG-2015.

Y2Q1 UTHealth received HRPO continuing review acknowledgement for the retrospective study on 09-OCT-2015.

Y2Q2 BCM and UTHSCSA received continuing review approval for the retrospective study from their local IRBs on 19-JAN-2016 and 17-FEB-2016, respectively.

Y2Q3 UTHealth received approval for the retrospective study continuing review on 23-MAY-2016. UTHSCSA and BCM continuing review acknowledgments for the retrospective study were also received from HRPO on 04-APR-2016 and 22-MAR-2016, respectively. USAISR received IRB and HRPO approval and acknowledgement of continuing review on 18-JUN-2016.

Y2Q4 UTHealth received acknowledgement of continuing review for the retrospective study on 17-AUG-2016.

Y3Q1 BCM received continuing review approval for the retrospective study on 20-OCT-2016.

Y3Q2 UTHealth and USHSCSA received continuing review approval for the retrospective study on 17-FEB-2017 and 14-FEB-2017, respectively. HRPO continuing review acknowledgement for the BCM retrospective study was received 07-MAR-2017.

Y3Q3 UTHealth requested continuing review acknowledgement from HRPO for the retrospective study on 09-MAR-2017. HRPO continuing review acknowledgement for the UTHSCSA retrospective study was received 23-MAY-2017.

Y3Q4 USAISR received continuing review approval for the retrospective study on 20-June-2017.

Y4Q1 All regulatory approvals were up-to-date in Y4Q1.

Y4Q2 BCM and UTHealth received HRPO acknowledgment of continuing review for the retrospective study on 22-FEB-2018 and 09-MAR-2018, respectively. UTHSCSA received approval of continuing review on 15-FEB-2018.

Y4Q3 All regulatory approvals were up-to-date in Y4Q3.

Y4Q4 USAISR received continuing review approval for the retrospective study on approximately 20-June-2018, although they haven't sent us a copy of their approval to date. BCM sent in continuing review documents to HRPO this quarter. All other regulatory approvals were up-to-date in Y4Q4.

Milestone 2: Initiate retrospective data collection study.

Y1Q1 Before the UTHealth IRB submission, we had a series of internal meetings as well as phone calls and emails with external investigators to discuss, revise, and finalize the protocol and case report forms for the retrospective study. The protocol and case report forms were finalized as of 15-NOV-2014. We also submitted information and study documents to UTHealth's Sponsored Projects Administration in order to begin drafting of the subcontracts for the three external sites as the next step to initiating data collection.

Y1Q2 The subcontracts with the three sites were drafted by UTHealth's Sponsored Projects Administration and sent to the three external sites as the first step to initiating data collection. The subcontracts were sent to the sites on 07-JAN-2015. Contract negotiation has taken longer than expected and at the end of Y1Q2, all three subcontracts were not yet executed. USAISR has requested a Cooperative Research and Development Agreement (CRADA) and a Data Use Agreement (DUA) for this study instead of the standard Federal Demonstration Partnership (FDP) contract we use for all other sites and projects. We expect that the contracts for BCM and UTHSCSA will be executed in early Q3. Because we have not received approval from the GOR

for the change in PI for USAISR, we cannot move forward with the CRADA; however, the DUA can move forward. We have developed a REDCap application for the Phase 1 retrospective study, including a data dictionary, codebook and data entry forms. We are finalizing this database application. Once completed, UTHealth will start entering data into the application.

Y1Q3 UTHealth, UTHSCSA and BCM have begun the trauma registry query and retrospective data review. We received approval from the GOR for the change in PI and research site to USAISR. Contract negotiations continue with USAISR because they are using a Cooperative Research and Development Agreement (CRADA) instead of the standard Federal Demonstration Partnership (FDP) contract we developed for all sites. The Data Use Agreement (DUA) that ISR also required has been executed by both parties. The Program Manager at USISR contacted UTHealth on 25-June-2015 to request additional documents be sent to the Contract Officer at USAMRAA in order for the change in site to take effect. UTHealth sent the documents to her on 29-JUNE-2015. The REDCap application has been finalized and data entry into the system has begun.

Y1Q4 UTHealth requested a status update from the Contract Office at USAMRAA on 13-July-2015, and a response was received on 22-JULY-2015 stating that a modification was being prepared to change the study site. We received a request for additional documents on 08-OCT-2015 from USAMRAA.

Y2Q1 UTHealth, UTHSCSA and BCM completed trauma registry query and retrospective data review and data entry in Y2Q1. 239 patients from UTHealth, 189 from BCM, and 208 from UTHSCSA were enrolled. The Cooperative Research and Development Agreement (CRADA) between UTHealth and USAISR was also fully executed in Y2Q1. USAISR entered registry information on all of their eligible patients (N=51) and are continuing to enter additional detailed data from the medical record abstraction.

Y2Q2 USAISR completed retrospective study data entry in Y2Q2. A total of 683 for the four sites were therefore available for analysis. This number was considerably less than the expected total for enrollment (n=3500) due to the operationalization of the eligibility criteria. The eligibility criteria from both the proposal and the IRB-approved protocol were:

Inclusion Criteria

To be eligible, subjects must meet all of the following:

- 1) Has NCTH defined as
 - a. Named axial torso vessel disruption
 - b. Solid organ injury with AIS \geq 4 (liver, kidney, or spleen) plus concomitant shock or immediate operation
 - c. Thoracic cavity injury (including lung)
 - d. Pelvic fracture with ring disruption
- 2) Estimated age of 15 years or older or greater than/equal to weight of 50 kg if age unknown
- 3) Admitted to one of four participating Level 1 trauma centers

Exclusion Criteria

Subjects will be excluded if they meet one or more of the following:

- 1) Patients who are <15 years old or under 50 kg body weight if age unknown
- 2) Known pregnancy reported by EMS personnel
- 3) Isolated hip fractures
- 4) Injury resulting from a fall from standing

For the original submitted grant proposal, we received data from all 4 sites in order to estimate the potential number of patients we would be able to enroll in the retrospective using these inclusion and exclusion criteria. Using these criteria only, we estimated that we would enroll 3500 patients. However, in order to operationalize these criteria for the retrospective study using site trauma registries to identify appropriate patients and to get detailed information regarding the specific vessels of interest, the following rules were used at all 4 sites:

- a. Run the following inclusions/exclusions first:
 - i. Inclusions:
 1. Age 15 or older
 2. Admitted
 3. Time of injury < 12 hours from admission
 - a. Not all of our patients have a time of injury in the registry, so we also used the date/time of EMS notification to try to catch any of those patients
 - ii. Exclusions:
 1. Prisoners
 2. Isolated hip fractures
 3. Injury resulting from a fall from standing (< 6 feet)
 4. Prisoners, defined as those who have been directly admitted from a correctional facility
- b. Use that data set to separately find the patients with abdominal, thoracic, and pelvic injuries
 - i. Abdominal
 1. We searched for patients with AIS ≥ 3 plus base deficit > 4
 2. We searched for patients with AIS ≥ 3 plus immediate operation (limited it to patients that went directly from the ER to the OR within 90 minutes of arrival)
 3. We then combined those two lists
 - ii. Thoracic
 1. We searched for patients with AIS ≥ 3 plus base deficit > 4
 2. We searched for patients with AIS ≥ 3 plus immediate operation (limited it to patients that went directly from the ER to the OR within 90 minutes of arrival)
 3. We then combined those two lists
 - iii. Pelvic
 1. We searched for patients with AIS05 codes equal to: 856161.3, 856162.4, 856163.4, 856164.5, 856171.4, 856172.4, 856173.5, or 856174.5
 - iv. Combine the above 3 lists (abdominal, thoracic, and pelvic)

- c. Use that data set to separately find the patients with named axial torso vessel disruption using both AIS codes and ICD9 codes (to try to find as many as possible)
 - i. AIS codes
 - 1. Thoracic arteries: 420206.4, 420208.4, 420210.5, 420216.5, 420218.6, 420404.3, 420406.3, 420408.4, 421004.3, 421006.3, 421008.5, 421009.6, 421404.3, 421406.3, 421408.4, 422004.2, 422006.2, 422008.3
 - 2. Thoracic veins: 420602.3, 420604.3, 420606.4, 420608.5, 421202.3, 421204.3, 421206.5, 421207.6, 421602.3, 421604.3, 421606.4, 421802.3, 421804.3, 421806.4, 421808.5, 422202.2, 422204.2, 422206.3
 - 3. Abdominal arteries: 520204.4, 520206.4, 520208.5, 520404.3, 520406.4, 520408.5, 520604.3, 520606.3, 520608.4, 521104.3, 521106.3, 521108.4, 521404.3, 521406.3, 521408.4, 541828.5
 - 4. Abdominal veins: 520802.3, 520804.3, 520806.4, 521002.2, 521004.2, 521006.3, 521202.3, 521204.3, 521206.4, 521602.3, 521604.3, 521606.4
 - 5. Common carotid arteries: 320206.3, 320208.3, 320209.3, 320210.4, 320211.4, 320212.4, 320213.4, 320214.5, 320215.5, 320216.3, 320217.3, 320218.4, 320219.4
 - ii. ICD9 codes
 - 1. Thorax: 901.0, 901.1, 901.2, 901.3, 901.41, 901.42
 - 2. Abdomen: 902.0, 902.10, 902.20, 902.22, 902.23, 902.25, 902.31, 902.33, 902.41, 902.42, 902.53, 902.54
 - 3. Common carotid: 900.01
 - iii. Combine the AIS and ICD9 lists and produced our final patient list.

Using these rules to generate the sampling frame for patients, further exclusions were made if no specifically-named vessels were reported in the medical record. In the prospective study, we will be able to include solid organ injuries as well as vessel injuries.

Y2Q3 We initiated a study of CT data for vascular injuries in order to begin collecting data for questions we had originally planned to address in the prospective study. This substudy uses data only from UTHealth, where we have adequate image storage capabilities, and is approved under the retrospective study UTHealth IRB and HRPO approvals. The plan for this substudy is to accurately quantify the applicable vascular morphometry of the human torso, which can be done with images previously stored during the retrospective study. For the scan-based measurements, standard imaging software is used to measure diameter and length of the torso vessels and relative distances between major aortic branch vessels as related to aortic zones defined by Stannard, et al. We are also including a CT measurement component in the prospective study at UTHealth to continue this work.

Y2Q4 Data collection, entry and cleaning for the substudy of CT images for vascular injuries was largely completed in Y2Q4. One more field for 100 patients remains to be entered and will be completed in Y3Q1. We also negotiated Data Use Agreements (DUAs) with Madigan Army

Medical Center (PI: COL Matthew Martin) and with Denver Health Medical Center (PI: Charles Fox) for their use of the retrospective study data. Both were executed early in Y3Q1.

Y3Q1 The retrospective study was completed as described in the SOW in Y2Q2. Data for the additional CT measurement substudy was completed in this quarter for a training set of data to predict catheter insertion length using external measurements and patient data such as sex, height, weight and body mass index (BMI). We performed a preliminary analysis of the data and identified likely algorithms to predict appropriate insertion to Zones I and III. The developed algorithm will be tested on data from an additional 100 patients that are now being collected. We also executed a Data Use Agreements (DUA) with Madigan Army Medical Center (PI: COL Matthew Martin) for use of the retrospective study data on 26-SEP-2016.

Y3Q2 We performed a preliminary analysis of the CT measurement substudy data and identified likely algorithms to predict appropriate insertion to Zones I and III. We continued to collect data from an additional 100 patients in order to validate the algorithm and expected to complete this additional data collection in early Y3Q3.

Y3Q3 We completed data collection from the additional 100 patients in Y3Q3 and are currently validating the algorithm for the final development of the nonogram which we plan to copyright.

Y3Q4 We have completed data analysis for the CT measurement substudy and the manuscript is currently under development.

Y4Q1 Milestone complete, nothing to report

Y4Q2 Milestone complete, nothing to report

Y4Q3 Milestone complete, nothing to report

Y4Q4 Milestone complete, nothing to report

Milestone 3: Analysis of retrospective data

Y2Q1 We identified a Co-Investigator Statistician, Stacia DeSantis, PhD, who worked on preliminary statistical analysis code and programs. She obtained access to the dataset, the data dictionary, the protocol, and updated the statistical plan with assistance from a statistical programmer (T. Jay Greene, MS).

Y2Q2 Data analysis for the Delphi Meeting was completed during this quarter. Additional analysis was undertaken during this quarter as a result of suggestions made at the Delphi Meeting. These analyses will be reported in an upcoming manuscript. Additionally, all attendees of the Delphi Meeting were offered the opportunity to analyze the retrospective data. We are currently working with these external institutions and negotiating Data Use Agreements (DUAs) with them. Our goal is that additional manuscripts and/or abstracts will be submitted as a result of sharing these important data.

Y2Q3 The additional analyses initiated last quarter are ongoing. These analyses will be reported in an upcoming manuscript. Two external institutions (Madigan Army Medical Center and Denver Health Medical Center) requested the retrospective data for their own analysis. The UTHealth Sponsored Projects office completed the draft of the Data Use Agreement, which was sent to the two institutions for negotiation and execution in June 2016.

Y2Q4 We submitted an abstract of the retrospective study to the Eastern Association for the Surgery of Trauma (EAST) Annual Meeting and it was accepted for an oral presentation at the meeting in January. We also drafted a manuscript for the main results of the retrospective study during Y2Q4 and it will be finalized in Y3Q1. Negotiation of the two DUAs continued this quarter.

Y3Q1 The main results manuscript for the retrospective study was finalized and submitted for review during this quarter.

Y3Q2 The main results manuscript for the retrospective study was presented at EAST and is under review at the *Journal of Trauma and Acute Care Surgery*. COL Matthew Martin of Madigan Army Medical Center continued to work on a secondary analysis that hypothesizes that the FAST exam has a high false negative rate when used in the evaluation of NCTH patients. The DUA with Denver Health Medical Center (PI: Charles Fox) was partially executed by UTHealth and awaiting full execution by Denver.

Y3Q3 The main results manuscript for the retrospective study was accepted at the *Journal of Trauma and Acute Care Surgery* on 1-APR-2017. COL Matthew Martin of Madigan Army Medical Center continued to work on a secondary analysis that hypothesizes that the FAST exam has a high false negative rate when used in the evaluation of NCTH patients. The DUA with Denver Health Medical Center (PI: Charles Fox) was fully executed.

Y3Q4 Retrospective data were sent to Denver Health Medical Center on 30-JUN-2017. The main results manuscript for the retrospective study was published in the July edition of the *Journal of Trauma and Acute Care Surgery*. COL Matthew Martin of Madigan Army Medical Center submitted his secondary analysis that hypothesizing that the FAST exam has a high false negative rate when used in the evaluation of NCTH patients to EAST on 1-JUL-2017. Copies of the published manuscript and submitted abstract can be found in Appendix 2.

Y4Q1 The main results manuscript for the retrospective study was accepted at the *Journal of Trauma and Acute Care Surgery* on 1-APR-2017. It will be published in the July edition of the journal.

COL Matthew Martin of Madigan Army Medical Center is continuing to work on a secondary analysis that hypothesizes that the FAST exam has a high false negative rate when used in the evaluation of NCTH patients. The DUA with Denver Health Medical Center (PI: Charles Fox) was fully executed and the data will be sent to Denver in early Y4Q1.

For the CT measurement substudy, we are currently validating the algorithm for the final development of the nonogram which we plan to copyright.

Y4Q2 COL Matthew Martin of Madigan Army Medical Center has access to the retrospective data and continues to perform analysis. Charles Fox, MD, from Denver Health Medical Center is also actively analyzing the retrospective data

A manuscript for the additional CT measurement substudy to predict catheter insertion length using external measurements and patient data such as sex, height, weight and body mass index (BMI) has been under development. Unfortunately, the interpretation of these data has hit a snag because the algorithm to predict catheter insertion length is giving biologically implausible results. Therefore, we are reluctant to publish a manuscript on the algorithm and are having difficulty revising the algorithm because the data are retrospective and confirmatory variables such as actual insertion length are not available. We are not likely to pursue this manuscript any longer, however, higher quality prospective data including actual insertion length are available with the completion of the prospective study in Phase II of this project. Those data do include insertion length, so we will have a gold standard comparison for any algorithm.

Y3Q3 COL Matthew Martin of Madigan Army Medical Center has access to the retrospective data and continues to perform analysis. Charles Fox, MD, from Denver Health Medical Center is also actively analyzing the retrospective data

Y4Q4 Milestone complete. COL Martin and Dr. Fox currently have retrospective data and may pursue other analyses if they desire.

Milestone 4: Hold Delphi Meeting

Y2Q1 We updated the list of 20 potential Delphi Panel meeting attendees and received input on additional potential attendees from Col. Todd Rasmussen, an expert in non-compressible torso hemorrhage

Y2Q2 The Delphi Panel Meeting was held on March 7, 2016 at the University of Texas Health Science Center at Houston. A total of 27 people attended the meeting. Attendees included the site investigators and coordinators, trauma and vascular surgeons from civilian and military institutions, and the Houston Data Coordinating Center. The group reviewed the results of the retrospective study and provided input for the upcoming Phase II prospective, observational study. See the Y2Q2 report for the agenda and review of retrospective data used at the Delphi Meeting, notes from the meeting, and a list and picture of participants.

Y2Q3 Milestone complete, nothing to report

Y2Q4 Milestone complete, nothing to report

Y3Q1 Milestone complete, nothing to report

Y3Q2 Milestone complete, nothing to report

Y3Q3 Milestone complete, nothing to report

Y3Q4 Milestone complete, nothing to report

Y4Q1 Milestone complete, nothing to report

Y4Q2 Milestone complete, nothing to report

Y4Q3 Milestone complete, nothing to report

Y4Q4 Milestone complete, nothing to report

Milestone 5: Obtain regulatory amendment approvals for prospective study

Y2Q2 We refined a draft of the prospective study protocol based on recommendations and comments at the Delphi Meeting.

Y2Q3 We finalized the Phase II prospective protocol with the other site PIs and staff. The protocol was submitted to the UTHealth IRB on 27-MAY-2016.

Y2Q4 UTHealth received IRB approval on 20-JUL-2016. BCM submitted the protocol to their IRB during Y2Q4. Approval for BCM was received 21-SEP-2016. UTHSCSA applied for IRB reciprocity during this quarter and received approval from the UTHealth IRB on 12-SEP-2016. UTHealth and UTHSCSA submitted their approval documents to HRPO for review. USAISR prepared their documents for submission to the MRMC IRB/HRPO.

Y3Q1 UTHealth and UTHSCSA received HRPO approval for the prospective study on 05-OCT-2016. UTHSCSA used reciprocity and therefore received approval from UTHealth's IRB. BCM received Harris Health System approval on 21-SEPT-2016 (local BCM approval occurred on 17-AUG-2016), and HRPO approval was received on 17-OCT-2016 for the prospective study.

Y3Q2 UTHealth submitted a continuing review application to their local IRB this quarter. USAISR submitted to HRPO for initial review and approval at their site for the prospective study on 17-MAR-2017.

Y3Q3 UTHealth and UTHSCSA received continuing review approval from UTHealth's local IRB this quarter on 27-MAR-2017 and received HRPO acknowledgment on 12-JUN-2017. UTHealth also changed the PI from Dr. Holcomb to Dr. Moore and received approval for the change from the local IRB on 22-MAY-2017. The PI change was acknowledged by HRPO in the 12-JUN-2017 document.

Y3Q4 USAISR received initial local IRB and HRPO approval for the prospective study on 29-JUN-2017.

Y4Q1 All regulatory approvals for the prospective study were up-to-date in Y4Q1

Y4Q2 UTHealth and UTHSCSA (via reciprocity) received continuing review approval for the prospective study on 26-JAN-2018. All other regulatory approvals for the prospective study were up-to-date in Y4Q2

Y4Q3 All regulatory approvals for the prospective study were up-to-date in Y4Q3.

Y4Q4 BCM submitted a continuing review application to their local IRB for the prospective study this quarter. USAISR received continuing review approval on approximately 29-JUN-2018, but have not yet sent UTHealth a copy as of the date of this report. All other regulatory approvals are up-to-date.

Milestone 6: Conduct prospective observational study

Y2Q4 We drafted modifications of subawards for BCM and UTHSCSA to extend the date of contract and add the Phase II funds. Both contracts have been executed (BCM on 29-SEP-2016 and UTHSCSA on 30-SEP-2016). We are negotiating a CRADA modification with USAISR for the change in PI from LTC Kevin Chung to LTC Jennifer Gurney. It was signed by UTHealth on 20-SEPT-2016 and we are awaiting signature and full execution by USAISR. In preparation of study initiation, we developed a draft of the Manual of Operations and have circulated it to the 3 external sites for review and comment. We expect to enroll patients in Y3Q1.

Y3Q1 Modifications of subawards for BCM and UTHSCSA to extend the date of contract and add the Phase II funds were executed this quarter (BCM on 29-SEP-2016 and UTHSCSA on 30-SEP-2016). A CRADA modification with USAISR for the change in PI from LTC Kevin Chung to LTC Jennifer Gurney was executed on 27-JUL-2016. A second modification of the CRADA was initiated by USAISR during this quarter. The partially executed CRADA was returned to USAISR on 27-OCT-2016.

Training occurred at UTHealth, UTHSCSA and BCM during Y3Q1. Patient enrollment began at UTHealth on 07-NOV-2016 and 18 patients were enrolled by the end of Y3Q1. UTHSCSA is currently screening patients (started 12-DEC-2016), but had no enrollments by the end of Y3Q1.

Y3Q2 The second modification of the CRADA with USAISR was fully executed on 28-OCT-2016. At UTHealth, 125 patients were screened and 56 patients were enrolled by the end of Y3Q2. UTHSCSA screened 84 patients with 18 enrollments in total by the end of Y3Q2. BCM screened 17 patients and enrolled 7 by the end of Y3Q2.

Y3Q3 At UTHealth, 526 patients were screened and 108 patients were enrolled by the end of Y3Q3. UTHSCSA screened a total of 265 patients and 37 enrollments by the end of Y3Q3. BCM screened 40 patients in total with 15 patients enrolled by the end of Y3Q3. One hundred sixty patients were enrolled by the end of Y3Q3.

Y3Q4 Total screened and enrollment by site at the end of Y3Q4 is shown below.

Site	Screened	Enrolled
UTHealth	1094	153
UTHSCSA	265	37
BCM	144	36
USAISR	127	2
Total	1630	228

Y4Q1 Total enrollment by site at the end of Y4Q1 is shown below.

Site	Enrollment start date	Enrolled
UTHealth	07-NOV-2016	177
UTHSCSA	12-DEC-2016	75
BCM	30-JAN-2017	38
USAISR	27-JUL-2017	4
Total		294

Y4Q2 Enrollment is now complete for the prospective study. Three hundred eighteen total patients were enrolled. Enrollment for all sites ended on 31-JAN-2018 and the data coordinating center at UTHealth will complete major data cleaning by 30-APR-2018.

Site	Enrollment start date	Enrolled
UTHealth	07-NOV-2016	187
UTHSCSA	12-DEC-2016	88
BCM	30-JAN-2017	38
USAISR	27-JUL-2017	5
Total		318

Y4Q3 The data coordinating center at UTHealth is working with the sites on data queries and completing data cleaning. Data from BCM had a high level of missing information, so we spent a large amount of time working with them to get the data cleaned. Preliminary data analysis has begun.

Y4Q4 The team completed initial major data cleaning, developed dummy tables, and drafted five tables for a future publication on the descriptive epidemiology of non-compressible torso hemorrhage (NCTH). Milestone completed as the study has been conducted.

Milestone 7: Data Analysis/Publications

Y2Q2 We worked on finalizing data analyses and developing a manuscript for the retrospective study.

Y2Q3 We continued to work on finalizing data analyses and developing a manuscript for the retrospective study.

Y2Q4 We submitted an abstract of the retrospective study to the Eastern Association for the Surgery of Trauma (EAST) Annual Meeting on 01-JUL-2016 and it was accepted on 01-AUG-2016 for oral presentation at the meeting. We also drafted a manuscript for this presentation during Y2Q4.

Y3Q1 The main results manuscript for the retrospective study was finalized and submitted for review during this quarter.

Y3Q2 The main results manuscript for the retrospective study was presented at the Eastern Association for the Surgery of Trauma (EAST) Annual Meeting in January 2017. The

manuscript was revised and resubmitted for publication in the *Journal of Trauma and Acute Care Surgery* this quarter

Y3Q3 The main results manuscript for the retrospective study was accepted by the *Journal of Trauma and Acute Care Surgery* this quarter. Charles Wade, PhD, also attended the JPC-6/CCCRP FSERCC Portfolio In-Progress Review on 02-MAY-2017.

Y3Q4 The main results manuscript for the retrospective study was published in the July edition of the *Journal of Trauma and Acute Care Surgery*.

Chang R, Fox EE, Greene TJ, Eastridge BJ, Gilani R, Chung KK, DeSantis SM, DuBose JJ, Tomasek JS, Fortuna GR Jr, Sams VG, Todd SR, Podbielski JM, Wade CE, Holcomb JB; NCTH Study Group. Multicenter retrospective study of noncompressible torso hemorrhage: Anatomic locations of bleeding and comparison of endovascular versus open approach. *J Trauma Acute Care Surg.* 2017 Jul;83(1):11-18. doi:10.1097/TA.0000000000001530. PubMed PMID: 28632581; PubMed Central PMCID: PMC5484539.

Y4Q1 We are working to complete enrollment, data cleaning and analysis for the prospective study.

Y4Q2 We are working to complete data cleaning and analysis for the prospective study.

Y4Q3 We are working to complete data cleaning and analysis for the prospective study.

Y4Q4 The team completed initial major data cleaning, developed dummy tables, and drafted five tables for a future publication on the descriptive epidemiology of non-compressible torso hemorrhage (NCTH).

What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to communities of interest?

Nothing to report. Results will be disseminated at the end of the project and as publications and presentations are accepted.

What do you plan to do during the next reporting period to accomplish the goals?

Milestone 1: Obtain USAMRMC HRPO and participating sites' IRB approvals

During Y5 of the project, we will ensure that the sites continue to submit continuing review approvals for the retrospective study to their local IRBs and HRPO in order to continue data analysis and manuscript development. We will also ensure that any Delphi Meeting attendees who have signed DUAs in order to perform their own data analysis will maintain appropriate regulatory approvals.

Milestone 2: Initiate retrospective data collection study
Milestone complete.

Milestone 3: Analysis of retrospective data

Analysis of the retrospective data will continue for development of additional secondary manuscripts, especially by COL Matthew Martin and Dr. Charles Fox. We will check in with both investigators to encourage further analysis of the data.

Milestone 4: Hold Delphi Meeting

Milestone complete.

Milestone 5: Obtain regulatory amendment approvals for prospective study

During Y5 of the project, we will ensure that the sites submit continuing reviews for the prospective study to their local IRBs and HRPO in order to complete analyses for the study.

Milestone 6: Conduct prospective observational study

Milestone complete.

Milestone 7: Data Analysis/Publications

We expect to have a completed draft of the main manuscript for the prospective study by the end of Y5Q1. An extension of 12 months will allow the team to improve the main results manuscript, making it more likely to obtain publication; perform additional secondary analyses on topics such as 1) effectiveness of hemorrhage control treatment for NCTH and 2) predictors of mortality and complications after major vascular and solid organ injuries; prepare all analyses for publication as abstracts and/or manuscripts; and prepare and submit the final deidentified datasets to the National Trauma Research Repository (W81XWH-15-2-0089) maintained by the National Trauma Institute by the end of EWO3. Submitting project data to the NTRR will facilitate the publication of additional abstracts and manuscripts and increase the DoD's return on investment for this project.

IMPACT

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfers?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

CHANGES/PROBLEMS

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

We are awaiting a third one-year extension without funds to improve the main results analysis and pursue additional analyses, particularly using data from the prospective study.

Changes that had a significant impact on expenditures

Because of a later start than anticipated, sites spent their Phase I funding more slowly than expected and all remaining funds were rolled into Phase II. At UTHealth, we also decreased paid effort on the project between July and September 2016 while awaiting regulatory approvals in order to save remaining funding for the prospective study.

USAISR did not submit any invoices for the prospective study until late August 2018 and reported expenditures of only \$36,948.03. This amount is much lower than the \$175,943 that they budgeted, and resulted in \$137,869 available for EWOF3. This delay in expenditures can be classified as both government and recipient-caused.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

PRODUCTS

Publications, conference papers, and presentations

Manuscripts

Chang R, Fox EE, Greene TJ, Eastridge BJ, Gilani R, Chung KK, DeSantis SM, DuBose JJ, Tomasek TS, Fortuna GR, Sames VG, Todd SR, Podbielski JM, Wade CE, Holcomb JB and the NTCH Study Group. Multicenter retrospective study of non-compressible torso hemorrhage: anatomic locations of bleeding and comparison of endovascular versus open approach. *J Trauma Acute Care Surg.* 2017;83(1):11-18. PMID: 28632581. PMCID: PMC5484539.

Presentations

Chang R, Fox EE, Greene TJ, Eastridge BJ, Gilani R, Chung KK, DeSantis SM, DuBose JJ, Tomasek JS, Fortuna GR, Sams VG, Todd SR, Podbielski JM, Wade CE, Holcomb JB. Multicenter retrospective study of non-compressible torso hemorrhage: anatomic locations of bleeding and comparison of endovascular versus open approach. Eastern Association for the Surgery of Trauma, Hollywood, FL, January 2017.

Website(s) or other Internet site(s)

Nothing to report.

Technologies or techniques

Nothing to report

Inventions, patent applications, and/or licenses

Nothing to report

Other Products

Nothing to report

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Laura J. Moore, MD
Project Role: Principal Investigator
Nearest Person Months Worked: 1
Contribution to Project: Dr. Moore oversaw all aspects of study management and execution for both the retrospective and prospective studies starting April 1, 2017. She oversaw all study staff, regulatory submissions, patient screening, subject enrollment, and data collection. She actively communicated with all clinical sites for this study, coordinated administration across institutions and ensured accurate and timely data collection and transfer.
Funding Source: DOD W81XWH-14-1-0112

Name: Erin Fox, PhD
Project Role: Co-Investigator; Project Manager
Nearest Person Months Worked: 2
Contribution to Project: Dr. Fox oversees the day-to-day communication and overall study coordination for both the retrospective and prospective multisite studies. She ensures timely and accurate reporting, including financial and interim research reports. She participated in the creation of the data management system and the Manual of Operation, data cleaning and integration, and coordination of requested data to research investigators in the retrospective study and will perform similar duties in the prospective study. She coordinated the subcontracts and budgets for the research sites. Dr. Fox is also involved with the analysis of data, interpretation of results, and development of manuscripts for this project.
Funding Source: DOD W81XWH-14-1-0112

Name: Charles Wade, PhD
Project Role: Co-Investigator
Nearest Person Months Worked: 1
Contribution to Project: Dr. Wade participated in the creation of the data management system and the Manual of Operation, data cleaning and integration, and coordination of requested data to research investigators.
Funding Source: DOD W81XWH-14-1-0112

Name: Jeanette Podbielski, RN
Project Role: Clinical Program/Regulatory Director

Nearest Person Months Worked: 1
Contribution to Project: Ms. Podbielski managed all regulatory aspects of this study. She assisted with study coordination as well as IRB preparation and submission. She managed the activities of the Research Coordinator and Assistant. Ms. Podbielski is the main point of contact for the external sites for regulatory issues, patient enrollment, and data collection.
Funding Source: DOD W81XWH-14-1-0112

Name: Denise Hinds, RN
Project Role: Research Coordinator
Nearest Person Months Worked: 2
Contribution to Project: Ms. Hinds assisted with all aspects of study coordination, including the attainment and maintenance of all necessary regulatory approvals and guidelines as well as patient enrollment, data collection, data entry, and answering queries at the UTHealth site for the prospective study.
Funding Source: DOD W81XWH-14-1-0112

Name: Marc Dipasupil
Project Role: Research Assistant
Nearest Person Months Worked: 1
Contribution to Project: Mr. Dipasupil assisted in identifying eligible patients, performing data collection, and entering data at the UTHealth site in the prospective study.
Funding Source: DOD W81XWH-14-1-0112

Name: Kandice Motley
Project Role: Research Assistant
Nearest Person Months Worked: 3
Contribution to Project: Ms. Motley assisted in identifying eligible patients, performing data collection, and entering data at the UTHealth site in the prospective study.
Funding Source: DOD W81XWH-14-1-0112

Name: Christy Allen
Project Role: Research Assistant
Nearest Person Months Worked: 1
Contribution to Project: Ms. Allen assisted in identifying eligible patients, performing data collection, and entering data at the UTHealth site in the prospective study.
Funding Source: DOD W81XWH-14-1-0112

Name: Tamara Matthew
Project Role: Research Assistant
Nearest Person Months Worked: 1

Contribution to Project: Ms. Matthew assisted in identifying eligible patients, performing data collection, and entering data at the UTHealth site in the prospective study.

Funding Source: DOD W81XWH-14-1-0112

Name: Xu Xun

Project Role: Data Manager

Nearest Person Months Worked: 2

Contribution to Project: Ms. Xun was hired in December 2017 as a Data Manager for CeTIR and has worked on this project to assist with identifying data issues, as well as running queries for data cleaning and management for the prospective study.

Funding Source: DOD W81XWH-14-1-0112

Name: Carolyn Grimes, DrPH

Project Role: Grants and Contracts Specialist

Nearest Person Months Worked: 1

Contribution to Project: Dr. Grimes has been assisting with financial and contractual management of this study.

Funding Source: DOD W81XWH-14-1-0112

Name: Stacia DeSantis, PhD

Project Role: Co-Investigator (Statistician)

Nearest Person Months Worked: 1

Contribution to Project: Dr. DeSantis is the lead statistician for this project. She oversees all data management and analysis for both the retrospective and prospective studies.

Funding Source: DOD W81XWH-14-1-0112

Name: T. Jay Greene, MS

Project Role: Graduate Research Assistant (Statistical Programmer)

Nearest Person Months Worked: 1

Contribution to Project: Mr. Green acted as the statistical programmer for both the retrospective and prospective studies and was supervised by Dr. DeSantis. He left UT in November 2017.

Funding Source: DOD W81XWH-14-1-0112

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

We reported Dr. Moore's active other support last year, and her current support is as follows:

Title: FiO2 Closed Loop Control in the ZOLL 731 Series Ventilator
Time Commitment: 4%
Agency: University of Cincinnati/ZOLL Medical/USAF/AFMC, Jay Johannigman, MD
Agency POC: S. Theresa Yockey, University of Cincinnati, Sponsored Research Services, 51 Goodman Avenue, Suite 530, Cincinnati, OH 45221-0222; 513-556-4390
Performance Period: 05/2015-05/2018
Role: Principal Investigator
Level of Funding:
Goals: To demonstrate that physiologic closed-loop control (PCLC) is at least as safe and effective as manual control in keeping hemoglobin oxygen saturation (SpO₂) within the target range of 92-96%.

Title: Multicenter, Observational Clinical Study of the ER-REBOA Catheter
Time Commitment: 25%
Agency: Prytime Medical Devices, Inc./USAMMA/W911QY-15-C-0099
Agency POC: David Spencer, CEO, Prytime Medical Devices, Inc., 229 N. Main Street, Boerne, TX 78006; dspencer@prytimemedical.com
Performance Period: 04/2017-06/2018
Role: Principal Investigator
Level of Funding:
Goals: The purpose of this multicenter, prospective, observational study is to collect detailed information at selected Level 1 trauma centers currently utilizing the Prytime REBOA catheter as part of their standard clinical practice.

What other organizations were involved as partners?

Baylor College of Medicine
Houston, TX
Research collaborator

University of Texas Health Science Center at San Antonio
San Antonio, TX
Research collaborator

US Army Institute of Surgical Research
San Antonio, TX

Research collaborator

SPECIAL REPORTING REQUIREMENTS

Quad Chart uploaded as Appendix 1.

APPENDIX 1

Hemorrhage Control for Major Traumatic Vascular Injuries

EDMS: 5840 and Quad Chart for Year 4 Annual Report
W81XWH-14-1-0112



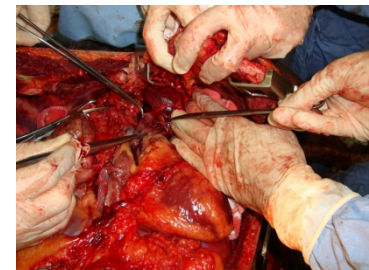
PI: Laura J. Moore, MD Org: University of Texas Health Science Center at Houston Award Amount: \$1,991,317

Study Aims

- Determine current practice patterns for the treatment of patients with non-compressible torso hemorrhage (NCTH) among 4 clinical sites using a retrospective study design;
- Conduct a 2-day Delphi Panel meeting of military and civilian experts to gain consensus regarding anatomic, technology, credentialing, competency, and training issues for catheter-based hemorrhage control and inform the development of the prospective study.
- Conduct a 4-site prospective observational study to test the hypothesis that less-invasive device-driven and expert-led hemorrhage control techniques improve survival in NCTH patients and definitively inform development of catheters, devices and training required for catheter-based hemorrhage control.

Approach

This is a 2-phase study which will include a retrospective study and Delphi Meeting in Phase I, then a prospective study in Phase II informed by the Phase I activities.



These pictures represent the care of the severely injured NCTH patient, which will be studied in this project.

Accomplishments this quarter: Phase II- Completed major data cleaning , drafted dummy tables for main results manuscript and continued data analysis. All regulatory approvals are current.

Timeline and Cost

Activities	Y1	Y2	Y3	Y4
Phase 1 milestones	→			
Obtain IRB approvals for prospective study		→		
Conduct prospective study			→	
Data analysis/ publication				→
Estimated Budget (\$K)	994	996	EWOFF 1	EWOFF 2

Goals/Milestones

CY14 -15 Goals – Phase I

- Obtain DoD HPRO and local IRB approvals
- Conduct retrospective data collection
- Analysis of retrospective data
- Hold Delphi Panel meeting

CY15-16 and EWOFF Goals – Phase II

- Obtain regulatory approvals for prospective study
- Conduct prospective observational study
- Data Analysis/Publications

Comments/Challenges/Issues/Concerns

- The prospective study has been completed and data analysis and manuscript development continues. There are no financial or scientific concerns.

Budget Expenditure to Date

Projected Expenditure: Y4Q4 \$0K; YTD \$0K; ITD \$1,991K
Estimated Actual Expenditure: Y4Q4: \$35K; YTD \$251K; ITD \$1,816K