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TITLE: Trauma Outcomes and UroGenital Health in OEF/OIF (TOUGH) - A Retrospective Cohort Study with Long-Term Follow-up

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INTRODUCTION

The goal of this study is to identify the characteristics of service members (SMs), their genitourinary injuries (GU), the care received for these injuries, and other factors that predict long-term outcomes. The knowledge gained will help optimize acute injury treatment planning as well as help inform development of more effective long-term care strategies.

KEY WORDS

Genitourinary injury; epidemiology; urotrauma

ACCOMPLISHMENTS

Goals:

The major goals of this project are: 1) Using a cohort design, estimate the incidence of adverse outcomes and identify prognostic factors including comorbid injuries that predict poor long-term outcomes; 2) Using a patient-centered approach, describe the natural history of recovery from GU injuries based on patient-reported outcome measures obtained via an annual health survey; and 3) Investigate the physiologic impairments and associated adverse outcomes based on an in-person physical examination (for a local subset of the study population).

Progress:

There has been one peer-reviewed publication during the current reporting period (01 July 2017 to 30 June 2018): Reed, AM, Judson CJ, Orman JA, Hudak SJ. Genitourinary Injuries Among Female U.S. Service Members During Operation Iraqi Freedom and Operation Enduring Freedom: Findings from the Trauma Outcomes and Urogenital Health (TOUGH) Project. *Mil Med.* 2018; <https://doi.org/10.1093/milmed/usx079>. GU injuries among female Service Members (SMs) have comprised a small proportion of all GU injuries sustained by U.S. SMs during OIF/OEF. Renal injuries pre-dominated and genital/reproductive injuries were rare. With more females now serving in direct combat roles, the number of female SMs injured in future conflicts will likely increase. Thus, the unique anatomical and functional aspects of female GU injuries must be considered in future research, prevention, and long-term multidisciplinary care efforts.

During the current reporting period, several key milestones have been achieved: **(1)** In conjunction with the move of the former UT Health San Antonio Site Principal Investigator (PI) (Dr. Mary Jo Pugh) to another institution, Dr. Roxana Delgado replaced Dr. Pugh as the UT Health San Antonio Site PI. The UT Health San Antonio IRB approved the PI change on December 11, 2017. **(2)** The second and third years of subcontract funding for the University of Texas Health Science Center at San Antonio (now called UT Health San Antonio) were awarded. **(3)** As reported last year, the Brooke Army Medical Center (BAMC) Office of the Institutional Review Board (OIRB) Chief recommended the study team develop a new protocol for Phase II of the project. However, after meeting with the study team in October 2017 and further reviewing the protocol, the OIRB Chief recommended the study team amend the current protocol instead of developing a new one. As a result, the study team revised the structure of the study from two phases into two parts with three sub phases in Part II of the study. (The protocol revisions are further discussed below.) The UT Health San Antonio IRB approved the protocol amendments on February 28, 2018. **(4)** The OIRB Chief also recommended that the BAMC IRB defer to UT Health San Antonio's IRB since UT Health San Antonio is performing the vast majority of the study activities in Part II. Since the deferral is to a non-Department of Defense (DoD) organization, the BAMC IRB deferral is conditioned on second-level regulatory approval from the U.S. Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP) Human Research Protection Office (HRPO). Prior to submitting the protocol to USAMRMC ORP HRPO, the OIRB Chief also recommended the study team further revise the protocol to clarify

that BAMC IRB is deferring to UT Health San Antonio IRB and to specify what study activities will occur at BAMC versus UT Health San Antonio. The study team revised the protocol based on the BAMC OIRB Chief's recommendations and submitted the additional protocol amendments to the UT Health San Antonio IRB for approval. Following successful approval by the UT Health San Antonio IRB on May 7, 2018, the study team submitted the amended protocol and deferral request to the BAMC IRB. On May 21, 2018, the BAMC OIRB Chief submitted the amended protocol to USAMRMC ORP HRPO for second-level regulatory review and for Component Level Administrative Review (CLAR) for reliance on a non-DoD IRB. On June 27, 2018, USAMRMC ORP HRPO requested additional supporting documentation for the protocol, clarification of team roles/responsibilities, and a minor revision to the telephone script. The study team submitted all of the requested protocol documentation and clarifications to USAMRMC ORP HRPO on June 27, 2018 and the transcript revision to the UT Health San Antonio IRB on June 28, 2018. The UT Health San Antonio IRB approved the transcript revision on June 29, 2018. We will submit the IRB approval memo and revised transcript to USAMRMC ORP HRPO and await approval of the amended protocol and completion of the CLAR, as required for BAMC IRB's deferral to the UT Health San Antonio IRB. **(5)** UT Health San Antonio hired the medical records chart abstractor who will be validating the cases of GU injury identified in Part I of the study. (Although UT Health San Antonio had originally planned to issue a subaward to a third-party contractor to perform this work, to avoid further delay, UT Health San Antonio hired the medical records chart abstractor directly and completed the onboarding process for this staff person at UT Health San Antonio.) Prior to hiring the medical records chart abstractor, the study team requested and received approval from the BAMC Department of Clinical Investigation (DCI) to utilize UT Health San Antonio's existing master Cooperative Research and Development Agreement (CRADA) with BAMC to perform the medical records chart abstraction/validation work. The study team then prepared and submitted the CRADA SOW to UT Health San Antonio's Office of Sponsored Programs (OSP) and received OSP approval on February 20, 2018. Per BAMC DCI, DCI cannot approve the SOW and the chart abstraction/records validation work cannot commence until the amended protocol receives final approval and the BAMC IRB deferral to the UT Health San Antonio IRB is complete. Once BAMC IRB's deferral is complete, the study team will submit the chart abstraction/records validation SOW to BAMC DCI for approval. **(6)** Since the dataset BAMC will transfer to UT Health San Antonio in Part II of the study involves data managed by the Defense Health Agency (DHA), DHA must approve a Data Sharing Agreement (DSA) between UT Health San Antonio and the DHA prior to the data transfer. The study team completed the DSA Application (DSAA) in January 2018, but cannot submit the application to BAMC DCI to initiate the multi-step DHA approval process until BAMC DCI approves the chart abstraction/records validation SOW. **(7)** The UT Health San Antonio IRB and the BAMC IRB approved continuation of the study in May 2018 and both IRBs deemed the study minimal risk. In addition, USAMRMC ORP HRPO acknowledged receipt of the continuing review documents on June 8, 2018 and required no further action for continuation of the study. **(8)** The study team is planning an analysis of medical records evaluation/validation with the DoDTR data repository. **(9)** Due to personnel changes (e.g., UT Health San Antonio Site PI) and the multiple regulatory approvals required for the BAMC IRB deferral, master CRADA SOW, and DSA, a face-to-face meeting with the TOUGH External Advisory Board was not yet convened, but we plan to have our face-to-face meeting in the late fall of 2018. **(10)** The study team further revised the study survey to ensure that data elements directly map to the protocol aims and objectives in order to keep the survey to a reasonable length and reduce respondent burden. The study team also revised the survey to align with the change in format from a telephone to a predominantly online administered REDCap (Research Electronic Data Capture) survey. The study team is planning to submit the survey to the TOUGH External Advisory Board members for further review and fine-tuning. Once the DSA is approved, the study team will beta-test the survey with a small pilot sample. **(11)** The study team finalized the data dictionary for the survey, including full definition of data coding, formats, values, value labels and allowable ranges. We have also prepared

a preliminary accrual schedule, which provides a quarterly estimate of chart reviews, validated case enrollments and surveys (both baseline and follow-up) to be administered, survey completions, and administrative data requests that will occur during Part II of the study. We will finalize a comprehensive study GU Injury Database, study electronic case report forms (eCRFs), and associated hard copy CRFs after we receive approval and transfer the validated medical records dataset to UT Health San Antonio for Part II of the study. Once the data transfer occurs, the study team will configure the UT Health San Antonio IT system to collect data from REDCap eCRFs. (12) The study team held several face-to-face meetings during the reporting period to revise the protocol, discuss manuscript development, and to further delineate the chart abstraction/records validation process.

Opportunities for Training and Professional Development

Nothing to report

Dissemination to Communities of Interest

The study team is currently making plans to create a blog post via the TOUGH study website that summarizes the study purpose and goals. The purpose of the blog is to generate interest in military/veteran/caregiver communities that may have a connection to the underlying targeted study population and/or want to learn more about the study impact/goals. We are also purchasing a unique project domain name and will establish a central TOUGH Study website to coordinate and disseminate study information.

Plans for the next reporting period

1. Finalize the study survey based on the beta-testing and feedback from the TOUGH External Advisory Board.
2. Convene a face-to-face meeting of the TOUGH External Advisory Board.
3. Develop the TOUGH study website and initiate advertisement of the study through the website blog.
4. Finalize the data dictionary for the GU Injury Database.

IMPACT

The incidence and characteristics of GU injuries treated in Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) have been described in recent literature. However, the information about the care received and needed and lasting morbidity from these injuries has yet to be described. The information obtained from this study will ensure that wounded warriors have and are receiving the care required for their injuries. The information will be used to guide military leadership to ensure programs are in place to better serve SMs with GU injuries.

Care for returning SMs is and will be a lasting duty that is entrusted to all healthcare providers in the Departments of Defense and Veterans Affairs. Ensuring that those who have served receive all necessary care is paramount to this duty. The initial treatment in theatre may have been temporizing or definitive. However, the lasting impact is unknown and patterns of healthcare utilization and unmet needs for care for the outcomes of GU injury are also unknown. Identifying the group of SMs with lower/external GU injuries and asking them about their health status and healthcare needs will allow us to ensure that they have received and are receiving proper care as well as identify changes over time. Because some of the SMs in our study will have been injured more than 10 years ago during the early years of the war, we will have very long-term outcome data (i.e., 20 years or more) on a subset of the participants in this study.

CHANGES/PROBLEMS

There has been a delay with Part II of the study commencing due to the multiple regulatory approvals required for the BAMC IRB deferral, master CRADA SOW, and DSA, as discussed earlier in the report. Once the amended

protocol is approved and the BAMC IRB deferral to the UT Health San Antonio IRB is complete, the study team will immediately submit the chart abstraction/records validation SOW to BAMC DCI. Pending BAMC DCI's approval of the SOW, Part II of the study can begin with the chart abstraction/records validation. Importantly, while the survey content will remain the same, moving from an individually administered telephone interview to an online survey will significantly improve the efficiency and timeliness of our data collection efforts thus allowing us to achieve the study goals within the original planned project duration.

The following changes occurred during the current reporting period: **(1)** Since no records will be reviewed at the VA, the VA was removed from the protocol and is no longer a study site. The UT Health San Antonio IRB approved this change on January 19, 2018. **(2)** As discussed above, the study team revised the structure of the study from two phases into two parts. Part I, identifying medical records in the DoD Trauma Registry (DoDTR) involving GU injuries (1,300 total records) has been completed. The records are currently with the BAMC on-site PI, LTC Steven Hudak. Part II of the study was further divided into three sub phases: data extraction to validate the DoDTR data; data requisition and analysis; and survey/interviews data collection. In addition to revising the study structure, the survey methodology was changed from a telephone interview to an online/paper survey, to make the data collection more feasible and effective in this study population; the number of follow-up surveys was reduced from ten to three (and limited to data fields likely to change during the follow-up interval); the participant payment amount and form of payment was revised; the protocol appendices were updated to reflect the revised survey methodology; and study personnel were updated to reflect the change in the UT Health San Antonio Site PI to Dr. Delgado. **(3)** Last year we reported a new Memorandum of Agreement (MOA) with the Joint Trauma System (JTS) would be required for BAMC to transfer the cases validated via the chart abstraction to UT Health San Antonio. However, the study team subsequently confirmed with the BAMC DCI that since UT Health San Antonio has an existing master CRADA with BAMC, a project-specific MOU with JTS is not required. Instead, the chart abstraction/case validation can be performed utilizing a SOW under UT Health San Antonio's master CRADA with BAMC. **(4)** We also reported last year that the U.S. Army Institute of Surgical Research (USAISR) on-site PI would no longer be USAISR staff and would be meeting with USAISR leadership to confirm whether an ISR investigator must be assigned to the study. Dr. Delgado and Dr. Kimberly Peacock (UT Health San Antonio Co-Investigator) met with USAISR leadership and confirmed that since the study only involves data transfer, LTC Hudak's role as the on-site BAMC PI satisfies USAISR's PI requirements.

There are no significant changes in use of care of human subjects, vertebrate animals, biohazards, and/or select agents.

PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS DURING THE REPORTING PERIOD

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SPECIAL REPORTING REQUIREMENTS

None

APPENDICES

None