The TSOS Effectiveness-Implementation Hybrid Study: Health Care System Level Theoretical Considerations & Pragmatic Trial Results

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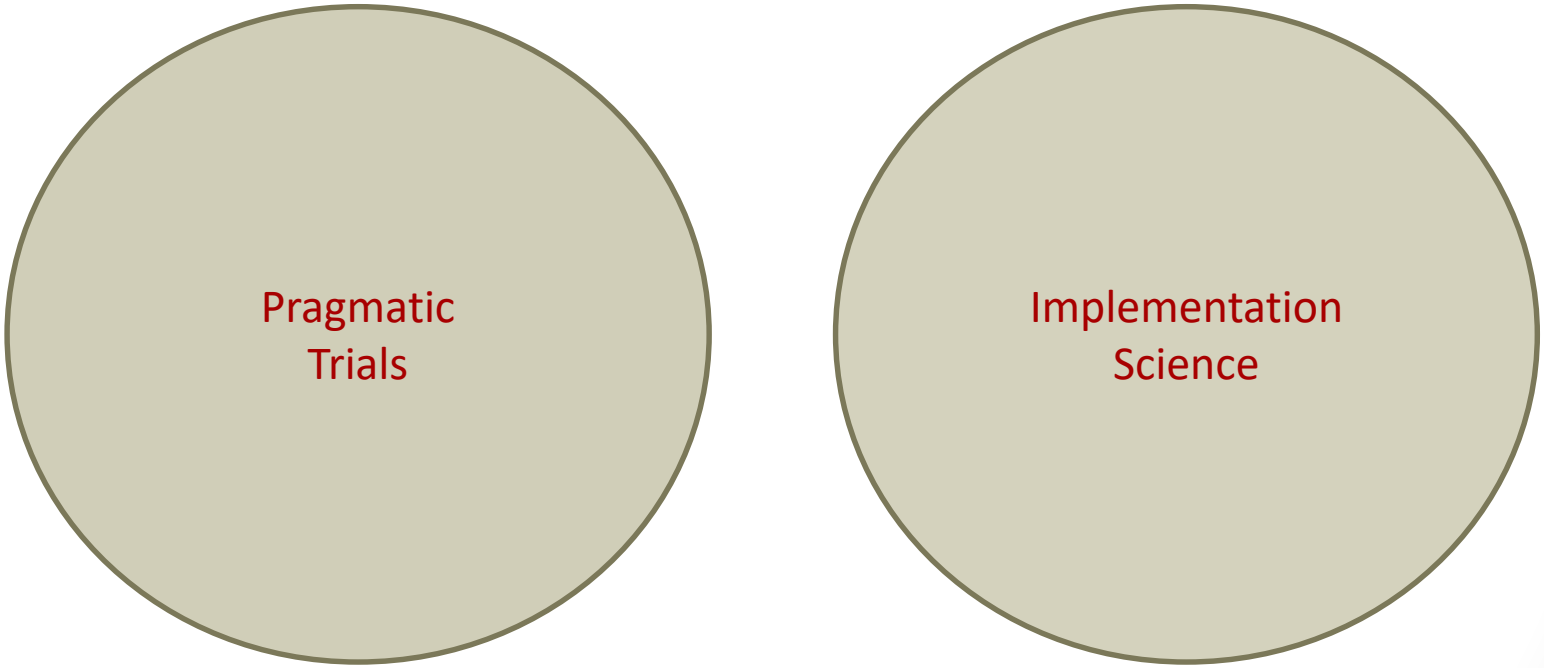
Overview

1) Theoretical considerations: Comparative health care system level integration of pragmatic trial and implementation science frameworks

2) TSOS pragmatic trial results: Reducing PTSD symptoms for injured patients, including firearm injury survivors, at US Trauma Centers

3) Preview of American College of Surgeons injury psychological sequelae screening and referral policy requirement

Theoretical Considerations: Integrating Pragmatic Trial & Implementation Science Approaches



Potential Integration: Pragmatic trials can strive to have a targeted policy impact

Article

CLINICAL TRIALS

Clinical Trials
2015, Vol. 12(5) 436–441

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Exploring the ethical and regulatory issues in pragmatic clinical trials

Robert M Califf[1,2,*] and Jeremy Sugarman[3,4]

Abstract

The need for high-quality evidence to support decision making about health and health care by patients, physicians, care providers, and policy-makers is well documented. However, serious shortcomings in evidence persist. Pragmatic clinical trials that use novel techniques including emerging information and communication technologies to explore important research questions rapidly and at a fraction of the cost incurred by more "traditional" research methods promise to help close this gap. Nevertheless, while pragmatic clinical trials can bridge clinical practice and research, they may also raise difficult ethical and regulatory challenges. In this article, the authors briefly survey the current state of evidence that is available to inform clinical care and other health-related decisions and discuss the potential for pragmatic clinical trials to improve this state of affairs. They then propose a new working definition for pragmatic research that centers upon fitness for informing decisions about health and health care. Finally, they introduce a project, jointly undertaken by the National Institutes of Health Health Care Systems Research Collaboratory and the National Patient-Centered Clinical Research Network (PCORnet), which addresses 11 key aspects of current systems for regulatory and ethical oversight of clinical research that pose challenges to conducting pragmatic clinical trials. In the series of articles commissioned on this topic published in this issue of *Clinical Trials*, each of these aspects is addressed in a dedicated article, with a special focus on the interplay between ethical and regulatory considerations and pragmatic clinical research aimed at informing "real-world" choices about health and health care.

Keyword

Clinical trials, cluster-randomized trial, ethics, evidence-based medicine, learning health-care system, patient-centered outcomes research, pragmatic clinical trial

Pragmatic trials are…

"Designed for the primary purpose of informing decision-makers regarding the comparative balance of benefits, burdens and risks of a biomedical or behavioral health intervention at the individual or population level."

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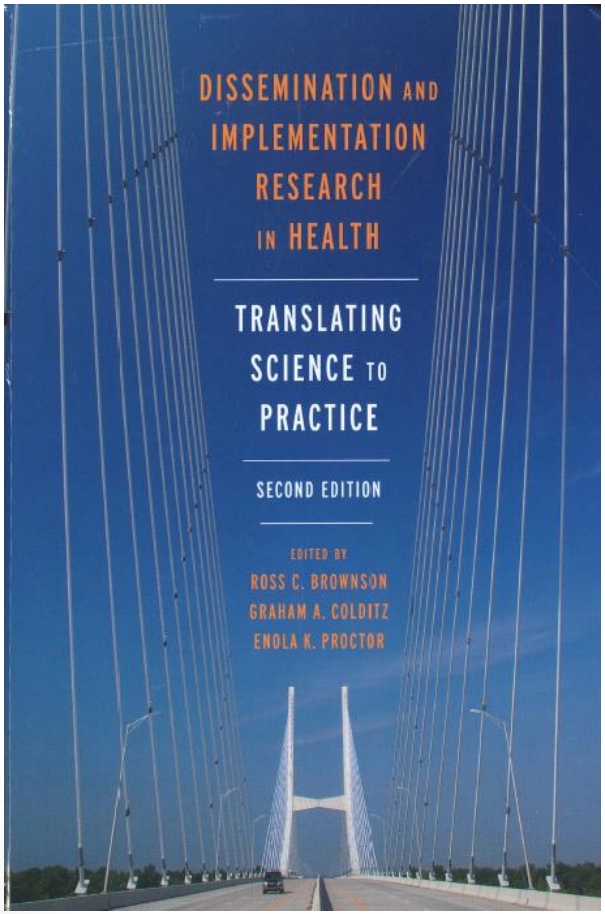
Potential Integration: Implementation Science Focused on Accelerating Research to Practice Translation



FOREWORD

Five years on down the road . . .

Perhaps the most frequently quoted statistic in dissemination and implementation (D&I) research is one that derives from Balas and Boren's seminal article in 2000: "It takes 17 years to turn 14 percent of original research to the benefit of patient care."[1] It is thus interesting to be writing research is expanding, including greater focus on understanding adaptation of interventions in the context of implementation, sustainability of evidence-based practices (EBPs) over time, and even the de-implementation of ineffective or harmful practices still in use.[2–4] Over the past 5 years, tens of D&I research studies, including small grants,

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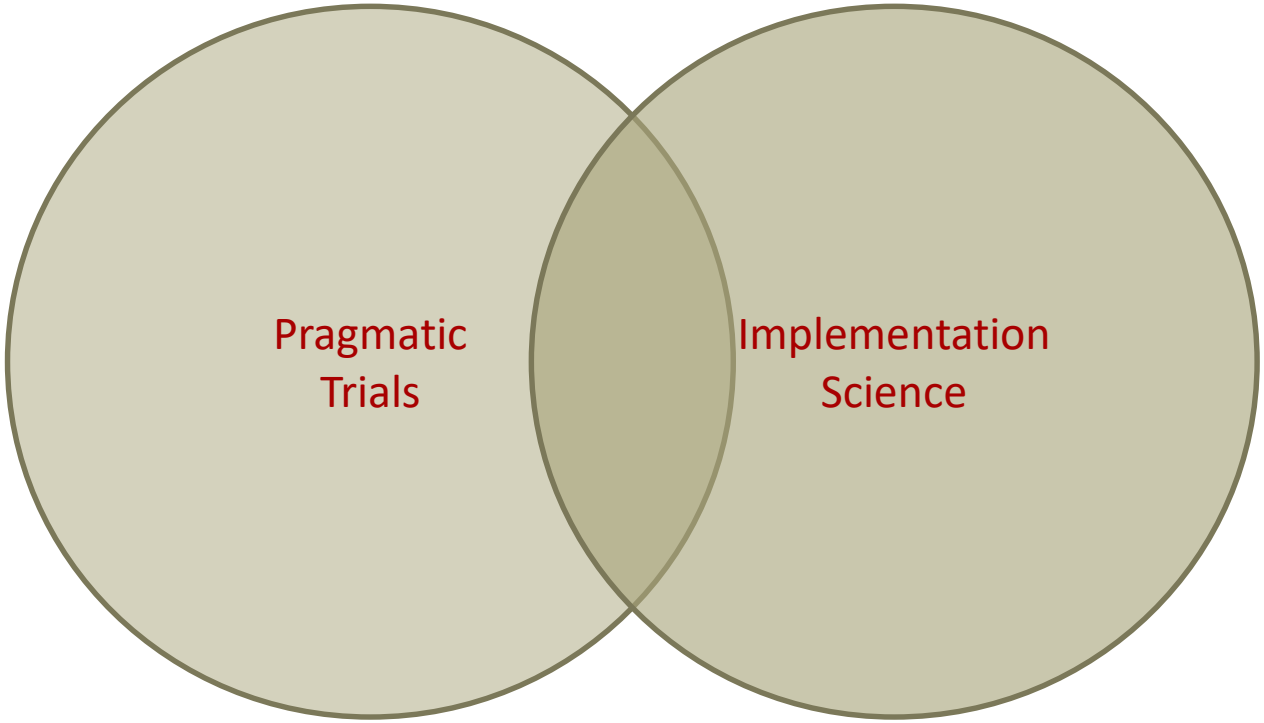
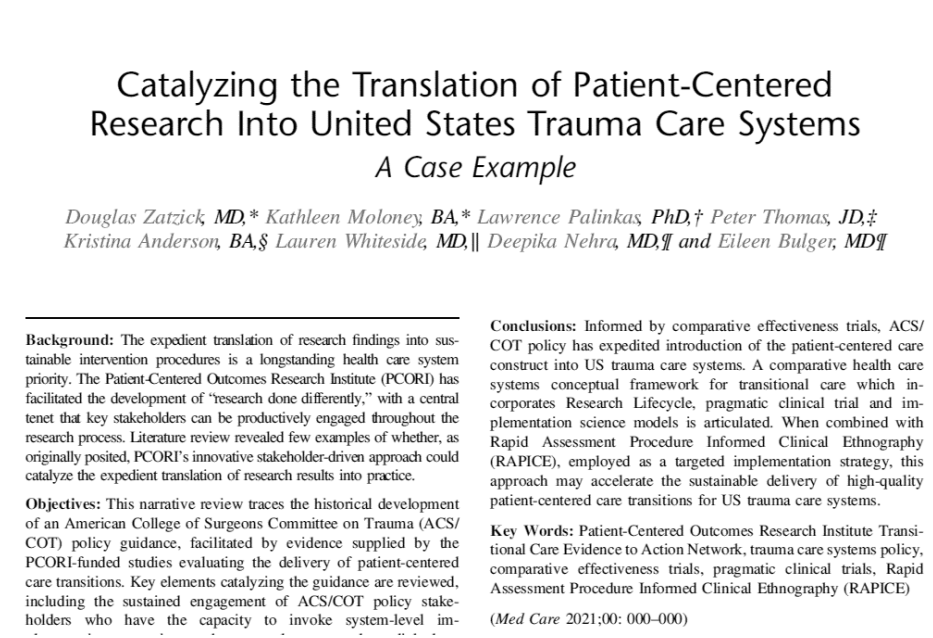
Potential Integration: Pragmatic Trial Results Can Influence Practice Change by Targeting Health Care System Policy



Catalyzing Research to Practice Translation by Honing Effectiveness-Implementation Hybrid Pragmatic Trials to Target Health Care System Policy



Catalyzing the Translation of Patient-Centered Research Into United States Trauma Care Systems

A Case Example

Douglas Zatzick, MD, Kathleen Moloney, BA,* Lawrence Palinkas, PhD,† Peter Thomas, JD,‡ Kristina Anderson, BA,§ Lauren Whiteside, MD,‖ Deepika Nehra, MD,¶ and Eileen Bulger, MD¶*

Background: The expedient translation of research findings into sustainable intervention procedures is a longstanding health care system priority. The Patient-Centered Outcomes Research Institute (PCORI) has facilitated the development of "research done differently," with a central tenet that key stakeholders can be productively engaged throughout the research process. Literature review revealed few examples of whether, as originally posited, PCORI's innovative stakeholder-driven approach could catalyze the expedient translation of research results into practice.

Objectives: This narrative review traces the historical development of an American College of Surgeons Committee on Trauma (ACS/COT) policy guidance, facilitated by evidence supplied by the PCORI-funded studies evaluating the delivery of patient-centered care transitions. Key elements catalyzing the guidance are reviewed, including the sustained engagement of ACS/COT policy stakeholders who have the capacity to invoke system-level im-

Conclusions: Informed by comparative effectiveness trials, ACS/COT policy has expedited introduction of the patient-centered care construct into US trauma care systems. A comparative health care systems conceptual framework for transitional care which incorporates Research Lifecycle, pragmatic clinical trial and implementation science models is articulated. When combined with Rapid Assessment Procedure Informed Clinical Ethnography (RAPICE), employed as a targeted implementation strategy, this approach may accelerate the sustainable delivery of high-quality patient-centered care transitions for US trauma care systems.

Key Words: Patient-Centered Outcomes Research Institute Transitional Care Evidence to Action Network, trauma care systems policy, comparative effectiveness trials, pragmatic clinical trials, Rapid Assessment Procedure Informed Clinical Ethnography (RAPICE)

(*Med Care* 2021;00: 000–000)

- A comparative health care systems conceptual framework
- Effectiveness results directly target health care system level policy requirements for screening and intervention
- Planned end-of-study policy summit facilitates research-to-practice integration within 5-year grant cycle

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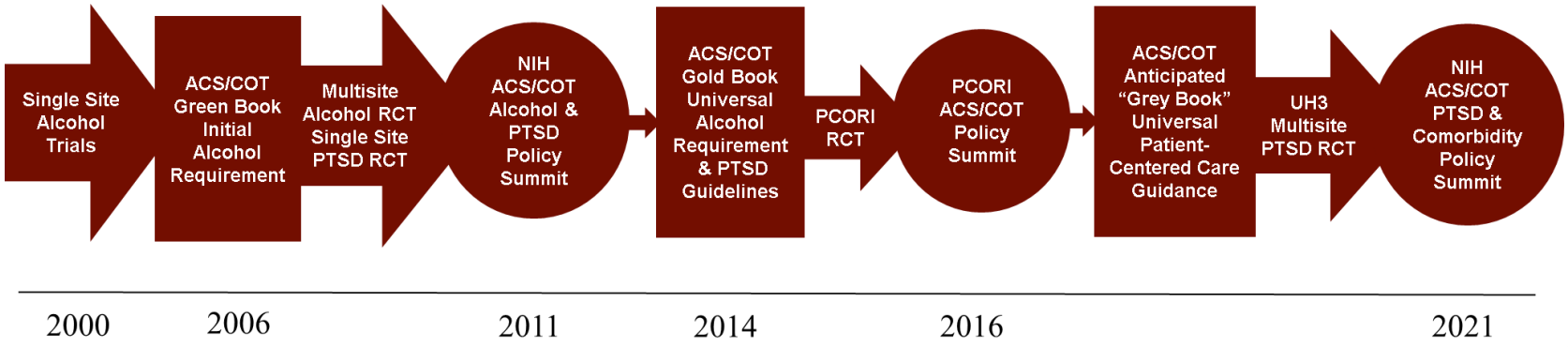
TSOS Study Team Hybrid Pragmatic Clinical Trials & American College of Surgeons Committee on Trauma Policy



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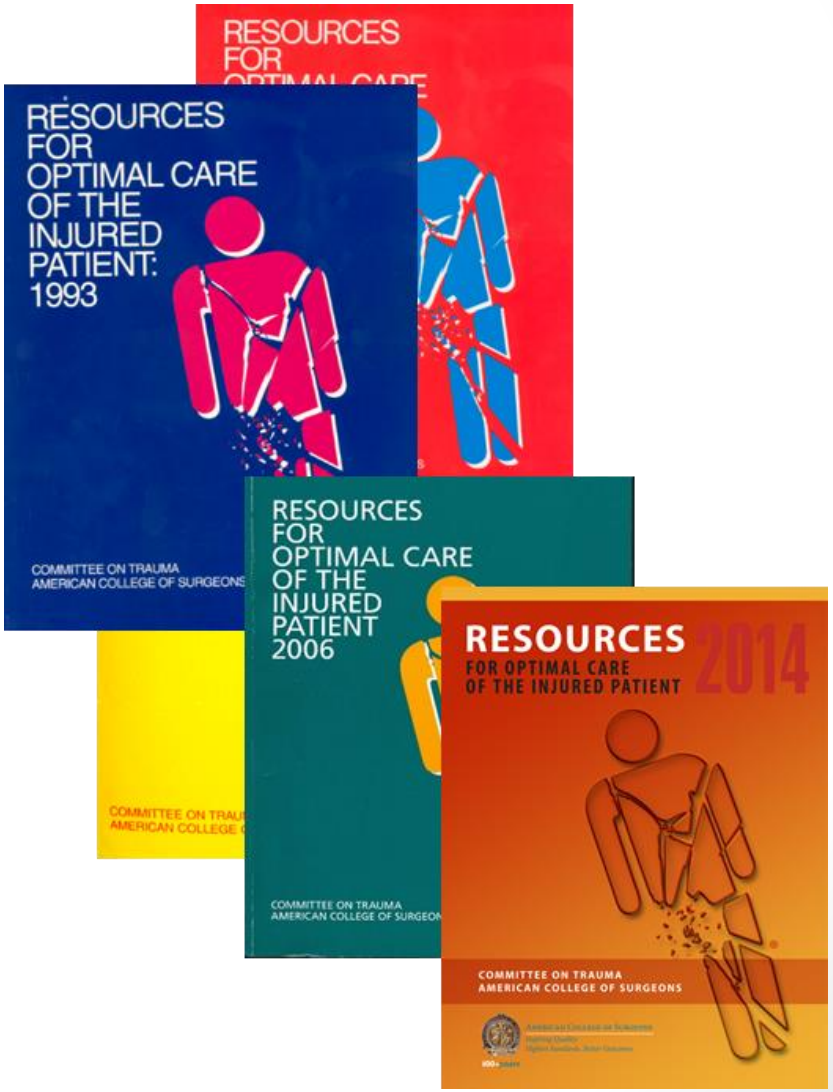
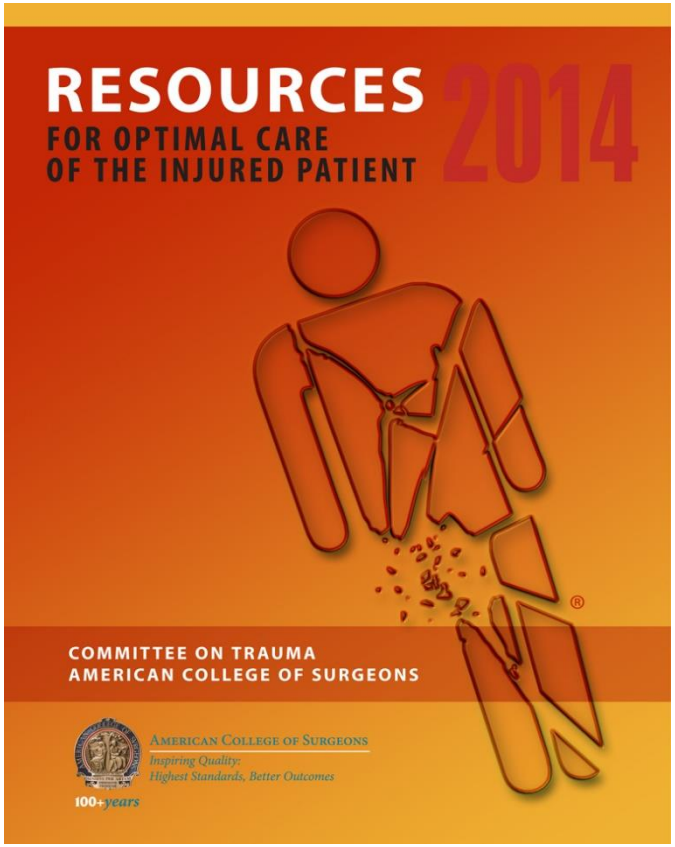
American College of Surgeons' Committee on Trauma: Resources Guide

- 1976 1st Book
- 2006 "Green Book"
- 2014 "Orange Book"





Alcohol Requirement

Universal Screening & Intervention Mandate at Level I & II trauma centers

Verification Site Visit by College Every 3 Years

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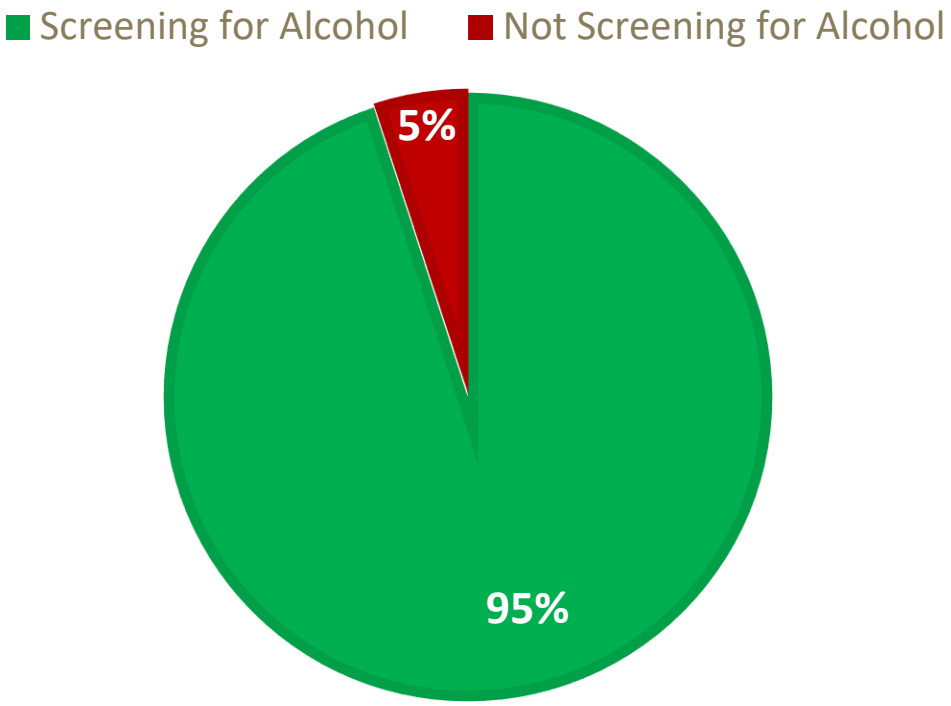
TSOS UH3 Nationwide Trauma Center Survey
(322/627; 51% Response)



≥ 95% of responding trauma centers report screening/ intervening for alcohol

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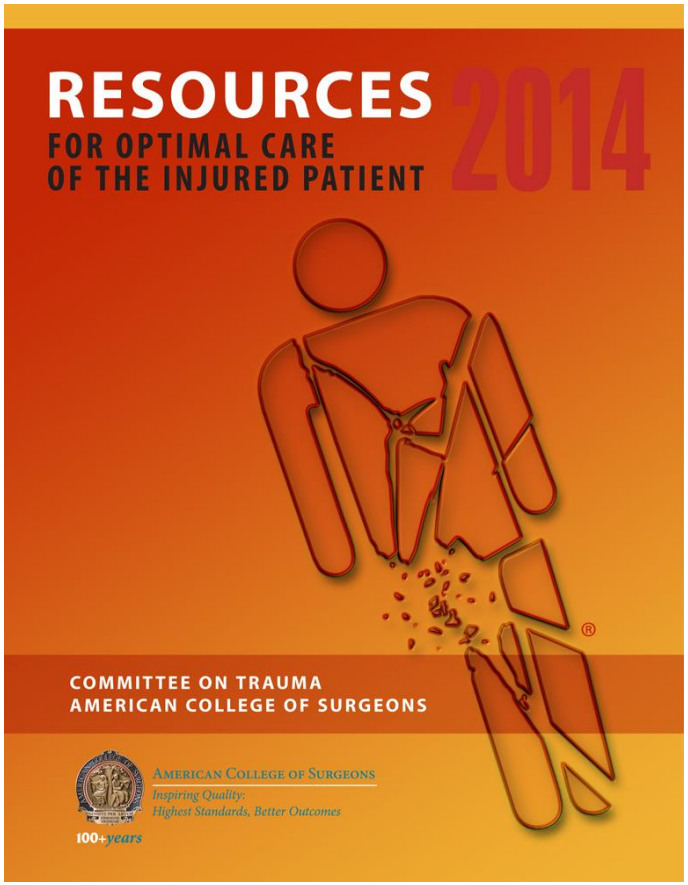
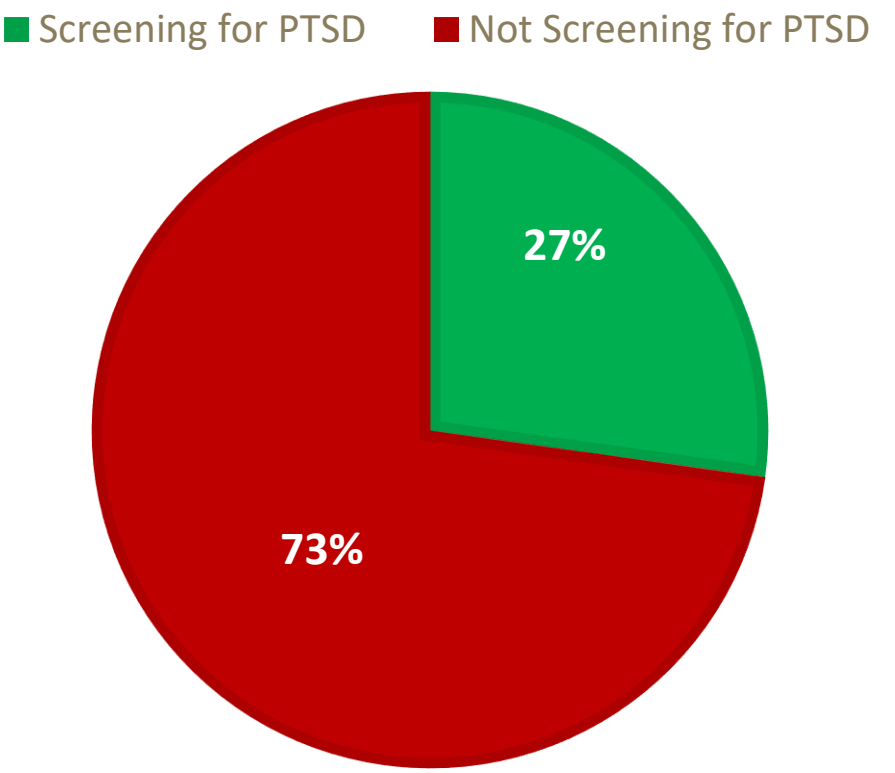


PTSD Guidance

Contains guideline-level recommendation for PTSD screening, intervention, and referral

TSOS UH3 Nationwide Trauma Center Survey
(322/627; 51% Response)



27.2% of responding trauma centers report currently screening for PTSD

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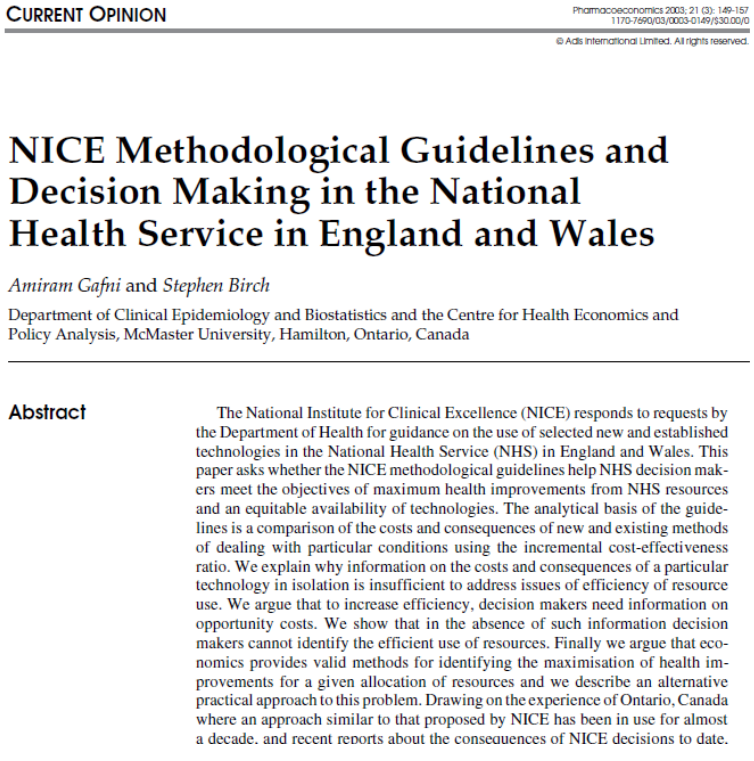
A Comparative Health Care Systems Framework: TSOS Australia

- Current dissemination of TSOS intervention to Melita Giummarra and team in Melbourne, Australia
- In Australia, no capacity to target acute care policy
- TSOS Australia is in a “help it happen” rather than a “make it happen” health care system implementation context

A Comparative Health Care Systems Framework: NICE Guidelines & NHS Practice in the United Kingdom



CURRENT OPINION

Pharmacoeconomics 2003; 21 (3): 149-157
1170-7690/03/0003-0149/$30.00/0

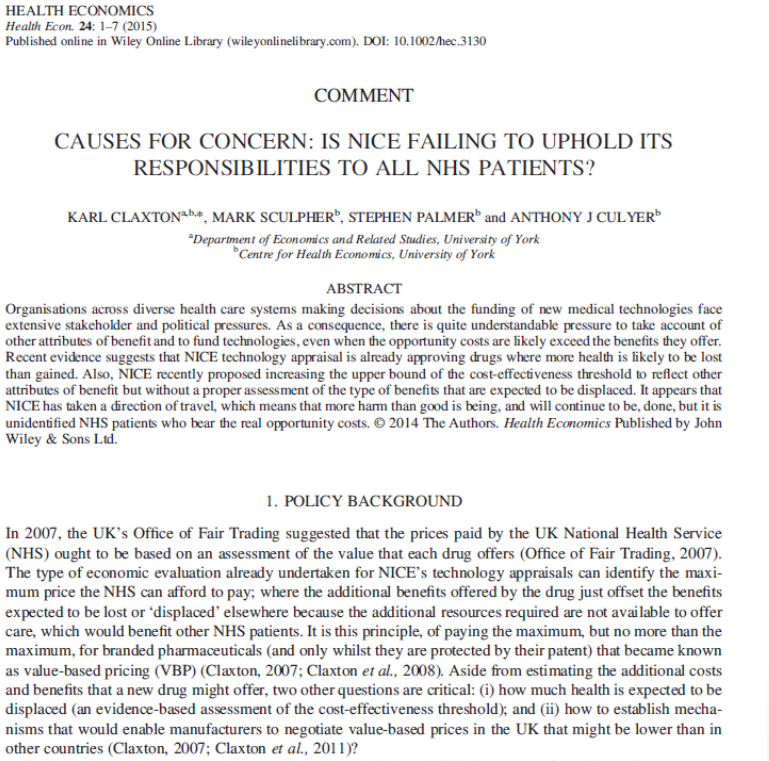
NICE Methodological Guidelines and Decision Making in the National Health Service in England and Wales

Amiram Gafni and *Stephen Birch*

Department of Clinical Epidemiology and Biostatistics and the Centre for Health Economics and Policy Analysis, McMaster University, Hamilton, Ontario, Canada

Abstract

The National Institute for Clinical Excellence (NICE) responds to requests by the Department of Health for guidance on the use of selected new and established technologies in the National Health Service (NHS) in England and Wales. This paper asks whether the NICE methodological guidelines help NHS decision makers meet the objectives of maximum health improvements from NHS resources and an equitable availability of technologies. The analytical basis of the guidelines is a comparison of the costs and consequences of new and existing methods of dealing with particular conditions using the incremental cost-effectiveness ratio. We explain why information on the costs and consequences of a particular technology in isolation is insufficient to address issues of efficiency of resource use. We argue that to increase efficiency, decision makers need information on opportunity costs. We show that in the absence of such information decision makers cannot identify the efficient use of resources. Finally we argue that economics provides valid methods for identifying the maximisation of health improvements for a given allocation of resources and we describe an alternative practical approach to this problem. Drawing on the experience of Ontario, Canada where an approach similar to that proposed by NICE has been in use for almost a decade, and recent reports about the consequences of NICE decisions to date,



HEALTH ECONOMICS
Health Econ. **24**: 1–7 (2015)
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/hec.3130

COMMENT

CAUSES FOR CONCERN: IS NICE FAILING TO UPHOLD ITS RESPONSIBILITIES TO ALL NHS PATIENTS?

KARL CLAXTON[a,b,*], MARK SCULPHER[b], STEPHEN PALMER[b] and ANTHONY J CULYER[b]

[a]*Department of Economics and Related Studies, University of York*
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ABSTRACT

Organisations across diverse health care systems making decisions about the funding of new medical technologies face extensive stakeholder and political pressures. As a consequence, there is quite understandable pressure to take account of other attributes of benefit and to fund technologies, even when the opportunity costs are likely exceed the benefits they offer. Recent evidence suggests that NICE technology appraisal is already approving drugs where more health is likely to be lost than gained. Also, NICE recently proposed increasing the upper bound of the cost-effectiveness threshold to reflect other attributes of benefit but without a proper assessment of the type of benefits that are expected to be displaced. It appears that NICE has taken a direction of travel, which means that more harm than good is being, and will continue to be, done, but it is unidentified NHS patients who bear the real opportunity costs. © 2014 The Authors. *Health Economics* Published by John Wiley & Sons Ltd.

1. POLICY BACKGROUND

In 2007, the UK's Office of Fair Trading suggested that the prices paid by the UK National Health Service (NHS) ought to be based on an assessment of the value that each drug offers (Office of Fair Trading, 2007). The type of economic evaluation already undertaken for NICE's technology appraisals can identify the maximum price the NHS can afford to pay; where the additional benefits offered by the drug just offset the benefits expected to be lost or 'displaced' elsewhere because the additional resources required are not available to offer care, which would benefit other NHS patients. It is this principle, of paying the maximum, but no more than the maximum, for branded pharmaceuticals (and only whilst they are protected by their patent) that became known as value-based pricing (VBP) (Claxton, 2007; Claxton *et al.*, 2008). Aside from estimating the additional costs and benefits that a new drug might offer, two other questions are critical: (i) how much health is expected to be displaced (an evidence-based assessment of the cost-effectiveness threshold); and (ii) how to establish mechanisms that would enable manufacturers to negotiate value-based prices in the UK that might be lower than in other countries (Claxton, 2007; Claxton *et al.*, 2011)?

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Additional Examples of Pragmatic Trials Directly Targeting Health Care System Level Policy/Practice Change

- NIH Collaboratory ABATE and REDUCE team trials influence ICU bacterial decolonization practice
- NIH Collaboratory Grand Rounds Jan. 2019, Dublin et al Kaiser Permanente gestational diabetes screening de-implementation
- NIMH RAISE trial “deployment focused” approach

TSOS Effectiveness-Implementation Hybrid Design Paper

(Zatzick et al. *Implementation Science,* 2016)

Zatzick *et al. Implementation Science* (2016) 11:58
DOI 10.1186/s13012-016-0424-4

Implementation Science

STUDY PROTOCOL Open Access

An effectiveness-implementation hybrid trial study protocol targeting posttraumatic stress disorder and comorbidity

Douglas F. Zatzick[1,5*], Joan Russo[1], Doyanne Darnell[1], David A. Chambers[2], Lawrence Palinkas[3], Erik Van Eaton[4], Jin Wang[5], Leah M. Ingraham[1], Roxanne Guiney[1], Patrick Heagerty[6], Bryan Comstock[6], Lauren K. Whiteside[7] and Gregory Jurkovich[8]

Abstract

Background: Each year in the USA, 1.5–2.5 million Americans are so severely injured that they require inpatient hospitalization. Multiple conditions including posttraumatic stress disorder (PTSD), alcohol and drug use problems, depression, and chronic medical conditions are endemic among physical trauma survivors with and without traumatic brain injuries.

Methods/design: The trauma survivors outcomes and support (TSOS) effectiveness-implementation hybrid

Trial Aims:

1. Complete pragmatic trial testing effectiveness
2. Conduct implementation process assessment in order to inform real world roll-out of study procedures
3. End-of-study policy summit informs potential policy requirement

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TSOS Pragmatic Trial Results

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Why TSOS? PTSD & Comorbidity

- Traumatic injury
  - ~30 million visits each year
  - ~2.5 million injury admissions
- PTSD, depression, suicidal ideation, substance use (e.g., alcohol, opioids, stimulants) and associated risk behaviors all common
- Patients “sail off of a flat earth” after trauma center care
- Early acute care-based intervention potentially effective

TSOS UH3 Pragmatic Trial: Key Points
(*JAMA Surgery*, March 2021)

Key Points

Question Can a brief stepped collaborative care intervention for injured patients at a trauma center delivered by front-line clinicians reduce posttraumatic stress disorder symptoms compared with usual care?

Findings In a randomized clinical trial with 635 injured patients from 25 US trauma centers, intervention patients demonstrated significant posttraumatic stress disorder symptom reductions compared with those who received usual care at 6 months, but not 12 months, postinjury. Subgroup analyses revealed larger posttraumatic stress disorder treatment effects at trauma centers with good or excellent protocol implementation.

Meaning In this study, a well-implemented brief intervention for injured patients reduced posttraumatic stress disorder symptoms; policy efforts should incorporate these findings into national trauma center requirements and verification criteria.

- Significant 6-month but not 12-month PTSD symptom reductions in intent-to-treat sample
- Subgroup analyses revealed larger treatment effects for patients, including firearm injury survivors, treated at trauma center with good/excellent protocol implementation

TSOS Pragmatic Trial: Design

Research

JAMA Surgery | Original Investigation

Stepped Collaborative Care Targeting Posttraumatic Stress Disorder Symptoms and Comorbidity for US Trauma Care Systems
A Randomized Clinical Trial

Douglas Zatzick, MD; Gregory Jurkovich, MD; Patrick Heagerty, PhD; Joan Russo, PhD; Doyanne Darnell, PhD; Lea Parker, BA; Michelle K. Roberts, MPH; Riddhi Moodliar, BA; Allison Engstrom, MSW; Jin Wang, PhD; Eileen Bulger, MD; Lauren Whiteside, MD; Deepika Nehra, MD; Lawrence A. Palinkas, PhD; Kathleen Moloney, BA; Ronald Maier, MD

IMPORTANCE To date, few multisite investigations have evaluated early interventions for injured patients with posttraumatic stress disorder (PTSD) symptoms.

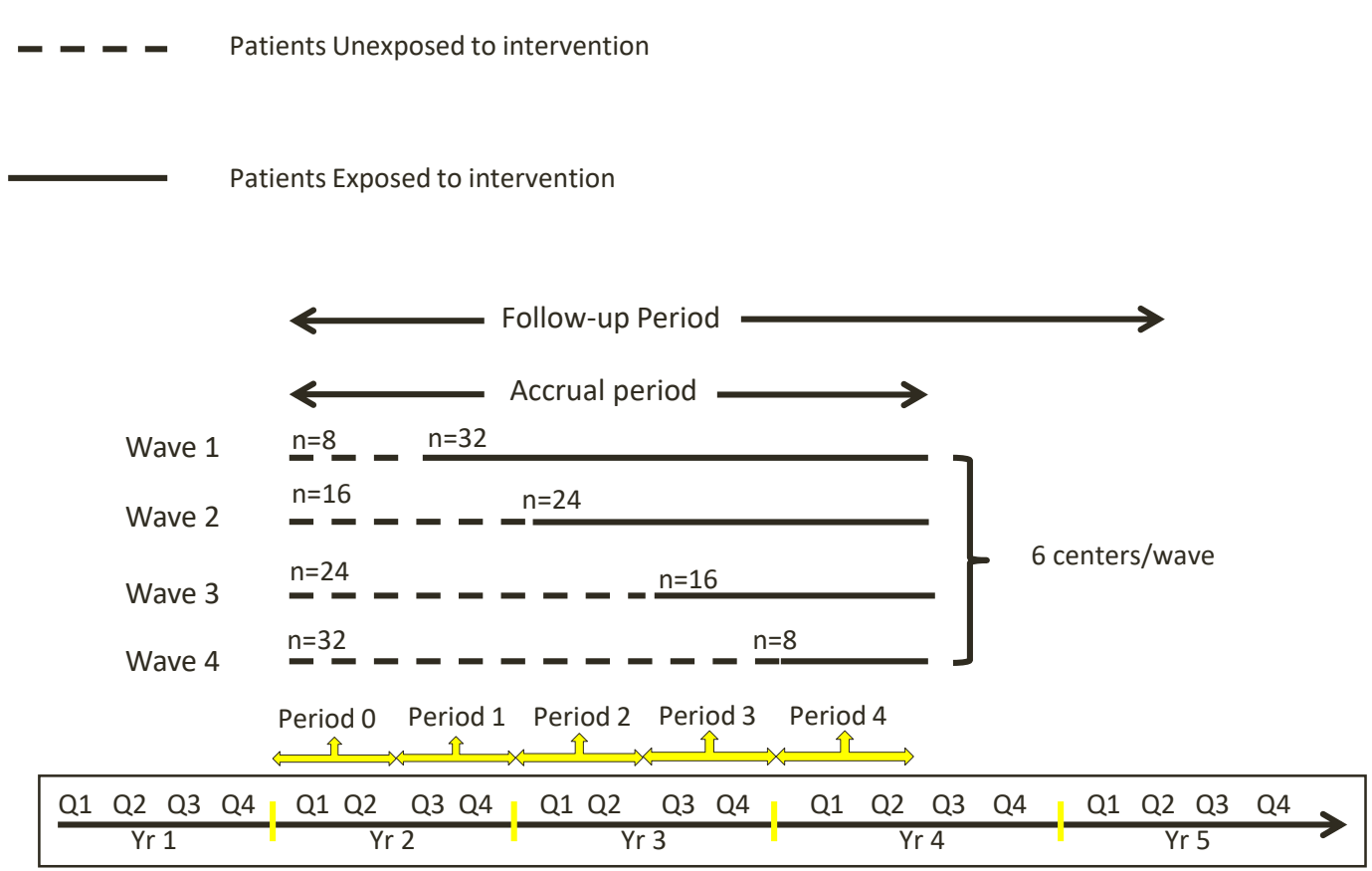
OBJECTIVE To simultaneously assess the effectiveness and implementation of a brief stepped collaborative care intervention targeting PTSD and comorbidity.

DESIGN, SETTING, AND PARTICIPANTS A stepped-wedge cluster randomized clinical trial was conducted at 25 US level I trauma centers. Participants included hospitalized survivors of physical injury who underwent a 2-step evaluation for PTSD symptoms. Patients reporting high levels of distress on the PTSD Checklist (PCL-C) were randomized (N = 635) per the stepped-wedge protocol to enhanced usual care control (n = 370) or intervention (n = 265) conditions. The study was conducted from January 4, 2016, through November 2018. Data analysis was performed from November 4, 2019, to December 8, 2020.

Invited Commentary
Supplemental content

- 25 US level I trauma centers
- 635 patients randomized
- Stepped wedge cluster randomized design
- Baseline PTSD EHR screen
- 3-, 6-, 12-month follow-up
- Usual care control
- Stepped collaborative care intervention
- Front-line trauma center providers trained

TSOS Stepped Wedge Cluster Randomized Design



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TSOS Pragmatic Trial: Patient Characteristics (N = 635)

Research

JAMA Surgery | Original Investigation

Stepped Collaborative Care Targeting Posttraumatic Stress Disorder Symptoms and Comorbidity for US Trauma Care Systems
A Randomized Clinical Trial

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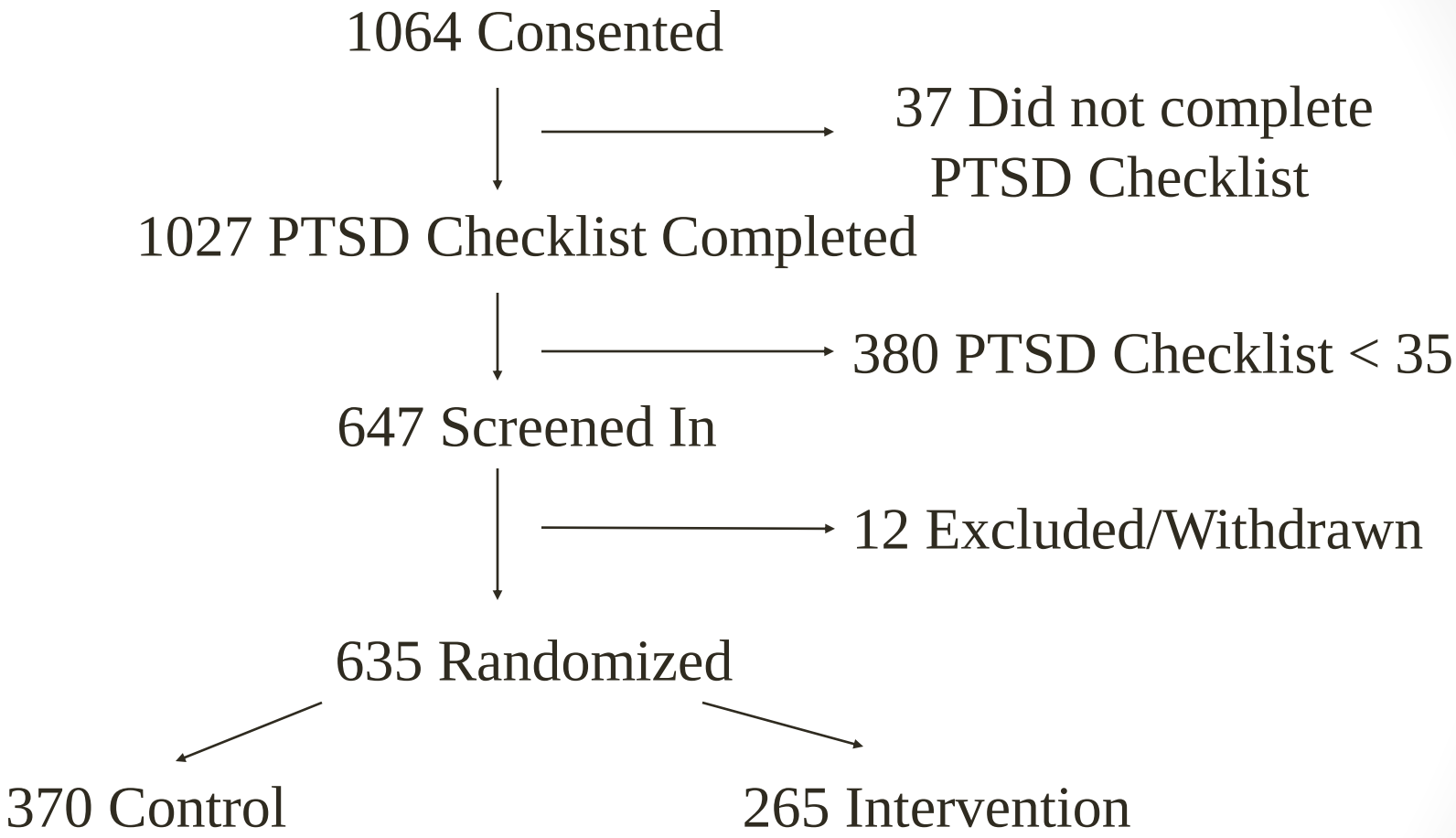
Invited Commentary
Supplemental content

- 49% Female
- 50% White
- 34% Black
- 16% Hispanic/Latinx
- 20% Firearm injury
- 65% Public/uninsured
- 28% Alcohol positive
- 10% Pre-injury opioids
- 4.5 serious prior trauma on average

TSOS Results: Patient Flow



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TSOS Baseline Control vs. Intervention: EHR Characteristics

Characteristic	Control (n=370)	Intervention (n=265)	P
Female	43%	55%	< 0.01
Non-White	54%	50%	ns
Age	40 yrs	38 yrs	< 0.05
ICU Admit	62%	56%	ns
Prior PTSD DX	15%	23%	< 0.05

TSOS Baseline Control vs. Intervention (N=635)

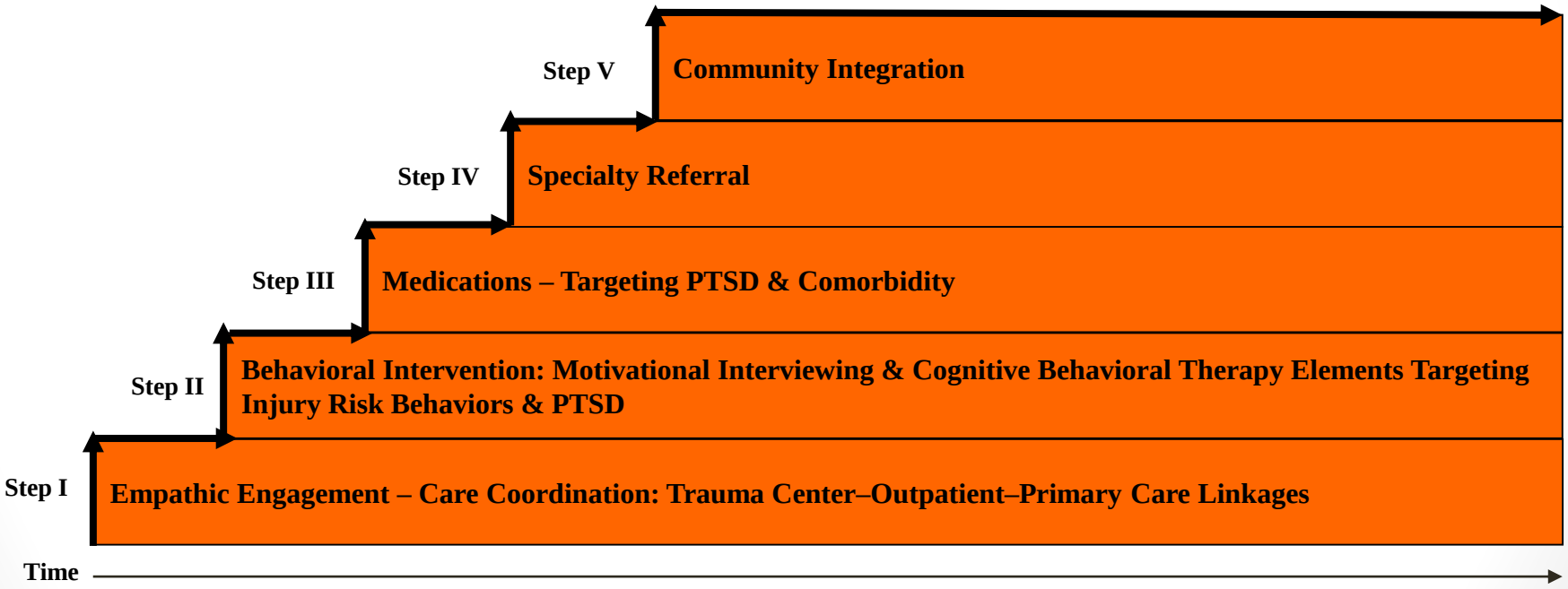
Characteristic	Control (n=370)	Intervention (n=265)	P
PTSD Checklist	50.7	54.0	< 0.01
Pre-injury traumas	4.4	4.5	ns
Firearm injury	21%	19%	ns

TSOS Follow-up Interview Completion

- 80.2% 3-month
- 77.3% 6-month
- 75.1% 12-month
- No differential attrition across control and intervention conditions

Stepped Care Targeting the PTSD & Comorbidity

(2 hours of front-line provider time over 6-12 months)



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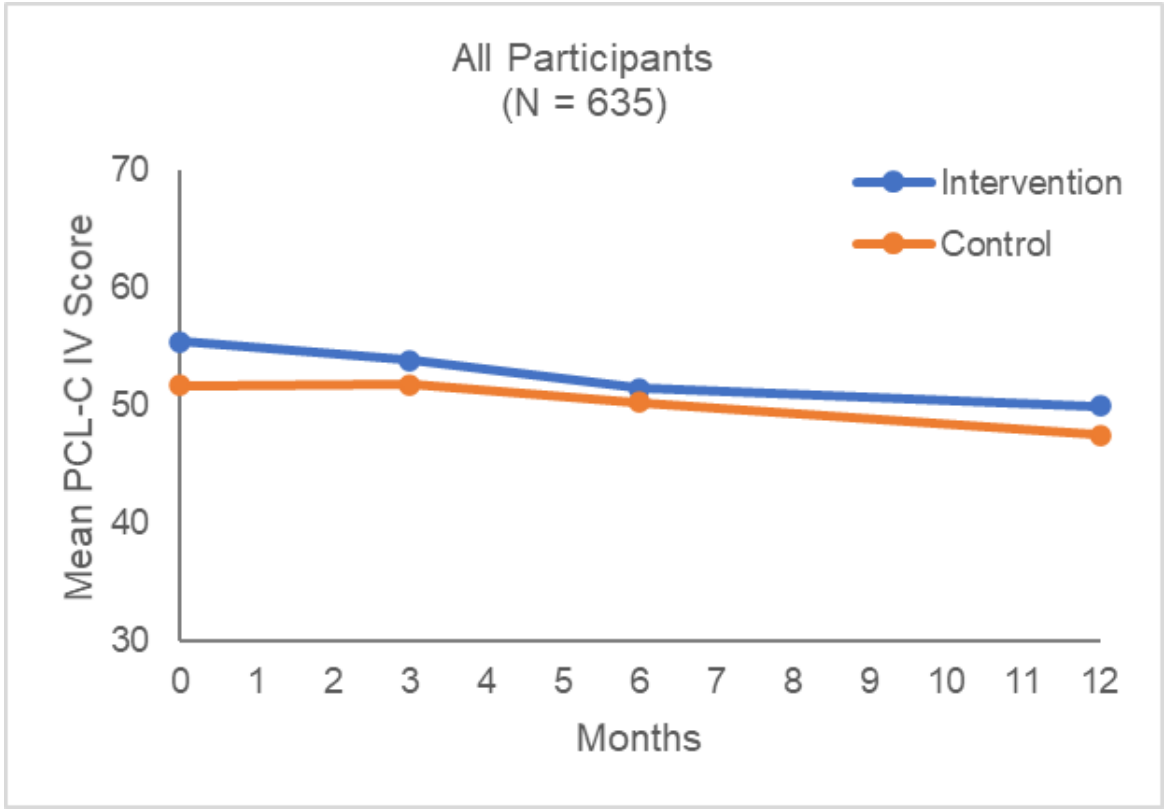
PTSD Symptom Levels Over Time: All Participants



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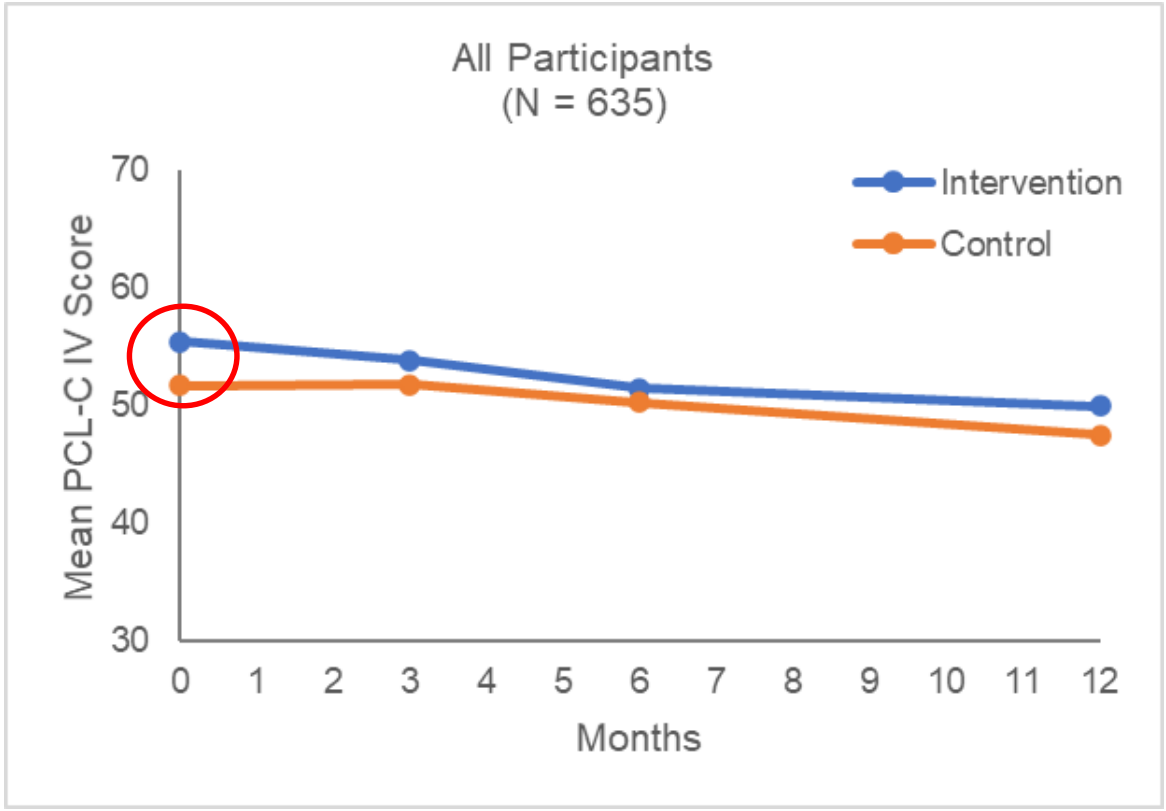
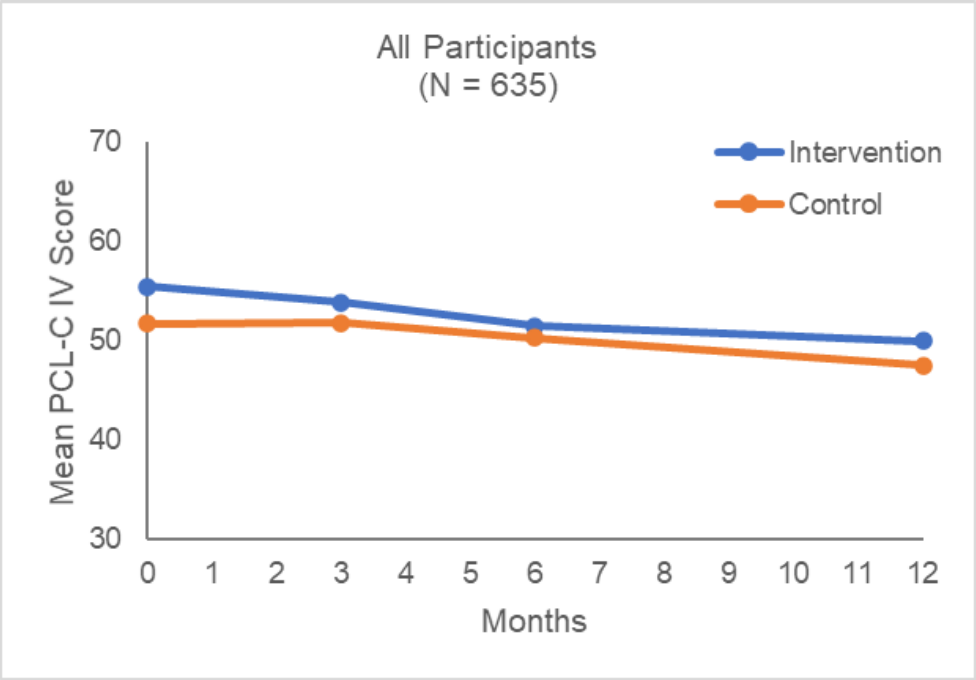


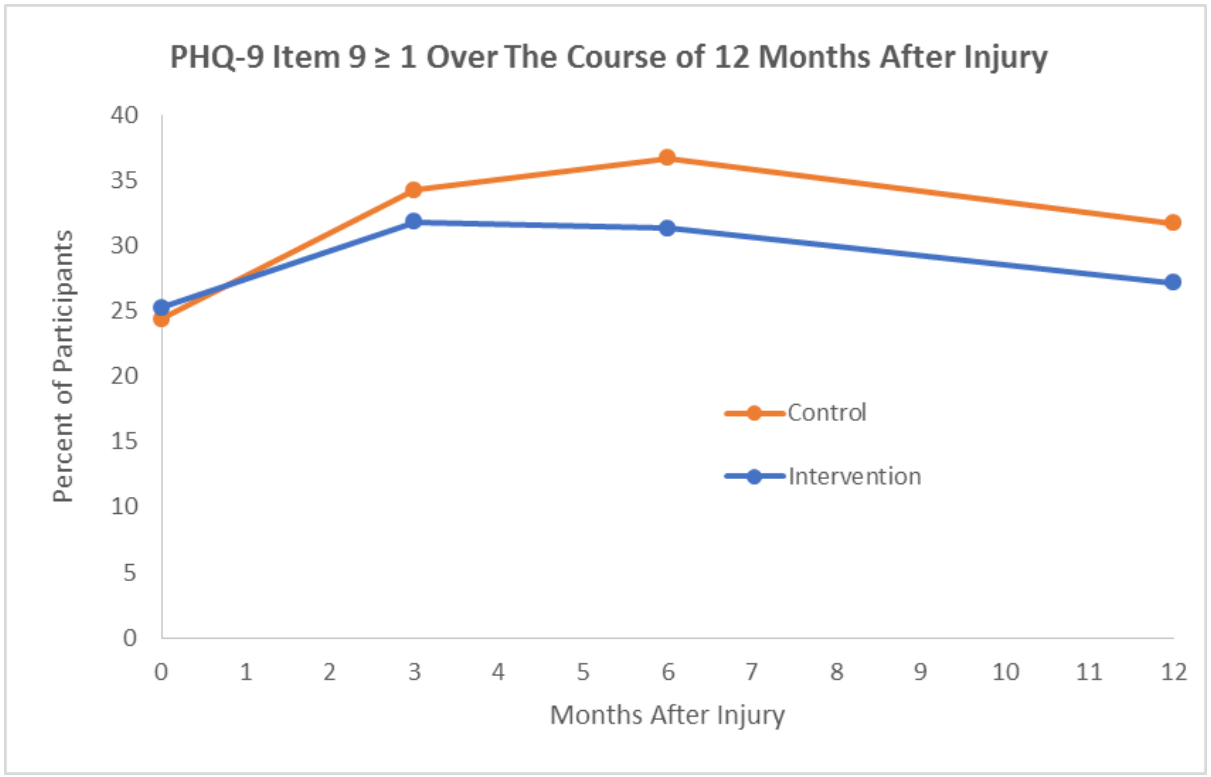
PTSD Symptom Levels Over Time: All Participants



Intervention vs. Control

- 6-month follow-up:
  - Net Δ = -2.57 (-5.12, -0.03)
  - Effect size = 0.18
- 12-month follow-up:
  - Net Δ = -1.27 (-4.26, 1.73)
  - Effect size = 0.08

UH3 Comorbidity Results: Suicidal Ideation (N = 635)



$p = 0.53$

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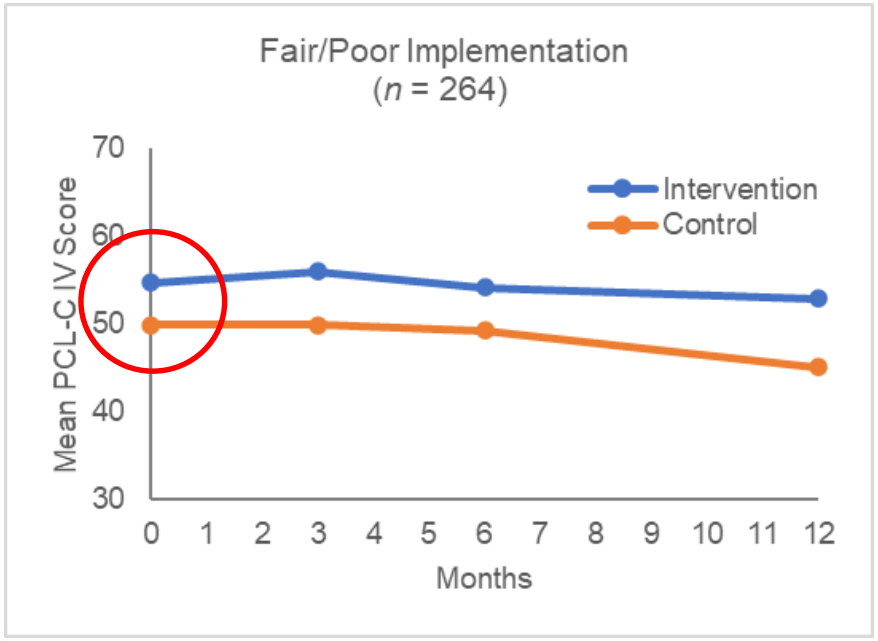
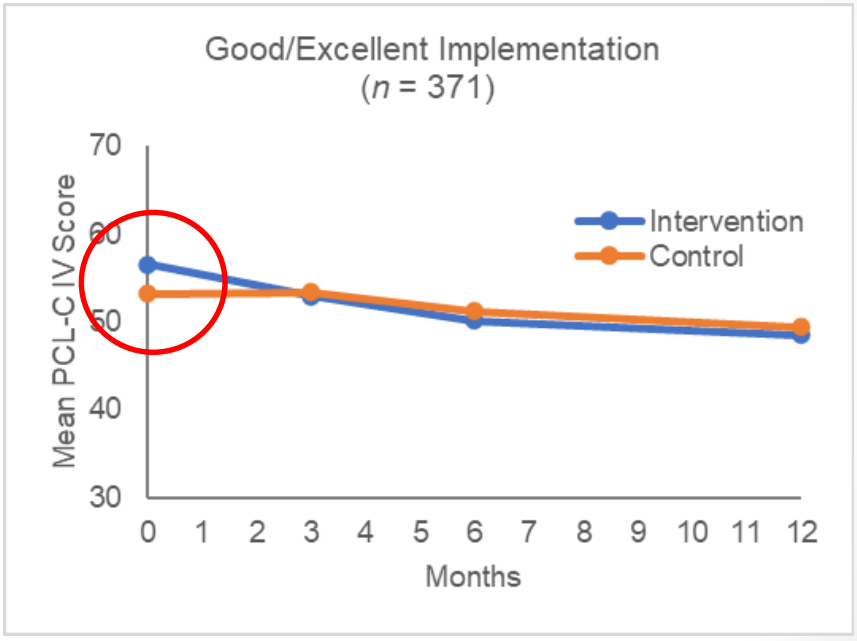
TSOS Incorporates a Rapid Assessment Procedure Informed Clinical Ethnography (RAPICE) Implementation Process Assessment

- Marked variability in site quality of implementation across multiple domains:
  - Quality of intervention delivery
  - Recruitment milestones (range 12-40 patients)
  - Leadership stability/turnover
  - Regulatory compliance
- Each domain rated on a 0 (poor) to 3 (excellent) scale
- For subgroup analyses scores summed & dichotomized:
  - Fair/poor implementation sites (n = 13)
  - Good/excellent implementation sites (n = 12)

PTSD Symptom Levels Over Time: Stratification by Quality of Trauma Center Implementation

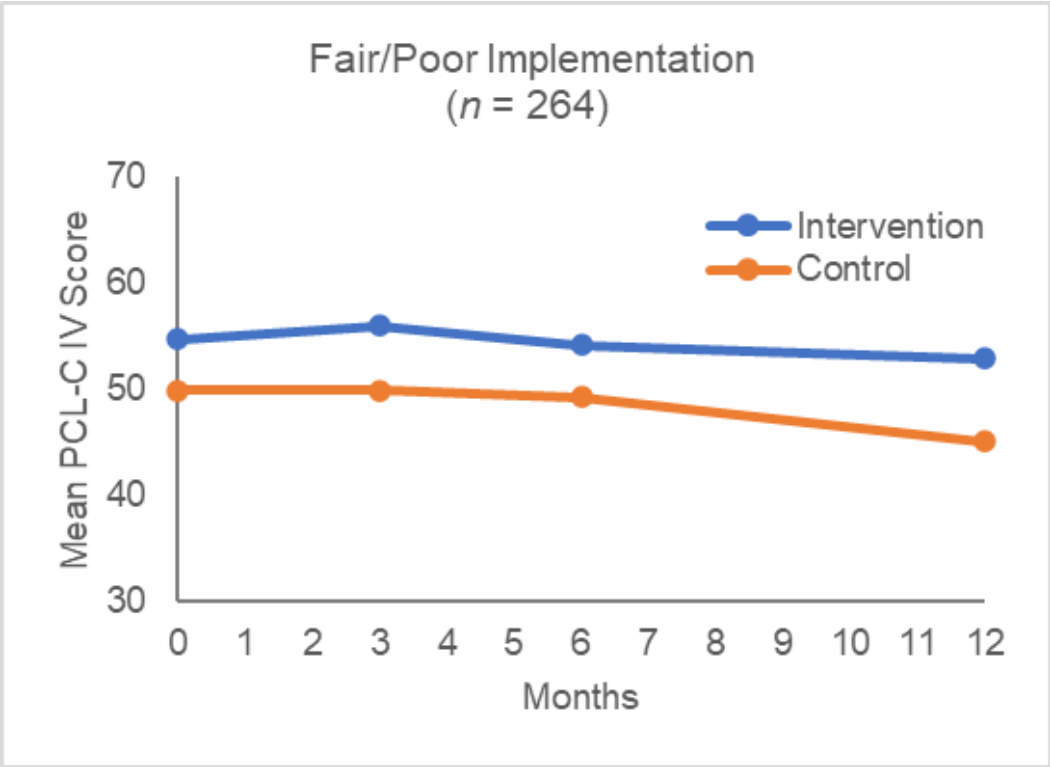




NIH Collaboratory

Health Care Systems Research Collaboratory

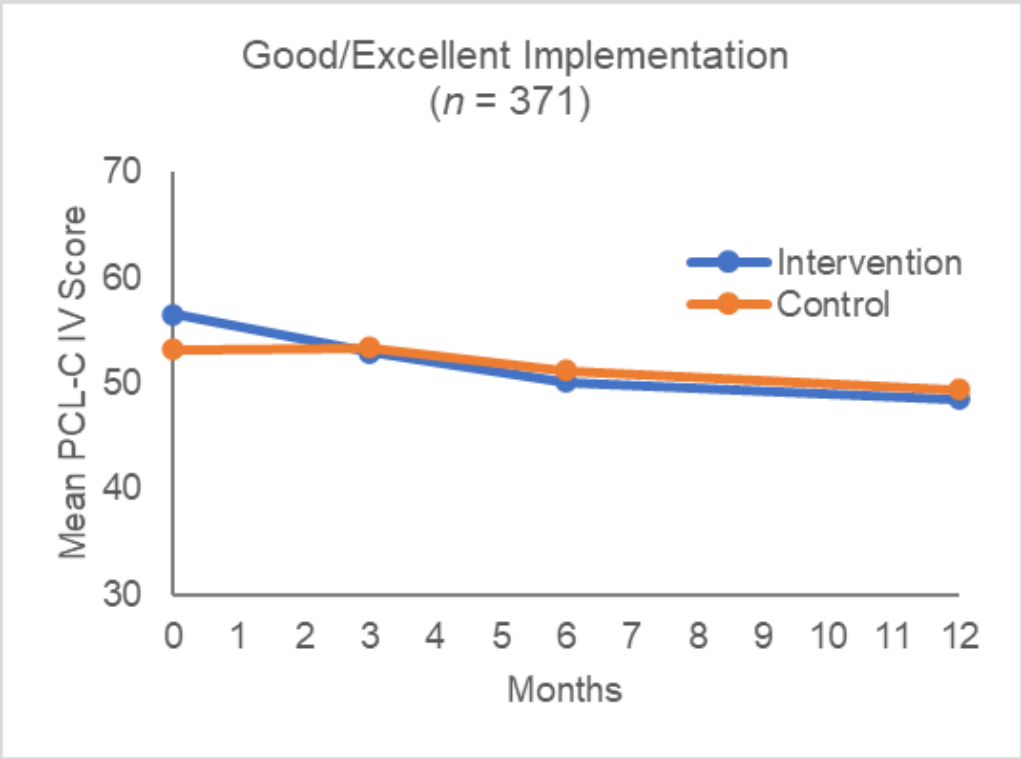
PTSD Symptom Levels Over Time: Stratification by Quality of Trauma Center Implementation - Fair/Poor



Intervention vs. Control

- 6-month follow-up:
  - Net Δ = 0.04 (-3.95, 4.03)
  - Effect size = 0.00
- 12-month follow-up:
  - Net Δ = 2.93 (-1.73, 7.59)
  - Effect size = 0.18

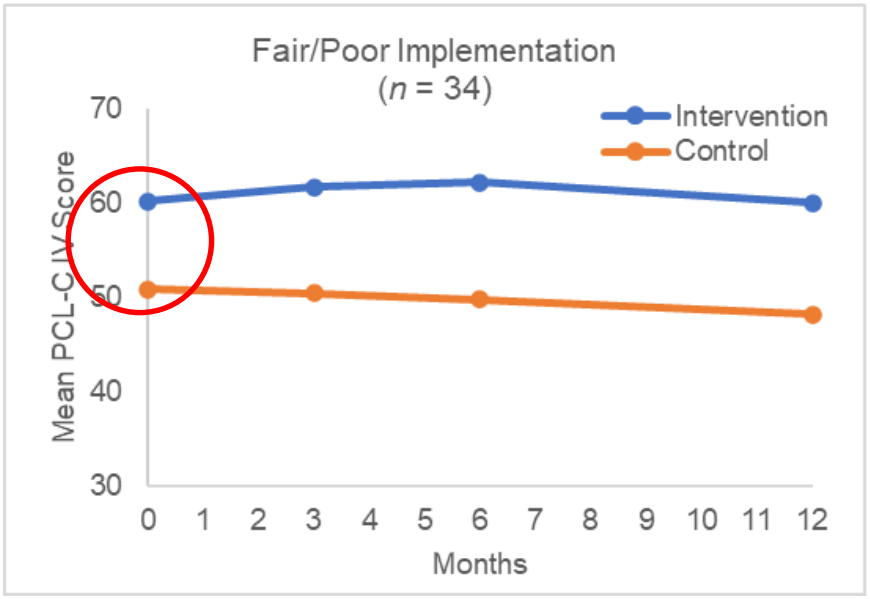
PTSD Symptom Levels Over Time: Stratification by Quality of Trauma Center Implementation - Good/Excellent



Intervention vs. Control

- 6-month follow-up:
  - Net Δ = -4.41 (-7.70, -1.12)
  - Effect size = 0.31
- 12-month follow-up:
  - Net Δ = -4.23 (-8.12, -0.34)
  - Effect size = 0.26

PTSD Symptom Levels Over Time: Firearm Injury Stratification by Quality of Trauma Center Implementation



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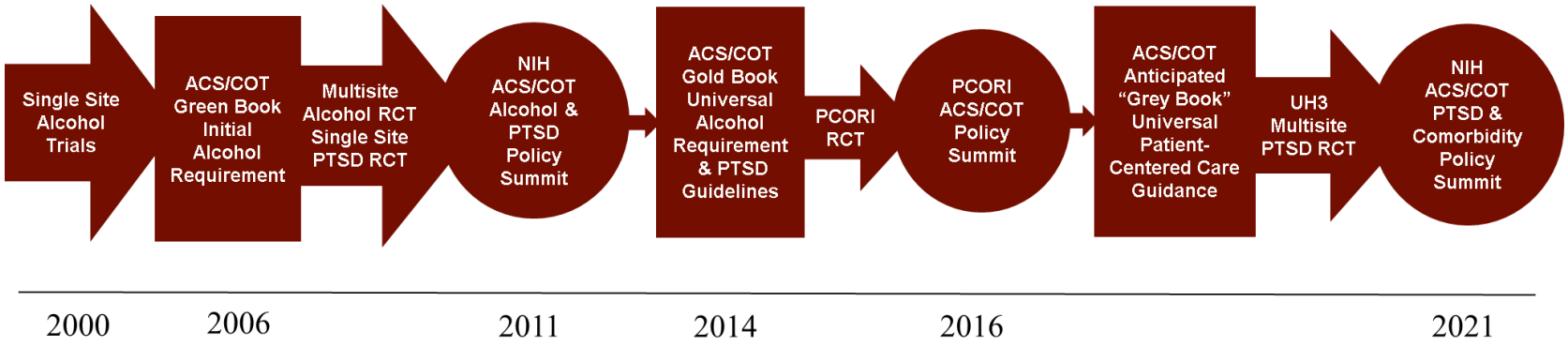
PTSD Symptom Levels Over Time: Firearm Injury Stratification by Good/Excellent Implementation

Intervention vs. Control

- 6-month follow-up:
  - Net Δ = -7.81 (-15.61, -0.02)
  - Effect size = 0.52
- 12-month follow-up:
  - Net Δ = -10.37 (-19.2, -1.59)
  - Effect size = 0.61

TSOS Study Team Hybrid Pragmatic Clinical Trials & American College of Surgeons Committee on Trauma Policy



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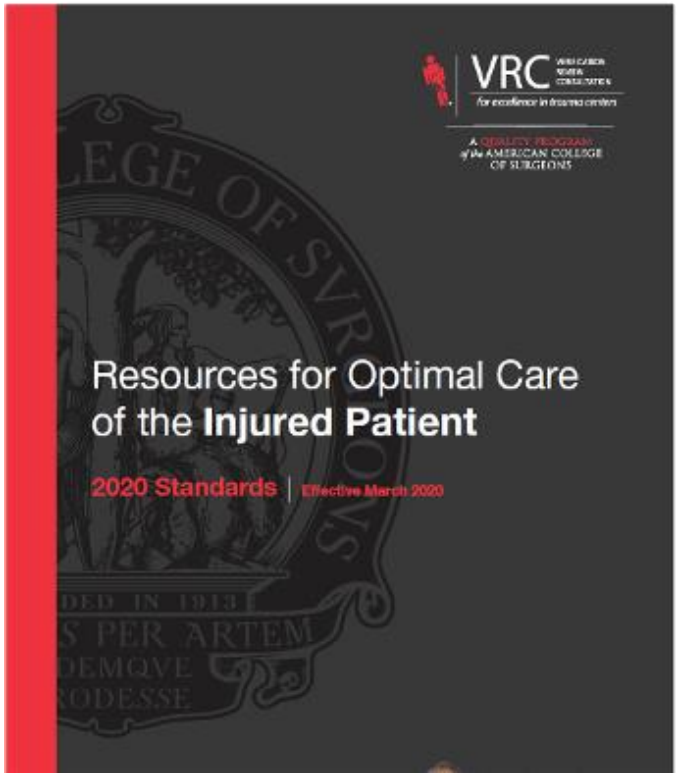
The "Grey Book" Mental Health Screening & Referral Requirement



- Trauma Centers must have the following in place to meet the mental health needs of trauma patients:
  1. Protocols to identify patients at high risk for psychological sequelae
  2. A referral process for patients who have been identified as high risk for psychological sequelae
- Verification procedures under development

TSOS Summary

- Pragmatic trials can harness effectiveness results to directly target health care system policy change
- Hybrid trials that target policy change within a 5-year grant cycle may further the integration of pragmatic trial and implementation science approaches

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Questions & Comments