A Policy Relevant US Trauma Care System Pragmatic Trial for PTSD and Comorbidity (TSOS6)

Study Protocol

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1. Overview and Aims

The overarching goal of this UH2-UH3 proposal is to work with the NIH Health Care Systems Research Collaboratory 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 with presentations of Posttraumatic Stress Disorder (PTSD) and related comorbidity. Each year in the United States (US), over 30 million individuals present to trauma centers, emergency departments, and other acute care medical settings for the treatment of physical injuries. Multiple chronic conditions including enduring PTSD, depression and associated suicidal ideation, alcohol and drug use problems, pain and somatic symptom amplification, and chronic medical conditions (e.g., hypertension, coronary artery disease, diabetes, and pulmonary diseases) are endemic among physical trauma survivors with and without traumatic brain injuries (TBI). Evidence-based, collaborative care/care management treatment models for PTSD and related comorbidities exist. These care management models have the potential to be flexibly implemented in order to prevent the development of chronic PTSD and depressive symptoms, alcohol use problems, and enduring physical disability in survivors of both TBI and non-TBI injuries; care management models may also be effective in mitigating the impact of the acute injury event on symptom exacerbations in the large subpopulation of injury survivors who already carry a substantial pre-injury burden of multiple chronic medical conditions.

Effective collaborative care/care management treatment models however, have yet to be broadly implemented throughout US Trauma Care Systems; prior investigation by members of the interdisciplinary study team suggest that less than 10% of US trauma centers routinely provide post-injury screening or integrated care management treatment targeting the chronic disease cluster of PTSD and related comorbidities. Injured patients presenting to trauma care systems are often from low income, ethnoculturally diverse backgrounds. These “safety net” patient populations face major challenges in care coordination from trauma care systems to primary care and community services. The enduring challenges presented by the chronic disease cluster of PTSD and comorbidities after injury require innovative research approaches that cut across the traditional domains of multiple NIH institutes.

The primary aim of the UH3 period, years 2-5 of the project, is to conduct a pragmatic randomized effectiveness trial of a collaborative care intervention targeting PTSD and comorbid conditions after acute care injury hospitalization. The investigation aims to determine if injured patients receiving the collaborative care intervention demonstrate significant reductions in PTSD symptoms when compared to control patients receiving care as usual. The study also aims to determine if the intervention patients when compared to control patients will demonstrate significant reductions in depressive symptoms and alcohol use problems, and improvements in physical function. An exploratory aim of the investigation is to assess whether the intervention is effective in injury survivors with and without pre-existing chronic medical conditions and with and without TBI. Exploratory analyses will also assess whether the intervention successfully reduced enduring symptom development for other co-morbid presentations (e.g., suicidal ideation, physical pain, drug use problems).

A second aim of the UH3 project is to understand the processes of pragmatic trial implementation. The study team will use the RE-AIM model to comprehensively assess factors related to intervention reach, effectiveness, adoption, implementation, and maintenance. An exploratory assessment of the impact of the intervention on post-injury health service utilization and costs will also be conducted. The RE-AIM and health economic analyses aim to further understand trial implementation experiences, in order to elucidate barriers to and facilitators of sustainable screening and intervention procedures for PTSD and comorbidities across US trauma care systems.

A final project dissemination aim is to conduct a policy summit with the key study stakeholder, the American College of Surgeons in UH3 year 5. The policy summit targets the broader goal of further engaging trauma centers in the research process by integrating pragmatic trial results into mandates and clinical practice guidelines for screening and intervention for PTSD and related comorbidities across trauma care systems nationwide.

2. Significance

A. Physical injury trauma occurs frequently in the US and constitutes both a substantial source of individual suffering and a significant public health burden.[1-5] Each year in the US, over 30 million individuals present to acute care medical trauma center and emergency department settings for the treatment of traumatic physical injury.[1-5] Injured trauma survivors present to acute care medical settings after both intentional (e.g., gunshots, stabbings, physical assaults) and unintentional (natural disasters, motor vehicle crashes) injury events.[6] Annually 1.5-2.5 million Americans are so severely injured that they require inpatient hospitalization.[1-5] Estimates suggest that approximately 1.5 million American youth and adults experience traumatic brain injury (TBI) annually.[7,8] Physical injury with and without TBI, constitutes a major public health problem for both civilian and veteran trauma-exposed patient populations.[9,10] Traumatic injury is a leading cause of death for individuals under the age of 45 and accounts for 12% of medical expenditures in the US.[1-3,5] In one nationwide US study, over 40% of injured trauma survivors reported they were unable to return to work 12 months after their hospital admission.[11] Globally, traumatic injury accounts for approximately 16% of the world's burden of disease.[12-14]

Multiple chronic conditions including PTSD and pre-existing medical co-morbidities (e.g., hypertension (HTN), coronary artery disease (CAD), diabetes, and pulmonary disease) are endemic in populations of injured trauma survivors.[15-24] Recent commentary has defined chronic conditions as "conditions that last one year or more and require ongoing medical attention and/or limit activities of daily living".[25-27] Prior investigation suggests that complex comorbid conditions meeting these definitional criteria are endemic among injured patient populations treated at US trauma centers and their affiliated trauma care systems.[21,28,29] Highly prevalent comorbidities include PTSD, depression and associated suicidal ideation, alcohol and drug use problems, enduring physical pain and somatic symptom amplification, and chronic medical conditions such as HTN, CAD, diabetes, and pulmonary disease.[17,28,30] Initial studies suggest that enduring personality disturbances may also occur in some sub-populations of injured trauma survivors.[31]

A series of US prospective cohort investigations suggest that between 20-40% of physically injured trauma survivors may go on to develop symptoms consistent with chronic PTSD after hospitalization for injury.[21,32-36] Chronic PTSD symptoms develop between 3-12 months after exposure to a traumatic injury event. A recent Institute of Medicine Report articulates that a majority of individuals presenting with PTSD have one or more comorbid conditions.[37] In injury survivors, chronic PTSD often occurs in conjunction with comorbid depressive symptoms.[21,32-34,36,38-42]

PTSD and related comorbidity including depression, pain and somatic symptom amplification occur as a "cluster" among patients with TBI and non-TBI related injury.[41,43-45] The constellation of enduring PTSD, depression, suicidal ideation, somatic symptom amplification post-injury pain, and TBI share common presentations and symptom overlap; prior study suggests that broad spectrum medication and psychotherapeutic treatments can target this constellation of chronic conditions and symptoms.[45-51]

After injury, chronic PTSD and depression lasting 12 months or more are associated with a broad profile of functional impairments and costs, including diminished physical function and inability to return to work.[34,35,52-54] In both TBI and non-TBI patient populations, PTSD and depression independently account for post-injury functional impairments.[43,44] In one nationwide 69-site trauma center investigation, PTSD and depression made an independent "dose" related contribution to the inability to return to work after injury hospitalization;[55] PTSD and comorbidity are associated with increased health care and societal costs.[56-60]

Alcohol use problems and other high risk behaviors are also endemic among injured trauma survivors.[6,17,61] In one study of 1118 consecutively admitted injured trauma survivors, the lifetime prevalence of alcohol abuse/dependence was 37% and 24% had a diagnosable alcohol abuse or dependence at the time of injury admission.[17] Alcohol use problems in injured trauma survivors are associated with the occurrence of chronic recurrent traumatic life events.[18,61] Multiple prior reports suggest that drug use problems may also be endemic among injured trauma survivors.[17,30]

Pre-existing chronic medical conditions also occur frequently among injured trauma survivors. In a national US study of approximately 3000 injured trauma survivors admitted to 69 hospitals, approximately 35% of injury survivors had one or more chronic medical conditions including HTN (20.4%), CAD (11.8%), and diabetes (7.4%).[21,28,29] In a recent investigation by the study team that utilized automated electronic health record (EHR) *International Classification of Diseases, 9th Revision, Clinical Modification (ICD)* code screening to recruit patients, approximately two thirds of patients had one or more chronic medical conditions including

HTN (36%), CAD (38%), diabetes (20%), pulmonary (17%), or other medical diagnoses (e.g., renal disease, liver disease, HIV, 21%).[29] Table 1 below delineates medical and chronic condition comorbidity rates in the study team's prior investigations.

Table 1. Characteristics of Patients with Multiple Chronic Conditions in Prior Studies

Characteristic	69 Site Cohort Study (N=2931)	20 Site Alcohol R01 RCT (N=878)	Single Site PTSD R01 RCT (N=207)	Single Site PTSD IT Pilot (N=121)
Mean (SD) of Chronic Conditions	1.4 (2.0)	2.0 (1.2)	2.4 (1.8)	3.8 (2.2)
≥ 3 Multiple Chronic Conditions %	12.9% (605)	25.2% (221)	44.0% (91)	62.8% (76)
Chronic Condition Breakdown %				
- Chronic PTSD Symptoms %	21.8% (602)	14.1% (124)	39.0% (60)	43.8% (53)
- Chronic Depressive Symptoms %	6.7% (175)	14.7% (92)	31.8% (49)	41.3% (50)
- Chronic Alcohol Use Problems %	17.1% (797)	68.5% (600)	52.7% (109)	57.0% (69)
- Chronic Drug Use Problems %	3.2% (146)	37.0% (320)	28.5% (59)	28.1% (34)
- Traumatic Brain Injury %	46.3% (2643)	50.2% (441)	38.2% (79)	35.5% (43)
- ≥1 Chronic Medical Disorders %	33.7% (2039)	21.4% (137)	41.1% (85)	64.5% (78)
1) Hypertension (HTN)	16.5% (984)	12.0% (77)	18.4% (38)	35.5% (43)
2) Coronary Artery Disease (CAD)	11.8% (876)	1.9% (12)	16.9% (35)	38.0% (46)
3) Diabetes	7.4% (438)	3.6% (23)	3.9% (8)	19.8% (24)
4) Pulmonary (Asthma, COPD)	6.9% (379)	7.3% (47)	15.0% (31)	17.4% (21)
5) Other Disorders (e.g., Renal, HIV)	6.1% (405)	3.0% (19)	12.6% (26)	20.7% (25)
Insurance Status %				
- Public (e.g., Medicaid, Medicare)	20.9% (1252)	22.5% (198)	53.6% (111)	62.8% (76)
- Uninsured	28.2% (1130)	26.9% (236)	21.7% (45)	15.7% (19)
- Private	50.9% (2661)	28.9% (254)	24.6% (51)	21.5% (26)

B. Nationwide trauma care systems provide care for injured patients.[1,62-64] The nation's trauma care system is the service delivery sector in which injury victims receive their treatment. A trauma care system is an organized and coordinated effort in a defined geographic area that is designated to deliver the full spectrum of care to populations of injured trauma survivors. This care begins immediately after the injury and includes inpatient trauma center surgical hospitalization.

Injured patients presenting to US trauma care systems are often from low-income diverse backgrounds and include a substantial proportion of uninsured/under-insured and dual Medicaid/Medicare recipients.[21,65-71] Prior investigation suggests that a substantive majority of injured patients in trauma care systems receive insurance coverage either through public funding sources (e.g., Medicare, Medicaid) or are uninsured; the proportion of uninsured may continue to be high in states that have elected not to expand their Medicaid programs as part of health care reform.[11,21,28,62,72]

Patients treated in trauma care systems often receive fragmented care that is not coordinated from emergency department and trauma centers to primary care and community settings.[73,74] Recent commentary has suggested the extension of trauma care to include primary care and community linkages.[63,75] Quality of care improvements in trauma care systems could address issues of care coordination across acute care hospitalization, and primary care and community services.[73,74,76-82] In particular, low-income, diverse "safety net" patient populations face major challenges in care coordination across trauma care system and primary care service delivery sectors.[71]

Early intervention models that bridge supportive care and evidence-based treatment delivery are crucial elements in the prevention of chronic PTSD and related comorbidity.[83-89] Epidemiologic data suggests that it may take years for trauma-exposed individuals with PTSD to enter treatment.[90] Intervention models that serve to link acutely exposed individuals to evidence-based PTSD treatment services remain to be widely implemented and represent a crucial next step in the prevention of PTSD and the mitigation of symptoms for pre-injury medical comorbidity.[25,83,84,86-88,91-94]

Currently, few patients treated in trauma care systems receive evaluations or evidence-based treatment for PTSD and related comorbidity. Prior investigation by members of the interdisciplinary study

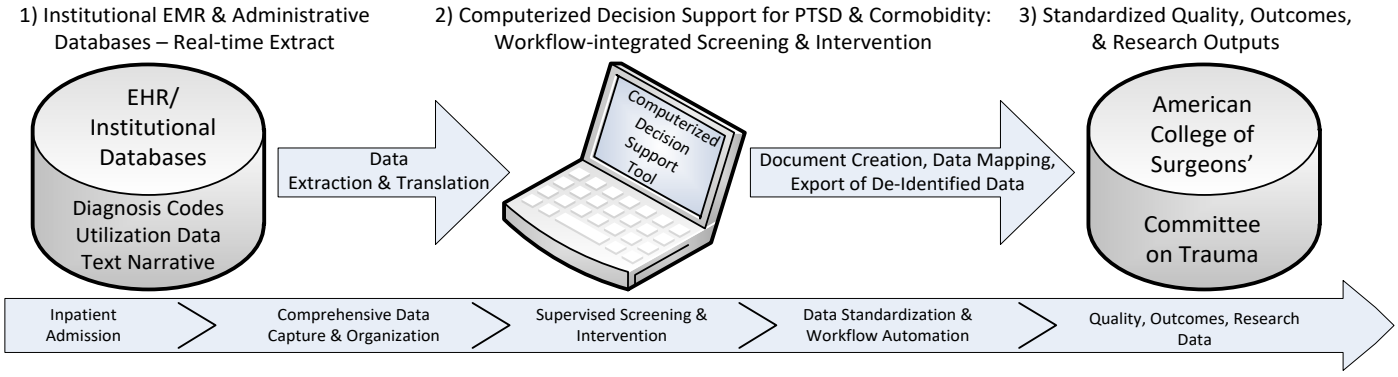
team suggest that less than 10% of US trauma centers routinely provide early post-trauma screening and intervention services for PTSD.[95]

Health care reform including the introduction of accountable care organizations and the patient-centered medical home present a series of potential opportunities for the incorporation of novel intervention strategies targeting injured patients with multiple chronic conditions who require hospital to primary care and community care transitions.[96-102] Trauma care systems are currently grappling with the advent of health care reform.[100,101,103-105] While much dialogue has occurred, few evidence-based intervention models have been widely implemented for injured patients with comorbid conditions including physical injury, mental health disorders and substance use problems, as well as pre-injury chronic medical conditions.[50,51] The establishment of systematic trauma center to primary care and community linkages could potentially impact unplanned, costly, emergency department and trauma center readmissions.[97,99,103-105]

The American College of Surgeons oversees the development of national policy mandates and clinical best practice guidelines that inform the integrated operation of US trauma centers and affiliated trauma care systems.[63] The College has successfully linked trauma center funding to verification site visits and other quality indicators.[63,106,107]

C. Trauma care systems constitute high volume integrated health care systems that are increasingly supported by sophisticated EHRs. Recent investigation by members of the interdisciplinary study team document that trauma care systems are increasingly integrating advanced EHR systems.[108] The investigative team is aware that an overarching goal of the NIH Collaboratory is to integrate all aspects of the research including screening, enrollment, treatment assignment and monitoring of outcomes into routine practice workflows and data capture mechanisms.[109] Although potential exists, currently most trauma care systems do not utilize information technology (IT) innovations to support real-time, workflow integrated, automated data screening, intervention, and quality documentation procedures.[108]

Figure 1. Comprehensive Trauma Center Screening, Intervention & Quality Documentation for PTSD & Comorbidity



Members of the study team are implementing a series of IT care enhancements for patients treated in trauma care systems (Figure 1).[110-113] These innovations include: 1) automated population-based EHR screening procedures for PTSD and comorbidity, 2) trauma center-based computerized decision support tools that facilitate the delivery of care management interventions, and 3) methods for documentation of high quality screening and intervention procedures.[29,49] The investigative group is experienced in creating EHR-linked screening tools that use generalized business-rules logic engines, both in locally constructed EHR systems and in nationally adopted EHR systems.[108,110-113] Applying these principles, study team members have developed a PTSD risk prediction algorithm that uses 10 EHR domains to identify patients at high risk for PTSD.[21,36,49,114-122] Novel applications developed by Dr. Van Eaton and colleagues also include a computerized decision support tool that targets study team care management of surgical, medical, mental health and substance related comorbidities.[29,113] In addition, members of the study team are participating in American College of Surgeons' policy workgroups that establish policy for US trauma care systems quality documentation. Finally, in the UH2 start-up phase of the protocol, study team collaborators, including Dr. Van Eaton, have developed and piloted an open-source method for automated de-identification and mapping of patient data to the National Trauma Data Bank (Appendix 9).[123] The National Trauma Data Bank provides de-identified data for nationwide trauma care systems quality benchmarking. An overarching goal of the study team is to work with the NIH Collaboratory and the American College of Surgeons' to refine this constellation of IT innovations in order to develop real-time, workflow integrated, automated screening, intervention, and

quality documentation procedures for PTSD and related comorbidities that can be deployed across trauma care systems nationally (Figure 1).

D. Collaborative care/care management treatment models that combine effective intervention elements and incorporate IT innovations have the potential to enhance the prevention and management of multiple chronic conditions; these models have the capacity to maximize flexibility and integration of approaches to addressing the chronic disease cluster of PTSD and comorbidity after injury (Table 2 and Figure 2).[124,125] Derived from the chronic care mode, collaborative care/care management interventions hold promise for the integration of treatment for patients with multiple chronic conditions within trauma care systems.[51,126-129] A large body of research now has established the effectiveness of integrated care delivery models such as "collaborative care" in reducing depressive, anxiety, pain and other somatic symptom presentations in conjunction with comorbid medical conditions in primary care settings.[51,128-145] Collaborative care treatments bring together efficacious medication and psychotherapeutic intervention elements with care management strategies that target reductions in care fragmentation and enhanced care coordination for patients with multiple chronic conditions (Table 2). The novel application of collaborative care models for injury survivors at risk for PTSD and comorbidity has the potential to address myriad aspects of the "Multiple Chronic Conditions Strategic Framework" (Table 2).[25,91,92]

Medication coordination and reconciliation can improve care transitions for patients with chronic medical conditions.[146-149] Previous investigation has documented high rates of errors in chronic condition pharmacotherapy during acute care to primary care and community care transitions. Interventions targeting care transition pharmacotherapy for patients with chronic medical conditions have been developed; these interventions include care management care coordination, obtaining accurate inpatient medication histories, reconciliation of medication discrepancies and careful and ongoing medication coordination with primary care and other community providers.[146-149]

Medication interventions are effective in the management of PTSD and comorbidities.[48,150-162] The Selective Serotonin Reuptake Inhibitor (SSRI) class of medications is efficacious in the treatment of PTSD and depression.[153,154,163-165] Medication treatment targeting trauma-related insomnia may be effective in reducing global PTSD symptoms and associated somatic symptom presentations.[51,128,145,159-161,166,167] Clinical practice guidelines based on these research studies have been formulated.[89,150-152,168]

Table 2. Core Elements of Intervention Targeting Multiple Chronic Conditions (MCC) After Injury [91]

Essential Element	Which of multiple (≥ 3) MCC Targeted	MCC strategic framework goals addressed*
Population-based EHR PTSD & comorbidity risk prediction	PTSD, depression, alcohol & drug use problems, pain and somatic symptoms, & chronic medical conditions after acute injury	Goal 1 Objective D, Implement and efficiently use health information technology; Automated screening efficiently identifies constellation of PTSD and comorbidity in injured populations
Care management with trauma center to primary care linkage	Coordination of acute injury mental health and pre-existing chronic medical condition care	Goal 2 Facilitate use of community based services and self-care management
Early post-injury medication history, reconciliation, and care coordination	PTSD, depression, pain, somatic symptom amplification & TBI symptoms prevention. Chronic medical condition (e.g. HTN, CAD, Diabetes) reconciliation and coordination	Goal 1 Objective E Prevent occurrence of new chronic conditions and mitigate the consequences of existing conditions & Goal 2 Objective C, Provide tools for medication management
Evidence-based MI embedded within care management	Targets alcohol and drug use problems and enhanced patient engagement	Goal 1 Objective E Prevent occurrence of new chronic conditions and mitigate the consequences of existing conditions
Evidence-based CBT embedded within care management	Targets PTSD, depression, pain, somatic symptom amplification and TBI sequelae. Also targets enhanced patient self-efficacy	Goal 1 Objective E Prevent occurrence of new chronic conditions and mitigate the consequences of existing conditions, & Goal 2 Objective A Facilitate self-care management
Patient and caregiver-centered posttraumatic concern elicitation and improvement	Patient-centered concerns elicitation and improvement targets patient and family engagement in care of full MCC constellation	Goal 2 Optimize self-care management and coordinated use of services by patient and caregivers
Caseload supervision & stepped measurement-based care implementation	PTSD, depression & associated suicidal ideation, alcohol & drug use problems, chronic medical conditions & acute physical injury	Goal 3 Provide better information and education on treatment of MCCs to health-care workers
* All study elements address MCC Goal 4 of Enhancing Research Knowledge on MCCs		

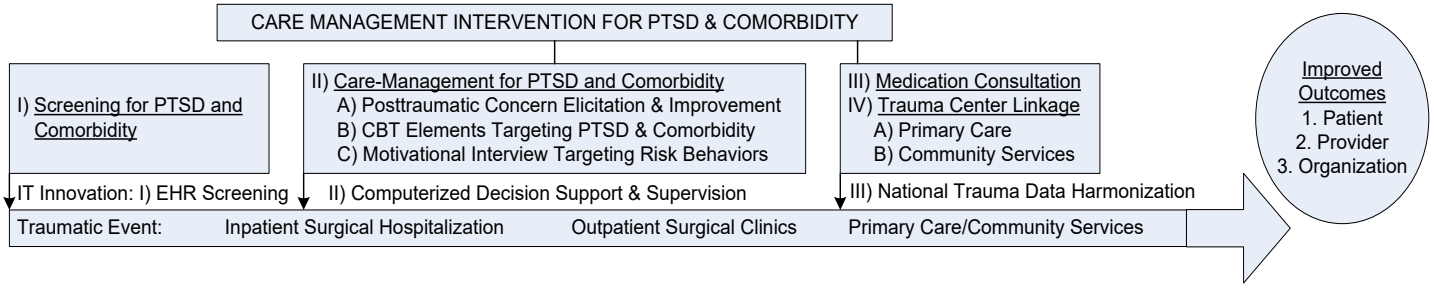
Flexibly delivered Cognitive Behavioral Therapy (CBT) interventions have been used to successfully target PTSD.[24,136,169-171] A series of investigations have described the feasibility, acceptability, and effectiveness of telephone and care management based CBT intervention strategies targeting PTSD and depression; these interventions can also enhance chronic disease management self-efficacy.[129,170,172,173]

A body of evidence supports the effectiveness of brief Motivational Interviewing (MI) interventions targeting alcohol use problems.[18,129,174-183] A series of randomized clinical trials (RCTs) support MI as an evidence-based treatment for alcohol use problems in the acute care inpatient setting.[18,129,175-179]

Recent investigations document the effectiveness of stepped care management treatment models targeting PTSD and related comorbidities for injured patients treated within trauma care systems (Figure 2)**.** Two recent trials have demonstrated the effectiveness of care management models targeting PTSD and related comorbidity.[129,172] The collaborative care treatment models begin with population-based PTSD screening.[129,172] Next, care managers elicit patient and family member post-injury concerns and target these concerns for amelioration. Early supervised psychopharmacologic intervention elements including SSRI antidepressants and other related agents target the constellation of overlapping PTSD, depressive, somatic and TBI symptom presentations.[29,50,51] Prior investigation demonstrates enhanced post-injury quality of care for multiple chronic conditions as documented by increased rates of primary care linkage and adherence to pharmacotherapy regimes.[51,172] Simultaneously, care managers deliver evidence-based MI and CBT elements during routine post-injury patient encounters in trauma wards and emergency departments, in outpatient clinics, in community settings, and over the telephone. Finally, care managers work to link injured patients' care from inpatient and emergency department settings to primary care and community services.

These collaborative care models show promise both in preventing the development of chronic PTSD symptoms and associated enduring disability after acute injury episodes, and in mitigating the impact of the injury event in the large subpopulation of injury survivors who already carry a substantial pre-injury burden of ≥ 3 chronic medical, mental health, and substance related conditions. In the proposed pragmatic trial, early CBT and pharmacological interventions target high early acute symptoms of PTSD and other mental health, substance related comorbidity and chronic medical condition exacerbation. Early medication history and reconciliation can comprehensively address the need to continue/restart medications targeting pre-existing chronic medical conditions. Sustained pharmacotherapy intervention and treatment linkage target more chronic presentations of PTSD and comorbidity while simultaneously bolstering early treatment gains.

Figure 2. Essential Elements of Trauma Center Screening & Intervention Targeting PTSD & Comorbidity



E. Conceptual framework informing pragmatic trial design and implementation.

Overview. By necessity, multiple theoretical and applied perspectives inform the conceptual framework underlying the Trauma Survivors Outcomes and Support (TSOS) study design and implementation. The conceptual framework for implementation incorporates collaborative care intervention models targeting the PTSD and comorbidity cluster that includes PTSD, depression and associated suicidal ideation, alcohol and drug use problems, enduring physical pain and somatic symptom amplification, and chronic medical conditions in patients with TBI and non-TBI related injury. The conceptual framework also must incorporate key features of pragmatic trial design and implementation captured in the pragmatic-explanatory continuum indicator summary or PRECIS model.[184]

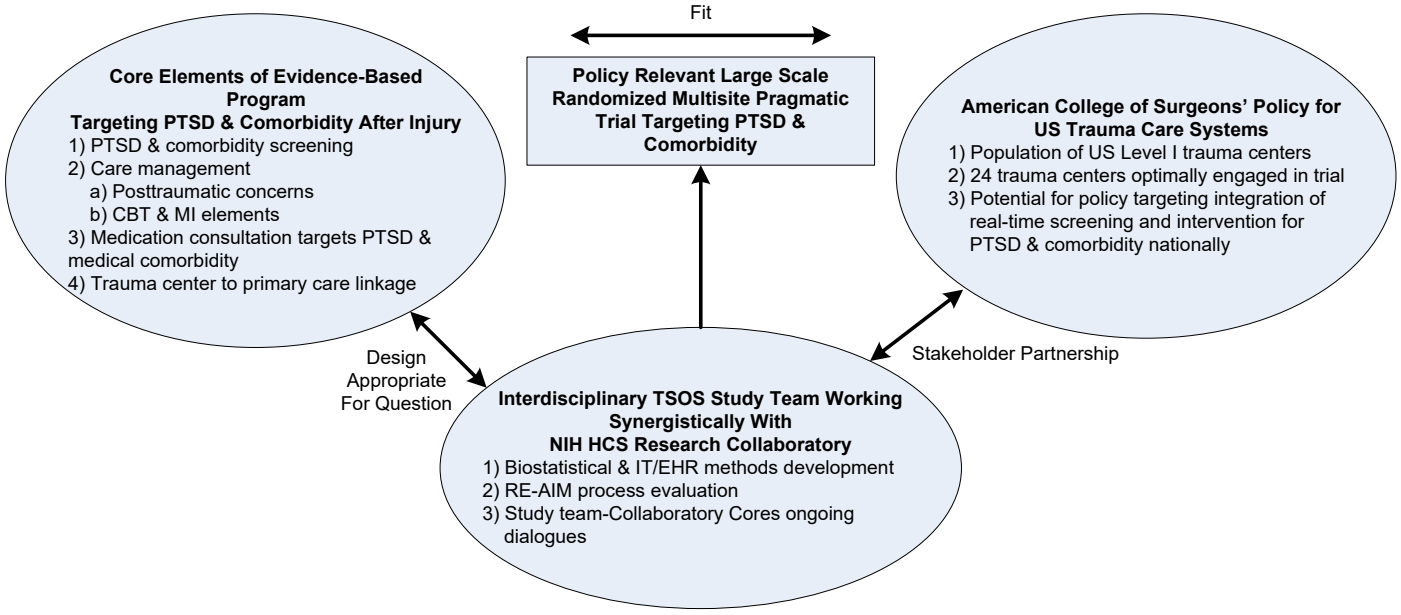
The PRECIS model and the TSOS trial.[184] Gold standards for pragmatic trial design and implementation include broad participant eligibility criteria, flexible intervention delivery, application by the full

range of practitioners, and incorporation of rigorous prospective controls, preferably by randomization. Usual practice comparison conditions are frequently used in pragmatic trials.[184-189] The optimal pragmatic trial is characterized by an intent-to-treat data analytic approach that includes all patients regardless of adherence.[184] The TSOS trial encompasses these pragmatic trial attributes by fielding a readily implementable collaborative care intervention that targets injured patients with the full spectrum of PTSD and related comorbidity with minimal exclusionary criteria.

Pragmatic trial outcomes are often centrally measured, clinically meaningful, and require minimal adjudication.[184-189] With regard to pragmatic trials in US trauma care systems no one or even multiple administrative databases can be used to track outcomes among injured trauma survivors; thus for trauma care system pragmatic trials, outcome assessments may by necessity occur as an addition to naturalistic follow-up. The PRECIS framework suggests that for some trials, outcome assessments must by necessity be obtained through contact with participants.[184] Similarly the PRECIS framework takes into consideration the observation that in some trials that rely heavily on patient reported outcomes, some training in the assessment and adjudication may be desirable.[184]

The "Robust, Sustainable, Rapid Pragmatic Trials Framework," that includes the RE-AIM model as a central component, is a conceptual framework that can guide the synergistic work of the TSOS study team and NIH Health Care Systems Research Collaboratory in the implementation of the UH3 trial (Figure 3).[185,190] This framework outlines a series of pragmatic trial approaches including the reach, effectiveness, adoption, implementation and maintenance model as a systematic method for understanding the processes of pragmatic trial implementation. To enhance trial impact, the Robust, Sustainable, Pragmatic Trials Framework encourages trial policy relevance and the collection of policy relevant cost-effectiveness data. The use of mixed quantitative and qualitative methods that comprehensively assess the potential for pragmatic trial/health care system sustainability are also encouraged. Deriving from this framework, the TSOS study pragmatic cluster randomized trial may be best characterized as an hybrid effectiveness-implementation RCT.[29,50,51,191] The TSOS trial simultaneously aims to determine the effectiveness of the stepped collaborative care intervention model while also assessing the potential utility of the implementation strategy for trauma care systems nationally.[185,190]

Figure 3. Integration of Large-Scale Pragmatic Trials, Robust Implementation, & Policy Relevance Conceptual Frameworks for Trauma Care Systems



F. A series of innovative methodological approaches are suggested by the combined application of the PRECIS and RE-AIM frameworks in a single pragmatic trial demonstration project targeting PTSD and related comorbid conditions (Figure 3). RE-AIM provides additional pragmatic domains that corroborate and

enhance the PRECIS framework.[192,193] The RE-AIM framework provides a model for the integration of pragmatic trial results into routine trauma center practice.[190] RE-AIM pragmatic trial criteria include: can the program reach those most often in need and most often left out of health care systems interventions? RE-AIM adoption criteria ask the question: can the intervention program be adopted by low-resource settings and by front-line staff serving high risk populations? RE-AIM maintenance criteria include the question: can the settings sustain the program over time without added resources and leadership? By targeting low income, ethnoculturally diverse injured trauma survivors treated in trauma care systems, and by including an American College of Surgeons' policy component, the TSOS study incorporates these RE-AIM pragmatic trial domains.

Implementation science investigation can also inform a better understanding of the processes of pragmatic trial implementation and ultimately pragmatic trial sustainability. Organizational behavior and process research can provide insight into trauma center implementation and maintenance of interventions for PTSD and comorbidity.[107,194-202] Prior study suggests that training workshops, plus feedback and coaching are the optimal procedures for training in evidence-based interventions.[203-208] An emerging body of research suggests that mixed method investigations can also inform transparency and understanding of the manner in which multiple stakeholders can work collaboratively to understand implementation processes and translate research findings into policy.[209-214]

Policy relevant cost-effectiveness analyses are key methodological approaches for optimizing pragmatic injury trial public health impact.[11,215-220] At trauma centers, both general cost-effectiveness approaches and approaches relevant to specific acute care issues, such as injured trauma survivors returning to work, are germane.[11,219,220] Members of the investigative group have previously conducted cost-effectiveness and analyses related to the impact of mental health and substance abuse care management interventions in acute, primary care, and general medical settings.[11,219-224] The integration of mixed, quantitative and qualitative research methods can optimally inform the results and policy implications of pragmatic trials.[225-229]

G. The potential for the project to develop transformative methods and reusable resources. The significance of the TSOS study extends beyond specific investigative aims to the potential development of transformative research approaches for the multiple chronic condition framework and reusable pragmatic trial resources for US health care systems. The investigation brings to the Collaboratory a unique American College of Surgeons-TSOS study team stakeholder partnership. This partnership has been cultivated over the past decade and has the potential to directly translate UH3 pragmatic trial results into American College of Surgeons' policy targeting real-time workflow integrated screening and intervention procedures for PTSD and related comorbidity for US trauma care systems. The American College of Surgeons' stakeholder partnership can potentially generate a novel model for the dissemination and sustainability of Collaboratory research results; the TSOS study team policy arm is poised to advocate for American College of Surgeons' best practice recommendations that incorporate theoretical and applied research products including information technology innovations.

With regard to the generation of innovative and reusable research methods, the TSOS pragmatic trial employs a novel cluster randomized stepped wedge design that begins with control phase recruitment and then "switches on" the intervention; this design addresses study implementation challenges raised by the inclusion of 24 diverse trauma center sites in the trial. The stepped wedge design also optimizes implementation science approaches to training at 24 US level I trauma center sites that may wish to incorporate PTSD screening and intervention procedures as part of future American College of Surgeons' policy. The study introduces across 24 US level I trauma center hospitals with diverse electronic health record (EHR) capacity, a novel EHR screening procedure for PTSD and related comorbidity. The procedure is designed to be flexibly implemented at sites that can either automate the screen or apply the screen in a manual chart review fashion. The TSOS stepped screening and intervention procedures target a multiple chronic condition/comorbidity cluster that includes PTSD and associated mental health comorbidity such as depression and suicidal ideation, alcohol and drug use comorbidity, pain and somatic symptom amplification, TBI and non-TBI injury, as well as a heterogeneous clustering of chronic medical comorbidities. The investigation addresses complex challenges raised by the introduction of the need to screen for multiple chronic conditions within the EHR and complexities related to accurate diagnoses of patients with mental health conditions. A single care management based intervention program targets this heterogeneous comorbidity cluster with minimal exclusions.

3. Study Design

A. Design Overview

The pragmatic trial demonstration project is designed to test the implementation of efficient, high quality screening and intervention for PTSD and comorbidities across 24 US level I trauma center sites. The investigation will employ a stepped wedge cluster randomized design. In the stepped wedge design, level I trauma center sites are randomized sequentially to initiate the intervention. In the UH3 implementation phase, after IRB approval is obtained, each of the 24 trauma center sites will be randomized to one of four waves. All sites will begin with control patient recruitment and each wave is assigned a specific proportion of control and intervention patient recruitment. Wave one recruits 8 control and 32 intervention patients, wave two recruits 16 control and 24 intervention, wave three recruits 24 control and 16 intervention, and wave four recruits 32 control and 8 intervention patients. The demonstration project aims to recruit 960 patients, 40 at each trauma center site.

A routine trauma center provider, the site PTSD intervention champion, will be selected to orchestrate screening and intervention procedures. All sites will work with the study team to implement an EHR initial PTSD risk evaluation. Patients identified by EHR evaluation as at-risk for high early PTSD symptom levels (i.e., a score of ≥ 3 risk domains positive) will then be formally screened for study entry with the patient reported outcome measure, the PTSD Checklist. Formal study cohort definition occurs with the PTSD Checklist; patients scoring ≥ 35 on the PTSD Checklist will be followed in the longitudinal portion of the investigation.

Patients in the control condition will receive enhanced trauma center care as usual. Enhanced trauma center care as usual consists of nurse notification of control patients who screen into the study with high PTSD symptom levels. Patients in the intervention condition will receive a stepped collaborative care intervention targeting PTSD and related comorbidities. The intervention phase will begin with a one-day workshop training in care management, medication, MI, and CBT elements targeting PTSD and related comorbidity. These workshop trainings will occur on site at each of the 24 level I trauma center sites. The site PTSD intervention champion, as well as trauma surgical, nursing, psychiatric, social work, and other allied mental health providers who are already routinely delivering care at each of the sites will be invited to attend the workshop training. After the one-day workshop, the site will receive ongoing decision support facilitated supervision from the University of Washington study team.

Intent-to-treat outcome analyses will incorporate baseline patient reported outcome and trauma registry derived EHR data, as well as patient reported outcome assessment data from the 3-, 6-, and 12-months post-injury patient interviews. The investigation aims to determine if injured patients receiving the collaborative care intervention demonstrate significant reductions in PTSD symptoms when compared to control patients receiving care as usual. The study also aims to determine if the intervention patients, when compared to control patients, will demonstrate significant reductions in depressive symptoms and alcohol use problems, and improvements in physical function. The investigation is designed as an effectiveness-implementation hybrid that simultaneously aims to determine the effectiveness of the care management intervention while also assessing the potential utility of the implementation strategy.[191] Thus, the investigative team will also use the RE-AIM framework and exploratory health economic analyses to better understand the processes of intervention implementation, as well as the resource implications for trauma care systems nationwide.

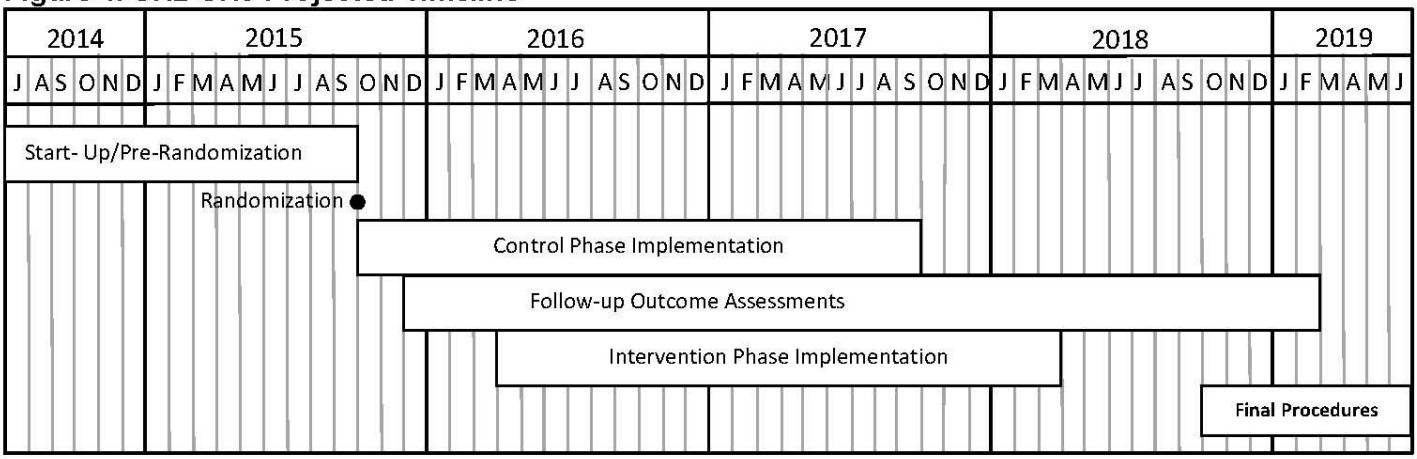
In the UH3 year 5 of the proposal, the results of the pragmatic trial will be presented at an American College of Surgeons' policy summit. A key focus of the summit will be discussion of the implications of trial results for screening and intervention for PTSD and comorbidity, clinical practice guidelines, and policy mandates. In particular, the study team will discuss findings that facilitate the implementation of real-time workflow integrated screening and intervention procedures for PTSD and comorbidity across trauma care systems nationally. The summit will be timed to optimally impact the next version of trauma center guidelines for PTSD and comorbidity.

B. Study Phases (see Figure 4)

Phase 1: Planning and start-up. In the start-up phase, the University of Washington (UW) study team has identified the 24 participating trauma center sites; potential wait list or "back-up sites" that could participate in the trial should initially contacted sites drop from the study have also been identified. At each potential site, the study team has identified three different types of "Champions", or individuals who have the background and experience at a trauma center to advocate for a particular component or element of the study protocol. The

three identified champions at each site are the trauma surgical champion, PTSD intervention champion and information technology champion. Also during the start-up phase, each site will be asked to assess their capacity for automated versus manual health record PTSD screening and to characterize their potential method for identifying injured patient cohorts and implementing the 10 domain PTSD risk factor screening elements.

Figure 4. UH2-UH3 Projected Timeline



Phase 2: Start-Up/Pre-randomization. Appropriate regulatory approvals (e.g., IRB, DSMB) will be obtained prior to initiation of this phase. Ten provider subjects will be consented and will complete a baseline organizational survey to assess their views and experiences of working in their respective trauma centers. Data quality assessments (e.g., whether 10 domain PTSD risk factor screening items are identified in the health record or from ward observation) will also begin during this phase.

Phase 3: Randomization. Randomization of the 24 trauma centers occurs during this phase.

Phase 4: Control phase initiation. Sites will be trained in the study protocol, recruitment procedure, consent process, and how to use the decision support tool recruitment modules. Recruitment of control patient subjects will begin following this training. Data quality assessment procedures and baseline standardized patient interviews with care manager provider subjects will also occur in this phase.

Phase 5: Follow-up outcome assessments. Follow-up interviewer training will begin prior to the initiation of this phase. The 3-, 6- and 12-month, blinded follow-up interviews will begin and continue ongoing throughout this phase.

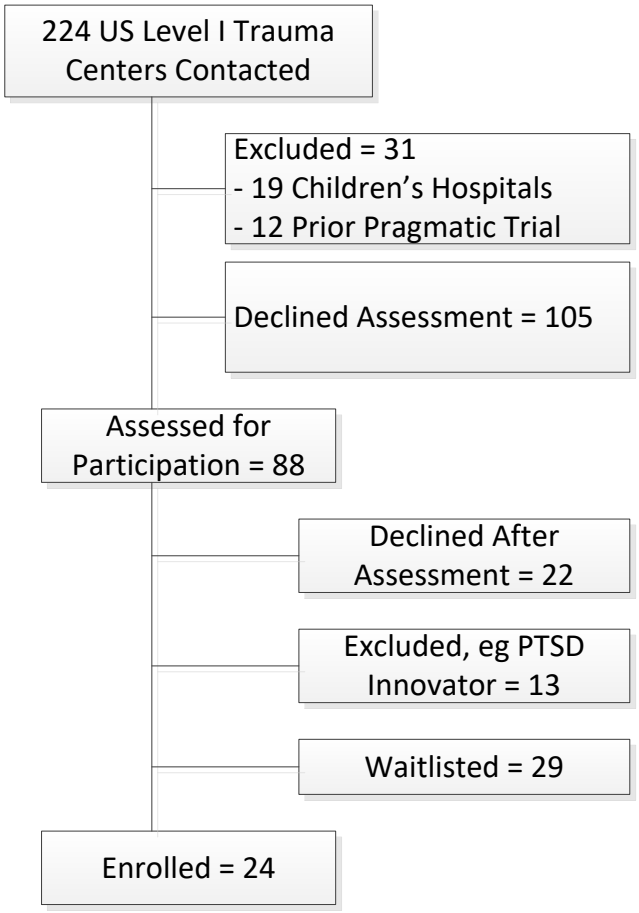
Phase 6: Intervention phase initiation. Recruitment of control patient subjects will end at each site based upon the wave they are assigned in the stepped wedge design. The UW intervention study team members will conduct a one-day intervention training workshop at each site at this time. Following this training, each site begins recruitment of intervention patient subjects and their care manager subjects begin charting notes in the decision support tool and have regular supervision with the UW study team. Intervention feedback and coaching will occur during this phase. Standardized patient sessions continue during this phase. Data quality assessment procedures will also continue at each site in this phase. All provider subjects will be asked to complete another organizational survey, after this phase is completed.

Phase 7: Final study procedures. Final data cleaning and analyses will be conducted in this phase. Manuscript preparation and the end of study policy summit will occur in this phase. The UW study team will coordinate with the American College of Surgeons' Committee on Trauma, as well as other stakeholders to hold a policy summit.

C. Site Eligibility and Recruitment

Over the course of the start-up phase, the TSOS study team has recruited the 24 trauma center sites that will participate in the trial. The goal of the selection process was to recruit 24 level I trauma centers nationally that would be capable of efficiently implementing the study procedures. The study team sent notification emails and/or contacted by telephone all US level I trauma centers (Figure 5). Responding centers were asked questions about current PTSD screening and intervention practices; the study excluded the less than 10% of sites nationally that were already routinely screening and intervening for PTSD and related comorbidity. Pediatric specialty trauma centers were also excluded from the investigation, as elements of the intervention (e.g., the administration of psychopharmacological agents targeting PTSD) are less well established for patients under the age of 18.

Figure 5. Site Recruitment CONSORT



With the exception of pediatric trauma center specialty status, the organizational characteristics of the 24 participating sites does not substantially differ from the characteristics of all US level I trauma centers potentially eligible for the study (Table 3). Site level generalizability/reach is an important aim of the investigation as it aims to influence American College of Surgeons' policy for PTSD and comorbidity screening and intervention for all trauma centers nationwide (see the RE-AIM investigation implementation assessments in the Statistical and Data Analysis Plan section). Potential sites were also required to identify three champions to assist with study implementation; the trauma surgical champion, the PTSD intervention champion, and the information technology champion (Table 4).

Table 3. Organizational Characteristics of TSOS study versus all US level I trauma centers

Characteristic	UH3 TC N=24 N(%)	Other TCs N=198 N(%)	*P*
Region of country			0.40
Midwest	7(29.2)	64(32.3)	
South / Southeast	4(16.7)	30(15.2)	
Northeast /East	5(20.8)	63(31.8)	
West	4(16.7)	28(14.1)	
Central	4(16.7)	13(6.6)	
Rural status	3(12.5)	24(12.1)	1.0
Population served			0.03
Adult	7(29.2)	92(46.5)	
Adult & pediatrics	17(70.8)	82(41.4)	
Pediatrics	0(0.0)	23(11.6)	
Missing	0(0.0)	1(0.5)	
Teaching hospital	23(95.8)	162(81.8)	0.14
Council of teaching hospitals	22(91.7)	143(72.2)	0.04
University affiliation	24(100.0)	189(95.5)	0.60
		Median(IQR)	
Number of interns/residents	327(282)	224(297)	0.11
Number of hospital beds	575(296)	534(318)	0.40
Number of inpatient admits	26971(16311)	25699(14978)	0.28

A champion is an individual who has the background and experience at a trauma center to advocate for a particular component or element of the study protocol. For example, a trauma surgeon champion is a surgeon opinion leader at the trauma center who can advocate with other surgical staff regarding the importance of PTSD screening and intervention. The champion at the trauma center site will interface with study personnel (e.g., trauma surgeon champion at each study site interfaces with study trauma surgery policy lead/co-investigator, Gregory Jurkovich, MD).

Senior trauma surgical co-investigator, Dr. Jurkovich will be in contact with the trauma surgeons-in-chief at all sites to coordinate investigative activities and to insure data is collected in a timely manner. All trauma centers will receive $20,000-$25,000 in payments and equipment/supplies (e.g., a laptop computer) over the course of the study in order to offset costs incurred by the requisite study research and information technology implementation activities. Also, as a further incentive for study participation all trauma centers may receive American College of Surgeons' research participation credit; centers residing in College verified states will receive a waiver on alcohol screening and brief intervention verification documentation criteria (Appendix 2).

Table 4. Site Champions

Site	Trauma Surgeon Champion	PTSD Intervention Champion	IT Champion
Baylor	Michael Foreman	Ann Marie Warren	Inga Gerard
Cedars-Sinai	Dan Margulies	Heidi Hotz	Meaghan Harada
Georgia Regents	Steven Holsten	Cassie Alexander	David Fallaw
Hartford	D'Andrea Joseph	Colleen Mulkerin	Marc Palter
Iowa	Patrick Kealey	Dionne Skeete	Dwight Barnes
L.S.U.	Alan Marr	Erich Conrad	Alan Marr
Madison	Suresh Agarwal	Becky Turpin	Jeff Burnett
North Memorial	Greg Beilman	Patty Reicks	Amina Baha
Ohio State	David Evans	Ken Yeager	Jeremy Harper
Regions	Michael McGonigal	Jen Gabbey	Kurt Isenberger
Santa Clara	John Sherck	Vickie Pham	Michael Hwa
Scott & White	Alex Thompson	Alex Thompson	Jeana O'Brien
Scottsdale	Charles Hu	Linda Sinwell	Nicole Reyes
Strong Memorial	Paul Bankey	Ray McLean	David Krusc
U.C. Davis	Joseph Galante	Bonnie McCracken	Kent Anderson
Wake Forest	Preston Miller	Laura Veach	Dee Emon
Wishard	Michelle Laughlin	Wendy St. John	Seth Brooks
UT Galveston	Bill Mileski	Lance Griffin	Paolo Mangahas
Cincinnati	Bryce Robinson	Dina Gomaa	Brett Hartnett
Vermont	Bill Charash	Jennifer Gratton	Matt Price
U. Kentucky Chandler Hospital	Andrew Bernard	David Maynard	Joe Bobadilla
Inova FairFax	Maggie Griffith	Anna Bradford	Alex Solorzano
Jacobi Medical Center	Sheldon Teperman	Melvin Stone	Janet Cucuzzo
U.T. Southwestern	Joseph Minei	Jessica Mitchell	Garrett Hall
U.C.L.A. Harbor	Dennis Kim	Nicole Perez	Dr. Moazzez
Utah	Giavonni Lewis	Amy Vincent	Shay Taylor

All 24 level I trauma center sites have completed subcontract agreements that are included with this UH3 transition request (see Table 5 and budget documents). The Western IRB (WIRB) approved the UH3 on March 16, 2015; the five sites that cede to WIRB have approved the UH3 protocol (Table 4). As of May 26, 2015, all of the 19 sites that have elected an individual IRB review had submitted the protocol to their respective IRBs; 7/19 sites had obtained IRB approval (Table 5).

Table 5. Regulatory Documentation Status			
Site/State	**Subcontract Complete**	**IRB Authority**	**IRB Status**
Baylor/Texas	Yes	Institutional IRB	Approved
Cedars-Sinai/California	Yes	Institutional IRB	Submitted
Georgia Regents/Georgia	Yes	WIRB	Approved
Hartford/Connecticut	Yes	Institutional IRB	Submitted
University of Iowa/Iowa	Yes	WIRB	Approved
L.S.U./Louisiana	Yes	Institutional IRB	Revision, Post-Review
UW Madison/Wisconsin	Yes	Institutional IRB	Submitted
Ohio State University/Ohio	Yes	Institutional IRB	Revision, Post-Review
Regions/Minnesota	Yes	Institutional IRB	Submitted
Scott & White/Texas	Yes	Institutional IRB	Approved
Scottsdale/Arizona	Yes	Institutional IRB	Submitted
Strong Memorial/New York	Yes	Institutional IRB	Submitted
U.C. Davis/California	Yes	Institutional IRB	Approved
Wake Forest/Virginia	Yes	Institutional IRB	Approved
Wishard/Indiana	Yes	Institutional IRB	Revision, Post-Review
U.T. Galveston/Texas	Yes	Institutional IRB	Approved
Cincinnati/ Ohio	Yes	WIRB	Approved
University Hospital/Vermont	Yes	Institutional IRB	Submitted
Chandler Hospital/Kentucky	Yes	Institutional IRB	Revision, Post-Review
Inova FairFax/Virginia	Yes	WIRB	Approved
Jacobi Medical Center/ New York	Yes	WIRB	Approved
U.T. Southwestern/ Texas	Yes	Institutional IRB	Approved
U.C.L.A. Harbor/ California	Yes	Institutional IRB	Submitted
University Hospital/Utah	Yes	Institutional IRB	Submitted
Santa Clara/California	Pending Final Signatures	Institutional IRB	Approved
North Memorial/Minnesota	Pending Final Signatures	Institutional IRB	Submitted

D. Provider Subject Eligibility and Recruitment

All provider recruitment procedures described below were successfully piloted during the UH2 start-up phase of the project. There is no formal screening for providers aside from a recommendation by another trauma center provider at a site or a search of the site's public website. No study activities will begin with providers until consent is obtained.

Providers participating in the study at each site will be consented into the study as provider subjects, as they will complete interviews in addition to their roles working with patient subjects. At the beginning of the study prior to randomization, all provider subjects, staff and care managers, will fill out an online organizational survey to assess their opinions of their work environment, experiences with trauma and traumatic stress, and potential for job turnover (see Measures and Assessments: Provider assessments section and provider measures in Appendix 11). Providers will be asked to complete this survey again after termination of recruitment/intervention activity at their respective sites. To compensate them for their time spent completing these surveys, provider subjects will be paid $35 at each time point.

For the roughly one to five PTSD interventionist care manager subjects at each site, there are additional study procedures. Throughout the study, a member of the UW study team will conduct standardized patient interviews (see also Treatment Conditions: Fidelity Assessments section and Appendix 12) with the care manager subjects. These standardized patient interviews will assess the care manager subject's skill set in interviewing patient subjects and will be tape recorded and later coded by study team members. A standardized patient interview consists of the UW study team member trained in conducting these interviews calling the care manager subject, introducing a mock patient situation, and running through an approximately 15-20 minute roll play in which the care manager subject addresses the mock patient's presenting issues (e.g., symptoms of PTSD, depression, alcohol use, etc.). These sessions are recorded and later reviewed by the UW intervention supervision team to incorporate in regular intervention supervision calls. These four standardized patient interviews occur at baseline prior to stepped wedge randomization, approximately just before training in the intervention, after intervention workshop training has taken place, and at the end of recruitment. The care manager subject(s) will be paid $50 for their time for each standardized patient interview.

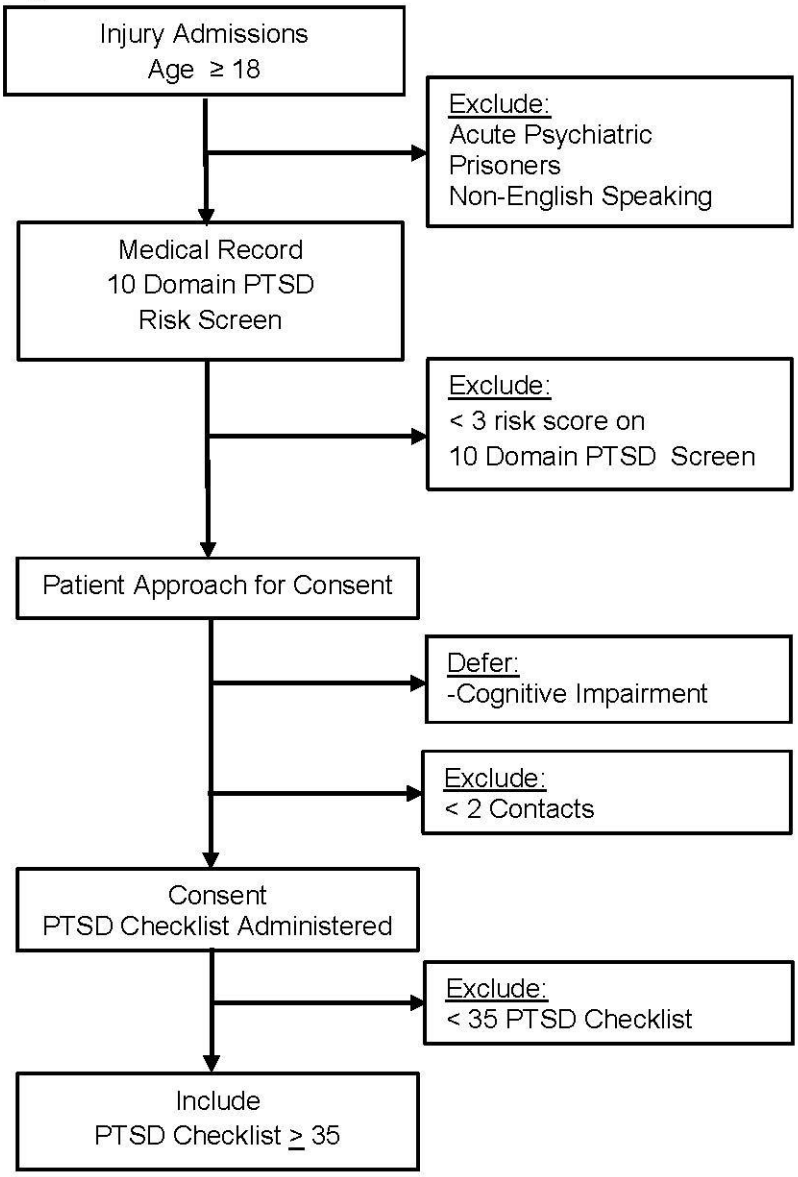
At the end of the study, one or more care manager subject(s) at each site may be asked to take part in a semi-structured qualitative interview that will be audio-recorded (see also the discussion of RE-AIM investigation implementation assessments in the Statistical and Data Analysis section and Appendix 12). This

qualitative interview will be conducted by a member of the UW study team. This assessment will elicit perspectives on participation in the study as a whole. They will be paid $50 for their time. Care manager subjects will be allowed to withdraw from the assessment portion of the study and still continue in their respective roles in the study at their site without any further interviews.

E. Patient Subject Eligibility, Recruitment, and Follow-up (Figure 6 & Appendices 5-6)
Patient identification and recruitment procedures described below were successfully piloted during the the UH2 start-up phase of the project. PTSD interventionist and other providers will identify potential patient subjects by reviewing inpatient rosters and identifying individuals who are most likely to have PTSD using the UW study team's validated PTSD screening algorithm further described below. Care manager subjects will then approach potential patient subjects about the study.

1. Potential patient subjects are identified by searching health records at each site for inpatients brought into the hospital for a traumatic injury. In order to review those records for this purpose, the study team will apply for and receive a waiver of consent and a waiver of HIPAA authorization.

Figure 6. Patient Recruitment Flow



2. In order to enhance the efficiency of trauma care system PTSD case finding, the study team has developed and implemented a 10 domain PTSD risk factor screen (Appendix 5).[49] The 10 domains used for screening are: 1) Female gender, 2) Non-white race/ethnicity, 3) Intentional injury, 4) Public or Veterans insurance status, 5) Intensive Care Unit (ICU) admission, 6) Previous hospitalizations 7) Substance use, 8) Tobacco use, 9) Evidence of PTSD diagnosis, 10) Other mental health diagnosis.
3. The PTSD screening evaluation can either be applied in an automated or manual format. The automated form of the evaluation can be programmed into the hospital computing system, while the manual form of the evaluation involves screening individual health records for the 10 PTSD risk factor domains. At both automated and manual sites that select the manual screening, UW study team members will train PTSD intervention care manager subjects to adhere to the chart abstraction checklists developed and validated by the UW study team (see also the Data Quality Assurance and Harmonization section).
4. Each day the PTSD interventionist will oversee a hospital-based review for admitted injured patients. The review will aggregate data from the 10 PTSD risk factor domains. Patients with higher scores on the evaluation (i.e., more positive risk elements) will be prioritized for approach for formal PTSD symptom assessment with the PTSD Checklist. Providers will identify potential patient subjects who meet the criteria of having ≥ 3 PTSD risk factor domains positive. Once a patient is approached for the investigation, in order to be eligible for this study and move on to the consent process, the provider will inform the potential patient subject that they must be able to provide at least two pieces of contact information that

consists of at least one phone number and a second alternate contact (e.g., another phone number, email address). This requirement helps ensure that the patient subject has a better likelihood of being able to be contacted for future interviews. During the approach and prior to the consent process, the provider will review this with a potential patient subject and will not enroll someone if they do not have at least two contacts. This is being done because the internal validity of the study relies on adequate follow-up rates. The study team has employed this procedure before and obtained greater than 70-80% 6-12 month follow-up rates of nationwide studies with low income, ethnically diverse, acute care medical patients.

5. The recruitment process will vary at sites depending on a number of factors including the ability of sites to automate screening procedures, the number of patients selected for recruitment each day and the availability of health record data. Any of the exclusions (e.g., 18 > age, acute psychosis, prisoner) or any of the 10 PTSD risk factor domains may be obtained from the health record, ward observation, or patient approach.

F. Patient Follow-up Contact

The study team will ask patient subjects for at least two pieces of contact information. One piece will need to be a phone number, while the second piece of contact information could include the patient's address, email address or any of the previous contacts for a relative or friend. In the event that the patient subject changes residence (a common event after injury admission), the follow-up team may use these alternate sources.

Over the 12 months after the injury, the follow-up team may perform check in phone calls with patient subjects to insure that the contact information on file is up-to-date; at the 9-month follow-up time point this phone check-in may be performed in order to remind subjects that their final follow-up interview will be coming in about three months. Patient subjects at this time will have all contact information on file confirmed and asked for any new information.

After a trauma, patient subjects sometimes relocate temporarily in order to receive better care, such as movement from independent living to a skilled nursing facility. Therefore, in addition to contacting patient subjects through the information they provide during the initial interview, the follow-up team will utilize several approaches to try and stay in touch with patient subjects across the study window. These approaches are:

1. Contacting other people in the patient subject's life. At recruitment, patient subjects will be asked for phone numbers/addresses of at least two contact sources (for example friends or relatives). In the event that a patient subject is no longer at their residence, the alternative follow-up numbers listed will be another way of contacting them.
2. Looking at hospital records. If the follow-up team is unable to reach a patient subject after repeatedly trying to contact them through the information provided, they may have the UW research coordinator contact the respective hospital sites to review their hospital records for any updated contact information.
3. Conduct a public records search. The follow-up team may also conduct a public records search to find new contact information. Examples of public records searches conducted may include the Yellow Pages, or using a Google search to find additional contact information. The follow-up team will search for records or information on forums that are open to the public either for free or at a cost. Patient subjects will not incur this charge; it will come from the study budget.
4. Contact through a social media page. If the follow-up team finds a social media page (e.g., Myspace, Facebook, Google+, etc.), they may attempt to contact a patient subject on these sites via private message. They will only send this message if they are able to match at least three identifiers with information the patient subject already provided, including: first name, last name and middle initial, date of birth, address, hometown, phone number or photo identification. This information will be sent to the patient subject's inbox and will not be viewable to the public. No information identifying the study or its purpose will be included in this message.
5. Sending an interview in the mail, email or other means (e.g., FAX). If the follow-up team cannot reach a patient they may send the interview through the mail, by email or by other means such as FAX. The interview form would not include a name or any identifying information. Patient subjects will be reminded they should complete the interview in a confidential space where no one else can have access or see the interview.

4. Treatment Conditions

A. Enhanced Usual Care Control Condition

The control patient subjects will receive enhanced usual trauma center care from the care manager subjects. Prior investigation suggests that usual posttraumatic care includes routine surgical, primary care, and emergency department visits, as well as the occasional use of specialty mental health services. The enhanced portion of the usual care will consist of the recruiting provider informing the ward nurse currently covering the patient subject's care of any distress they are experiencing as identified by a PTSD Checklist score of ≥ 35 or Patient Health Questionnaire (PHQ-9) item 9 ≥ 1 administered during the baseline interview (Appendix 10). During the control phase of the protocol, providers who are recruiting will utilize components of the decision support tool to document screening activity, but will not receive any study team supervision in the application of the tool intervention elements; these elements will be kept "blinded" from the recruiters during the control phase. Data quality procedures for the usual care control training include assessment of PTSD risk factor domain screening, PTSD Checklist interview reliability assessments, and decision support tool data documentation checks.

B. Stepped Collaborative Care Intervention Condition (Appendix 7)[51,129]

As with control patients, intervention patients will receive nurse notification of PTSD Checklist scores of ≥ 35 and/or PHQ-9 item 9 scores of ≥ 1 (Appendix 7). Dr. Zatzick and potentially other UW study staff (e.g., Dr. Darnell) will visit the trauma center sites in order to perform a one-day intervention workshop training. The workshop will provide an overview of the core elements of the PTSD and comorbidity intervention (Appendix 7). The workshop will begin with a review of the experiences of the control phase. Front-line providers at each site will be asked to review control phase cases and consider what potential interventions may have been appropriate to deliver had they had adequate time and supervision. Next, the trainers will review the intervention elements including care management, medications, MI and CBT elements and community linkage. An in-depth review of the decision support tool modules that support the intervention will also occur. Finally, the ongoing plan for caseload staffing and supervision will be discussed with each site. Aspects of each training workshop may be audio-recorded and rated to assess fidelity to the intervention model.

After the one-day workshop training, Drs. Zatzick and Darnell will initiate between 1-4 care management supervisory calls each month (e.g., weekly calls) for the duration of the intervention period at each site. Utilizing the computerized decision support tool, the care managers will present cases to the supervisory team. These regular meetings may range between approximately 15 minutes and 2 hours depending on the number of patient subjects and symptomatic intensity of caseloads. These sessions will include coaching in concern elicitation, CBT and MI techniques, as well as problem-solving surrounding organizational obstacles to screening and intervention implementation for PTSD and related comorbidity. These calls will also include coaching on evidence-based medication prescription for PTSD and comorbidity. The computerized decision support tool will also be used to assess fidelity to specific care management, behavioral therapy, and pharmacotherapy elements of the clinical treatment protocol. The care managers will be able to contact Drs. Zatzick and Darnell by phone if specific questions regarding patients arise; of particular note, Drs. Zatzick and Darnell, will provide written feedback on questions via the staffing notes function in the decision support tool. With care manager subject permission, elements of any training/supervision procedures may be audio-recorded for educational or fidelity purposes.

The care management intervention elements are distilled from manualized procedures derived from the study team's previous intervention trials (Appendix 7). The delivery of specific elements will be dependent on care manager time allocation and patient subject intensity of symptoms. In the protocol, care management will occur up to six months after the injury. It is anticipated that the care manager will spend approximately 2-4 hours working on intervention and treatment linkage for each intervention patient. The care manager will attempt to meet all intervention patients during their trauma center or emergency department stay. During this meeting, the care manager will begin to elicit and target for improvement each patient's unique constellation of posttraumatic concerns. This will help to enhance initial treatment engagement and therapeutic alliance. The care manager will give the patients their hospital contact number and encourage calls for spontaneous questions and concerns. The care manager will also elicit treatment preferences (e.g., CBT only, medication only, combined treatment) for PTSD and comorbidity and will schedule ongoing times to meet/call the patients during the initial days and weeks post-injury. Whenever possible, patients' family members will be integrated

into treatment planning and longitudinal care. The care manager will elicit information regarding patients' plans for physical and mental health care follow-up, and will inquire about whether or not the patients have a primary care provider (PCP). During caseload supervision, this information will be relayed back to the supervising UW study team members. After team discussion, the care manager subject will discuss treatment options with the patient and come to a shared decision about the initial treatment plan with the patient, their family members, and providers.

The elements and progression of the MI, CBT, and medication modules are described below. The intervention includes a MI psychotherapy element embedded within care management that targets both treatment engagement and high risk behaviors, such as alcohol and drug use problems that risk recurrent injury. The MI intervention element consists of a graded sequence of clinical tasks including: a) eliciting from patient subjects their views of the importance of changing and of their confidence in being able to change, b) giving patient subjects personalized feedback, and c) clarifying the patient subject's behavior change goals and action plans.[230] The MI intervention component has been successfully developed and implemented by the UW group over the past decade in single and multi-site pragmatic clinical trials targeting alcohol use problems. By empathically exploring ambivalent feelings about alcohol use, MI approaches encourage movement in the direction of reductions in at-risk drinking behaviors.

The CBT intervention component builds upon the engagement and therapeutic alliance developed with concern elicitations and MI. The intervention team has embedded aspects of evidence-based CBT within routine care management. The PTSD interventionist will utilize a non-demanding, MI interpersonal style when discussing possible behavioral interventions to target symptoms of PTSD, depression, and other comorbidities. The care manager subject will work to gauge patient subject willingness and ability to complete CBT exercises and adjust recommendations to match patient subject readiness to change current ineffective behaviors. Consistent with CBT principles and the principles of chronic condition self-management, the PTSD interventionist will incrementally increase sophistication and difficulty of behavioral tasks in order to help the patient subject achieve early successes and increase self-efficacy.

CBT approaches also have proven efficacious in the reduction of PTSD, depression, and related comorbid presentations such as suicidality; CBT elements will be embedded within care management to target PTSD, depressive, and other related (e.g., insomnia, pain) symptoms during trauma center inpatient, acute care outpatient, and telephone follow-up contact with patient subjects. Specific elements targeting PTSD include psychoeducation, problem-solving, breathing exercises, and behavioral activation homework assignments. Specific elements targeting depression include psychoeducation, problem-solving, activities scheduling, attention to experience, and behavioral activation homework assignments. For patient subjects who demonstrate adequate CBT readiness and motivation, homework assignments are given.

In prior single site investigations, the study team has developed pharmacotherapy protocols that simultaneously target prevention of PTSD and comorbidity, and mitigation of symptom exacerbations among injury survivors with pre-existing chronic medical conditions. As in previous trials, the medication element will coordinate pre-injury medication prescriptions for chronic medical conditions with post-injury medication decisions. Due to high documented rates of medication errors in the acute care to primary care transition, the initial step in the care coordination intervention for chronic medical conditions will be taking an accurate medication history from the patient subject; next the study team may reconcile any discrepancies between the patient subject, hospital, and outpatient provider medication records.

The medication intervention element also aims to initiate and insure adequate follow-up of pharmacologic treatment targeting PTSD and related comorbid presentations. The investigative team will train the site teams in preventive pharmacotherapy targeting PTSD and comorbidity. A series of placebo-controlled blinded RCTs have established the SSRI class of anti-depressants as efficacious in treating PTSD and depression. Recent guidelines endorse these agents as the first line medication treatment for PTSD and depression. Other trials in adults suggest that psychopharmacological agents may also be effective in treating sleep, pain, TBI and somatic symptom amplification disturbances that occur concurrently with PTSD and depressive symptoms. In terms of treatment, symptomatic intervention patient subjects electing PTSD pharmacotherapy will be recommended to begin, advanced to, and maintained on guideline-level therapeutic doses of SSRI anti-depressant agents (e.g., Sertraline 50-200mg) either as surgical patients or through primary care linkage and consultation.

The site team will potentially perform psychotropic medication evaluations and medication prescriptions in a number of settings including trauma inpatient wards, emergency departments, trauma surgery outpatient

clinics, over the telephone, and in the community. For all psychotropic medication prescriptions, the intervention team will attempt to consult with inpatient, outpatient, or primary care teams with regard to medication recommendations. Medication recommendations will preferably derive from team discussions and staffing with the study principal investigator and psychiatric supervisor Douglas Zatzick, MD. These discussions will be recorded in the study clinical decision support tool and may be documented in the health record by non-research clinical staff. The team will not become the primary prescriber of psychotropic medications. However, in the transitional care period between hospitalization and the solidification of outpatient follow-up, the study team may temporarily prescribe medications. On occasion, when patient subjects have demonstrated symptomatic need/distress and cannot obtain timely prescriptions from a non-study team provider, a study team member may provide psychotropic medication prescriptions to patient subjects. Study team members in this role are likely to vary and could include psychiatrists, nurse practitioners, or other surgical or medical providers (e.g., trauma surgeon, PCPs). All study team prescriptions will be reviewed by Dr. Zatzick.

A key role for the PTSD interventionist care manager is to insure that high quality trauma center-to-community linkages occur.[49,129,231] Prior investigation by the study team has documented that approximately 40% of injured trauma survivors do not have a PCP at the time of injury admission. The care coordination component will include a series of intervention elements that have previously improved acute care to primary care and community transitions.[146-149] Intervention elements will include hospital to primary care medication reconciliation, clear care manager-to-patient communication regarding discharge instructions and follow-up, MI and CBT intervention elements targeting the promotion of patient self-efficacy regarding acute care to community transition, engaging the help of family members and other patient subject social support (when available), ensuring appropriate PCP follow-up, and ongoing coordination and monitoring of care during and after the transition with the patient subject, family members, and inpatient/outpatient care providers. In coordinating care with other health care providers or a patient subject's family or friends, care manager subjects may speak with individuals in person, over the telephone, or communicate by text, email, or other electronic means, such as FAX.

Proactive, perseverant linkage efforts are a key element of the care management intervention. The investigators have previously developed aggregated lists of trauma center to community linkage resources. After a site has officially become part of the study, the research team may work with the care manager subjects to compile a list of community resources specific to their trauma center; this list may be entered into the computerized decision support tool. With the advent of health care reform, the team may also work to procure appropriate insurance coverage for trauma inpatients (e.g., through health benefit exchanges).

A key aspect of the study will be to select appropriate PTSD intervention champion(s). The investigative team is aware that the champion could potentially be housed within a number of trauma center organizational work units.[201,232,233] Procedures for identifying appropriate trauma center work units and individual PTSD intervention champions have been derived from the prior DO-SBIS investigation.[130,136] This will allow the clinical research team first hand experiences with trauma surgery nursing, trauma center social work and psychiatric consultation liaison service care management options that could potentially support the activities of the PTSD intervention champion. The study team anticipates that the PTSD intervention champion will either be a nursing (RN), social work (MSW), or PhD-level routine trauma center practitioner.[130,136] Dr. Zatzick will oversee the PTSD intervention care manager subject selection process.

C. End of Participation

While final patient subject follow-up interviews take place approximately 12 months post-consent, intervention activities with intervention patients are anticipated to conclude approximately 6 months after patient subjects consent into the trial. The objective of the final contact is to negotiate a specific plan for ongoing care. The care manager subjects will discuss strategies for maintaining treatment gains with each intervention patient. This means proper handoff of medication prescription management to a patient subject's preferred primary care or other medical provider, linkage to community resources, and psychotherapy referrals. Resources to be recruited into treatment maintenance include ongoing relationships with the primary care or other providers, the patient subject's family, and other community support services.

Once the 12-month follow-up interview has been completed with control patient subjects, they will be informed of the end of their involvement with the research study. As these subjects will not receive any care other than what is usually provided at the hospital they were recruited at, there will be no transition of care

other than what they may already receive from their respective hospital. PTSD interventionist care manager may be invited at the end of their involvement to take part in a semi-structured exit interview with the UW study team (see below and Appendix 12).

D. Fidelity Assessments

The intervention fidelity assessments aim to simultaneously optimize the goals of fastidiously documenting intervention implementation process while also addressing the pragmatic trial requisite for minimal research specific resources dedicated to trial adjudication.[184] The three fidelity domains assessed attempt to optimize these two at times competing implementation science and pragmatic trial aims.

1. Workshop training. The PTSD interventionists and other on-site staff will attend a one-day intervention training workshop. The workshop training will be rated by study team members to ensure that key elements of the training are delivered (Appendix 7); aspects of each training workshop may be audio-recorded and rated to assess fidelity to the intervention model. Trauma center staff attending the workshops may be asked to provide post-workshop evaluations (Appendix 12).
2. Intervention fidelity. Level I trauma centers typically employ psychiatrists and psychologists as members of psychiatric consultation/liaison services, rehabilitation medicine services, and behavioral medicine and clinical pain teams. These highly trained mental health professionals are at the present time infrequently assigned supervisory roles in the delivery of services for injured patients suffering from PTSD and related disorders. The early intervention model restructures trauma center care by assigning two highly trained providers form the TSOS study team to supervise the delivery of evidence-based treatments by the front-line care management providers. For the current study, Dr. Zatzick (Psychiatrist) and the supervising psychologist will provide weekly supervision individually with each of the PTSD interventionists and other site team members. The interventionist team will present new cases and treatment plans during the weekly team meeting. After this team discussion, the care managers will discuss treatment options with the patients and come to a shared decision about the initial treatment plan. Follow-up on active patients will also occur at team meetings, as will decision making around stepped-up care and psychopharmacology suggestions. Intervention team members will enter all assessments and treatment contacts into web-based forms contained within the study decision support tool.[110-113,234] Because information is available in real time the system can be used by the MD/PhD intervention team supervisors to monitor and support the standardized implementation of the stepped care procedure. The automated decision support tool will also be used to assess adherence to specific care management, behavioral therapy, and pharmacotherapy elements of the clinical treatment protocol (Appendix 12).[111,234,235]
3. Standardized patients. In the study team's prior pragmatic trial focusing on alcohol screening and intervention, standardized patient fidelity assessments were used to assess fidelity to MI interventions delivered by front-line trauma center providers. In order to assess MI skills, intervention and control screening and brief intervention (SBI) providers participated in a total of seven, 20-minute standardized patient telephone interviews during which brief interventions were simulated.[208,236] Prior to randomization, baseline standardized patient interviews took place with SBI providers at all 20 sites. Intervention site providers were scheduled for standardized patient interviews one week after workshop training and then again at 1-, 4-, 7-, 17-, and 27-months. Control site providers underwent a comparable sequencing of standardized patient assessments. Standardized patient scenarios were designed to reflect increasing clinical complexity over time. Initially, standardized patient actors role-played injured patient scenarios that reflected optimal readiness to change at-risk drinking behaviors (e.g., the baseline, pre-randomization standardized patient was in "action"), while later standardized patients presented more difficult scenarios (e.g., the final 27-month standardized patient was "pre-contemplative").[208,230]

   Each standardized patient interview was scored using the Motivational Interviewing Treatment Integrity (MITI) coding system.[237] Domains assessed by the MITI include the frequency of specific MI concordant behaviors such as counts of the delivery of open-ended questions. The MITI has established reliability and validity, and MITI coding procedures have been manualized.[237]

   The MITI will again be used to code patient standardized interviews in the UH3 study; in the UH3 protocol for the PTSD care manager interventionist subjects at each site, there are additional study procedures. Throughout the study, a member of the UW study team will conduct standardized

patient interviews (Appendix 12) with the care manager subjects. These standardized patient interviews will assess the PTSD interventionist subject's skill set in interviewing patient subjects and will be tape recorded and later coded by study team members. A standardized patient interview consists of the UW study team member trained in conducting these interviews calling the care manager subject, introducing a mock patient situation, and running through an approximately 15-20 minute role play in which the care manager subject addresses the mock patient's presenting issues (e.g., symptoms of PTSD, depression, alcohol use, etc.). These sessions are recorded and later reviewed by the UW intervention supervision team to incorporate in regular intervention supervision calls. These four standardized patient interviews occur at baseline at the initiation of the stepped wedge randomization and again just before training in the intervention and after intervention workshop training has taken place, and at the end of recruitment. The care manager subject(s) will be paid $50 for their time for each session. This procedure was successfully piloted for four care managers (total of 16 standardized patient interviews) during the UH2 pilot. Standardized patient scenarios to be employed in the study are included in the appendices (Appendix 12).

5. Data Quality Assurance and Harmonization

A. Overview

The data quality assurance plan provides a framework for data quality assessment and ongoing data quality monitoring for the TSOS study. The TSOS study is a large scale 24 trauma center site pragmatic clinical trial that aims to directly inform national trauma care system policy for injured patients presenting with PTSD and related comorbidity. A series of prior single- and multi-site pragmatic trials have informed the design and implementation of the UH3 data quality and harmonization procedures; these procedures were piloted and refined during the UH2 start-up period.[51,29,43,129,172,236]

The study will use electronic health record (EHR) data gathered at the sites during the course of routine clinical care to integrate patient eligibility screening into clinical workflow. A wide variety of EHR systems and variations in local capacity to leverage technology to deliver data for research projects is expected.[108] This document describes strategies that will permit all sites to deliver highly reliable data, regardless of their technology leveraging capacity. These strategies include methods for creating local datasets of candidate patients, transforming data into a data model, techniques for detecting and reporting missing/erroneous data, and a process for harmonizing delivered data.

After patients are enrolled in the study, front-line trauma center providers will collect and record new information used only for this research project, including patient reported outcomes (PROs). These data are gathered by front-line providers working across all 24 sites and are managed in a single electronic system maintained by the UW study data coordinating center. The TSOS data management plan describes strategies that will ensure all providers collect and record data uniformly across the 24 participating sites. These strategies include: (1) description of workflow, (2) standardization of injury cohort definition, (3) provider training, (4) validation of EHR PTSD risk domain screening, (5) training in standard operating procedures for patient interviewing and data collection, (6) periodic reviews of site providers to assess for process drift, and (7) the data coordinating center will conduct an independent review of each patient's EHR-derived trauma registry data; these results will be compared to site-submitted data to assess variance and data discrepancies.

B. Conceptual Frameworks Informing the TSOS Data Quality Assurance Procedures: NIH Health Care Systems Research Collaboratory Assessing Data Quality – Version 1.0

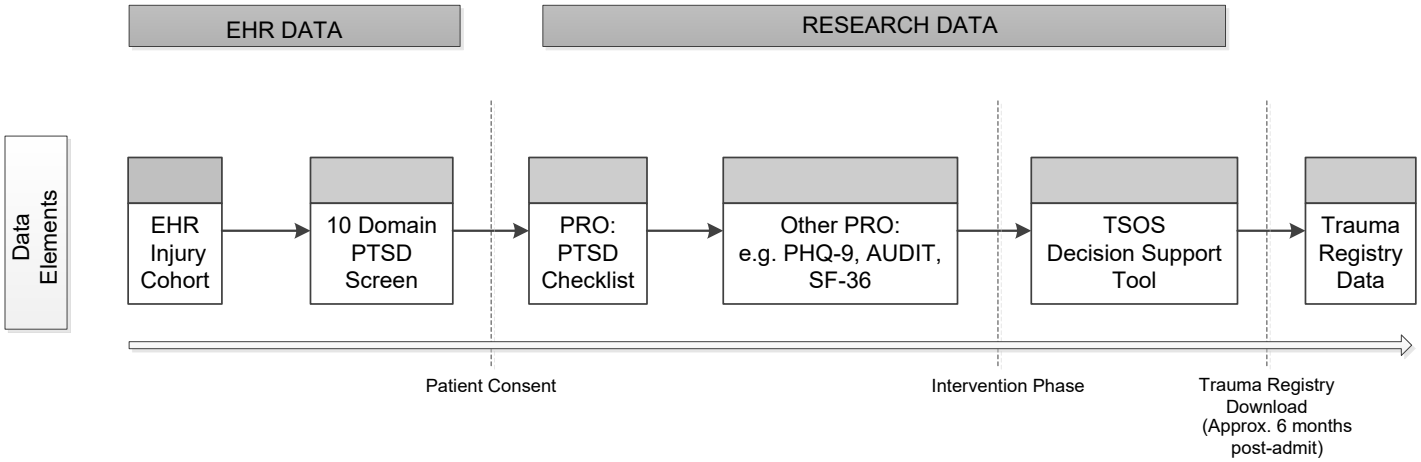
The methodological approach to developing data quality assessment and ongoing data quality monitoring procedures for the TSOS study has relied heavily upon conceptual frameworks developed by the NIH Health Care Systems Research Collaboratory Phenotypes Core (see Assessing Data Quality for Healthcare Systems Data Used in Clinical Research, Version 1.0).[238] The following information derived from these guidelines informs the approach to data quality assurance in the TSOS study.

1. Category of data collected. The NIH Health Care Systems Research Collaboratory Phenotypes Core explicitly defines two categories of data to be collected in pragmatic trials (Figure 7): 1) collection of data specifically for a pragmatic trial, where the investigative team is able to influence or control the data collection process,[239] and 2) use of data generated in routine care, where the investigative team has little or no control over the data collection.[238] (see Assessing Data Quality for Healthcare Systems Data Used in Clinical Research, Version 1.0; page 4).[238] For both the first and second category of data, the Collaboratory Phenotype Data Standards and Data Quality core has articulated specific criterion for ascertaining data quality (see Assessing Data Quality for Healthcare Systems Data Used in Clinical Research, Version 1.0; page 13).[238]
2. Data quality criterion. Specific Collaboratory guidelines have been developed for assessing the ability of pragmatic trials to produce data that sufficiently supports research conclusions (see Assessing Data Quality for Healthcare Systems Data Used in Clinical Research, Version 1.0; page 17).[238] The Collaboratory recommends that demonstration projects address the following criterion pertaining to data collection, data quality assurance, harmonization and ongoing UH3 data quality control:

Criterion 1: "Are data collection methods adequately validated?"
Criterion 2: "Validated methods for the electronic health record information?"
Criterion 3: "Demonstrated quality assurance and harmonization of data elements across healthcare systems/sites?"
Criterion 4: "Plans adequate for data quality control during the UH3 (trial conduct) phase?"

The Collaboratory further recommends that each question be considered distinctly for each of the two categories of data: data collected in routine care and research data (see Assessing Data Quality for Healthcare Systems Data Used in Clinical Research, Version 1.0; Table A1).[238] Criterion 1, validation of data collection methods, applies only research data. Criterion 2, data quality assurance methods validation, applies only to data collected in routine care. Criterion 3 and 4 apply to both routine care and research data collection. The Collaboratory Phenotypes Data Standards and Data Quality core also recommends the creation and ongoing use of data flow and workflow diagrams for pragmatic trials (see Assessing Data Quality for Healthcare Systems Data Used in Clinical Research, Version 1.0 and Appendix 9).[238] The Collaboratory recommends using generic workflow diagrams when assessing sites for incorporation into the study's comprehensive data impact and harmonization strategy. Site-specific limitations and variances in clinical care processes can then dictate changes to the generic workflow to create a site-specific diagram that provides specific details regarding work flow and data flow that should inform data quality assurance processes for each site.

Figure 7. TSOS Data Flow Chart



C. Categories of Data Collected in the TSOS Study

The investigation will include six key types of data (Table 6): 1) EHR data informing trauma cohort definition, 2) EHR data informing the 10 domain PTSD risk screen, 3) The PTSD Checklist [240] PRO measure used to define the PTSD phenotype, 4) Other patient reported outcomes for definition of secondary outcomes including the Patient Health Questionnaire (PHQ-9),[241] the Alcohol Use Disorders Identification Test,[242] and the Medical Outcomes Study SF-12/36 Physical Components Summary Score,[243,244] 5) Additional clinical data collected in the TSOS decision support tool and, 6) Trauma registry derived electronic health record data including traumatic brain injury and pre-injury chronic medical condition ICD codes. Each of the six data types are explicated in greater detail below.

1. Traumatic injury cohort definition and exclusions. The trauma cohort definition describes the inclusion criteria a site will use to identify the pool of inpatients that are eligible to be screened for inclusion in the TSOS project. Potential patient subjects are identified by searching health records at each site for inpatients brought into the hospital for a traumatic injury. In order to review those records for this purpose, the study team will apply for and receive a waiver of consent and a waiver of HIPAA authorization. Further phenotypic review of these domains can be found in the Data Quality/Phenotyping Manual (Appendix 9.
2. 10 domain PTSD risk screen. Once a list of eligible traumatically injured patients is derived, all patients on the list will be screened for the following 10-item risk factors. This evaluation utilizes 10 data elements that are readily available in a typical robust EHR to identify patients at high risk for the development of PTSD.[49] The use of the 10 domain screen will increase screening efficiency in a clinical workflow integrated fashion for identifying patients at high risk for the development of high early PTSD symptom levels. However it is important to note that the PTSD cohort definition occurs after a patient is consented, and with the administration of the 17 item PTSD Checklist PRO measure. The 10 PTSD risk

domains include: 1) Female gender, 2) Non-white race/ethnicity, 3) Intentional injury, 4) Public or Veterans insurance status, 5) Intensive Care Unit (ICU) admission, 6) Previous hospitalizations 7) Substance use, 8) Tobacco use, 9) Evidence of PTSD diagnosis, 10) Other mental health diagnosis. Patients with ≥ 3 PTSD Risk Domains will screen into the study. The 10 domain screen can either be utilized as an automated or manual EHR abstraction procedure. Further discussion of the 10 domains can be found below and in Appendix 9.

3. TSOS PTSD phenotype: PTSD Checklist 17 item patient reported outcome (see Measures and Assessments section and Appendix 10).
4. Other patient reported outcomes for definition of secondary outcomes (see Measures and Assessments and Appendix 10). Other patient reported outcomes assessments that will be used to define the key secondary outcomes of depressive symptoms, alcohol use problems and impairments in physical function are described below.
    a. Depressive symptoms. The 9-item Patient Health Questionnaire (PHQ-9) brief depression severity measure will be used to assess depressive symptoms.[241] The PHQ-9, item 9 will be used to assess for suicidal ideation, with an additional item to assess more recent suicidal intent. The PHQ-9 has established reliability and validity in acute and primary care medical patients.[29,51,241,245,246]
    b. Alcohol use problems. The AUDIT, a 10-item screening instrument for the early identification of problem drinkers,[242] will be used to assess alcohol use problems before and after the injury hospitalization. The AUDIT's reliability and validity are well established and the scale has been widely used in general medical settings.[247]
    c. Limitations in physical function MOS SF-12/36.[243] The investigation will use the MOS SF-12 at baseline, and SF-36 at 3-, 6-, and 12-month follow-up to assess physical functional outcomes. The SF-12/36 has established reliability and validity and the measure has been used extensively with traumatically injured populations.[244]
5. TSOS decision support tool data. Data collected in the TSOS decision support tool will be used to assess intervention activities and time (Appendix 7).
6. Trauma registry derived electronic health record data. Key variables derived from the trauma registry include ICD codes required to assess the severity of covariates, such as the severity of traumatic brain injury and the presence or absence of chronic medical condition comorbidity and injury severity scores (ISS). Trauma registry data will also allow comparisons of the clinical, injury and demographic characteristics of patient subjects selected for the study with all other non-consented patient subjects admitted during the time period of the study at each of the 24 trauma centers but not included in the clinical trial. Electronic health record data collected in the trial will be compared to national trauma registry standards.[63,248,249]

D. Summary of TSOS Data Characterization

TSOS data for traumatic injury cohort definition, 10 PTSD risk domain assessment, and trauma registry data constitute data that is collected as part of routine trauma center care that will be utilized by the study to identify the traumatic injury cohort and to identify selected covariates such as the presence/absence of ICD injury codes, the presence/absence of pre-injury chronic medical conditions (see Table 6).

Table 6. TSOS Data Types: Research versus Routine Care Categorization

Data Type	Category 1: Prospectively Collected Research Data	Category 2: Routine Care Data	Notes
1) Injury Cohort Definition		X	
2) 10 PTSD Risk Domains		X	
3) PTSD Checklist PRO	X		
4) Other PROs	X		
5) TSOS Decision Support Tool	X		
6) Trauma Registry		X	EHR Derived Registry Data

PTSD Checklist and other PRO and TSOS clinical tool data constitute data that will be collected specifically for the research study (see table below). For the study, PTSD and comorbidity cohort definition will occur with the use of the patient reported outcome, PTSD Checklist data. Patient reported outcome measures will also be used to define secondary outcomes including depression, alcohol use problems and physical functioning. Providers will assess organizational factors related to the implementation of PTSD screening and intervention services with provider reported outcome measures. The TSOS decision support tool data will document intervention patient activities.

E. Data Quality Assessment and Harmonization for TSOS Data

Data quality assessment and harmonization procedures for the TSOS study derive from application of the Collaboratory conceptual framework and TSOS study team previous investigation and piloting procedures (see Figures 8-10).

Figure 8. Framework Informing Traumatic Injury Cohort Definition and 10 PTSD Risk Domains Routine Care Data

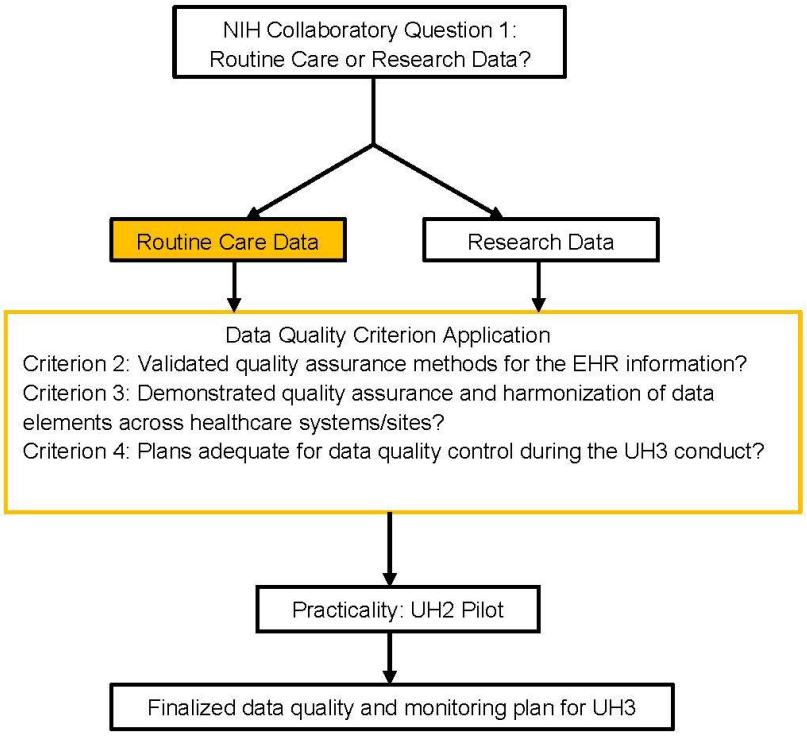


Figure 9. Framework Informing Trauma Registry Data

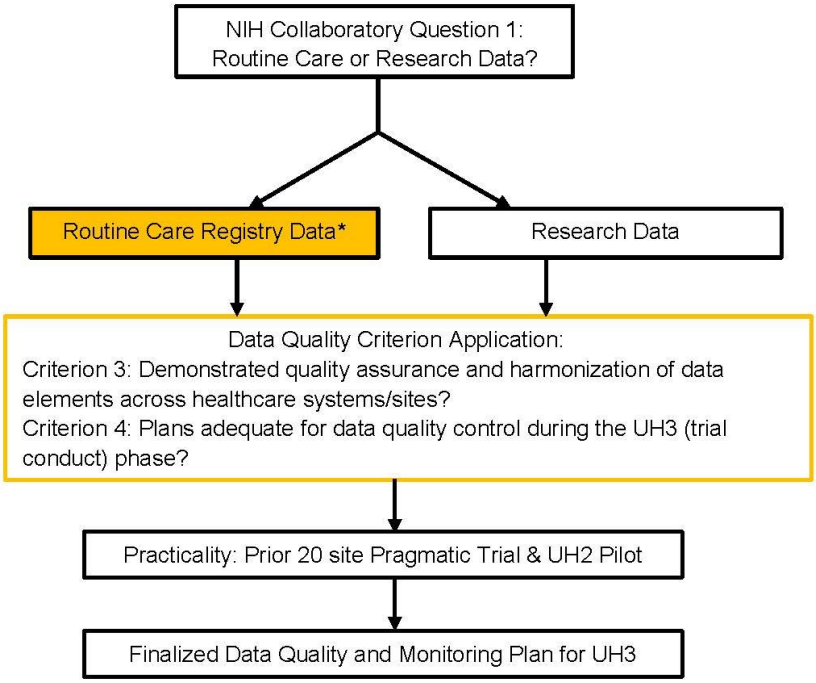
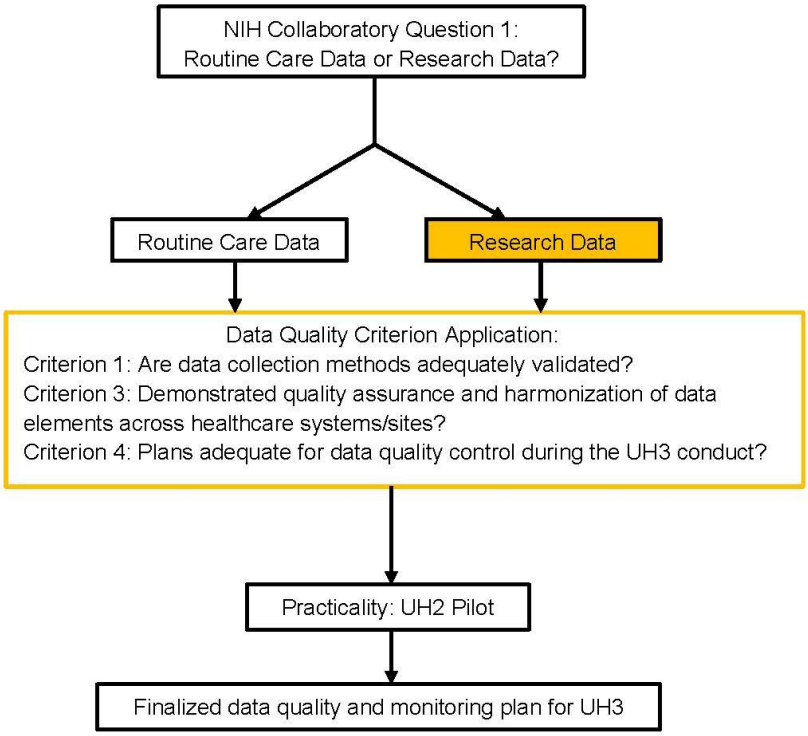


Figure 10. Framework Informing PTSD Checklist, Other Patient/Provider Reported Outcome, and TSOS Decision Support Tool, Research Data



F. Proposed TSOS UH3 Data Quality and Harmonization Procedures

The UH3 data quality and assurance procedures will follow general phases of the UH2-UH3 protocol (Figures 8-10 & Table 7).

Table 7. TSOS UH3 Data Quality Assurance Procedures by Study Phase

Study Phase	TSOS Data Category	Procedure	Component of Collaboratory Conceptual Framework Addressed
Pre-Randomization	Injury cohort, 10 domain PTSD risk screen	Detailed survey Detailed workflow map	Criterion 2: Methods for EHR data validation
Pre-Randomization	Injury cohort, 10 domain PTSD risk screen	5-patient sample evaluation	Criterion 2: Methods for EHR data validation
Pre-Randomization	PTSD phenotype, Other PROs	Baseline interviewer training	Criterion 1: Methods for research data validation
Randomization			
Control Initiation	PTSD phenotype, Other PROs	Initiate weekly intra- and inter-site data review	Criterion 1: Methods for research data validation Criterion 3: Harmonization
Control Initiation	Injury cohort, 10 domain PTSD risk screen	5-patient sample evaluation	Criterion 2: Methods for EHR data validation
Control Initiation	PTSD phenotype	Drift assessment baseline of % PTSD positive on PTSD Checklist	Criterion 2: Methods for EHR data validation Criterion 3: Harmonization Criterion 4: Quality control
Control Initiation	Injury cohort, 10 domain PTSD risk screen and TSOS decision support tool	Weekly intra- and inter-site data review/checks	Criterion 4: Quality control
Control Initiation	Trauma registry	Data comparisons across the 24 sites	Criterion 3: Harmonization
Follow-up	PTSD phenotype, Other PROs	Follow-up interviewer training	Criterion 1: Methods for research data validation Criterion 4: Quality control
Intervention Initiation	TSOS decision support tool	Baseline intervention team training	Criterion 1: Methods for research data validation Criterion 3: Harmonization
Intervention Initiation	PTSD phenotype, Other PROs	Continue weekly intra- and inter-site data review	Criterion 1: Methods for research data, Criterion 4: Quality control
Intervention Initiation	Injury cohort, 10 domain PTSD risk screen	1-5-patient drift assessment	Criterion 2: Methods for EHR data validation Criterion 3: Harmonization Criterion 4: Quality control
Intervention Initiation	PTSD phenotype	Assessment baseline of % PTSD positive on PTSD Checklist	Criterion 1: Methods for research data validation Criterion 3: Harmonization Criterion 4: Quality control
Intervention Initiation	Injury cohort, 10 domain PTSD risk screen and TSOS decision support	Weekly intra- and inter-site data review/checks	Criterion 4: Quality control
Intervention Initiation	Trauma registry	Data comparisons across the 24 sites	Criterion 3: Harmonization
Final Procedures	Trauma registry	Data comparisons across the 24 sites	Criterion 3: Harmonization

Phase 1: Planning and start-up. In the planning phase, the UW study team has identified the 24 participating trauma center sites; potential wait list or "back-up" sites that could participate in the trial should initially contacted sites drop from the study have also been identified. During the planning phase, the UW team also piloted data collection and quality assessment procedures. These procedures included training providers in the 10 domain PTSD risk factor screening procedure, training providers in the patient recruitment procedures, implementing and evaluating the one day provider workshop training, piloting the standardized patient procedures, testing and refining the provider coaching procedure that employs the computerized decision support tool, and establishing the feasibility of the investigation's electronic data capture and transfer protocol from the pilot trauma center sites to the central University of Washington site. Data quality checks and harmonization procedures were also piloted and refined.

Phase 2: Pre-randomization. Appropriate regulatory approvals (e.g., IRB and NIMH DSMB) will be obtained prior to initiation of this phase. All provider subjects will be consented and will complete a baseline organizational survey to assess their views and experiences of working in their respective trauma centers. The pre-randomization phase will include more detailed assessments of workflow at each site, capacity and specific assessments of injury cohort definition and 10 PTSD risk domain data quality procedures. Data quality assessments (e.g., validating process by which injury cohort definition and 10 domain PTSD risk factors are identified) will be initiated during this phase. A test transfer of de-identified data will occur during the pre-randomization phase.

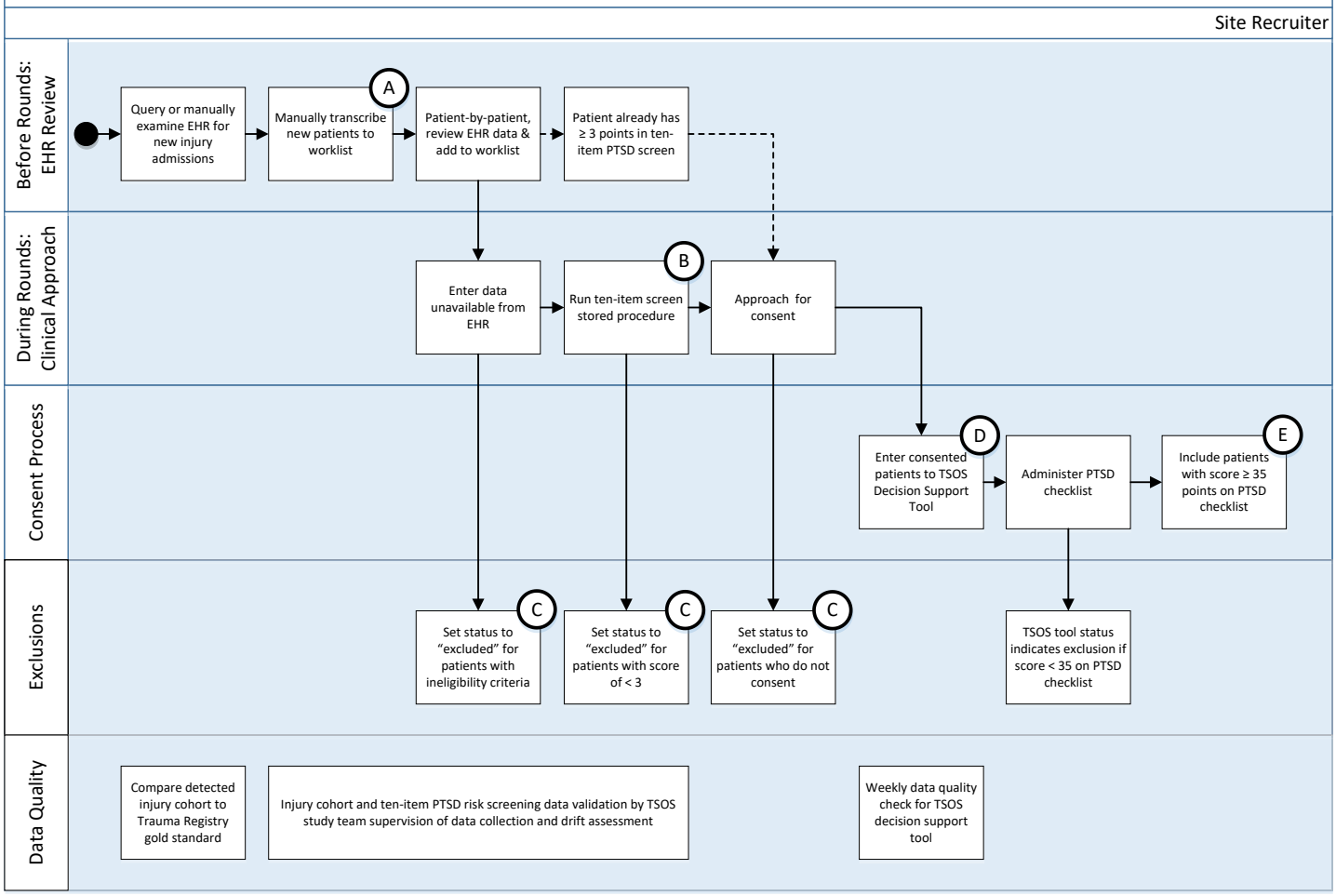
a. Injury cohort definition, exclusions and 10 domain PTSD risk screening

The overarching first step to identifying potential inpatient subjects requires utilizing the EHR systems at each site. We recognize the diversity of EHR systems and procedures that can be used to produce a daily list of inpatients brought into the hospitals for traumatic injuries. In order to review those records for this purpose, the study team will apply for and receive a waiver of consent and a waiver of HIPAA authorization. The procedures used to define injury cohorts and characterize potential inpatient subjects for the recruitment process will vary between sites depending on a number of factors; the major factor is the capacity of the individual sites to automate the screening procedure within or external to the EHR (Figures 11 and 12). The automated form of the evaluation can be performed using EHR data queries or scheduled reports, while the manual form of the abstraction procedure involves reviewing individual health records. The fully automated form of the initial screening evaluation can be programmed into EHR systems resulting in a spreadsheet containing information about potential inpatients available for approach by the study team each morning. This report could have programmed study parameters or be a spreadsheet containing the injury ICD definitions, exclusion criteria, and the 10 risk domains. In contrast, the manual form of the abstraction procedure may involve using a manual list or printout of the daily inpatient census and manual screening of the individual's EHR for injury definition, exclusion criteria or the 10 risk factors. Some sites will lie somewhere between the two examples and will be partially automated. In this case, a hospital may have a daily list sent electronically with injured patients; these hospitals may employ manual screening and patient approach to fully capture the 10 risk factors and exclusion criteria. Therefore, the TSOS study team's first task will be to work with each site to characterize the methods they will employ for defining their daily cohort of injured inpatients, assessing exclusion criteria, and determining the 10 risk factors. The study team will then create documents characterizing these procedures that will be reviewed by the sites. Example workflow diagrams of the methods used to ascertain the daily list of potential patients according to the injury cohort definition with either automated or manual EHR review procedures are included (Appendix 9).

1. Injury cohort definition. Appendix 9 has the study team definition of injury in terms of ICD codes and natural language indicators. These definitions will be applied by all sites. These definitions will be provided to each site during the pre-randomization phase. The study team will then have in-depth conversations with the IT champions and/or PTSD intervention champions at each site to identify the procedures used to generate the daily list of inpatients based on the definition. In these conversations, the study team will determine how the list of injured inpatients will be generated, what the list will contain, whether there needs to be manual editing of the list, and what criteria or risk factors will need to be gathered directly from the EHR. The study team also determines whether patients on the daily list include inpatients from a variety of services in order to increase generalizability. These services will include general surgery, orthopedics, neurosurgery, ENT/Maxillofacial, trauma ICU, and ER admissions

for ≥ 24 hours. Services available for the cohort will be noted for each site. This information will be incorporated into the workflow manual individualized for each site. These procedures have been piloted during the UH2 phase of the protocol and manuals and worksheet guides for these procedures have been refined and are included (Appendix 9).

Figure 11. Manual Data Flow Diagram



Legend:

- A — Compare de-identified eligible cohort statistics to site trauma registry and publish discrepancy rates.
- B — Temporal trends within sites are analyzed periodically to detect sudden shifts in ten-item screen positive results.
- C — Temporal trends within sites are analyzed periodically to detect sudden shifts in excluded patient volume.
- D — Pre-randomization UAT: first five patients entered to TSOS Decision Support Tool are validated back to EHR data to confirm process validity.
- E — Compare granular data on included patients to site trauma registry and publish discrepancy rates.

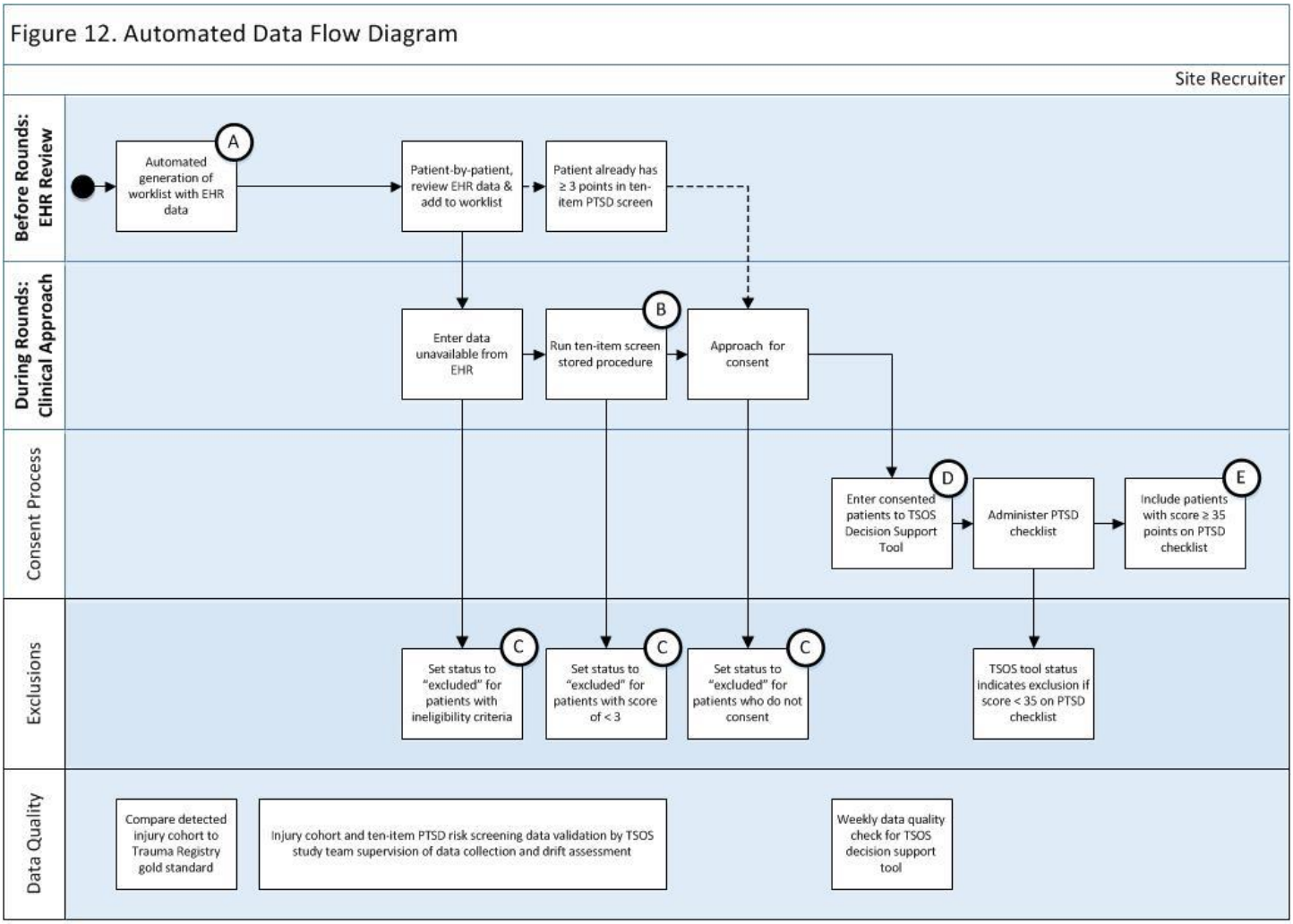
Ineligibility criteria:
Non-injury admission diagnosis
Non-English speaking
Acutely suicidal/self-inflicted injury
Cognitive impairment
Incarcerated or violent
Acutely psychotic
Deceased

2. Exclusion criteria. The study recruitment consort (Figure 6) and Appendix 9 define exclusion criteria. At each hospital, these criteria can be addressed in several ways, depending upon the capacity of the EHR and its programming potential. The fully automated sites will eliminate inpatients from the injury cohort daily list within the EHR query or using spreadsheet macros and those excluded individuals may

or may not be visible to the recruiter. In contrast, sites may use the manual abstraction procedure in which the first group of patients are chosen, and the exclusion criteria are examined in the EHR individually by the recruiter. As soon as an exclusion is identified, the recruiter would go on and choose the next inpatient on the list for further examination. Some sites will use a combination of automated and manual exclusion procedures. These criteria can be determined from the EHR, by patient observation, or by patient interview.

3. 10 domain PTSD risk screen. Appendix 9 describes in detail each of the 10 risk factors. These factors range from very easy to ascertain from the EHR, such as gender, to risk factors that involve the aggregation of past EHR elements such as previous inpatient hospitalizations or prior psychiatric ICD. Fully automated sites will be able to query the risk factors automatically from the EHR, and attach these 10 indicators to the daily inpatient cohort report for the inspection of the recruiter. Hospitals not fully automated will have to determine these indicators from either the EHR, patient observation, or patient self-report. These procedures have also been piloted during the UH2 phase of the protocol and manuals and worksheet guides for these procedures have been refined and are included (Appendix 9).
4. Training and validation of injury cohort definitions and PTSD risk screen. In an attempt to standardize injury cohort definition, both across sites in the initial pre-randomization training and also during the control and intervention phase drift assessments (Table 7), the study team will work with the site to understand the process by which the injury cohort is defined and patients are selected for PTSD screening at each site (Appendix 9).
    a. All sites will undergo a validation process whereby study team members, either in person or via secure web-based video conferencing, perform a validation check on injury cohort and risk domain identification (Appendix 9). This rating process will occur in the pre-randomization phase. Five patients will be evaluated with the expectation of 100% rating concordance; if the site recruiter and study coordinator do not reach rating concordance with the initial five patients, ratings will continue until 100% concordance is reached with five consecutive patients. General procedures for automated and manual screening sites are as follows: 1) At sites that have automation capacity (Figure 11), the phenotypes manual will be sent to the site complete with ICD and E-code identifiers (Appendix 9). Sites will proceed to write EHR queries; the study team will examine each site's code. The study team will also validate with automated sites the 10 domain risk screen results of five patients through web-based EHR review (see procedure below). 2) At manual EHR review sites (Figure 12), the study team will provide the appropriate manuals (Appendix 9); validation will also occur through web-based EHR review. Drift assessments that follow this procedure will occur once during the control phase recruitment and once during the intervention phase recruitment. The concordance between the cohort definition and 10 risk domain variables from the recruiters and our study coordinator will provide an indication of the drift in cohort definition. If significant drift is identified pre-randomization training procedures will be repeated.
    b. We recognize that within both the automatic and manually driven screening procedures, there will be variability in the capacity of the 24 hospitals to extract screening variables from the EHR, and that some hospitals will be able to automate varying numbers of the 10 risk factors and exclusion factors. In both cases, in the pre-randomization phase after appropriate regulatory approvals are in place, sites will implement at least one, pre-study de-identified (non-PHI) electronic data transfer to the UW data coordinating center.
    c. Trauma registry data checks. Trauma registry usually requires approximately 6 months to accrue after a patient subject is recruited. Using trauma registry data, the TSOS study team will compare the clinical and demographic characteristics of all patients included in the investigation with the characteristics of the population of injured patients potentially eligible for the study at approximately six-month intervals after recruitment initiation After these comparisons are performed, sites may receive feedback regarding any observed idiosyncrasies in injury cohort definition relative to other participating sites. Where possible (45 percent of items), the injury cohort data elements are directly normalized to the trauma registry (NTDB) data dictionary for this comparison.[250] Where possible (70 percent of items), the 10 domain PTSD risk factor screening elements is also directly normalized to the trauma registry (NTDB) data dictionary for this comparison.

Figure 12. Automated Data Flow Diagram



Legend:

A Compare de-identified eligible cohort statistics to site trauma registry and publish discrepancy rates.

B Temporal trends within sites are analyzed periodically to detect sudden shifts in ten-item screen positive results.

C Temporal trends within sites are analyzed periodically to detect sudden shifts in excluded patient volume.

D Pre-randomization UAT: first five patients entered to TSOS Decision Support Tool are validated back to EHR data to confirm process validity.

E Compare granular data on included patients to site trauma registry and publish discrepancy rates.

Ineligibility criteria:
Non-injury admission diagnosis
Non-English speaking
Acutely suicidal/self-inflicted injury
Cognitive impairment
Incarcerated or violent
Acutely psychotic
Deceased

Phase 3: Randomization. Randomization of the 24 Trauma Centers occurs during this phase.

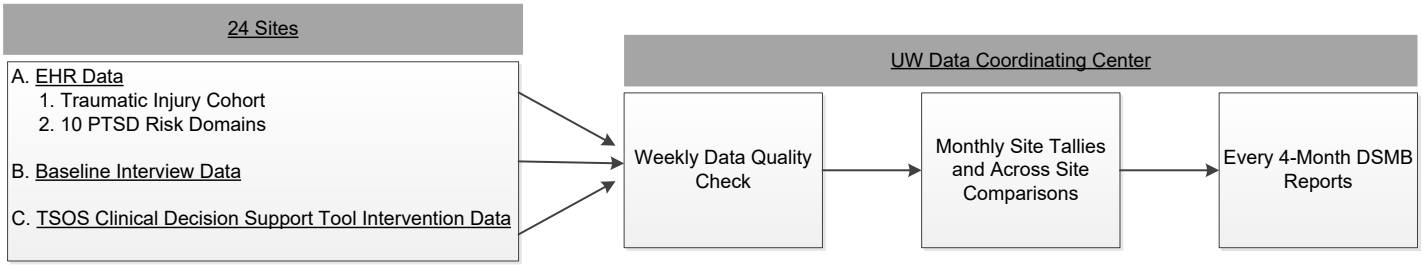
Phase 4: Control phase initiation. Sites will be trained in the study protocol, recruitment procedures, consent process, and how to use the recruiter portion of the decision support tool; these trainings will either occur in-person or over secure video conferencing. Before recruitment begins each site will be trained in the consent procedure and each site will be trained in the administration of the 17 item PTSD Checklist PRO measure. Sites will also be trained in the administration of the other PRO measures included in the baseline study interview. This training process will either occur in-person or via secure web-based video conferencing. Each site recruiter will undergo a pre-defined mock interview with a research associate trained as a standardized

patient. As the standardized patient interview occurs, the research study coordinator or other research staff will co-rate the interview that is performed by the site recruiter. Afterward, the site recruiter will receive feedback with a specific focus on discrepancies. As needed, repeat standardized patient interviews may occur. Trauma registry downloads also will begin during this phase.

During the control phase intra- and inter-site assessments of baseline percentage of PTSD Checklist positive rates will occur. The investigative team expects by chance alone a 20% screen in rate for PTSD Checklist ≥ 35; utilizing the complete 10 domain risk screen rates of up to 67% on the PTSD Checklist ≥ 35 have been achieved.[49] Beginning with subject recruitment in the control phase, the study team will assess site rates of PTSD Checklist ≥ 35. Rate comparisons will also be made across sites. The study team hypothesizes that those sites that have a greater percentage of patients who have complete 10 domain PTSD risk screen data, will have greater rates of PTSD Checklist ≥ 35. As a result of this process, tailored feedback will be given to sites with lower PTSD Checklist screen in rates. Feedback will also be given to sites with high screen in rates.

a. Weekly electronic data transfer (Figure 13)
Recruitment data are aggregated in real-time as part of the site workflow. The de-identified data are submitted electronically from each of the 24 sites to the UW data coordinating center during this study phase. Weekly data include the following: 1) All de-identified data on non-consenting subjects required to construct the study consort diagrams; 2) All identified consenting patient baseline data. Once patients are consented and enrolled, their research data are directly entered in to the TSOS decision support tool and are available in real time to the data coordinating center.

Figure 13. Weekly Data Transfer: 24 Sites



b. Weekly data integrity (Table 8)
Weekly data checks will occur for incoming data from each site; data will be reviewed by the investigation's data analyst, Dr. Wang, under the supervision of Dr. Russo. Incoming data from each site will be evaluated for missing data, contradictory, or out-of-bounds values.

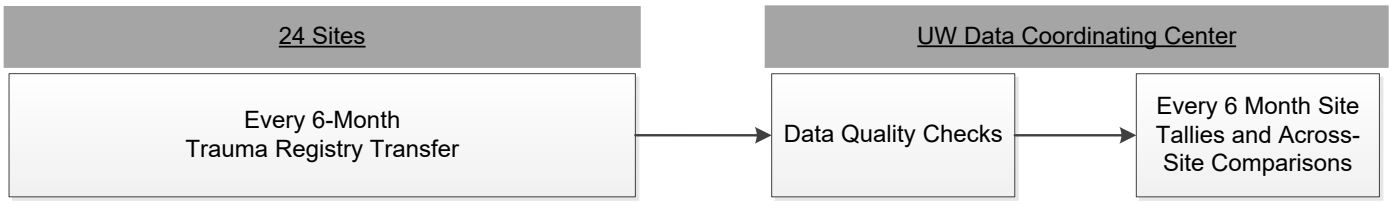
Table 8. Weekly Data Integrity Checks & Monthly and Tri-annual Progress Reports

Data Category	Weekly Data Check	Monthly Progress Report	Tri-annual DSMB Report
Non-Consented Patient Data			
- Check for missing values	X		
- Check for erroneous values	X		
- Check for other data entry or transmission errors	X		
Consented Patient Research Data			
- Check for missing values	X		
- Check for erroneous values	X		
- Check for other data entry or transmission errors	X		
-PHQ-9 item 9 positive	X		X
Summary Assessments			
PTSD Checklist screen in rate		X	
PTSD Checklist positive /10 domain screen in positive rates		X	
Single and 24-site CONSORT		X	X

Dr. Wang will also perform additional assessments of data completion and consistency within and across sites. In cases where missing, contradictory or out-of-bounds values are identified, sites may be queried by the study coordinator; this querying process uses an escalation review process: 1) sites are asked to manually review questionable data against the EHR; 2) site workflow and data generation processes are reviewed in conference; 3) site workflow examples are observed in real time using secure remote desktop sharing software. The study data analyst will also begin single site assessments and across site comparisons of the percentages of patients consented and assessed versus the number of PTSD Checklist ≥ 35 followed longitudinally in the pragmatic trial during the control phase.

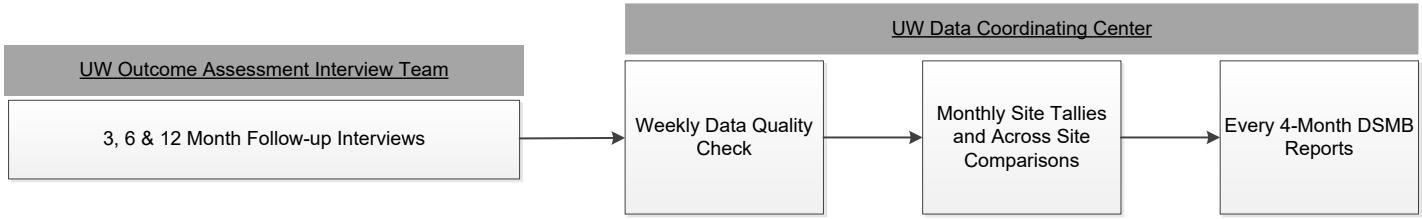
c. Trauma registry downloads (Figure 14)
Trauma registry data will be obtained for each site beginning at six months after control phase recruitment begins, and continuing at six-month intervals until study termination. Trauma registries will be used to compare the clinical and demographic characteristics of patients recruited into the study at each site to the final, cleaned and submitted NTDB data for the eligible population of patients at each site. These data will be used to conduct within-site consistency checking; between-site comparisons will also occur.

Figure 14. Trauma Registry Data Transfer: 24 Sites



Phase 5: Follow-up outcome assessments (Figure 15). Blinded follow-up interviews will begin and continue ongoing throughout this phase. Blinded follow-up interviewers will be trained using manualized procedures prior to this phase (Appendix 6).

Figure 15. Patient Reported Outcome Interview Data



Phase 6: Intervention phase initiation. Recruitment of control patient subjects will end at each site based upon the wave they are assigned to in the stepped wedge design, and the UW study team will conduct a one-day intervention training workshop at each site at this time. Following this training, each site begins recruitment of intervention patient subjects and their care manager subjects begin charting notes in the decision support tool and have regular supervision with the UW study team. Data quality assessment procedures including weekly data checks will also continue at each site in this phase. All provider subjects will be asked to complete another organizational survey, after this phase is completed.

Phase 7: Final study procedures. Final data cleaning and analyses will be conducted in this phase. Manuscript preparation and the end of study policy summit will occur in this phase.

6. Measures and Assessments

A. Patient Baseline, and 3-, 6-, and 12-month Independent Outcome Assessments (Appendix 10)
The baseline, 3-, 6- and 12-month outcome assessments are briefly described below; a full listing of the outcome assessments complete with questionnaire items is detailed in Appendix 10. The timing of assessment administration is detailed in Table 9. All scales will be available both in the computerized decision support tool and as paper and pencil administered measures, so that the study can proceed in the event of information technology complications.

1. Primary study outcome and PTSD phenotype: The PTSD Checklist[240,251] PTSD Symptoms. The PTSD Checklist is a 17 item self-report questionnaire that will be used to assess PTSD symptoms. The instrument yields both a continuous PTSD symptom score and a dichotomized diagnostic cut-point for symptoms consistent with a DSM diagnosis of PTSD.[252] A series of investigations have demonstrated the reliability and validity of the PTSD Checklist across trauma-exposed populations.[253-257] Blanchard et al. reported a correlation of 0.93 between the PTSD Checklist total score and the CAPS in a study of injured trauma survivors.[258,259] Cronbach's alpha for the 17 item scale in a prior investigation with injured trauma survivors by the study team was 0.92.[51,136] In previous investigations, PTSD symptoms assessed with the PCL in the surgical ward were the strongest single independent predictor of PTSD symptom level over the course of the year after injury; PTSD Checklist scores of ≥ 35 in the days and weeks after injury admission have been shown to be associated with the development of higher PTSD symptom levels over the course of the year after injury.[49]

2. Secondary study outcomes: depressive symptoms, alcohol use problems and physical function
Other patient reported outcomes assessments that will be used to define the key secondary outcomes of depressive symptoms, alcohol use problems and impairments in physical function are described below.

a. Depressive symptoms. The 9 item Patient Health Questionnaire (PHQ-9) brief depression severity measure will be used to assess depressive symptoms.[241] The instrument yields both a continuous depressive symptom score and a dichotomized diagnostic cut-point for symptoms consistent with a DSM diagnosis of depression. The PHQ-9 has established reliability and validity in acute and primary care medical patients.[29,51,245] Cronbach's alpha for the PHQ-9 in prior study team investigations was 0.83.[29] The PHQ-9, item 9 will be used to assess for suicidal ideation; the PHQ-9 item 9 question asks, "How often have you been bothered by any of the following problems…Thoughts that you would be better off dead or of hurting yourself in some way?" In the current investigation an additional item has also been added to assess more recent suicidal intent, for those individuals who have any positive response on PHQ-9 item 9.
b. Alcohol use problems. The Alcohol Use Disorder Identification Test (AUDIT), a 10 item screening instrument for the early identification of problem drinkers will be used to assess alcohol use problems before and after the injury hospitalization.[242] The AUDIT's reliability and validity are well established and the scale has been widely used in acute and primary care medical settings.[242,260,261,29,51] Cronbach's alpha for the AUDIT in prior investigations by the study team was 0.80.[208]
c. Physical limitations. The investigation will use the MOS SF-12 at baseline and SF-36 at 3-, 6-, and 12-month follow-up to assess physical, role, and social functional outcomes. The SF-12/36 has established reliability and validity,[243] and the measure has been used extensively with traumatically injured populations.[35,52,262] Cronbach's alpha for the MOS SF-36 PCS in prior investigations by the study team was 0.90.[136,51]

3. Baseline patient trauma center/emergency department electronic health record assessment
EHR data will be collected from each of the 24 sites during the recruitment of study patients; this data will be de-identified for non-consenting patients and identified for consenting patients. Similarly, trauma registry data will be obtained from each of the 24 sites that will contain EHR derived ICD and other patient data.
EHR 10 item PTSD risk factor screen. A previously developed EHR screen will be used to assess admitted injured trauma survivors at risk for the development of PTSD.[49] The screen utilized 10 data elements that are both associated with increased risk for PTSD and that are readily available in any robust EHR system. When the 10 data elements were used to predict scores on the PTSD Checklist of ≥ 35, the EHR screen demonstrated adequate sensitivity (0.71), specificity (0.66), and area under the ROC curve (0.72).[49] The

evaluation utilizes 10 data elements that are readily available in a typical robust EHR to identify patients at high risk for the development of PTSD. The 10 domains used for screening are: 1) Female gender, 2) Non-white race/ethnicity, 3) Intentional injury, 4) Public or Veterans insurance status, 5) Intensive Care Unit (ICU) admission, 6) Previous hospitalizations 7) Substance use, 8) Tobacco use, 9) Evidence of PTSD diagnosis, 10) Other mental health diagnosis.

a. Traumatic brain injury. Traumatic brain injury will be identified and categorized from hospital chart-abstracted ICD codes indicative of traumatic injury. Specific ICD-9-CM codes used to prospectively identify traumatic brain injuries include 800.0-801.9, 803.0-804.9, 850.0-854.1, and 959.01.[263,264] TBI severity will be coded based on a previously validated algorithm for hospitalized inpatients.

b. Injury severity. Injury severity will be abstracted from surgical records using a conversion software program that transforms recognized ICD-9CM codes into Abbreviated Injury Scale (AIS) and subsequent injury severity scores (ISS).[265]

c. EHR derived chronic medical conditions. Comorbid chronic medical conditions will also be taken from EHR and trauma registry data and will be derived from ICD diagnostic codes.[36,266] Chronic medical comorbidity will also be assessed through patient self-report during the follow-up interviews.

Table 9. Assessments & Timing of Administration (Appendix 10)

Study Measure	Ward	3-Mo	6-Mo	12-Mo
EHR 10 Item PTSD Evaluation	X			
ICD injury severity	X			
ICD TBI severity	X			
ICD/Self-report Chronic Medical Conditions	X	X		
EHR & Self-reported demographics	X			
Consciousness/Glasgow Coma Scale	X			
PTSD (PTSD Checklist DSM-IV & DSM-5)	X	X	X	X
Depression (PHQ-9)	X	X	X	X
Alcohol (AUDIT)	X	X	X	X
Illegal and Prescription Drug Use (DAST)	X	X	X	X
Pain (Brief Pain Inventory)	X	X	X	X
Postconcussive (NSCOT/Rivermead)	X	X	X	X
Functioning (MOS SF12/36)	X	X	X	X
Violence risk behaviors	X	X	X	X
Pre-Injury Trauma (NCS)		X		
Recurrent Traumatic Events (NCS)			X	X
Reactions to Research Participation (RRPQ)	X	X	X	X
Satisfaction with Care (NSCOT)	X	X	X	X
Health Services, Work & Cost (NSCOT/TSOS)	X	X	X	X
Medication Use (NSCOT/TSOS)	X	X	X	X
EHR/Trauma Registry Utilization Data	Ongoing - Automated Data			

4. Other Patient baseline and longitudinal assessments

a. The Glasgow Coma Scale and Mini-Mental State exam will be used to assess level of consciousness in hospitalized surgical inpatients.

b. Drug use: Single Items and the Drug Abuse Screening Test (DAST). Single items will be used to assess the use of specific substances. Illegal and prescription drug use after the injury will also be assessed with the 10-item DAST.[267] The DAST has established validity among substance abusing inpatients.[65,268-271] Tobacco use will also be assessed using a single-item screen.[271,272]

c. Pain. A modified version of the Brief Pain Inventory will be used to assess pain longitudinally in the study. The Brief Pain Inventory has established reliability and validity.[273,274]

d. Postconcussive symptoms.[43,44,262] A self-reported cognitive symptom scale with established reliability and validity in injured patients will be used to assess impairments in cognitive function.[262] These items will be supplemented with the Rivermead assessment developed for TBI patients.[275]

e. Violence.[172] A set of previously developed items will be used to assess violence risk behaviors such as weapon carrying.

f. Recurrent traumatic and stressful life events.[6,90,276] The trauma history screen developed for the National Comorbidity Survey will be used to assess pre-injury trauma and recurrent traumatic and stressful life events.

g. Reactions to Research Participation Questionnaire (RRPQ).[277,278] A single item from the RRPQ will be used to assess injured patient experiences with participation in the research protocol.

h. Patient satisfaction with care. Items assessing satisfaction with general health care services and emotional health care services are included at each assessment point.[29,51]

5. Health care utilization and other costing/economic assessments

a. Health Service Utilization, Work and Cost Items (NSCOT).[11,28] The investigation will collect detailed information on post-injury health service utilization including inpatient, skilled nursing facility, emergency room, and outpatient utilization visits. Health service utilization will be primarily assessed from patient self-report items that were developed and used in the NSCOT study; EHR derived trauma registry data will be used to augment patient self-report whenever possible. Assessment of psychotherapeutic services targeting PTSD and comorbidity will be specifically assessed using previously derived items.[29] The investigation will assess pre-injury employment and return to work over the course of the months post-injury.[55] Patient-centered injury cost assessments will also be collected. Technology use in communication with health care providers will also be briefly evaluated.[29]

b. Medication use.[11,28,29,51] Patient self-report will be used to assess medication use targeting chronic medical and psychiatric conditions longitudinally. For psychiatric medications the initiation of appropriate medications, and the maintenance on adequate doses over time will be assessed. Dosing and missed medication days will be assessed over a 3-month period.

c. The Time Trade Off (TTO). [279-281] The modified version of the TTO approach for determining the desirability of a health state and estimating health state utilities will be included as part of the patient assessment.

d. Other costing/economic assessments. Start-up and ongoing personnel costs associated with the delivery of the screening and intervention procedures will be ascertained through review of interventionist case management notes and study team member costing logs (Appendix 12). Study team members will use logging procedures developed during previous pragmatic trials to document the nature and duration of all intervention activities.[208,236]

6. Intervention specific assessments

In order to not replicate instruments delivered in the independent assessments, a number of intervention specific measures will be included for the assessment of PTSD, depressive and other symptoms in the trial. Interventionists will use the Impact of Events Scale (Revised-IESR) [282] and the 10-item Center for Epidemiologic Studies Depression Scale (CES-D) [283] to assess anxiety and depression in the current study. The Cog-Log[284,285] will be used to assess cognitive impairment in the wake of traumatic brain or other injury. Other single item assessments will be used for the evaluation of alcohol and drug use problems.[270]

7. Provider assessments

a. Trauma center organizational assessments.[286-291] The study will modify previously developed organizational culture and climate assessment scales to evaluate trauma center organizational characteristics related to PTSD and comorbidity service implementation. Organizational implementation scales will assess the extent trauma centers were able to adapt to the changes required by PTSD and comorbidity screening and intervention service development. Trauma center provider attrition from the study and turnover will also be examined. Following the procedure established in the DO-SBIS trial, 10 providers will be identified through an organizational mapping procedure to be part of the organizational work unit impacted by screening and intervention service delivery. These 10 providers will complete the organizational assessment packet at baseline in UH3 year 2, and again in UH3 year 4 after all patient intervention is complete.

b. Trauma center provider exposure to critical incidents and job stress. Previously developed items will be used to assess trauma center provider job related stress (e.g., call frequency, work volume). [292] The secondary traumatic stress scale will be used to assess trauma center provider work related stress exposures.[293]

c. Provider lifetime traumatic stress exposure and PTSD symptoms. Provider lifetime traumatic stress exposures will be assessed with the trauma history screen developed for the National Comorbidity Survey.[6,90,276] Provider PTSD symptom development in the wake of trauma exposures will be assessed with the PTSD Checklist.[240,251]

8. Nationwide trauma center information technology survey[108]

In study year 4, Drs. Van Eaton and Zatzick will develop a nationwide trauma center IT survey that derives from and builds upon the previous survey implemented during the DO-SBIS investigation. Survey domains will

again include EHR capacity for routine clinical documentation and pharmacy procedures. Additional survey items may include questions regarding the ability to expose de-identified standardized data for federated queries and questions regarding the potential for the implementation of open source platforms that would permit the real-time, workflow integrated, automated EHR screening, computerized decision support tool, and trauma registry documentation procedures for PTSD and comorbidity. The survey will also evaluate the potential for trauma center participation in nationwide data aggregation that would facilitate inclusion in distributed research networks. Survey results will be presented at the year 5 College policy summit.

9. Trauma center provider semi-structured interviews

In the final year of the project (UH3 year 5), after completion of patient recruitment and intervention activities, study team members will conduct semi-structured interviews with PTSD intervention care managers at each of the 24 level I trauma center sites. The study team has developed a year 5 interview guide derived in part from the DO-SBIS site champion key informant interviews (Appendix 12). The UH3 year 5 interviews with site champions will explore barriers and facilitators of implementation of screening, intervention, and quality documentation procedures for PTSD and comorbidity at trauma center sites. The interviews will also assess the potential sustainability/maintenance of study procedures. Semi-structured interviews may also be conducted with UH3 year 5 policy summit attendees.

7. Statistical and Data Analysis Plan

A. Statistical Analysis Plan

1. Study aims and hypotheses

The **primary aim** of the UH3 period is to conduct a pragmatic randomized effectiveness trial of a collaborative care intervention targeting PTSD and comorbid conditions after acute care injury hospitalization. The investigation aims to determine if injured patients receiving the collaborative care intervention demonstrate significant reductions in PTSD symptoms when compared to control patients receiving care as usual. The study also aims to determine if the intervention patients when compared to control patients will demonstrate significant reductions in depressive symptoms and alcohol use problems, and improvements in physical function. An exploratory aim of the investigation is to assess the effectiveness of the intervention in injury survivors with and without pre-existing chronic medical conditions and with and without TBI. Exploratory analyses will also assess whether the intervention successfully reduced enduring symptom development for other co-morbid presentations (e.g., suicidal ideation, physical pain, drug use problems).

The **primary hypothesis** is that the intervention group when compared to the control group will demonstrate significant reductions in PTSD symptoms over the course of the year after injury. **Secondary hypotheses** are that intervention patients when compared to control patients will demonstrate, significant reductions in depressive symptoms, significant reductions in alcohol use problems, and improved post-injury physical function.

2. UH3 statistical analysis plan

All primary statistical analyses will be conducted using intent-to-treat methods. The primary goal of the statistical analyses is to examine and compare trends over time in the symptoms of PTSD. The major test of the intervention effect will be the change in PTSD symptoms from baseline to the 12-month study endpoint. We will also examine changes in PTSD symptoms from baseline to the 3- and 6-month study time points, as well as the treatment group by time by interaction for PTSD symptoms over the course of the 12 months after injury. This analytic approach will be replicated for all secondary outcomes; secondary analyses will examine trends over time for depression and alcohol use, and physical function. The major outcome variables are the continuous and dichotomous assessments of PTSD (PTSD Checklist), alcohol use problems (AUDIT), depression (PHQ-9), and physical function (MOS SF-36 PCS).

The study team will use ANCOVA/mixed effects regression models to test the hypotheses. The investigative group has extensive experience with these analytic approaches in the analyses of longitudinal data after injury. These analytic approaches allow for the modeling of longitudinal data on patients, nested within trauma center sites (see also sample size and power discussion below for a more in-depth discussion of clustering). An important potential advantage of using longitudinal mixed models is the ability to use partial data on those of subjects with missing data, and therefore potentially ameliorate selection bias due to drop-out. In addition, mixed models naturally structure patient and center heterogeneity specifically allowing for random effects such as individual intercepts and slopes on time. Longitudinal regression models also allow the use of baseline covariates that may be prognostic or reflective of the study design.

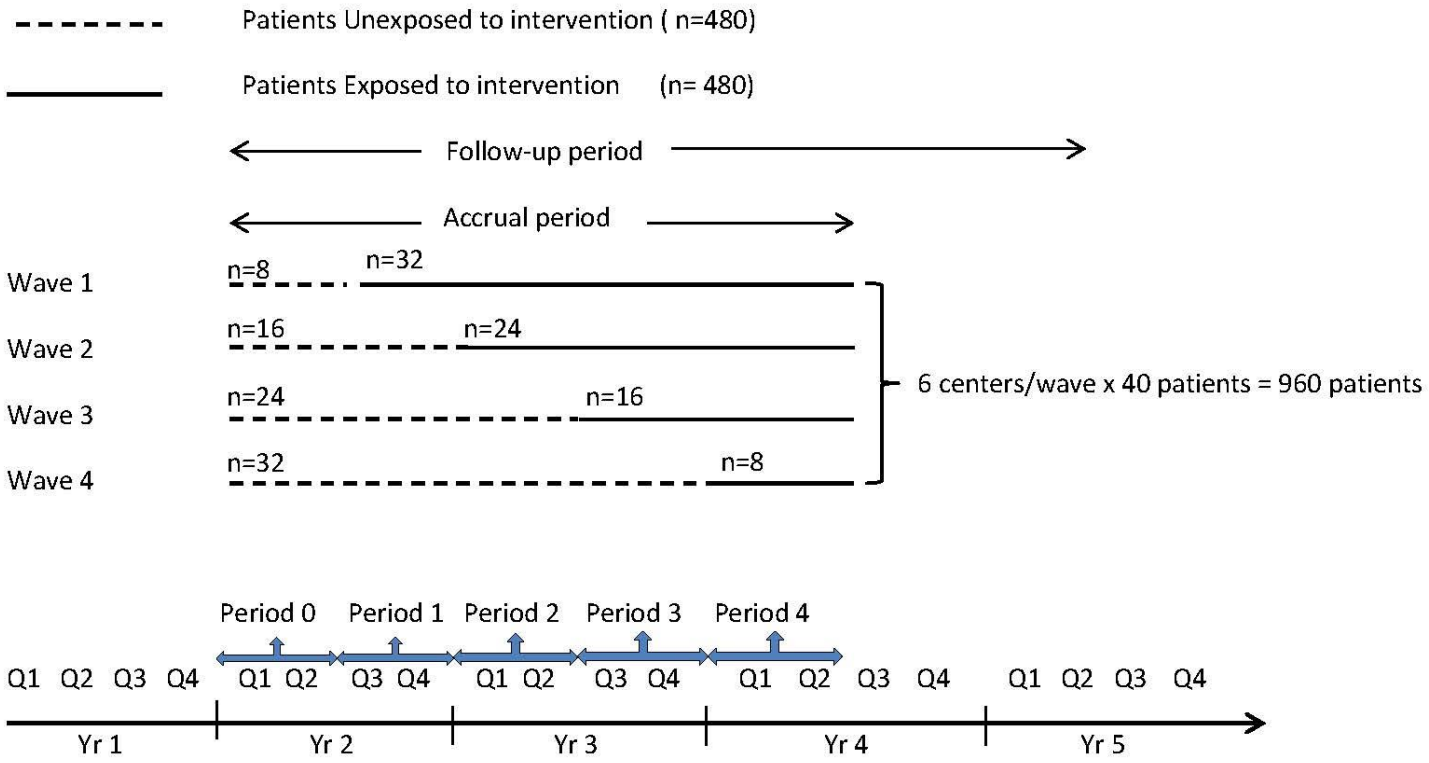
Exploratory analyses will assess the impact of the intervention on primary and secondary outcomes for patients with and without pre-injury chronic medical conditions and with and without TBI. Exploratory analyses will also assess for significant reductions in suicidal ideation, pain and drug use problems in intervention patients when compared to control patients. The study team will again use ANCOVA/mixed effects regression for these exploratory analyses.[294-297] In order to assess for potential selection bias across clusters, demographic characteristics (e.g., gender, ethnicity, insurance status) will also be tested as main effects and interactions with treatment status.

3. Stepped wedge cluster randomized design

Variability in multiple trauma center characteristics can impact rates of recruitment (e.g., admission volumes, EHR capacity), rates of PTSD (e.g., percentages of patients with violent injury admissions, intensive care unit admission rates), and the ability to follow patients longitudinally (e.g., patient demographic characteristics such as being homeless, clinical characteristics such as substance use problems). The study team initially considered using a stratified randomization procedure; however given the potential variability in multiple trauma center characteristics the study team will use a stepped wedge cluster randomized design for the UH3

protocol. The stepped wedge design randomizes level I trauma center sites to sequentially initiate the intervention, thus allowing within site pre-, post- intervention comparisons, as well as between site comparisons. An additional advantage of the stepped wedge design for the UH3 protocol is that it would be impractical to roll out the entire intervention at 24 sites simultaneously. Finally, from an implementation science perspective there is an advantage to having the intervention ongoing at the end of the study at every site, should the intervention demonstrate a significant impact on PTSD and comorbidity. Given that there is little threat of contamination at each site across intervention and control patients and that the UH3 can accommodate the increased potential length of active recruitment and follow-up, the stepped wedge design appears to be an optimal choice for the UH3 protocol. In the proposed UH3 protocol stepped wedge design, all 24 participating level I trauma centers are randomly assigned to 1 of four waves. Each wave is assigned a specific proportion of control and intervention patient recruitment. Wave 1 recruits 8 control and 32 intervention patients, wave 2 recruits 16 control and 24 intervention, wave 3 recruits 24 control and 16 intervention and wave 4 recruits 32 control and 8 intervention patients. Interventions are initiated in the second six months of the UH3. The proposed stepped wedge design is outlined in the figure below.

Figure 16. Stepped Wedge Cluster Randomized Design



The stepped wedge regression model will adapt the functional form given below, and uses a time-dependent variable to code treatment status for cluster *k* at calendar time *t*, denoted as $condition_{kt.}$ For the stepped wedge study design there are now two key time scales: Period, which denotes the study period measured relative to the calendar time when the overall study begins; and Follow-up time which is a patient-specific time scale relative to when they enrolled in the study. In this model mean outcomes may have a temporal trend in calendar time and this will be captured by modeling "Period", while the primary outcome will still be the 12-month patient outcome denoted by Y_{ijkt} where i=4.

A) The primary analysis regression model will adapt the functional form given below:

$Y_{4jkt} = \beta_0 + \beta_1*Period_{4jk1} + \beta_2*Period_{4jk2} + \beta_3*Period_{4jk3} + \beta_4*Period_{4jk4} + \beta_5*Y_{1jkt} + \beta_6*condition_{kt} +$ Mean model

$b_{k,0} + e_{4jkt}$ Trauma center random effect and error

For this analysis the null hypothesis of no intervention effect is captured by H_0: $\beta_6=0$, and the primary statistical test will be a Wald test of this null hypothesis.

B) A secondary analysis will explore the potential for treatment effect heterogeneity at the center level through inclusion of an additional random effect that permits cluster-specific variability in the intervention impact, captured by a random coefficient on the time-varying condition covariate:

$Y_{4jkt} = \beta_0 + \beta_1*Period_{4jk1} + \beta_2*Period_{4jk2} + \beta_3*Period_{4jk3} + \beta_4*Period_{4jk4} + \beta_5*Y_{1jkt} + \beta_6*condition_{kt} +$ Mean model

$b_{k,0} + b_{k,1}*condition_{kt} + e_{4jkt}$ Trauma center random intercept, slope, and error

The key difference for this model is that the intervention effect at trauma center k would be allowed to vary across centers and would involve the overall average intervention effect and a center-specific random intervention effect: $\beta_6 + b_{k,1}$. For this analysis the null hypothesis of a null average intervention effect is still captured by H_0: $\beta_6=0$, and the primary test will be a Wald test of this null hypothesis, but now using an additional random intervention effect together with a standard random trauma center effect (random intercept).

C) A secondary analysis will evaluate the impact of intervention at all of the longitudinal follow-up times by including additional outcome measures and associated follow-up time variables, and interactions between follow-up time and intervention:

$Y_{ijkt} = \beta_0 + \beta_1*Period_{ijk1} + \beta_2*Period_{ijk2} + \beta_3*Period_{ijk3} + \beta_4*Period_{ijk4} + \beta_5*Followup_{2jkt} + \beta_6*Followup_{3jkt} + \beta_7*Followup_{4jkt} + \beta_8*condition_{kt} + \beta_9*Followup_{2jkt}*condition_{kt} + \beta_{10}*Followup_{3jkt}*condition_{kt} + \beta_{11}*Followup_{4jkt}*condition_{kt} +$ Mean model

$a_{jk,0} + a_{jk,1}*Followup_{ijkt} +$ Patient random effects

$b_{k,0} + b_{k,1}*condition_{kt} + e_{ijkt}$ Trauma center random effects and error

Y_{ijkt} denotes patient outcome at follow up time i (i=1,2,3,4) (baseline, 3m, 6m, 12m)

for patient j (j=1,2,…,n_k)

at trauma center k (k=1,2,…,24)

enrolled in time period t (t=0,1,2,3,4)

For secondary analysis using the repeated measurements from each subject there are two key hypotheses to test. First, the 12-month intervention effect would now be captured by the intervention-by-time interaction specific to the 12-month assessment time: H_0: $\beta_{11}=0$; and evaluation of the intervention effect under this model evaluates any impact of using the partially complete longitudinal data for all subjects to estimate the 12-month intervention effect. This analysis provides a sensitivity analysis evaluating the impact of missing 12-month data for subjects who do have partial follow-up data (e.g. 3 month, 6 month data). A second exploratory hypothesis would be the global null of no intervention effect at all follow-up times, and this would be captured by the multivariate null hypothesis: H_0: $\beta_8=\beta_9=\beta_{10}=\beta_{11}=0$; and evaluated using a multivariate Wald test. Under this hypothesis the intervention and control means within a given period would be equivalent for all patient follow-up times.

The primary analysis is a single hypothesis test based on Model (A) and will use alpha=0.05. All other statistical tests are conducted to evaluate the sensitivity of the primary analysis to either heterogeneity or missing data, and therefore multiple comparison corrections are not used for these secondary analyses.

Subject Attrition: Some attrition is expected in the study sample due to the research context and the population under study (i.e., low income, ethnoculturally diverse, injured trauma survivors). Prior studies by the

investigative group have consistently achieved follow-up completion rates ≥ 75-80% at 12 months post-injury with this population. Estimates derived from these rates are incorporated into the descriptions of subject flow and power analyses.

4. Sample size and power

A number of issues specific to the design and analyses of cluster randomized trials are addressed by the current power analyses.[298-302] A key consideration for the trial is the nesting of patients within trauma center sites and the ascertainment of associated intraclass correlations (ICC). The study team has extensive experience with prior multisite trauma center observational and pragmatic clinical trial investigations. Sample size estimates were therefore adjusted for the clustering of patients within trauma center sites, using appropriate ICCs derived from the study team's prior multisite investigations; original ICCs utilized included, PTSD Checklist ICC = 0.0083, PHQ-9 ICC = 0.0259, AUDIT ICC = 0.0059, SF-36 PCS ICC = 0.003.Original sample size estimates suggested recruiting 20 trauma center sites with a total study N = 800 patients (n = 40 patients per site).

Table 10. PTSD Checklist Effect Sizes

	Intraclass Correlation			
PTSD Checklist	0.005	0.010	0.020	0.030
Minimum Detectable Effect Size	0.216	0.220	0.227	0.231

In response to a series of discussions with the NIH Health Care Systems Biostatistics Core, sample size estimates were revised using more conservative ICCs. The power analyses model the baseline to 12-month treatment effect for the primary outcome and secondary outcomes. Table 10, provides effect sizes for the PTSD Checklist with a range of ICCs that includes empirically derived ICCs from the investigative team's prior studies as well more conservative ICC estimates suggested by the NIH Health Care Systems Collaboratory Biostatistics Core. Table 11 delineates the parameters used to estimate power for the PTSD Checklist, PHQ-9, AUDIT, and SF-PCS. Sample size estimates were derived using the STATA statistical package.[303] With each of the 24 trauma center sites recruiting 40 patients into the study, the study has 80% power to detect effect sizes ranging from 0.22 to 0.23. These effect sizes are smaller than our previously observed treatment effect for PTSD symptoms of 0.34. In prior investigations PTSD treatment effects of 0.34 have been associated with clinically significant and policy relevant functional outcome improvements.

Table 11. Stepped Wedge Power for UH3 Outcomes

Continuous outcomes	**PTSD Checklist**	**PHQ9**	**AUDIT**	**SF-36 PCS**
Cluster size at baseline	40	40	40	40
Cluster size estimation at 12m (25% attrition)	30	30	30	30
Total Number of clusters	24	24	24	24
alpha	0.05	0.05	0.05	0.05
Power	0.8	0.8	0.8	0.8
ICC	0.02	0.0259	0.02	0.02
Baseline mean(SD)	50(15)	14(6)	10(5)	50(10)
Autocorrelation	0.7	0.7	0.7	0.7
Follow-up time points (including baseline)	4	4	4	4
Minimal detectable effect size				
Stepped wedge (STATA)	0.23	0.23	0.23	0.23
Stepped wedge (Excel)	0.22	0.23	0.22	0.22

B. RE-AIM Analyses

A second aim of the UH3 project is to understand the processes of pragmatic trial implementation. The study team will use the RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance) model to comprehensively assess factors related to intervention reach, effectiveness, adoption, implementation, and maintenance. When combined with the PRECIS pragmatic trial conceptual framework, RE-AIM can provide a model for the integration of pragmatic trial results into routine trauma center practice (see also Significance section).[192,193] The study RE-AIM assessments and analyses are described in Table 12 below.

1. Reach[304-306]

Reach is defined as the percent and representativeness of participants. Reach is an individual level measure that can be assessed by comparing records of program participation with records from a complete sample or "census" of potential program participants. In the pragmatic trial context, reach can be seen as assessing the capacity of a program to attract a large and representative percentage of a target population. Other key questions related to pragmatic trial reach include: can the program reach those most in need and most often left out (e.g., low income, ethnoculturally diverse patients)?

In the UH3 investigation reach will be estimated for individual patients by comparing the characteristics of injured trauma survivors included in the investigation, with the characteristics of eligible trauma survivors admitted during the time period of the study as documented in the trauma registry. The study team has extensive theoretical and applied experience conducting trauma registry reach assessments; in published reports of randomized clinical trials the study team typically reports on investigation reach criteria.[51,172,307-309]

2. Effectiveness[51,172,304-309]

Effectiveness relates to the program's impact on key symptomatic outcomes and quality of life; RE-AIM effectiveness criteria are addressed in the Statistical Analysis Plan discussion of primary PTSD and secondary depression and alcohol use symptoms and physical function outcomes. Of note, the study team has conducted theoretical and applied work on the population impact construct that combines effectiveness and reach RE-AIM criteria.[307,309]

Table 3. UH3 Assessments and Corresponding RE-AIM Framework Domains

Patient, Provider or Site Assessment	N	How Assessed	Measures/ Assessment	RE-AIM Domain, Level
Site Recruitment	24/225	CONSORT	Characteristics of 24 study sites versus all other US sites	Adoption, Site
Trauma Center Providers	10* 24	Web	Organizational change, & climate and culture surveys	Implementation, Provider
PTSD Interventionist	24	Tool	Weekly decision support tool recruitment log activity	Implementation, Provider & Site
PTSD Interventionist	24	Tool	Clinical notes in decision support tool	Implementation, Provider
Patient Flow	960	CONSORT	Patient flow through protocol	Reach, Patient
Patient Outcomes	960	Phone	PTSD & comorbidity, gender & ethnicity groups	Effectiveness, Patient
Patient Outcomes	960	Multiple	EHR, trauma registry self-report logs	Implementation, Patient
Patient 3,6, &12-Mo. F/U	960	Phone	≥ 6 months follow-up after intervention	Maintenance, Patient
PTSD Interventionist	24	Phone	Semi-structured key informant interviews	Implementation & Maintenance, Provider
Policy Summit Participant	20	Phone	Semi-structured key informant interviews	Implementation & Maintenance, Site
All US Level I Centers	225	Web	National Trauma Center Questionnaire	Maintenance, Site

3. Adoption[304-306]
Adoption can be defined as the percent and representativeness of settings that participate in or adopt a specific program. For the TSOS study, adoption criteria are discussed in the Site Eligibility and Recruitment section. Of particular note, the 24 sites selected for the trial do not significantly differ from the potential population of sites eligible for the trial on the majority of key trauma center organizational characteristics (Table 3).

4. Implementation[304-306]
A number of potential constructs can be used to describe implementation, including the consistency and cost of delivering a program and adaptations made. At an individual patient level, measures of adherence are necessary for understanding study outcomes, and can be used as implementation criteria. Provider ability to deliver an intervention can also be an important assessment of implementation. For the current study a number of implementation fidelity criteria will be used (Also see Implementation Manual, Treatment Conditions, Fidelity and Appendix 12).

5. Maintenance[304-306]
Maintenance is the extent to which a program is maintained over time, as well as the long-term effects at individual and setting levels, and modifications made. In the TSOS study, maintenance at participating sites will be assessed through in-depth semi-structured end of study interviews. Nationally, the UH3 year 5 American College of Surgeons' Policy Summit will address maintenance of study procedures through regulatory guidelines and policy mandates. National trauma center surveys will also address questions related to maintenance of study procedures related to PTSD and comorbidity screening and intervention procedures.

6. Other RE-AIM analytic considerations
The TSOS longitudinal cohort is defined by the patient reported outcome of a PTSD Checklist ≥ 35, which is a reliable and valid measure of DSM-IV Posttraumatic Stress Disorder.[232,243,252] The 10 domain PTSD risk factor EHR evaluation serves to efficiently identify patients with high PTSD symptom levels.[49] The study team is aware that patients with < 3 risk domains are excluded and not approached at the 24 sites for consent and PTSD checklist screening.

Therefore, an additional consideration for the investigation is the observation that approximately 8-9% of patients in the cohort, or 20-25% of patients who have PTSD Checklist scores ≥ 35 will not be identified by the PTSD risk factor chart evaluation procedure. In a random sample of 878 injured trauma survivors at the Harborview level I trauma center approximately 1/4 patients with high early PTSD symptom levels had 10 domain PTSD screen scores of < 3.[208] Similarly, in a second nationwide US trauma center study approximately 1/4 patients with high early PTSD symptom levels had 10 domain PTSD screen scores of < 3.[21]

In an effort to determine the potential impact of excluding patients with PTSD risk domain scores < 3 in the current nationwide pragmatic trial, the study team performed a series of retrospective analyses of data derived from a prior NIMH funded R01 PTSD intervention trial.[51] The intervention tested a stepped collaborative care protocol similar to the intervention to be implemented in the UH3 protocol. Instead of EHR PTSD screening however, patients were screened with the PTSD Checklist twice; the 10 PTSD risk domains where retrospectively assessed for these 207 patients. In this way the trial included patients with high early PTSD symptoms as defined as a score of ≥ 35 on the PTSD checklist, with < 3 and ≥ 3 risk domain scores; of the 207 patients n = 163 had ≥ 3 risk domains positive, while n = 44 had < 3 risk domains positive. Mixed model regression that tested the treatment condition by time by risk domain score interaction found no significant differences in the intervention treatment effect for patients with < 3 versus ≥ 3 risk domains positive ($F_{5,792}$ = 0.56, p = 0.73). These results suggest that the intervention may be equally effective for subgroups of patients with PTSD Checklist scores ≥ 35 and risk domain scores < 3 or ≥ 3, and that exclusion of patients with < 3 PTSD risk factors may not substantially impact the results of the pragmatic trial demonstration project.

C. Qualitative Data Analyses
Drs. Palinkas[227,310-312] and Zatzick will oversee all qualitative analyses.[313-315] Audio-recorded key informant interviews will be transcribed verbatim. Personal information will be replaced with a participant ID during the transcription process. Drs. Palinkas and Zatzick will review a subsample of transcripts for accuracy while listening to the recorded interview.[316] The Atlas.ti computer software program will be used to assist with the

management and coding of all interview data. Using a grounded theory[317,318] methodology of "Coding Consensus, Co-occurrence, and Comparison,"[319] key informant interviews and field notes will be analyzed in the following manner: Drs. Palinkas and Zatzick will review all material to develop a broad understanding of content as it relates to the project's specific aims and to identify topics of discussion and observation. Investigators will prepare short descriptive statements or "memos" to document initial impressions of topics and themes and their relationships to define the boundaries of specific codes (i.e., the inclusion and exclusion criteria for assigning a specific code).[121] The material contained in the field notes and interview transcripts will then be independently coded by the project investigators to condense the data into analyzable units. Segments of text ranging from a phrase to several paragraphs will be assigned codes based on a priori (i.e., from the interview guide) or emergent themes (also known as open coding).[320] Following the open-coding, codes will be assigned to describe connections between categories (also known as axial coding).[320] Codes will also be assigned to material to reflect the social and demographic characteristics of study participants. Lists of codes developed by each investigator will be matched and integrated into a single codebook. Five transcripts will be independently coded by at least two investigators. Disagreements in assignment or description of codes will be resolved through discussion between investigators and enhanced definition of codes. The final list of codes or codebook, constructed through a consensus of team members, will consist of a numbered list of themes, issues, accounts of behaviors, and opinions that relate to coalition structure, function, development, and sustainment. Investigators will separately review a sample of transcripts to determine level of agreement in the codes applied. A level of agreement in the codes applied ranging from 66%-97% depending on level of coding (general, intermediate, specific), indicates good reliability in qualitative research.[321] Upon completion of the coding of the remaining transcripts, Atlas.ti will be used to generate a series of categories arranged in a treelike structure connecting text segments grouped into separate categories of codes or "nodes." These nodes and trees will be used to further the process of axial or pattern coding to examine the association between different a priori and emergent categories. They will also be used in selective coding of material to identify the existence of new, previously unrecognized categories. The number of times these categories occur together, either as duplicate codes assigned to the same text or as codes assigned to adjacent texts in the same conversation, will be recorded for descriptive purposes, and specific examples of co-occurrence illustrated with transcript texts. Through the process of constantly comparing these categories with each other, the different categories will be further condensed into broad themes. In the site PTSD intervention care managers' thematic analyses, we will focus on identifying commonalities and differences in responses to individual questions (e.g., how each participant defines barriers and facilitators of screening and intervention activities). We will explore and describe commonalities and differences in themes across the key informants. We will also identify the clinical contexts that drive any group differences.

D. Mixed Method Analysis

Mixed methods will be used to integrate the findings from the key informant interviews with pragmatic trial results. The design taxonomy follows a sequential (QUAN → qual) structure in which qualitative data collected from key informants will be used to explain quantitative data results from the pragmatic trial.[225] Qualitative data will therefore be used to expand upon the results of the pragmatic trial in order to understand the implementation and policy processes as experienced by key stakeholders. The investigative team will use a mixed method data analytic approach in two ways. First, findings from the quantitative data will be used to identify patterns in the qualitative data. Data derived from the pragmatic trial, such as intervention and control site recruitment periods, will be entered into Altas.ti as a "document family" or attribute of each site provider key informant interview. Analyses would subsequently categorize and compare themes across attribute defined subgroups such as intervention and control group status. Second, the sequential QUAN → qual mixed methods design will be used to provide an understanding of pragmatic trial results that require further explanation (e.g., control patients that demonstrate substantial improvement in outcomes, despite not receiving intervention). Results of the mixed method analyses will be presented through a number of modalities that may include key informant narratives, tabular representation of themes with illustrative quotes, and thematic counts.[225,314,315,322]

E. Exploratory Health Economic Evaluation

1. Background: Health care utilization analyses in trauma care systems

The cost assessments are intended to contribute to an understanding of the resource implications of the UH3 intervention and to American College of Surgeons' and other national policy dialogues of post-injury health service utilization and costs.[96-105] We note that in our prior policy collaboration with the American College of Surgeons', health care resource utilization and cost findings have contributed to, but have not dominated the discussions related to the establishment of mandates and best practice recommendations for PTSD and comorbidity.[63] The health care resource utilization and cost analyses therefore constitute an important exploratory aim of the investigation.

Multiple perspectives informed the approach to health service resource evaluation and cost analyses for the UH3 proposal. Recent commentary on the role of economic evaluation in dissemination and implementation research and the related costing of behavioral interventions contributed substantially.[215,216] The approach to these analyses is influenced in a large part by recent work by the project's health economic consultant, Dr. Basu, and psychometrician, Dr. Russo, on the costing of mental health care management interventions for comorbid medical and psychiatric conditions.[135,224] Also, prior investigation by members of the investigative group on the costing of health care utilization in trauma care systems that emphasized the costs of recurrent trauma center and emergency department admissions has also been incorporated into the economic analysis framework.[220] Finally, general recommendations regarding approaches to economic evaluations in health care have been integrated.[217,218]

2. Approach to cost analyses

The investigation will collect detailed information on the following: 1) the costs of intervention implementation and delivery, 2) post-injury health service utilization costs (inpatient, skilled nursing facility, emergency room, and outpatient utilization), and 3) the costs of patient medications post-injury. We will generally follow the principle of measuring the resource uses in each of these categories and then valuing them with unit costs that resemble the opportunity costs of these resources in the United States. The costs of the intervention would be comprised of the implementation costs, intervention time, and supervision time. These categories of costs are important in determining what resources would be needed to implement or replicate the intervention at other trauma center sites. Study development costs will not be included, since it would be a one-time fixed cost for developing the intervention, and would not be incurred in further implementation. Start-up and ongoing personnel costs associated with the delivery of the screening and intervention procedures will be ascertained through review of interventionist and study team member logs (see Appendix 12).

Health services utilization and medication use following index hospitalization will be collected based on self-reports. For the purposes of the analyses, hospital and emergency department admissions will be categorized as: 1) hospitalization/emergency department visits related to the original index injury admission, 2) hospitalization and emergency department visits related to a new injury, and 3) a non-injury related hospitalization (e.g., hospitalization for a chronic medical condition such as congestive heart failure).

Costs of intervention are likely to be dwarfed by the total costs of post-injury care, which would make it difficult to estimate the incremental costs of intervention precisely, given our sample size. This is mainly because our prior investigations suggest that up to 15-20% of injured trauma survivors in both intervention and control conditions experience recurrent injury emergency department and hospital admissions related to the index injury event, increasing the variance of the cost estimators. We will therefore provide detailed impact inventory for the intervention to identify specific components of total costs. Also of relevance, preliminary studies by the investigative group suggest that emergency department and hospital admissions for a new injury are policy relevant outcomes that are potentially malleable by care management interventions targeting PTSD and related comorbidity.[11,55,220]

3. Costing procedures

The following categories of costing information will be collected: 1) total charges for the index injury visit will be extracted either from the hospital trauma registry or the hospital EHR as available across the 24 level I trauma center sites, 2) all follow-up hospital, emergency department, and outpatient visits and re-hospitalizations over the course of the 12-months after the injury will also be collected from patient 3-, 6-, and 12-month self-report data or from the trauma registry, 3) structured patient interviews will be used to assess medication use.

All units of service will be assigned standard procedure codes (e.g., *Current Procedural Terminology, Fourth Revision* codes) for procedures, Diagnostic Related Groups (DRGs) for hospitalizations, and National Drug Codes for prescribed medication.[323] These codes will be converted into costs by using the Medicare reimbursement fee schedule for 2014. We will employ a validated and standardized program, EZ Fees 2014 http://www.rbrvs.net/, in this procedure.[324] The EZ Fees program has the 2014 Medicare fee schedule and is frequently updated as payment changes. For services not covered by Medicare, we will use the prevailing fees available from aggregate hospital data at http://hrsa.dshs.wa.gov/rbrvs./. These codes will be translated into unit prices using the Resource Based Relative Value Scales underlying Medicare payment rates for visits of different types, using EZ Fees http://www.rbrvs.net/. Medication costs will be ascertained using the Federal Supply Schedule for a given medication based on its NDC code.[325] All costs will be converted to 2018 using the PHC and PCE indices http://meps.ahrq.gov/about_meps/Price_Index.shtml.

Effectiveness/utility assessments. Exploratory analyses of cost-effectiveness will be conducted only if we find robust treatment effects for PTSD and comorbidity. Gold et al. have suggested the use of generic preference-based utility measures for cost-effectiveness analyses for comparability.[217] However, because of the unique characteristics of psychiatric populations, mental health services researchers frequently employ disease specific effectiveness measures.[221,224,326] The study team may explore a series of policy relevant effectiveness measures. The study team may use a method employed in a number of mental health effectiveness trials[221,224,326] to derive a disease specific clinical outcome entitled “PTSD-free days.” The investigative team will also use the Time Trade-Off procedure to estimate health-related quality of life weights longitudinally, which could be used to calculate Quality of Life Adjusted Years (QALYs). Finally, the investigation may also employ the MOS SF-12, to ascertain a generic preference-based utility estimate that has been previously used with injured patients in prior study team investigation.[243,262,327-329]

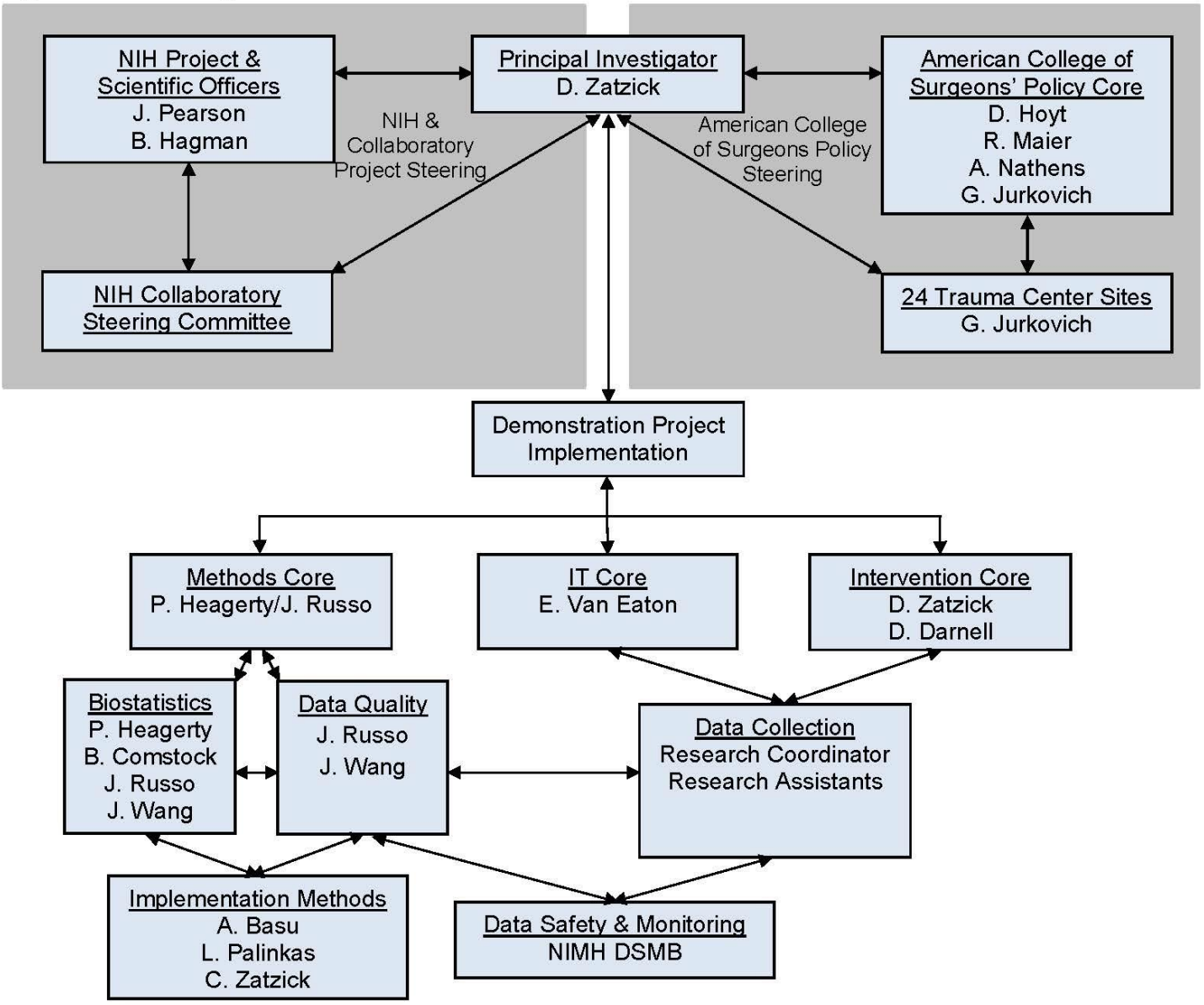
Cost analyses. The investigation’s exploratory cost analysis will first compare total costs for patients in the intervention and control conditions; total costs will be the primary dependent variable for this analysis. Total costs include the costs of the intervention, medication and health service utilization (i.e., inpatient, skilled nursing facility, emergency room, and outpatient utilization). After the total cost comparison is completed, other exploratory analyses will compare intervention and control costs restricted to intervention costs and costs of emergency department and hospital admissions. Randomization should ensure balance between the two groups in pre-injury utilization. So, our primary analyses will be to study incremental costs, effectiveness and cost-effectiveness without any adjustments. As a sensitivity analysis the study team will examine patient self-report data to assess balance between the two and to determine if adjustments are necessary.
If adjustments become necessary, we will use non-parametric methods previously employed by Drs. Basu and Russo.[135,224] The choice of non-parametric methods, such as propensity score weighting, is mainly because of the sample size of our analyses, where complicated regression models will be difficult to fit. Standard errors and 95% confidence intervals for incremental costs, effectiveness and cost-effectiveness will be obtained using clustered bootstrapping.[224,330,331]

8. Study Administration

A. Study Governance

The study organizational structure and governance plan aims to simultaneously optimize diverse stakeholder input into the trial design and implementation while maintaining the proposed study timeline and UH3 milestone completion. The study organizational structure is outlined in Figure 17.

Figure 17. TSOS Organizational Chart



The principal investigator in collaboration with NIH program staff and the NIH Health Care Systems Research Collaboratory, will be charged with the overall trial orchestration and steering. This steering group that includes NIH program staff Jane Pearson, PhD (NIMH) and Brett Hagman, PhD (NIAAA), have successfully worked with Douglas Zatzick, MD the study principal investigator over the course of the UH2 year to complete UH2-UH3 transition milestones. For the UH3 period, this group will again focus in on the completion of study milestones, reporting, and staff and budgetary management. As with the UH2 period, the principal investigator will have regular NIH and Collaboratory contact at monthly Collaboratory Steering Committee Conference calls, biannual in-person Collaboratory meetings, and on an as needed basis. The

roles and functions of other trial committees and subgroups outlined in the study organizational diagram are described below.

American College of Surgeons' Policy Steering Committee. The principal investigator in collaboration with the American College of Surgeons' Policy Steering Group will be charged with ensuring sites both adhere to study recruitment and data collection requirements, and receive appropriate American College of Surgeons' waivers and research participation credits for study participation. Gregory Jurkovich, MD American College of Surgeons policy lead and study 24 site liaison will oversee interchanges between the College and the sites.

The American College of Surgeons' Policy Steering Group that is led by Dr. Jurkovich and included Dr. Hoyt, Maier and Nathens, will assume overall orchestration and responsibility for planning and implementing the UH3 year 5 policy summit. In the initial years 2-3 of the UH3 award, this group will have an annual discussion to review the trial and plan for the policy summit. Beginning in year 4 of the award, this group will begin more regular meetings (e.g., monthly) to initiate policy summit planning (see also UH3 Milestones section below). The policy summit will occur in the final UH3 year.

TSOS Methods, Information Technology and Intervention Cores The principal investigator in collaboration with the study Methods, Information Technology and Interventions cores will be responsible for implementing the pragmatic trial, assuring data accuracy and harmonization and analyzing and preparing study results for presentations and manuscripts. Led by Dr. Heagerty, the biostatistics group will interface with the Collaboratory Biostatistics Core regarding issues related to stepped wedge cluster randomized trial design and implementation. Members of the data quality group, Drs. Russo, and Wang and will oversee data collection and data quality and will meet monthly with the principal investigator to review study progress. The study information technology core, led by Dr. Van Eaton will be responsible for information technology start-up and ongoing data transfer from the 24 level I US trauma center sites. The intervention core led by the principal investigator will be responsible for training and ongoing supervision in the stepped collaborative care procedures.

Data Safety and Monitoring. The NIMH DSMB will perform tri-annual review of the investigations data safety and monitoring procedures and progress (Appendix 4). The principal investigator in collaboration with members of the data quality group will prepare the tri-annual reports for NIMH DSMB review.

B. Plans and Annual Milestones for the UH3

Milestones for the UH3 years 2-5 that coincide with the UH3 timeline and study specific aims are articulated in Table 13. The TSOS study team will continue to work closely with NIH program staff and the Collaboratory towards the achievement of specific milestones.

With regard to aim 1, the conduct of the pragmatic trial demonstration project, in the beginning of the UH3 year 2, the study team will continue to work toward site readiness for protocol implementation across the 24 sites. This preparation includes finalizing IRB approvals, ensuring site information technology readiness for protocol implementation, and completing all other requisite pre-randomization procedures (Appendices 1, 3, 8, 9). Other year 2 milestones include protocol registration with clinicaltrials.gov, the initiation of tri-annual NIMH DSMB report submission, and submission of the clinical trial protocol manuscript for publication (Table 13). Milestones related to protocol control and intervention patient recruitment, and intervention training workshop completion will occur over the course of years 2-4 of the study as dictated by the stepped wedge intervention rollout (Figure 2, Figure 16, and Table 13). Data analyses and primary outcome manuscript submission will occur in UH3 year 5.

With regard to aim 2, evaluation of the trial implementation process, and ongoing RE-AIM and health economic data collection will occur over the course of the UH3 study. RE-AIM and health economic data analyses will coincide with primary trial data analyses in year 5 of the study (Table 13). For Aim 3, protocol dissemination and annual American College of Surgeons' stakeholder policy discussions will occur over the course of UH3 years 2-4. As with previous American College of Surgeons' policy summits orchestrated by the study team, in the later part of UH3 year 4 more regular (e.g., monthly) policy summit planning meeting phone conferences will occur. These planning calls will be designed to incorporate input from NIH program staff, Collaboratory Steering Committee members, and other key stakeholders. This intensive planning in UH3 years 4-5 will culminate in the UH3 year 5 American College of Surgeons' Committee on Trauma Policy Summit.

Contingency of UH3 milestone attainment on timely NIMH DSMB, IRB and information technology progression. The milestones progression presented in Table 13 below are contingent upon timely progression of coordinated NIMH DSMB and IRB review of the protocol. Delays in these or other regulatory approvals could push back the scheduled milestone completions presented in Table 13. Similarly, delays in site information technology assessments and/or implementation could serve to set back the scheduled milestone completion timeline.

Table 13. TSOS UH3 Milestones

UH3 Specific Aim	UH3 Milestone	Yr2	Yr3	Yr4	Yr5
1. Conduct pragmatic trial and assess effect of intervention on PTSD and comorbidity	Finalize 24 site readiness for protocol implementation	X			
	Clinicaltrials.gov protocol registration	X			
	Clinical trial protocol manuscript submitted	X			
	Tri-annual DSMB reports and monitoring	X	X	X	X
	Recruit control patients - 30% Complete Year 2 - 70% Complete Year 3 -100% Complete Year 4	X	X	X	
	Conduct one-day intervention trainings - 10% Year 2 - 60% Year 3 -100% Year 4	X	X	X	
	Recruit intervention patients -5% Year 2 -40% Year 3 -100% Year 4	X	X	X	
	Complete patient follow-up -15% Year 3 -50% Year 4 -100% Year 5		X	X	X
	Obtain final 24 site trauma registry data				X
	Prepare and submit main study outcome paper				X
2. Evaluate trial implementation process	RE-AIM & health economic data collection RE-AIM & health economic data analyses	X	X	X	X X
3. Disseminate study findings through American College of Surgeons' policy summit	American College of Surgeons' policy core meetings & policy discussions	X	X	X	X
	Convene American College of Surgeons' policy summit				X

C. Study Resource Sharing Plan

An overarching goal of the UH3 investigation and work with the NIH Health Care Systems Research Collaboratory is to produce and disseminate information and resources that will facilitate the widespread implementation screening and intervention procedures for PTSD and related comorbidity throughout trauma care systems nationwide. The resource and data sharing plan is in concert with this overarching goal. Any informational or other resources developed during the UH2 development and UH3 implementation of the pragmatic trial including treatment manuals, reports/white papers, and clinical/policy guidelines, are intended to be widely disseminated throughout trauma centers and affiliated trauma care systems nationwide.

Specifically with regard to data sharing, the interdisciplinary group encourages the use of data collected during the study to further the empiric basis for American College of Surgeons' policy mandates and clinical practice guidelines targeting screening, intervention, and referral for PTSD and related comorbidity. Of particular note, the investigative group has a history of this type of collaborative data and resource sharing in its previous efforts to share data derived from large scale NIH funded pragmatic trials to form the foundation for empirically-based American College of Surgeons' policy mandates and clinical best practice guidelines. The final data set will include patient, provider, and setting level demographic clinical, EHR, and trauma registry data from the 24 level I trauma centers and their affiliated trauma care systems that participated in the pragmatic trial. Along with the data set, we will create a code book documenting all variables (e.g., common names for trauma registry variables, names for single questionnaire items, scoring rules for derived variables).

After acceptance of the main manuscript for the study, which is anticipated to be 12-18 months after study completion, requests for access of data files will be considered. We will prioritize access to research groups that have a clearly articulated aim and rationale for how secondary data analyses will impact future policy and/or clinical practice for trauma care systems nationwide; the study team will also prioritize groups affiliated with the NIH Health Care Systems Research Collaboratory. Researchers requesting data will need to complete a request form outlining intended use of the data and agree to use the data for this intended purpose. Prior to data release, researchers requesting data will be required to sign a confidentiality agreement specifying that they will not identify any individual participant, that they will use secure technology to safeguard the data, and that they will destroy or return the data after their analyses are completed. The UH3 investigative team will also require documentation of IRB approval from the host institution prior to release of the data.

We do not expect to make a public use data file available from the study given the nature of our sample and trauma care system context. Study participants may have substance abuse or other diagnoses that may be stigmatizing and may prefer that the conditions of the traumatic injury event remain entirely confidential. Although the data analytic files will not have direct identifiers (only study IDs), the possibility of deductive disclosure of subjects with unusual demographic, injury, or clinical characteristics remains. In order to safeguard against the unlikely event of deductive disclosure, we will make the data files and codebook available to other researchers only on a case-by-case basis.

D. Study Software Sharing Plan

The software sharing plan is in concert with the overall application goal that targets the production and dissemination of resources that will facilitate the widespread implementation of PTSD screening and intervention procedures throughout trauma care systems nationwide. An aim of the proposed work is to create open access software that will allow trauma centers and affiliated trauma care systems to screen for PTSD using automated EHR data sources. Thus, the intent of the UH2-UH3 investigative team is to develop a software sharing plan that is in concert with the stated goals of the NIH Collaboratory RFA RM-13-012 “NIH Health Care Systems Research Collaboratory – Demonstration Projects for Pragmatic Clinical Trials Focusing on Multiple Chronic Conditions (UH3),”[332] including the following:

1. The software should be freely available to biomedical researchers, health care delivery systems, research institutions, and government health care systems and researchers.
2. The terms should also permit the dissemination and commercialization of enhanced or customized versions of the software, or incorporation of the software or components of it into other software packages.
3. The terms of software availability should include the ability of individuals outside the applicant institution and its collaborating organizations to modify the source code and to share modifications with other colleagues.
4. The investigative team will therefore choose a permissive open source software license that allows us to freely share any code/software developed for the UH3 project.

9. Dissemination Plan

American College of Surgeons' policy collaboration optimizes engagement of trauma care systems nationally as research partners and the potential public health impact of the pragmatic trial (Figure 18). Level I trauma centers care for the most severely injured patients and are mandated by the College to uphold the highest standards of trauma center care.[63] Level I trauma centers are distinct from Level II-V trauma centers and other emergency department settings in that they treat the most severely injured patients with highly prevalent multiple chronic conditions.[30,63]

The College oversees the development of national policy mandates and clinical best practice guidelines that inform the integrated operation of US trauma centers and affiliated trauma care systems.[63] The College has successfully linked trauma center funding to verification site visits and other quality indicators.[63,106,107] Gregory Jurkovich, MD, project consultant, has a longstanding history of collaboration with the College and helped to spearhead the 2005 alcohol policy mandate as Vice Chair of the College Committee on Trauma. Dr. Jurkovich has collaborated closely with David Hoyt, MD, FACS, current Executive Director of the College and UH2-UH3 project consultant, in these activities. Both Drs. Jurkovich and Hoyt have extensive applied and academic policy experience and expertise with PTSD and related comorbid conditions.[75,156] Simultaneously, as the investigation is being conducted, the study team will be actively developing with Drs. Jurkovich and Hoyt, a College policy agenda targeting the use of pragmatic trial results to directly impact mandates and practice guidelines for PTSD and related comorbidity.

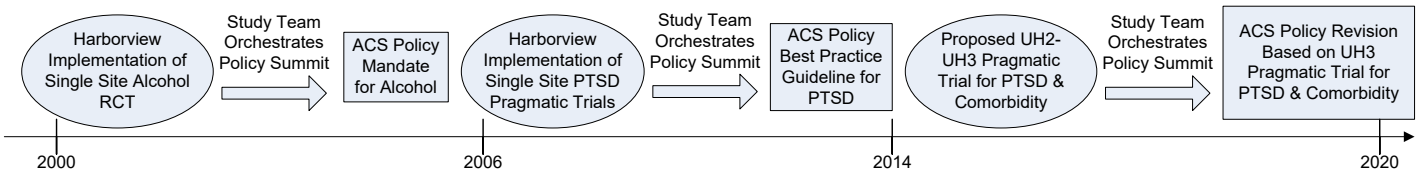
Trauma centers are required by the College to maintain registry information systems that document adherence to policy mandates and other clinical guidelines. Study consultant, Avery Nathens, MD, PhD, directs national efforts by the College to harness trauma registry data for ongoing quality improvement initiatives.[333,334] Currently, national trauma data efforts almost completely rely on post-hoc manual data extraction procedures that vary from site to site, and use vendor-specific data models.[63,106,107] These systems neither support real-time, workflow integrated screening and intervention for PTSD and comorbidity, nor do they provide a way for trauma centers to participate in national initiatives to create population-level, de-identified clinical data repositories for comparative effectiveness research.[335] The overarching goal of participation in the Collaboratory could be seen as a national trauma health care system that enforces and supports trauma quality mandates, facilitates automation and real-time, workflow integrated data capture, and contributes to nationwide research goals targeting PTSD and comorbidity.

This focus on trauma center policy directly addresses issues of engagement of trauma centers nationally as full research partners, as well as issues of intervention maintenance/sustainability. The scientific aims and results of the UH3 project have tremendous potential public health impact by directly informing nationwide policy mandates and clinical practice guidelines. The College policy support in the current investigation facilitates the endurance of new policy mandates and clinical guidelines, and ensures that sustained attention will be given to the underlying issue of wide-spread implementation of screening and intervention procedures for PTSD and related comorbidity, long after the completion of a single pragmatic trial.[190,336-338] Thus, the research team is fully committed to developing and implementing, with the aid of the Collaboratory, a flexible care management intervention targeting PTSD and comorbidity that is sustainable both within their own trauma center and also throughout trauma care systems nationally. This strategy is entirely in concert with the Collaboratory RFA-RM-13-012/MCC approach [332] that strongly encourages implementation of any developed care intervention model within the "home" health care systems (Figure 3).

The results of the trial will directly inform future American College of Surgeons' policy regarding screening and intervention for PTSD and comorbidity (Figure 18). In January of 2005, the College made a landmark policy decision to mandate health services targeting screening and intervention for alcohol related disorders as a requisite for trauma center accreditation.[63] Prior pragmatic randomized clinical trial investigations from the study team provided evidence supporting the College's alcohol mandate.[18,75,129] In May of 2011, the investigators presented results from effective NIH funded PTSD screening and intervention trials at a College policy summit.[129,136,137,172] Following the proposed summit in UH3 year 5, for the first time, the College intends to include PTSD screening and intervention as a best practice level recommendation in national guidelines for trauma center care. These new College clinical guidelines set the stage for a novel demonstration project that tests high quality, feasibly implemented, screening and intervention procedures for PTSD and related comorbidity. Dr. David Hoyt, the Executive Director of the College, is committed to a follow-up policy summit in 2019-2020 to integrate pragmatic trial results into the next edition of College guidelines for

the operation of trauma centers (Figure 18). Thus, simultaneously as the investigation is being conducted, the study team will be actively developing a College summit agenda targeting the broader aim of engaging trauma care systems nationwide in the research by using pragmatic trial results to directly impact policy mandates and clinical practice guidelines for PTSD and comorbidity. An overarching goal of the study team is to work with the Collaboratory to comprehensively refine procedures developed in prior investigation in order to develop real-time, workflow integrated, automated data screening, intervention and quality documentation procedures for the chronic disease cluster of PTSD and comorbidities that can be deployed across trauma care systems nationally. The proposed UH2-UH3 pragmatic trial is novel in suggesting both the specific technologic innovations that trauma centers could implement, and a national policy mechanism aimed to ensure that this IT innovation occurs.

Figure 18. Two Decades of Orchestration of American College of Surgeons' (ACS) Policy & NIH Funded Clinical Trials



UH3 American College of Surgeons' Policy Summit. In the UH3 year 5 of the proposal, the results of the pragmatic trial will be presented at a College policy summit. The preparation for the summit will follow similar guidelines as were developed for the May 2011 summit. Dr. Zatzick will convene a monthly meeting of the interdisciplinary team that will include Drs. Hoyt and Jurkovich; Collaboratory and NIH program staff will also be invited to participate. A key focus of the summit will be discussion of the implications of trial results for screening and intervention for PTSD and comorbidity, clinical practice guidelines, and policy mandates. In particular, the study team will discuss findings that facilitate the implementation of real-time, workflow integrated screening and intervention procedures for PTSD and comorbidity across trauma care systems nationally. Following the summit, the multi-stakeholder group will work together to develop a white paper that reviews the state of the science and recommendations for future directions for screening and intervention procedures for PTSD and related comorbidity at trauma centers nationwide. The summit will be timed to optimally impact the next version of trauma center guidelines (Figure 18).[63]

Ongoing American College of Surgeons' Stakeholder Commitment to UH3 Aims & Implementation (Appendix 2). The transition request includes letters from senior American College of Surgeons' policy advisors: Dr. David Hoyt, MD Executive Director of the American College of Surgeons', Dr. Ronald Maier, First Vice President of the American College of Surgeons' and Surgeon-in-Chief at the Harborview level I trauma center at the University of Washington, and Dr. Gregory Jurkovich, MD study policy lead and Chief of Trauma Surgery at Denver Health and the University of Colorado. The letters substantiate College support for the trial. This support includes commitment to convening an American College of Surgeons' policy summit to discuss implications for current practice guidelines and policy mandates targeting PTSD and comorbidity. This support also includes granting College research participation credit to the study 24 level I trauma centers and granting waivers of alcohol screening and brief intervention verification site visit requirements to participating centers.

10. References

1. Bonnie RJ, Fulco CE, Liverman CT, eds. *Reducing the burden of injury: Advancing prevention and treatment.* Washington, DC: National Academy Press; 1999.
2. McCaig LF. *National hospital ambulatory medical care survey: 1992 emergency department summary. Advance Data from Vital and Health Statistics.* Vol 245. Hyattsville: National Center for Health Statistics; 1994.
3. Rice DP, MacKenzie EJ, Jones AS, Associates. *Cost of injury in the United States: A report to congress.* San Francisco: Institute for Health and Aging, University of California; Baltimore, Md: Injury Prevention Center, The Johns Hopkins University;1989.
4. Bergen GS, National Center for Health Statistics (U.S.). *Injury in the United States: 2007 chartbook.* Hyattsville: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics; 2008.
5. Prevention NCfI. CDC 2012. In: Office of Statistics and Programming, ed. Atlanta: Center for Disease Control and Prevention; 2012.
6. Ramstad SM, Russo J, Zatzick D. Is it an accident? Recurrent traumatic life events in level I trauma center patients compared to the general population. *Journal of traumatic stress.* 2004;17(6):529-534.
7. Bergman K, Maltz S, Fletcher J. Evaluation of moderate traumatic brain injury. *J Trauma Nurs.* Apr-Jun 2010;17(2):102-108.
8. Faul M, Xu L, Wald MM, Coronado VG. Traumatic brain injury in the United States: Emergency department visits, hospitalizations, and deaths 2002-2006. *Center for Disease Control and Prevention.* 2010;National Center for Injury Prevention and Control.
9. United States. President's Commission on Care for America's Returning Wounded Warriors. *Serve, support, simplify: Report of the President's Commission on Care for America's Returning Wounded Warriors.* Washington, DC: President's Commission on Care for America's Returning Wounded Warriors; 2007.
10. National Institute of Neurological Disorders and Stroke. Traumatic brain injury: Hope through research. Bethesda: National Institute of Health; 2009: http://www.ninds.nih.gov/disorders/tbi/detail_tbi.htm.
11. Zatzick D, Jurkovich G, Rivara F, et al. A national US study of posttraumatic stress disorder, depression, and work and functional outcomes after injury hospitalization. *Ann Surg.* 2008;248(3):429-437.
12. Krug EG, Sharma GK, Lozano R. The global burden of injuries. *Am J Public Health.* 2000;90(4):523-526.
13. World Health Organization. Disease and injury country estimates. 2012; http://www.who.int/healthinfo/global_burden_disease/estimates_country/en/index.html.
14. Norton R, Kobusingye O. Injuries. *N Engl J Med.* May 2 2013;368(18):1723-1730.
15. Socie E, Duffy RE, Erskine T. Substance use and type and severity of injury among hospitalized trauma cases: Ohio, 2004-2007. *J Stud Alcohol Drugs.* 2012;73(2):260-267.
16. Soderstrom CA, Dischinger PC, Smith GS, McDuff DR, Hebel JR, Gorelick DA. Psychoactive substance dependence among trauma center patients. *Journal of the American Medical Association.* May 27 1992;267(20):2756-2759.
17. Soderstrom CA, Smith GS, Dischinger PC, et al. Psychoactive substance use disorders among seriously injured trauma center patients. *Jama.* 1997;277(22):1769-1774.
18. Gentilello LM, Rivara FP, Donovan DM, et al. Alcohol interventions in a trauma center as a means of reducing the risk of injury recurrence. *Ann Surg.* 1999;230(4):473-480.
19. Ramchand R, Marshall GN, Schell TL, et al. Alcohol abuse and illegal drug use among Los Angeles County trauma patients: Prevalence and evaluation of single item screener. *J Trauma.* May 2009;66(5):1461-1467.
20. Ehrlich PF, Brown JK, Drongowski R. Characterization of the drug-positive adolescent trauma population: Should we, do we, and does it make a difference if we test? *J Pediatr Surg.* May 2006;41(5):927-930.
21. Zatzick D, Rivara FP, Nathens AB, et al. A nationwide US study of post-traumatic stress after hospitalization for physical injury. *Psychol Med.* Oct 2007;37(10):1469-1480.

22. Zatzick D, Russo J, Rivara F, Roy-Byrne P, Jurkovich G, Katon W. The detection and treatment of posttraumatic distress and substance intoxication in the acute care inpatient setting. *Gen Hosp Psychiatry.* 2005;27(1):57-62.
23. Zatzick D, Kang S, Kim S, et al. Patients with recognized psychiatric disorders in trauma surgery: Incidence, inpatient length of stay, and cost. *Journal of Trauma.* 2000;49(3):487-495.
24. Geiss Trusz S, Wagner A, Russo J, Love J, Zatzick D. Assessing barriers to care and readiness for cognitive behavioral therapy in early acute care PTSD interventions. *Psychiatry.* 2011;74(3):207-223.
25. Parekh AK, Goodman RA, Gordon C, Koh HK. Managing multiple chronic conditions: a strategic framework for improving health outcomes and quality of life. *Public Health Rep.* Jul-Aug 2011;126(4):460-471.
26. Warshaw G. Introduction: Advances and challenges in care of older people with chronic illness. *Chronic Conditions in Later Life.* 2006;30(3):5-10.
27. Hwang W, Weller W, Ireys H, Anderson G. Out-of-pocket medical spending for care of chronic conditions. *Health Aff (Millwood).* Nov-Dec 2001;20(6):267-278.
28. MacKenzie EJ, Rivara FP, Jurkovich GJ, et al. A national evaluation of the effect of trauma-center care on mortality. *N Engl J Med.* Jan 26 2006;354(4):366-378.
29. Zatzick D, O'Connor SS, Russo J, et al. Technology enhanced stepped collaborative care targeting posttraumatic stress disorder and comorbidity after injury: A randomized controlled trial. *Journal of traumatic stress.* Accepted.
30. Zatzick D, Donovan D, Dunn C, et al. Substance use and PTSD in trauma center patients receiving mandated alcohol SBI. *Journal of substance abuse treatment.* 2012;43(4):410-417.
31. Ursano RJ, Fullerton CS, Epstein RS, et al. Acute and chronic posttraumatic stress disorder in motor vehicle accident victims. *American Journal of Psychiatry.* 1999;156(4):589-595.
32. Shih RA, Schell TL, Hambarsoomian K, Belzberg H, Marshall GN. Prevalence of posttraumatic stress disorder and major depression after trauma center hospitalization. *J Trauma.* Dec 2010;69(6):1560-1566.
33. Blanchard EB, Hickling EJ, Taylor AE, Loos W. Psychiatric morbidity associated with motor vehicle accidents. *J Nerv Ment Dis.* Aug 1995;183(8):495-504.
34. Holbrook TL, Anderson JP, Sieber WJ, Browner D, Hoyt DB. Outcome after major trauma: 12-month and 18-month follow-up results from the trauma recovery project. *Journal of Trauma.* 1999;46(5):765-773.
35. Michaels AJ, Michaels CE, Moon CH, et al. Posttraumatic stress disorder after injury: Impact on general health outcome and early risk assessment. *Journal of Trauma.* 1999;47(3):460-467.
36. Zatzick D, Kang SM, Muller HG, et al. Predicting posttraumatic distress in hospitalized trauma survivors with acute injuries. *Am J Psychiatry.* Jun 2002;159(6):941-946.
37. Institute of Medicine (U.S.), America CoQoHCi. Substance use disorders in the U.S. armed forces. In: Inc. e, ed. Washington, D.C.: National Academy Press; 2012: http://www.iom.edu/Reports/2012/Substance-Use-Disorders-in-the-US-Armed-Forces.aspx. Accessed 09/17/2012.
38. Shalev AY, Freedman S, Peri T, et al. Prospective study of posttraumatic stress disorder and depression following trauma. *American Journal of Psychiatry.* 1998;155(5):630-637.
39. O'Donnell ML, Creamer M, Pattison P. Posttraumatic stress disorder and depression following trauma: understanding comorbidity. *Am J Psychiatry.* 2004;161(8):1390-1396.
40. Ferrando L, Galea S, Sainz Cortón E, et al. Long-term psychopathology changes among the injured and members of the community after a massive terrorist attack. *European Pyschiatry: The Journal of the Association of European Psychiatrists.* 2010.
41. Bombardier CH, Fann JR, Temkin NR, Esselman PC, Barber J, Dikmen SS. Rates of major depressive disorder and clinical outcomes following traumatic brain injury. *Jama.* 2010;303(19):1938-1945.
42. Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *New England Journal of Medicine.* 2004;351(1):13-22.
43. Zatzick D, Rivara F, Jurkovich G, et al. Multi-site investigation of traumatic brain injuries, posttraumatic stress disorder, and self-reported health and cognitive impairments. *Arch Gen Psychiatry.* 2010;67(12):1291-1300.

44. Hoge C, McGurk D, Thomas J, Cox A, Engel CC, Castro CA. Mild traumatic brain injury in U.S. Soldiers returning from Iraq. *New England Journal of Medicine.* 2008;358(5):453-463.
45. Rivara FP, Mackenzie EJ, Jurkovich GJ, Nathens AB, Wang J, Scharfstein DO. Prevalence of pain in patients 1 year after major trauma. *Arch Surg.* Mar 2008;143(3):282-287; discussion 288.
46. Norman SB, Stein MB, Dimsdale JE, Hoyt DB. Pain in the aftermath of trauma is a risk factor for post-traumatic stress disorder. *Psychol Med.* Apr 2008;38(4):533-542.
47. Stein MB, McAllister TW. Exploring the convergence of posttraumatic stress disorder and mild traumatic brain injury. *Am J Psychiatry.* Jul 2009;166(7):768-776.
48. Holbrook TL, Galarneau MR, Dye JL, Quinn K, Dougherty AL. Morphine use after combat injury in Iraq and post-traumatic stress disorder. *New England Journal of Medicine.* 2010;362(2):110-117.
49. Russo J, Katon W, Zatzick D. The development of a population-based automated screening procedure for PTSD in acutely injured hospitalized trauma survivors. *Gen Hosp Psychiatry.* Sep-Oct 2013;35(5):485-491.
50. Zatzick D, Jurkovich G, Russo J, et al. Posttraumatic distress, alcohol disorders, and recurrent trauma across Level I trauma centers. *Journal of Trauma.* 2004;57(2):360-366.
51. Zatzick D, Jurkovich G, Rivara FP, et al. A randomized stepped care intervention trial targeting posttraumatic stress disorder for surgically hospitalized injury survivors. *Ann Surg.* 2013;257(3):390-399.
52. Zatzick D, Jurkovich GJ, Gentilello LM, Wisner DH, Rivara FP. Posttraumatic stress, problem drinking, and functioning 1 year after injury. *Arch Surg.* 2002;137(2):200-205.
53. Zatzick DF, Marmar CR, Weiss DS, et al. Posttraumatic stress disorder and functioning and quality of life outcomes in a nationally representative sample of male Vietnam veterans. *Am J Psychiatry.* Dec 1997;154(12):1690-1695.
54. Zatzick D, Weiss D, Marmar C, et al. Post-traumatic stress disorder and functioning and quality of life outcomes in female Vietnam veterans. *Military Medicine.* 1997;162(10):661-665.
55. Zatzick D, Jurkovich G, Fan MY, et al. The association between posttraumatic stress and depressive symptoms, and functional outcomes in adolescents followed longitudinally after injury hospitalization. *Archives of Pediatrics and Adolescent Medicine.* 2008;162(7):642-648.
56. Kessler RC. Posttraumatic stress disorder: The burden to the individual and society. *J Clin Psychiat.* 2000;61(suppl 5):4-14.
57. Greenberg PE, Sisitsky T, Kessler RC, et al. The economic burden of anxiety disorders in the 1990s. *J Clin Psychiat.* 1999;60(7):427-435.
58. Greenberg PE, Stiglin LE, Finkelstein SN, Berndt ER. The economic burden of depression in 1990. *J Clin Psychiatry.* 1993;54(11):405-418.
59. Walker E, Unutzer J, Rutter C, et al. Costs of health care use by women HMO members with a history of childhood abuse and neglect. *Arch Gen Psychiatry.* 1999;56(7):609-613.
60. Walker EA, Katon W, Russo J, Ciechanowski P, Newman E, Wagner AW. Health care costs associated with postraumatic stress disorder symptoms in women. *Arch Gen Psychiatry.* 2003;60(4):369-374.
61. Rivara FP, Koepsell TD, Jurkovich GJ, Gurney JG, Soderberg R. The effects of alcohol abuse on readmission for trauma. *Jama.* 1993;270(16):1962-1964.
62. MacKenzie EJ, Hoyt DB, Sacra JC, et al. National inventory of hospital trauma centers. *Jama.* March 26 2003;289(12):1515-1522.
63. American College of Surgeons Committee on Trauma. *Resources for optimal care of the injured patient.* Washington DC 2006.
64. National Center for Injury Prevention. *Cost of injury reports.* Atlanta2012.
65. Marshall GN, Orlando M. Acculturation and peritraumatic dissociation in young adult Latino survivors of community violence. *Journal of abnormal psychology.* 2002;111(1):166-174.
66. Smith RS, Fry WR, Morabito DJ, Organ CHJ. Recidivism in an urban trauma center. *Arch Surg.* 1992;127:668-670.
67. Poole GV, Griswold JA, Thaggard VK, Rhodes RS. Trauma is a recurrent disease. *Surgery.* 1993;113(6):608-611.
68. Sims DW, Bivins BA, Obeid FN, Horst HM, Sorensen VJ, Fath JJ. Urban trauma: A chronic recurrent disease. *Journal of Trauma.* 1989;29(7):940-947.

69. Santos M, Russo J, Aisenberg G, Uehara E, Ghesquiere A, Zatzick D. Ethnic/racial diversity and posttraumatic distress in the acute care medical setting. *Psychiatry.* 2008;71(3):234-245.
70. Stephens KA, Sue S, Roy-Byrne P, et al. Ethnoracial variations in acute PTSD symptoms among hospitalized survivors of traumatic injury. *Journal of traumatic stress.* 2010;23(3):384-392.
71. Wong EC, Schell TL, Marshall GN, Jaycox LH, Hambarsoomians K, Belzberg H. Mental health service utilization after physical trauma: The importance of physician referral. *Med Care.* Oct 2009;47(10):1077-1083.
72. Mackenzie EJ, Rivara F, Jurkovich G, et al. The national study on costs and outcomes of trauma. *Journal of Trauma.* 2007;63(6 Suppl):S54-67.
73. Institute of Medicine. *Emergency care for children: Growing pains.* Washington, DC: Institute of Medicine of the National Academies, Committee on the Future of Emergency Care in the United States Health System, Board on Health Care Services;2006.
74. Institute of Medicine. *Emergency medical services for children.* Washington, DC: Committee on Pediatric Medical Services; 1993.
75. Terrell F, Zatzick DF, Jurkovich GJ, et al. Nationwide survey of alcohol screening and brief intervention practices at US Level I trauma centers. *J Am Coll Surg.* Nov 2008;207(5):630-638.
76. Chesnut RM, Carney N, Maynard H, Patterson P, Mann NC, Helfand M. *Rehabilitation for traumatic brain injury.* Rockville: Agency for Health Care Policy and Research;1999.
77. Horowitz L, Kassam-Adams N, Bergstein J. Mental health aspects of emergency medical services for children: Summary of a consensus conference. *Academic Emergency Medicine.* 2001;8(12):1187-1196.
78. Zatzick D, Russo J, Katon W. Somatic, posttraumatic stress, and depressive symptoms among injured patients treated in trauma surgery. *Psychosomatics.* 2003;44(6):479-484.
79. Sabin JA, Zatzick D, Jurkovich G, Rivara FP. Primary care utilization and detection of emotional distress after adolescent traumatic injury: Identifying an unmet need. *Pediatrics.* 2006;117(1):130-138.
80. Boudreaux ED, Francis JL, Loyacano T. Family presence during invasive procedures and resuscitations in the emergency department: A critical review and suggestions for future research. *Ann Emerg Med.* Aug 2002;40(2):193-205.
81. Baren JM. Rising to the challenge of family-centered care in emergency medicine. *Acad Emerg Med.* Dec 2001;8(12):1182-1185.
82. Committee on Quality of Health Care in America. *Crossing the quality chasm: A new health system for the 21st century.* Washington, DC: National Academy Press; 2001.
83. Roberts NP, Kitchiner NJ, Kenardy J, Bisson JI. Systematic review and meta-analysis of multiple-session early interventions following traumatic events. *Am J Psychiatry.* 2009;166(3):293-301.
84. Roberts NP, Kitchiner NJ, Kenardy J, Bisson J. Multiple session early psychological interventions for the prevention of post-traumatic stress disorder. *Cochrane Database Syst Rev.* 2009(3):CD006869.
85. van Ommeren M, Saxena S, Saraceno B. Mental and social health during and after acute emergencies: Emerging consensus? *Bull World Health Organ.* Jan 2005;83(1):71-75; discussion 75-76.
86. National Institute of Mental Health. *Mental health and mass violence: Evidence-based early psychological intervention for victims/survivors of mass violence: a workshop to reach consensus on best practices.* BethesdaWashington, D.C.: National Institute of Mental Health: U.S. Government Printing Office; 2002.
87. National Center for Child Traumatic Stress and National Center for PTSD, Brymer M, Jacobs A, et al. *Psychological first aid: Field operations guide.* National Center for Child Traumatic Stress and National Center for PTSD; July 2006.
88. Hobfoll SE, Watson P, Bell CC, et al. Five essential elements of immediate and mid-term mass trauma intervention: Empirical evidence. *Psychiatry.* Winter 2007;70(4):283-315; discussion 316-269.
89. Foa EB, Keane TM, Friedman MJ, Cohen JA. *Effective treatments for PTSD: Practice guidelines from the International Society for Traumatic Stress Studies.* 2 ed. New York: The Guilford Press; 2009.
90. Kessler R, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry.* Dec 1995;52(12):1048-1060.
91. U. S. Department of Health and Human Services. *Multiple chronic conditions - a strategic framework: Optimum health and quality of life for individuals with multiple chronic conditions.* Washington, DCDecember 2010.

92. Wallace RB, Salive ME. The dimensions of multiple chronic conditions: Where do we go from here? A commentary on the special collection of preventing chronic disease. *Center for Disease Control and Prevention.* 2013;10:5.
93. Tuma F. Mass trauma intervention: A case for integrating principles of behavioral health with intervention to restore physical safety, order, and infrastructure. *Psychiatry.* Winter 2007;70(4):356-360.
94. Zatzick D, Galea S. An epidemiologic approach to the development of early trauma focused intervention. *Journal of traumatic stress.* 2007;20(4):401-412.
95. Love J, Zatzick D. A survey of screening & intervention for comorbid alcohol, drugs, suicidality, depression & PTSD at trauma centers. Manual Under Revision.
96. Services CfMM. Bundled payments for care improvement (BPCI) initiative: General information. http://innovation.cms.gov/initiatives/bundled-payments/.
97. Vashi AA, Fox JP, Carr BG, et al. Use of hospital-based acute care among patients recently discharged from the hospital. *Jama.* Jan 23 2013;309(4):364-371.
98. Adams JG. Emergency department overuse: perceptions and solutions. *Jama.* Mar 20 2013;309(11):1173-1174.
99. Burke RE, Coleman EA. Interventions to Decrease Hospital Readmissions Keys for Cost-effectiveness. *Jama Intern Med.* Apr 22 2013;173(8):695-698.
100. Shafi S, Barnes S, Nicewander D, et al. Health care reform at trauma centers--mortality, complications, and length of stay. *J Trauma.* Dec 2010;69(6):1367-1371.
101. Shafi S, Ogola G, Fleming N, et al. Insuring the uninsured: potential impact of Health Care Reform Act of 2010 on trauma centers. *J Trauma Acute Care Surg.* Nov 2012;73(5):1303-1307.
102. Bindman AB, Blum JD, Kronick R. Medicare Payment for Chronic Care Delivered in a Patient-Centered Medical Home. *Jama.* Aug 8 2013.
103. Khoury AL, Charles AG, Sheldon GF. The trauma safety-net hospital under the Affordable Care Act: Will it survive? *J Trauma Acute Care Surg.* Jul 2 2013.
104. Frankel HL, Butler KL, Cuschieri J, et al. The role and value of surgical critical care, an essential component of Acute Care Surgery, in the Affordable Care Act: a report from the Critical Care Committee and Board of Managers of the American Association for the Surgery of Trauma. *J Trauma Acute Care Surg.* Jul 2012;73(1):20-26.
105. Sacks GD, Hill C, Rogers SO, Jr. Insurance status and hospital discharge disposition after trauma: inequities in access to postacute care. *J Trauma.* Oct 2011;71(4):1011-1015.
106. United States Congress. The Patient Protection and Affordable Care Act. 2010.
107. Fixsen DL, Naoom SF, Blase KA, Friedman RM, Wallace F. *Implementation research: A synthesis of the literature.* Tampa: University of South Florida, Louis de la Parte Florida Mental Health Institute, National Implementation Research Network; 2005.
108. Van Eaton EG, Zatzick D, Gallagher T, et al. A nationwide survey of trauma center information technology and electronic medical record leverage capacity *JACS.* 2014;219(3):505-510.
109. Richesson RL, Hammond WE, Nahm M, et al. Electronic health records based phenotyping in next-generation clinical trials: a perspective from the NIH Health Care Systems Collaboratory. *J Am Med Inform Assoc.* Aug 16 2013.
110. Van Eaton EG, Horvath KD, Lober WB, Pellegrini CA. Organizing the transfer of patient care information: The development of a computerized resident sign-out system. *Surgery.* 2004;136(1):5-13.
111. Van Eaton EG, Horvath KD, Lober WB, Rossini AJ, Pellegrini CA. A randomized, controlled trial evaluating the impact of a computerized rounding and sign-out system on continuity of care and resident work hours. *J Am Coll Surg.* 2005;200(4):538-545.
112. Van Eaton EG, Lober WB, Pellegrini CA, Horvath KD. User-driven design of a computerized rounding and sign-out application. Paper presented at: AMIA Annual Sympossium Proceedings2005.
113. Van Eaton EG, McDonough KA, Lober WB, Johnson EA, Pellegrini CA, Horvath KD. Safety of using a computerized rounding and sign-out system to reduce resident workhours. *Academic Medicine.* 2010;85(7):1189-1195.
114. Michaels AJ, Michaels CE, Zimmerman MA, Smith JS, Moon CH, Peterson C. Posttraumatic stress disorder in injured adults: Etiology by path analysis. *Journal of Trauma.* 1999;47(5):867-873.

115. Zatzick D, Grossman D, Russo J, et al. Predicting posttraumatic stress symptoms longitudinally in a representative sample of hospitalized injured adolescents. *J Am Acad Child Adolesc Psychiatry.* 2006;45(10):1188-1195.
116. Zatzick D, Russo J, Pittman RK, Rivara F, Jurkovich G, Roy-Byrne P. Reevaluating the association between emergency department heart rate and the development of posttraumatic stress disorder: A public health approach. *Biol Psychiatry.* 2005;57(1):91-95.
117. Winston FK, Kassam-Adams N, Vivarelli-O'Neill C, et al. Acute stress disorder symptoms in children and their parents after pediatric traffic injury. *Pediatrics.* 2002;109(6):e90.
118. Davydow DS, Zatzick DF, Rivara FP, et al. Predictors of posttraumatic stress disorder and return to usual major activity in traumatically injured intensive care unit survivors. *Gen Hosp Psychiatry.* September-October 2009;31(5):428-435.
119. O'Donnell ML, Creamer MC, Parslow R, et al. A predictive screening index for posttraumatic stress disorder and depression following traumatic injury. *J Consult Clin Psychol.* 2008;76(6):923-932.
120. Ziedonis D, Hitsman B, Beckham JC, et al. Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. *Nicotine Tob Res.* Dec 2008;10(12):1691-1715.
121. Breslau N, Davis GC, Schultz LR. Posttraumatic stress disorder and the incidence of nicotine, alcohol, and other drug disorders in persons who have experienced trauma. *Arch Gen Psychiatry.* Mar 2003;60(3):289-294.
122. McFall M, Saxon AJ, Malte CA, et al. Integrating tobacco cessation into mental health care for posttraumatic stress disorder: A randomized controlled trial. *Jama.* 2010;304(22):2485-2493.
123. Trauma ACoSCo. National Trauma Data Bank (NTDB). http://www.facs.org/trauma/ntdb.html. Accessed May 5, 2015.
124. Wagner EH, Austin BT, Von Korff M. Organizing care for patients with chronic illness. *Milbank Q.* 1996;74(4):511-544.
125. Von Korff M, Gruman J, Schaefer J, Curry SJ, Wagner EH. Collaborative management of chronic illness. *Ann Intern Med.* Dec 15 1997;127(12):1097-1102.
126. Katon W. Health reform, research pave way for collaborative care for mental illness. Interview by Bridge M. Kuehn. *Jama.* Jun 19 2013;309(23):2425-2426.
127. Peek CJ. A collaborative care lexicon for asking practice and research development questions. Rockville: Agency for Healthcare Research and Quality; 2011.
128. Dobscha SK, Corson K, Perrin NA, et al. Collaborative care for chronic pain in primary care: A cluster randomized trial. *Jama.* Mar 25 2009;301(12):1242-1252.
129. Zatzick D, Roy-Byrne P, Russo J, et al. A randomized effectiveness trial of stepped collaborative care for acutely injured trauma survivors. *Arch Gen Psychiat.* 2004;61(5):498-506.
130. Zatzick D, Simon GE, Wagner AW. Developing and implementing randomized effectiveness trials in general medical settings. *Clinical Psychology: Science and Practice.* 2006;13:53-68.
131. Rollman BL, Belnap BH, LeMenager MS, et al. Telephone-delivered collaborative care for treating post-CABG depression: A randomized controlled trial. *Jama.* Nov 18 2009;302(19):2095-2103.
132. Rollman BL, Belnap BH, Mazumdar S, et al. A randomized trial to improve the quality of treatment for panic and generalized anxiety disorders in primary care. *Arch Gen Psychiatry.* Dec 2005;62(12):1332-1341.
133. Bruce ML, Ten Have TR, Reynolds CF, 3rd, et al. Reducing suicidal ideation and depressive symptoms in depressed older primary care patients: A randomized controlled trial. *Jama.* Mar 3 2004;291(9):1081-1091.
134. Katon W, Von Korff M, Lin E, et al. Collaborative management to achieve treatment guidelines: Impact on depression in primary care. *Jama.* 1995;273(13):1026-1031.
135. Katon WJ, Lin EH, Von Korff M, et al. Collaborative care for patients with depression and chronic illnesses. *New England Journal of Medicine.* 2010;363(27):2611-2620.
136. Zatzick D, Rivara F, Jurkovich G, et al. Enhancing the population impact of collaborative care interventions: Mixed method development and implementation of stepped care targeting posttraumatic stress disorder and related comorbidities after acute trauma. *Gen Hosp Psychiatry.* Mar-Apr 2011;33(2):123-134.
137. Zatzick D, Roy-Byrne P, Russo J, et al. Collaborative interventions for physically injured trauma survivors: A pilot randomized effectiveness trial. *Gen Hosp Psychiat.* 2001;23(3):114-123.

138. Roy-Byrne P, Craske MG, Sullivan G, et al. Delivery of evidence-based treatment for multiple anxiety disorders in primary care: A randomized controlled trial. *Jama.* 2010;303(19):1921-1928.
139. Katon W, Von Korff M, Lin E, et al. Stepped collaborative care for primary care patients with persistent depression: A randomized trial. *Arch Gen Psychiatry.* 1999;56(12):1109-1115.
140. Katon W, Von Korff M, Lin E, et al. Population-based care of depression: Effective disease management strategies to decrease prevalence. *Gen Hosp Psychiatry.* 1997;19(3):169-178.
141. Katon W, Rutter C, Ludman EJ, et al. A randomized trial of relapse prevention of depression in primary care. *Arch Gen Psychiatry.* 2001;58(3):241-247.
142. Wells KB, Sherbourne C, Schoenbaum M, et al. Impact of disseminating quality improvement programs for depression in managed primary care: A randomized controlled trial. *Jama.* 2000;283(2):212-220.
143. Unutzer J, Katon W, Callahan CM, et al. Collaborative care management of late-life depression in the primary care setting: A randomized controlled trial. *Jama.* 2002;288(22):2836-2845.
144. Katon W, Von Korff M, Lin EH, et al. The pathways study: A randomized trial of collaborative care in patients with diabetes and depression. *Arch Gen Psychiatry.* 2004;61(10):1042-1049.
145. Kroenke K, Theobald D, Wu J, et al. Effect of telecare management on pain and depression in patients with cancer: A randomized trial. *Jama.* Jul 14 2010;304(2):163-171.
146. Fermazin M, Tahan H, Lett JE, McGonigal L, Weis N. Improving transitions of care: Emergency department to home. 2009; http://www.ntocc.org/Portals/0/PDF/Resources/ImplementationPlan_EDToHome.pdf. .
147. Coleman EA, Parry C, Chalmers S, Min SJ. The care transitions intervention: results of a randomized controlled trial. *Arch Intern Med.* Sep 25 2006;166(17):1822-1828.
148. Baier RR, Gardner RL, Coleman EA, Jencks SF, Mor V, Gravenstein S. Shifting the dialogue from hospital readmissions to unplanned care. *The American journal of managed care.* Jun 2013;19(6):450-453.
149. Burke RE, Kripalani S, Vasilevskis EE, Schnipper JL. Moving beyond readmission penalties: creating an ideal process to improve transitional care. *Journal of hospital medicine : an official publication of the Society of Hospital Medicine.* Feb 2013;8(2):102-109.
150. Ursano RJ, Bell C, Eth S, et al. Practice guideline for the treatment of patients with acute stress disorder and posttraumatic stress disorder. *American Journal of Psychiatry.* 2004;161, 11 suppl:3-31.
151. Committee on Treatment of Post Traumatic Stress Disorder, Institute of Medicine, Board on Population Health and Public Health Practice. *Treatment of posttraumatic stress disorder: An assessment of the evidence.* Washington, DC: The National Academies Press; 2007.
152. Department of Veterans Affairs. Management of post-traumatic stress. 2003; http://www.oqp.med.va.gov/cpg/PTSD/PTSD_Base.htm. Accessed April 17, 2005.
153. Brady K, Pearlstein T, Asnis GM, et al. Efficacy and safety of sertraline treatment of posttraumatic stress disorder. *Jama.* 2000;283(14):1837-1844.
154. Marshall RD, Beebe KL, Oldham M, Zaninelli R. Efficacy and safety of paroxetine treatment for chronic PTSD: A fixed-dose, placebo-controlled study. *American Journal of Psychiatry.* 2001;158(12):1982-1988.
155. Pitman RK, Sanders KM, Zusman RM, et al. Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. *Biol Psychiatry.* 2002;51(2):189-192.
156. Stein MB, Kerridge C, Dimsdale JE, Hoyt DB. Pharmacotherapy to prevent PTSD: Results from a randomized controlled proof-of-concept trial in physically injured patients. *Journal of traumatic stress.* 2007;20(6):923-932.
157. Zatzick D, Roy-Byrne P. Psychopharmacological approaches to the management of posttraumatic stress disorders in the acute care medical sector. *Seminars in Clinical Neuropsychiatry.* 2003;8(3):168-174.
158. Zatzick D, Roy-Byrne P. From bedside to bench: How the epidemiology of clinical practice can inform pharmacological intervention development in the secondary prevention of PTSD. *Psychiatr Serv.* 2006;57:1726-1730.
159. Raskind MA, Peskind ER, Hoff DJ, et al. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. *Biol Psychiatry.* 2007;61(8):928-934.

160. Taylor FB, Lowe K, Thompson C, et al. Daytime prazosin reduces psychological distress to trauma specific cues in civilian trauma posttraumatic stress disorder. *Biol Psychiatry.* 2006;59(7):577-581.
161. Taylor FB, Martin P, Thompson C, et al. Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma posttraumatic stress disorder: A placebo-controlled study. *Biol Psychiatry.* 2008;63(6):629-632.
162. Agency for Health Care Policy and Research. *Depression in primary care volumes 1 and 2.* Rockville, Maryland: U.S. Department of Health and Human Services;1993.
163. Davidson J, Baldwin D, Stein DJ, et al. Treatment of posttraumatic stress disorder with venlafaxine extended release: A 6-month randomized controlled trial. *Archives General Psychiatry.* October 1, 2006 2006;63(10):1158-1165.
164. Davidson J, Pearlstein T, Londborg P, et al. Efficacy of sertraline in preventing relapse of posttraumatic stress disorder: Results of a 28-week double-blind, placebo-controlled study. *American Journal of Psychiatry.* 2001;158(12):1974-1981.
165. Solomon SD, Gerrity ET, Muff AM. Efficacy of treatments for posttraumatic stress disorder. *Jama.* 1992;268:633-638.
166. Boynton L, Bentley J, Strachan E, Barbato A, Raskind M. Preliminary findings concerning the use of prazosin for the treatment of posttraumatic nightmares in a refugee population. *Journal of Psychiatric Practice.* 2009;15(6):454-459.
167. Calohan J, Peterson K, Peskind ER, Raskind MA. Prazosin treatment of trauma nightmares and sleep disturbance in soldiers deployed in Iraq. *Journal of traumatic stress.* 2010;23(5):645-648.
168. Journal of Clinical Psychiatry Guidelines. Treatment of posttraumatic stress disorder. The expert consensus panels for PTSD. *J Clin Psychiat.* 1999;60:3-76.
169. Shalev AY, Ankri YL, Peleg T, Israeli-Shalev Y, Freedman S. Barriers to receiving early care for PTSD: results from the Jerusalem trauma outreach and prevention study. *Psychiatr Serv.* Jul 2011;62(7):765-773.
170. Simon GE, Ludman EJ, Tutty S, Operskalski B, Von Korff M. Telephone psychotherapy and telephone care management for primary care patients starting antidepressant treatment: A randomized controlled trial. *Jama.* 2004;292(8):935-942.
171. Mohr DC, Duffecy J, Jin L, et al. Multimodal e-mental health treatment for depression: a feasibility trial. *Journal of medical Internet research.* 2010;12(5):e48.
172. Zatzick D, Russo J, Lord SP, et al. Collaborative Care Intervention Targeting Violence Risk Behaviors, Substance Use, and Posttraumatic Stress and Depressive Symptoms in Injured Adolescents: A Randomized Clinical Trial. *JAMA Pediatr.* Apr 14 2014;168(6):532-539.
173. Somer E, Tamir E, Maguen S, Litz BT. Brief cognitive-behavioral phone-based intervention targeting anxiety about the threat of attack: A pilot study. *Behaviour research and therapy.* May 2005;43(5):669-679.
174. Madras BK, Compton WM, Avula D, Stegbauer T, Stein JB, Clark HW. Screening, Brief Interventions, Referral to Treatment (SBIRT) for illicit drug and alcohol use at multiple healthcare sites: Comparison at intake and 6 months later. *Drug Alcohol Depen.* Jan 1 2009;99(1-3):280-295.
175. Longabaugh R, Woolard RE, Nirenberg TD, et al. Evaluating the effects of a brief motivational intervention for injured drinkers in the emergency department. *J Stud Alcohol.* Nov 2001;62(6):806-816.
176. Monti PM, Colby SM, Barnett NP, Spirito A, Rohsenow DJ. Brief intervention for harm reduction with alcohol-positive older adolescents in a hospital emergency department. *J Consult Clin Psychol.* 1999;67(6):989-994.
177. Crawford MJ, Patton R, Touquet R, et al. Screening and referral for brief intervention of alcohol-misusing patients in an emergency department: A pragmatic randomised controlled trial. *Lancet.* 2004;364(9442):1334-1339.
178. Smith AJ, Hodgson RJ, Bridgeman K, Shepherd JP. A randomized controlled trial of a brief intervention after alcohol-related facial injury. *Addiction.* Jan 2003;98(1):43-52.
179. Schermer CR, Moyers TB, Miller WR, Bloomfield LA. Trauma center brief interventions for alcohol disorders decrease subsequent driving under the influence arrests. *J Trauma.* Jan 2006;60(1):29-34.
180. Tevyaw TO, Monti PM. Motivational enhancement and other brief interventions for adolescent substance abuse: foundations, applications and evaluations. *Addiction.* Nov 2004;99 Suppl 2:63-75.

181. Dunn C, Deroo L, Rivara FP. The use of brief interventions adapted from motivational interviewing across behavioral domains: A systematic review. *Addiction.* 2001;96:1725-1742.
182. Field CA, Baird J, Saitz R, Caetano R, Monti PM. The mixed evidence for brief intervention in emergency departments, trauma care centers, and inpatient hospital settings: What should we do? *Alcohol Clin Exp Res.* 2010;34(12):2004-2010.
183. Field CA, Caetano R. The effectiveness of brief intervention among injured patients with alcohol dependence: Who benefits from brief interventions? *Drug Alcohol Depend.* Sep 1 2010;111(1-2):13-20.
184. Thorpe KE, Zwarenstein M, Oxman AD, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): A tool to help trial designers. *J Clin Epidemiol.* May 2009;62(5):464-475.
185. National Center for Complementary and Alternative Medicine. *NIH Health Care Systems Research Collaboratory - Pragmatic Clinical Trials Demonstration Projects (UH2/UH3).* National Center for Complementary and Alternative Medicine,;2012.
186. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: Increasing the value of clinical research for decision making in clinical and health policy. *Jama.* 2003;290(12):1624-1632.
187. March J, Kraemer HC, Trivedi M, et al. What have we learned about trial design from NIMH-funded pragmatic trials? *Neuropsychopharmacology.* Aug 25 2010;35(13):2491-2501.
188. Zwarenstein M, Treweek S, Gagnier JJ, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *Bmj.* 2008;337:a2390.
189. Federal Coordinating Council for Comparative Effectiveness Research. Report to the President and the Congress. In: Services UDoHaH, ed. Washington, D. C.2009.
190. Glasgow RE, Chambers D. Developing robust, sustainable, implementation systems using rigorous, rapid and relevant science. *Clin Transl Sci.* Feb 2012;5(1):48-55.
191. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. *Med Care.* Mar 2012;50(3):217-226.
192. Gaglio B, Phillips SM, Heurtin-Roberts S, Sanchez MA, Glasgow RE. How pragmatic is it? Lessons learned using PRECIS and RE-AIM for determining pragmatic characteristics of research. *Implement Sci.* 2014;9:96.
193. Glasgow RE. What does it mean to be pragmatic? Pragmatic methods, measures, and models to facilitate research translation. *Health Educ Behav.* Jun 2013;40(3):257-265.
194. Simpson DD. A conceptual framework for transferring research to practice. *Journal of substance abuse treatment.* 2002;22(4):171-182.
195. Porras JI, Robertson PJ. Organizational development: Theory, practice, and research. In: Dunnette MD, Hough LM, eds. *Handbook of Industrial and Organizational Psychology*. Palo Alto: Consulting Psychologists Press, Inc; 1992.
196. Glisson C, Schoenwald SK. The ARC organizational and community intervention strategy for implementing evidence-based children's mental health treatments. *Mental Health Services Research.* 2005;7(4):243-259.
197. Glisson C. The organizational context of children's mental health services. *Clin Child Fam Psychol Rev.* 2002;5(4):233-253.
198. Glisson C, James LR. The cross-level effects of culture and climate in human service teams. *Journal of Organizational Behavior.* 2002;23:767-794.
199. Shortell SM, Marsteller JA, Lin M, et al. The role of perceived team effectiveness in improving chronic illness care. *Med Care.* 2004;42(11):1040-1048.
200. Shortell SM. Increasing value: a research agenda for addressing the managerial and organizational challenges facing health care delivery in the United States. *Medical Care Research and Review.* 2004;61(3 Suppl):12S-30S.
201. Zatzick CD, Zatzick DF. The effect of perceived person-job fit on employee attitudes toward change in trauma centers. *Health Care Manage Rev.* Feb 3 2012;38(2):115-124.
202. Aarons GA, Horowitz JD, Dlugosz LR, Ehrhart MG. The role of organizational processes in dissemination and implementation research. In: Brownson RC, Colditz GA, Proctor EK, eds. *Dissemination and Implementation Research in Health: Translating Science to Practice*. New York: Oxford University Press; 2012:128-153.

203. Miller WR, Yahne CE, Moyers TB, Martinez J, Pirritano M. A randomized trial of methods to help clinicians learn motivational interviewing. *J Consult Clin Psychol.* Dec 2004;72(6):1050-1062.
204. Sholomskas DE, Syracuse-Siewert G, Rounsaville BJ, Ball SA, Nuro KF, Carroll KM. We don't train in vain: A dissemination trial of three strategies of training clinicians in cognitive-behavioral therapy. *J Consult Clin Psychol.* 2005;73(1):106-115.
205. Miller WR, Mount KA. A small study of training in motivational interviewing: Does one workshop change clinician and client behavior? *Behavioral and Cognitive Psychotherapy.* 2001;29:457-471.
206. D'Onofrio G, Nadel ES, Degutis LC, et al. Improving emergency medicine residents' approach to patients with alcohol problems: A controlled educational trial. *Ann Emerg Med.* 2002;40(1):50-62.
207. D'Onofrio G, Pantalon MV, Degutis LC, Fiellin DA, O'Connor P G. Development and implementation of an emergency practitioner-performed brief intervention for hazardous and harmful drinkers in the emergency department. *Acad Emerg Med.* Mar 2005;12(3):249-256.
208. Zatzick D, Donovan DM, Dunn C, et al. Disseminating Organizational Screening and Brief Intervention Services (DO-SBIS) for alcohol at trauma centers study design. *Gen Hosp Psychiat.* 2013;35(2):174-180.
209. Naylor PJ, Wharf-Higgins J, Blair L, Green L, O'Connor B. Evaluating the participatory process in a community-based heart health project. *Soc Sci Med.* Oct 2002;55(7):1173-1187.
210. Brownson RC. Policy dissemination research: Are we making legislation or sausage? Paper presented at: 4th Annual NIH Conference on the Science of Dissemination and Implementation: Policy and Practice; March 21-22, 2011, 2011; Bethesda, MD.
211. Brownson RC, Dodson EA, Stamatakis KA, et al. Communicating evidence-based information on cancer prevention to state-level policy makers. *J Natl Cancer Inst.* Feb 16 2011;103(4):306-316.
212. Dreisinger ML, Boland EM, Filler CD, Baker EA, Hessel AS, Brownson RC. Contextual factors influencing readiness for dissemination of obesity prevention programs and policies. *Health Educ Res.* Sep 5 2011.
213. Mertens DM. Mixed methods as tools for social change. *Journal of Mixed Methods Research.* Jul 2011;5(3):195-197.
214. Johnson KE, Tachibana C, Coronado GD, et al. A guide to research partnerships for pragmatic clinical trials. *Bmj.* 2014;349:g6826.
215. Raghavan R. The role of economic evaluation in dissemination and implementation research. In: Brownson RC, Colditz GA, Proctor EK, eds. *Dissemination and Implementation Research in Health: Translating Science to Practice*. New York: Oxford University Press; 2012:94-113.
216. Ritzwoller DP, Sukhanova A, Gaglio B, Glasgow RE. Costing behavioral interventions: a practical guide to enhance translation. *Ann Behav Med.* Apr 2009;37(2):218-227.
217. Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost-effectiveness in health and medicine.* New York: Oxford University Press; 1996.
218. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes.* Oxford, England: Oxford University Press; 1997.
219. MacKenzie EJ, Weir S, Rivara FP, et al. The value of trauma center care. *J Trauma.* Jul 2010;69(1):1-10.
220. Gentilello LM, Ebel BE, Wickizer TM, Salkever DS, Rivara FP. Alcohol interventions for trauma patients treated in emergency departments and hospitals: A cost benefit analysis. *Ann Surg.* 2005;241(4):541-550.
221. Katon WJ, Roy-Byrne P, Russo J, Cowley D. Cost-effectiveness and cost offset of a collaborative care intervention for primary care patients with panic disorder. *Arch Gen Psychiatry.* Dec 2002;59(12):1098-1104.
222. Katon WJ, Lin E, Russo J, Unutzer J. Increased medical costs of a population-based sample of depressed elderly patients. *Arch Gen Psychiatry.* Sep 2003;60(9):897-903.
223. Katon W, Russo J, Sherbourne C, et al. Incremental cost-effectiveness of a collaborative care intervention for panic disorder. *Psychol Med.* Mar 2006;36(3):353-363.
224. Katon W, Russo J, Lin EHB, et al. Cost-effectiveness of a multicondition collaborative care intervention: A randomized controlled trial. *Arch Gen Psychiatry.* 2012;69(5):506-514.
225. Creswell JW, Plano Clark VL. *Designing and conducting mixed methods research.* 2nd ed. Los Angeles: SAGE Publications; 2011.

226. Creswell JW, Zhang W. The application of mixed methods designs to trauma research. *Journal of traumatic stress.* 2009;22(6):612-621.
227. Palinkas LA, Aarons GA, Horwitz S, Chamberlain P, Hurlburt M, Landsverk J. Mixed method designs in implementation research. *Adm Policy Ment Health.* 2011;38(1):44-53.
228. Donovan J, Mills N, Smith M, et al. Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. Commentary: presenting unbiased information to patients can be difficult. *Bmj.* Oct 5 2002;325(7367):766-770.
229. Sandelowski M. Focus on qualitative methods: Using qualitative methods in intervention studies. *Res Nurs Health.* Aug 1996;19(4):359-364.
230. Dunn C. Brief motivational interviewing interventions targeting substance abuse in the acute care medical setting. *Semin Clin Neuropsychiatry.* Jul 2003;8(3):188-196.
231. Zatzick D. Toward the estimation of population impact in early posstraumatic stress disorder intervention trials. *Depress Anxiety.* 2012;29(2):79-84.
232. Hemmelgarn AL, Glisson C, James LR. Organizational culture and climate: Implications for services and interventions research. *Clinical Psychology: Science and Practice.* 2006;13(1):73-89.
233. Hemmelgarn AL, Glisson C, Dukes D. Emergency room culture and the emotional support component of family-centered care. *Children's Health Care.* 2001;30(2):93-110.
234. Unützer J, Choi Y, Cook IA, Oishi S. A web-based data management system to improve care for depression in a multicenter clinical trial. *Psychiatr Serv.* 2002;53(6):671-673, 678.
235. Waltz J, Addis ME, Koerner K, Jacobson NS. Testing the integrity of a psychotherapy protocol: assessment of adherence and competence. *J Consult Clin Psychol.* 1993;61(4):620-630.
236. Zatzick D, Donovan DM, Jurkovich G, et al. Disseminating alcohol screening and brief intervention at trauma centers: A policy-relevant cluster randomized effectiveness trial. *Addiction.* May 2014;109(5):754-765.
237. Moyers TB, Martin T, Manuel JK, Hendrickson SM, Miller WR. Assessing competence in the use of motivational interviewing. *Journal of substance abuse treatment.* 2005;28(1):19-26.
238. Smerek MM. *Assessing data quality for healthcare systems data used in clinical research (Version 1.0).* NIH Collaboratory: Health Care Systems Research Collaboratory.
239. Management SfCD. Good Clinical Data Management Practices (GCDMP). Society for Clinical Data Management; 2013: http://www.scdm.org/sitecore/content/be-bruga/scdm/Publications/gcdmp.aspx. Accessed May 15, 2015.
240. Weathers FW, Litz BT, Herman DS, Huska JA, Keane TM. The PTSD checklist: reliability, validity, and diagnostic utility. Paper presented at: The 9th Annual Meeting of the International Society for Traumatic Stress Studies1994; San Antonio.
241. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med.* Sep 2001;16(9):606-613.
242. Babor TF, De La Fuente JR, Saunders J, Grant M. The Alcohol Use Disorders Identification Test: guidelines for use in primary health care. Geneva: World Health Organization; 1989.
243. Ware JE, Snow KK, Kosinski M. *SF-36 health survey: manual and interpretation guide.* Boston, MA: The Health Institute, New England Medical Center; 1993.
244. Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey: Construction of scales and preliminary tests of reliability and validity. *Med Care.* 1996;34(3):220-223.
245. Richardson LP, McCauley E, Grossman DC, et al. Evaluation of the patient health questionnaire-9 item for detecting major depression among adolescents. *Pediatrics.* 2010;126(6):1117-1123.
246. O'Connor SS, Dinsio K, Wang J, et al. Correlates of Suicidal Ideation in Physically Injured Trauma Survivors. *Suicide Life Threat Behav.* Feb 24 2014.
247. Bradley KA, DeBenedetti AF, Volk RJ, Williams EC, Frank D, Kivlahan DR. AUDIT-C as a brief screen for alcohol misuse in primary care. *Alcohol Clin Exp Res.* 2007;31(7):1208-1217.
248. American College of Surgeons Committee on Trauma. *Resources for optimal care of the injured patient.* Washington DC 2014.
249. Arts DG, De Keizer NF, Scheffer GJ. Defining and improving data quality in medical registries: A literature review, case study, and generic framework. *J Am Med Inform Assoc.* Nov-Dec 2002;9(6):600-611.

250. National Trauma Data Bank. *National Trauma Data Bank 2008 Annual Report: Version 8.0.* NTDB American College of Surgeons;2008.
251. Weathers FW, Huska JA, Keane TM. *The PTSD checklist-civilian version.* Boston, Ma.: The National Center For PTSD, Boston VA Medical Center; 1991.
252. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington, DC: American Psychiatric Association, American Psychiatric Press; 1994.
253. Weathers F, Ford J. Psychometric review of PTSD Checklist (PCL-C, PCL-S. PCL-M, PCL-PR). In: Stamm B, ed. *Measurement of stress, trauma, and adaptation*. Lutherville: Sidran Press; 1996:250-251.
254. Asmundson GJ, Frombach I, McQuaid J, Pedrelli P, Lenox R, Stein MB. Dimensionality of posttraumatic stress symptoms: A confirmatory factor analysis of DSM-IV symptom clusters and other symptom models. *Behaviour research and therapy.* February 2000 2000;38(2):203-214.
255. Walker EA, Newman E, Dobie DJ, Ciechanowski P, Katon W. Validation of the PTSD checklist in an HMO sample of women. *Gen Hosp Psychiatry.* 2002;24(6):375-380.
256. Dobie DJ, Kivlahan DR, Maynard C, et al. Screening for post-traumatic stress disorder in female Veteran's Affairs patients: Validation of the PTSD checklist. *Gen Hosp Psychiatry.* 2002;24(6):367-374.
257. Blanchard EB, Jones-Alexander J, Buckley TC, Forneris CA. Psychometric properties of the PTSD Checklist. *Behaviour research and therapy.* 1996;34:669-673.
258. Blake D, Weathers F, Nagy L, et al. *Clinician-Administered PTSD Scale (CAPS).* Boston, MA: National Center for Post-Traumatic Stress Disorder, Behavioral Science Division;1990.
259. Blanchard EB, Hickling EJ, Taylor AE, Loos W, Forneris CA, Jaccard J. Who develops PTSD from motor vehicle accidents? *Behaviour research and therapy.* 1996;34(1):1-10.
260. Reinert DF, Allen JP. The alcohol use disorders identification test: an update of research findings. *Alcohol Clin Exp Res.* Feb 2007;31(2):185-199.
261. Bradley K, Lapham G, Richards J, et al. Results of population-based, proactive outreach to non-treatment seeking primary care patients at high risk for AUD in the choice trial. 2014.
262. MacKenzie EJ, McCarthy ML, Ditunno JF, et al. Using the SF-36 for characterizing outcome after multiple trauma involving head injury. *J Trauma.* Mar 2002;52(3):527-534.
263. Thurman D, Sniezek J, Johnson D, al. e. *Guidelines for surveillance of central nervous system injury.* Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention;1995.
264. Butler JA, Langlois JA. *Central Nervous System Injury Surveillance Annual Data of Submission Standards—2000.* Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Injury Prevention and Control;2001.
265. The Johns Hopkins Health Services Research and Development Center. *Determining injury severity from hospital sischarges: A program to map ICD-9DM diagnoses into AIS, and ISS severity scores.* Baltimore, MD1989.
266. MacKenzie EJ, Morris JA, Edelstein SL. Effect of pre-existing disease on length of hospital stay in trauma patients. *Journal of Trauma.* 1989;29:757-764.
267. Skinner HA. The drug abuse screening test. *Addictive behaviors.* 1982;7(4):363-371.
268. Bohn MJ, Babor TF, Kranzler HR. Validity of the Drug Abuse Screening Test (DAST-10) in inpatient substance abusers. *Problems of Drug Dependence.* 1991;119:233.
269. Smith PC, Schmidt SM, Allensworth-Davies D, Saitz R. A single-question screening test for drug use in primary care. *Arch Intern Med.* Jul 12 2010;170(13):1155-1160.
270. Smith PC, Schmidt SM, Allensworth-Davies D, Saitz R. Primary care validation of a single-question alcohol screening test. *J Gen Intern Med.* Jul 2009;24(7):783-788.
271. Zatzick D, Koepsell T, Rivara F. Using target population specification, effect size, and reach to estimate and compare the population impact of two PTSD preventive interventions. *Psychiatry.* 2009;72(4):346-359.
272. Donovan DM, Bigelow GE, Brigham GS, et al. Primary outcome indices in illicit drug dependence treatment research: systematic approach to selection and measurement of drug use end-points in clinical trials. *Addiction.* Jul 22 2011.
273. Krebs EE, Bair MJ, Damush TM, Tu W, Wu J, Kroenke K. Comparative responsiveness of pain outcome measures among primary care patients with musculoskeletal pain. *Med Care.* 2010;48(11):1007-1014.

274. Krebs EE, Lorenz KA, Bair MJ, et al. Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference. *J Gen Intern Med.* 2009;24(6):733-738.
275. King NS, Crawford S, Wenden FJ, Moss NE, Wade DT. The Rivermead Post Concussion Symptoms Questionnaire: a measure of symptoms commonly experienced after head injury and its reliability. *J Neurol.* Sep 1995;242(9):587-592.
276. Kessler R, Berglund P, Demler O, Jin R, Merikangas K, Walters E. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry.* 2005;62(6):593-602.
277. Newman E, Kaloupek DG, Keane TM, Folstein SF. Ethical issues in trauma research: The evolution of an empirical model for decision making. In: Kantor GK, Jasinski J, eds. *Out of the Darkness: Contemporary Perspectives on Family Violence*. Newbury Park, CA: Sage Press; 1997:271-281.
278. Ruzek JI, Zatzick D. Ethical considerations in research participation among acutely injured trauma survivors: An empirical investigation. *Gen Hosp Psychiatry.* 2000;22:27-36.
279. Boye KS, Matza LS, Feeny DH, Johnston JA, Bowman L, Jordan JB. Challenges to time trade-off utility assessment methods: When should you consider alternative approaches? *Expert Review of Pharmacoeconomics & Outcomes Research.* 2014;14(3):437-450.
280. Badia X, Monserrat S, Roset M, Herdman M. Feasibility, validity and test–retest reliability of scaling methods for health states: The visual analogue scale and the time trade-off. *Quality of Life Research.* 1999;8(4):303-310.
281. Wright DR, Wittenberg E, Swan JS, Miksad RA, Prosser LA. Methods for measuring temporary health states for cost-utility analyses. *Pharmacoeconomics.* 2009;27(9):713-723.
282. Weiss DS, Marmar CR. The Impact of Event Scale - Revised. In: Wilson JP, Keane TM, eds. *Assessing Psychological Trauma and PTSD*. New York, NY: The Guilford Press; 1997:399-411.
283. Radloff LS. The CES-D scale a self-report depression scale for research in the general population. *Applied Psychological Measurement.* 1977;1(3):385-401.
284. Alderson AL, Novack TA. Reliable serial measurement of cognitive processes in rehabilitation: the Cognitive Log. *Arch Phys Med Rehabil.* May 2003;84(5):668-672.
285. Penna S, Novack TA. Further validation of the orientation and cognitive logs: Their relationship to the mini-mental state examination. *Arch Phys Med Rehabil.* Oct 2007;88(10):1360-1361.
286. Hogan SJ, Coote LV. Organizational culture, innovation, and performance: A test of Schein's model. *J Bus Res.* Aug 2014;67(8):1609-1621.
287. Caldwell SD, Herold DM, Fedor DB. Toward an understanding of the relationships among organizational change, individual differences, and changes in person-environment fit: A cross-level study. *Journal of Applied Psychology.* 2004;89:868-882.
288. Zatzick CD, Zatzick DF. The Effects of Job Impact and Person-Job Fit on Employee Attitudes towards Change in Trauma Centers. Academy of Management Annual Meeting; August 16, 2011, 2011; San Antonio, TX.
289. Hom P, Griffeth R. *Employee turnover.* Reading, MA: Addison-Wesley; 1995.
290. Mobley WH. *Employee turnover: Causes, consequences, and control.* Reading, MA: Addison-Wesley; 1982.
291. Zatzick CD, Elvira MM, Cohen LE. When is more better? The effects of racial composition on voluntary turnover. *Organization Science.* Sep-Oct 2003;14(5):483-496.
292. Bellal J, Pandit V, Hadeed G, et al. Unveiling posttraumatic stress disorder in trauma surgeons: A national survey. *J Trauma Acute Care Surg.* 2014;77(1):148-154.
293. Bride BE, Robinson MM, Yegidis B, Figley CR. Development and validation of the secondary traumatic stress scale. *Res Social Work Prac.* Jan 2004;14(1):27-35.
294. Gibbons RD, Hedeker D, DuToit S. Advances in analysis of longitudinal data. *Annu Rev Clin Psychol.* Apr 27 2010;6:79-107.
295. Gibbons RD, Hedeker D. Application of random-effects probit regression models. *J Consult Clin Psychol.* 1994;62(2):285-296.
296. Gibbons RD, Hedeker D, Elkin I, et al. Some conceptual and statistical issues in analysis of longitudinal psychiatric data. *Arch Gen Psychiat.* 1993;50:739-750.
297. McCulloch CE, Searle SR. *Generalized, linear, and mixed models.* Wiley; 2000.

298. Donner A, Klar N. *Design and analysis of cluster randomization trials in health research.* London: Arnold Publishers; 2000.
299. Murray DM, Pals SL, Blitstein JL, Alfano CM, Lehman J. Design and analysis of group-randomized trials in cancer: a review of current practices. *J Natl Cancer Inst.* Apr 2 2008;100(7):483-491.
300. Murray DM, Varnell SP, Blitstein JL. Design and analysis of group-randomized trials: A review of recent methodological developments. *Am J Public Health.* 2004;94(3):423-432.
301. Murray DM. *Design and analysis of group-randomized trials.* Vol 27. New York: Oxford University Press; 1998.
302. Raudenbush SW, Liu X. Statistical power and optimal design for multisite randomized trials. *Psychol Methods.* Jun 2000;5(2):199-213.
303. Hemming K, Girling A. A menu-driven facility for power and detectable-difference calculations in stepped-wedge cluster-randomized trials. *The Stata Journal.* 2014;14(2):363-380.
304. Glasgow RE, Nelson CC, Strycker LA, King DK. Using RE-AIM metrics to evaluate diabetes self-management support interventions. *Am J Prev Med.* 2006;30(1):67-73.
305. Glasgow RE, Lichtenstein E, Marcus AC. Why don't we see more translation of health promotion research to practice? Rethinking the efficacy-to effectiveness transition. *Am J Public Health.* 2003;93(8):1261-1267.
306. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *Am J Public Health.* Sep 1999;89(9):1322-1327.
307. Koepsell TD, Zatzick DF, Rivara FP. Estimating the population impact of preventive interventions from randomized trials. *Am J Prev Med.* 2011;40(2):191-198.
308. Zatzick D, Russo J, Grossman D, et al. Posttraumatic stress and depressive symptoms, alcohol use, and recurrent traumatic life events in a representative sample of hospitalized injured adolescents and their parents. *J Pediatr Psychol.* 2006;31(4):377-378.
309. Zatzick D, Koepsell T, Rivara FP. Using target population specification, effect size, and reach to estimate and compare the population impact of two PTSD preventive interventions. *Psychiatry.* 2009;72(4):346-359.
310. Aarons GA, Green AE, Palinkas LA, et al. Dynamic adaptation process to implement an evidence-based child maltreatment intervention. *Implement Sci.* Apr 18 2012;7(1):32.
311. Palinkas LA, Horwitz SM, Chamberlain P, Hurlburt MS, Landsverk J. Mixed-methods designs in mental health services research: a review. *Psychiatr Serv.* Mar 2011;62(3):255-263.
312. Palinkas LA, Weisz JR, Chorpita BF, et al. Continued Use of Evidence-Based Treatments After a Randomized Controlled Effectiveness Trial: A Qualitative Study. *Psychiatr Serv.* Aug 1 2013.
313. Zatzick D, Johnson FA. Alternative psychotherapeutic practice among middle class Americans: I: Case studies and follow-up. *Culture, Medicine and Psychiatry.* 1997;21(1):53-88.
314. Zatzick D, Kang SM, Hinton WL, et al. Posttraumatic concerns: A patient-centered approach to outcome assessment after traumatic physical injury. *Med Care.* 2001;39(4):327-339.
315. Zatzick D, Russo J, Rajotte E, et al. Strengthening the patient-provider relationship in the aftermath of physical trauma through an understanding of the nature and severity of posttraumatic concerns. *Psychiatry.* 2007;70(3):260-273.
316. Cohen MZ, Kahn DL, Steeves RH. How to analyze the data. In: Cohen MZ, Kahn DL, Steeves RH, eds. *Hermeneutic Phenomenological Research: A Practical Guide for Nurse Researchers*. Thousand Oaks, CA: Sage publications; 2000:71-82.
317. Charmaz K. *Constructing grounded theory: A practical guide through qualitative analysis.* London: SAGE Publications Ltd; 2006.
318. Glaser BG, Strauss AL. *The discovery of grounded theory; strategies for qualitative research.* Chicago,: Aldine Pub. Co.; 1967.
319. Willms DG, Best JA, Taylor DW, et al. A systematic approach for using qualitative methods in primary prevention research. *Med Anthropol Q.* 1990;4(4):391–409.
320. Corbin J, Strauss A. Grounded theory research: Procedures, canons, and evaluative criteria. *Qualitative Sociology.* 1990;13(1):3-21.
321. Boyatzis RE. *Transforming qualitative information : thematic analysis and code development.* Thousand Oaks, CA: Sage Publications; 1998.

322. Miles MB, Huberman M. *Qualitative data analysis: An expanded sourcebook.* 2nd ed. Thousand Oaks: SAGE Publications; 1994.
323. MAG Mutual, ed *ICD-9-CM Professional 2012, Volumes 1 and 2.* MAG Mutual Healthcare Solutions, Inc; 2012.
324. *RBRVS EZ-Fees 2012 "Physician Update Fix"* [computer program]. Wasserman Medical Publishers, Ltd; 2012.
325. Medical Economics Co, ed *Redbook 2010: Pharmacy's fundamental reference.* Montvale: Medical Economics Company,; 2010.
326. Lave JR, Frank RG, Schulberg HC, Kamlet MS. Cost-effectiveness of treatments for major depression in primary care practice. *Arch Gen Psychiatry.* Jul 1998;55(7):645-651.
327. Chuang LH, Kind P. Converting the SF-12 into the EQ-5D: An empirical comparison of methodologies. *Pharmacoeconomics.* 2009;27(6):491-505.
328. Franks P, Lubetkin EI, Gold MR, Tancredi DJ. Mapping the SF-12 to preference-based instruments: convergent validity in a low-income, minority population. *Med Care.* Nov 2003;41(11):1277-1283.
329. Franks P, Lubetkin EI, Gold MR, Tancredi DJ, Jia H. Mapping the SF-12 to the EuroQol EQ-5D Index in a national US sample. *Med Decis Making.* May-Jun 2004;24(3):247-254.
330. Efron B, Tibshirani R. Bootstrap methods for standard errors, confidence intervals, and other measures of statistical accuracy. *Statistical Science.* 1986;1(1):54-77.
331. Davison AC, Hinkley DV. *Bootstrap methods and their application.* Cambridge (UK): Cambridge University Press; 1997.
332. National Institute of Health. NIH health care systems research collaboratory - Demonstration projects for pragmatic clinical trials focusing on multiple chronic conditions (UH2/UH3). In: Services DoHaH, ed. Vol RFA-RM-13-0122013.
333. Newgard CD, Fildes JJ, Wu L, et al. Methodology and analytic rationale for the American College of Surgeons Trauma Quality Improvement Program. *J Am Coll Surg.* Jan 2013;216(1):147-157.
334. Mitchell CD, Truitt MS, Shifflette VK, Johnson V, Mangram AJ, Dunn EL. Who will cover the cost of undocumented immigrant trauma care? *J Trauma Acute Care Surg.* Mar 2012;72(3):609-612; discussion 612-603.
335. NIH Collaboratory. Health care systems research collaboratory: Rethinking clinical trials. https://www.nihcollaboratory.org/cores/Pages/default.aspx.
336. Proctor E, McMillen C, Luke D, Brownson R, Merz MA, Calhoun A. Sustainability of evidence-based healthcare: Research agenda and methods. Paper presented at: 5th Annual NIH Conference on the Science of Dissemination and Implementation: Research at the Crossroads2012; Bethesda, MD.
337. Proctor E, Silmere H, Raghavan R, et al. Outcomes for implementation research: Conceptual distinctions, measurement challenges, and research agenda. *Adm Policy Ment Health.* 2010;Epub ahead of print.
338. Scheirer MA. Sustainability research: What are the measurable outcomes? Paper presented at: 5th Annual NIH Conference on the Science of Dissemination and Implementation: Research at the Crossroads2012; Bethesda, MD.