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Health Care Systems Research Collaboratory

Ethics and Regulatory Core

UH2 Project: A Policy-Relevant U.S. Trauma Care System Pragmatic Trial for PTSD and Comorbidity *Trauma Survivors Outcomes and Support* (TSOS)

Douglas Zatzick, MD

Meeting Participants (April 20, 2015):

☒ Monique Anderson, MD *Duke Clinical Research Institute*	☒ Jeff Love *University of Washington*	☐ Galia Siegel, PhD *NIH / NIMH*
☒ Josie Briggs, MD *NIH / NCCIH*	☒ Jonathan McCall, MS *Duke Clinical Research Institute*	☒ Irene Stith-Coleman, PhD *OHRP*
☒ Elaine Collier, MD *NIH / NCATS*	☒ Jerry Menikoff, MD, JD *OHRP*	☒ Jeremy Sugarman, MD, MPH, MA *Johns Hopkins University*
☒ Doyanne Darnell, PhD, MA *University of Washington*	☒ Cathy Meyers, MD *NIH / NCCIH*	☒ Erik Van Eaton, MD *University of Washington*
☒ Leslie Derr, PhD *NIH / OD*	☐ Jeri Miller, PhD *NIH / NINR*	☒ Wendy Weber, MD, PhD, MPH *NIH / NCCIH*
☒ Brett Hagman, PhD *NIH / NIAAA*	☐ Andrew Narva, MD *NIH / NIDDK*	☒ Kevin Weinfurt, PhD *Duke Clinical Research Institute*
☒ Catherine Hammack, JD, MA *Duke Clinical Research Institute*	☒ Pearl O'Rourke, MD *Partners Healthcare*	☐ Barbara Wells, PhD *NIH / NHLBI*
☒ Adrian Hernandez, MD, MHS *Duke Clinical Research Institute*	☐ Jane Pearson, PhD *NIH / NIMH*	☒ Doug Zatzick, MD *University of Washington*
☐ Cheri Janning, BSN, RN, MS *Duke Translational Medicine Institute*	☒ Ivor Pritchard, PhD *OHRP*	
☒ Gregory J. Jurkovich, MD, FCAS *Denver Health Medical Center*	☒ Tammy Reece, MS, PMP, CCRA *Duke Clinical Research Institute*	
☒ Julie Kaneshiro, MA *OHRP*	☐ Marcel Salive, MD, MPH *NIH / NIA*	

The original discussion minutes were circulated to all attendees for two rounds of review and they reflect all corrections that were received.

Agenda Item	**Discussion** April 20, 2015	**Current Status** as of August 30, 2016

Brief review of *A Policy-Relevant U.S. Trauma Care System Pragmatic Trial for PTSD and Comorbidity* (Trauma Survivors Outcomes and Support (TSOS))	• Dr. Zatzick gave an overview of the TSOS project.
	  ○ The study's overarching goal is to develop and implement a large scale, cluster randomized pragmatic clinical trial demonstration project that directly informs national trauma care system policy targeting injured patients at risk of Posttraumatic Stress Disorder (PTSD) and related comorbidity.
	  ○ The study will involve twenty-four (24) sites, each a level one trauma center.
	  ○ It will implement a stepped wedge, cluster randomized design.
	  ○ The control group will receive enhanced usual care, while the intervention group will received stepped collaborative care.
	  ○ The intervention is the amalgam of standard of care, usual care, and best practices. In other words, each element is an acceptable, desirable, evidence-based method; it is the *integration*—the package—that is the novel intervention.
	  ▪ Specifically, the first step is the practitioner's empathic engagement at the bedside in an attempt to establish a therapeutic alliance with the patient; then the practitioner will coordinate care from the trauma center to primary care and
		• A 25th site was added to the project and randomized into the trial in the Spring of 2016.
		• Recruitment milestones for the project are being attained.

IRB status and approval	the community. The second step is to responds to PTSD and other comorbidities with the combination of various mechanisms, all of which are standard of care, usual care, and best practices. ▪ This package of interventions is ideal, but not often used in real-world. ○ Outcome assessments will occur at three- (3), six- (6), and twelve- (12) month intervals. ○ In response to questions regarding contamination, Dr. Zatzick explained that the project team will train a specific work unit within a hospital. ▪ It was suggested that the team could use historical data as a baseline for comparison with outcome changes. However, Dr. Zatzick explained that anything longitudinal would be very hard to document. ▪ The TSOS team and attendees acknowledged that the stepped-wedge design might very well have a community effect; indeed, the fact that the team is doing this study may itself impact care. • Dr. Zatzick explained that the American College of Surgeons' Committee on Trauma (ACS/COT) oversees trauma centers, but does not have an IRB. The University of Washington does not have centralized IRB capacity. Dr. Zatzick's team has approached Western IRB (WIRB) as the consolidated	• The TSOS team has experienced regulatory delays at individual sites in the study. The study has now achieved IRB approval at all 25 sites.

	IRB of record. Only five (5) sites were willing to cede to WIRB. Additionally, there are four (4) individual sites approved through their own institutions, eleven (11) being processed, and four (4) awaiting submission. TSOS has been approved as meeting the minimal risk criteria by WIRB (UH3 protocol) and the University of Washington IRB (UH2 pilot). • Additional information is included in the Summary Document attached to the original minutes.	
Risk *Does the project meet regulatory criteria for being considered minimal risk?*	• TSOS has been approved as minimal risk by WIRB and the University of Washington IRB. • In response to questions of whether or not the pilot study was informative with respect to risk, Dr. Zatzick explained that the pilot study was informative with respect to IT and administrative logistics but did not change any of the team's baseline assumptions about the study constituting minimal risk.	• *No changes reported*.
Consent *Planned processes for relevant subjects*	• Dr. Zatzick explained that a waiver of consent will be used to examine EHRs for risk population; those at risk will then approached for participation and consent. Patients are not asked to consent for the initial screening, but they are asked at the time of randomization regardless of the arm to which they are assigned. • Dr. Zatzick explained that trauma registries are kept in trauma care centers as standard practice, and the TSOS team will be obtaining the data therefrom.	• Informed consent has not changed.

	○ Within these data, there will be people who did not consent both because (i) they actually declined, and (ii) they were never asked. • In response to questions about assessing capacity and competency to consent, Dr. Zatzick explained that they will employ an initial pre-approach screening (including Glasgow Coma Scale (patients with a score of 15/15 plus an abbreviated version of the Mini–Mental State Examination). The informed consent process will be facilitated by a nurse or social worker with clinical experience. ○ Additionally, they will assess willingness to participate longitudinally by asking a participation question ("Had I known in advance what participating would be like for me I still would have agreed to participate") at varying intervals; thus far, most people respond with *true* or *mostly true*. • The attendees raised the concern that many patients will be prisoners at time of trauma or become prisoners as a result of the trauma. In response to questions regarding vulnerable subjects approval for those patients who will become prisoners, Dr. Zatzick explained that although this is a major issue, his team anticipates that less than 5% of their population will be incarcerated post-enrollment. Further, they will not approach those who are obviously "prisoners". Furthermore, if the team discovers that a patient was indeed incarcerated at a later time, they will not approach them for follow-up. ○ It was suggested that Dr. Zatzick's team may want to consider getting approval for the follow-up of prisoners, because if they lose many	

	patients to incarceration, they will lose trial integrity. [Post call note: Of 5,803 trauma center patients included in their previous multisite trauma center investigation, 119 or approximately 2% were incarcerated at the time of approach for the study (see attached Zatzick et al., Addiction 2014 Figure 1). In addition, in an ongoing TSOS study team longitudinal investigation, 2/104 patients were incarcerated at the time of study follow-up; also, incarcerated patients frequently exit jail settings within study follow-up windows. Given only potential limited gains in incarcerated patient accrual, and the likelihood that obtaining approvals to enroll prisoners in the research may delay IRB approvals across the 24 sites, the study team would prefer not to include prisoners as currently articulated in the approved WIRB UH3 protocol.]	
Privacy *Including HIPAA*	• The project will use a HIPAA waiver for initial screenings. *No questions or concerns raised.*	• *No changes reported*.

Monitoring and Oversight	• The NIMH DSMB will review the protocol mid-June, and if necessary modifications will be integrated into the final protocol and then submitted to the IRBs for review approval. • Dr. Zatzick explained that they anticipated sharing the following outcomes with the DSMB: adverse events (medication side effects, death (which is not unlikely in a trauma setting)), suicidality, loss to follow up, and demographics.	• The NIMH DSMB continues to provide oversight for the project. • The study will host a 4-day NIMH DSMB/regulatory University of Washington site visit the week of October 10th, 2016.
Issues beyond this project *Regulatory and ethics concerns raised by the project, if any*	• There was a brief discussion of the step-wedge design issue as a larger question, as well as secular changes in different interventions based on publicity of the trials. In addition, there is a need for additional guidance for data monitoring for these kinds of trials.	• *No additional information reported.*
Other	• Dr. Zatzick explained the TSOS team hopes to release their data at the end of the trial. The Collaboratory is based on data sharing; thus, the central papers that will come out should have a data set that is available to share with others. • [Post call note: A question was raised about whether FDA has jurisdiction in this study since part of it involves the use of approved psychotropic agents] • [NIH will follow up with staff at FDA to determine whether the proposed work is exempt from IND regulations]	As described in a memo (7/16/16) from the Project Officer (Jane Pearson, PhD) to the DSMB, the NIMH consulted with internal personnel with IND and FDA experience and concluded with concurrence of the PI that an IND was not needed for this study for a variety of reasons: • "The study does not aim to change the labeling of the antidepressant medications (primarily SSRIs and SNRIs), which are tested not individually, but rather as part of a recommended algorithm.

		• There is no intent to seek a change in the advertising for any medication product, nor for any algorithm (that could be construed as a mobile device). • The comparison group is not a placebo but 'treatment as usual,' which can include naturalistic use of the same medications in the algorithm. • The proposed use of the medications is not expected to generate greater risk for adverse events than other patient populations for whom these products are approved by the FDA (i.e., major depression)." Given this rationale, they elected not to consult directly with FDA.
Additional regulatory or ethics issue(s) that arose after the meeting		• *No additional issues reported.*
Additional follow-up information		• *No additional information reported.*