U.S. Department of Defense – Military Health System (MHS)

U.S. Combat Casualty Care Research Program (CCCRP)

Capability Gap Closure Analysis

June 26, 2015
Fort Detrick, MD

Table of Contents

List of Tables

List of Figures

Acronyms and Abbreviations

AAJT	Abdominal Aortic and Junctional Tourniquet
ALIRT	Acute Lung Injury Rescue Team
ARDS	Adult Respiratory Distress Syndrome
ATLS	Advanced Trauma Life Support
BANDITS	Biomarker Assessment for Neurotrauma Diagnosis and Improved Triage System
BRDSS	Burn Resuscitation Decision Support System
C4	Command, Control, Communications, and Computers
CASEVAC	Casualty Evacuation
CAT	Combat Application Tourniquet
CBRN	Chemical, Biological, Radiological, and Nuclear
CCATT	Critical Care Air Transport Team
CCCRP	Combat Casualty Care Research Program
CDC	U.S. Centers for Disease Control and Prevention
CDR	Clinical Data Repository
CICR	Comprehensive Intensive Care Research
CMA	Concussion Management Algorithm
CMR	Conduct Mental Rehabilitation
CN-NiNM	Cranial Nerve Non-Invasive Neuromodulation
COMBAT	Control of Major Bleeding after Trauma Study
CONUS	Continental United States
CoTCCC	Committee on Tactical Combat Casualty Care
COTS	Commercial-Off-The-Shelf
CPG	Clinical Practice Guideline
CR	Clinical Recommendation
CRADA	Cooperative Research and Development Agreement
CRASH	Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage
CRI	Compensatory Reserve Index
CRoC	Combat Ready Clamp
CSF	Cerebrospinal Fluid
CST	Clinical Support Tool
CT	Computed Tomography
CTSA	French Military Blood Institute
DCBI	Dismounted Complex Blast Injury
DCoE	Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury
DCR	Damage Control Resuscitation
DHB	Defense Health Board
DHP	Defense Health Program

DK	Develop Knowledge
DoD	Department of Defense
DRMRP	Deployment Related Medical Research Program
DVBIC	Defense and Veterans Brain Injury Center
ECLS	Extracorporeal Life Support
ECMO	Extracorporeal Membrane Oxygenation
EEG	Electroencephalography
ELSO	Extracorporeal Life Support Organization
EMS	Emergency Medical Service
EPA	Enhance Psychological Abilities
EPPA	Enhance Physiological and Physical Abilities
ETA	Eye-TRAC Advance
FDA	U.S. Food and Drug Administration
FDP	Freeze-Dried Plasma
FFP	Fresh-Frozen Plasma
FSICC	Forward Surgical and Intensive Critical Care
FWB	Fresh Whole Blood
GCS	Glasgow Coma Scale
GDF	Guidance for Development of the Force
GFAP	Glial Fibrillary Acidic Protein
GFM	Global Force Management
GU	Genitourinary
ICD	Initial Capabilities Document
IDF	Israel Defense Forces
IDF-MC	Israel Defense Forces Medical Corp
IED	Improvised Explosive Device
IID	Identify Infectious Disease
IMFW	Identify and Manage Fractures/Wounds
IMICP	Identify and Manage Infectious/Contaminated Patients
IND	Investigational New Drug
IPT	Integrated Product Team
IT	Information Technology
IV	Intravenous
JCD	Joint Capability Document
JCM	Joint Casualty Management
J-ERC	Joint En Route Care
JETT	Junctional Emergency Treatment Tool
JFHP	Joint Forces Health Protection
JHPE	Joint Human Performance Enhancement
JPC	Joint Program Committee

JPM	Joint Patient Movement
JTS	Joint Trauma System
JTTR	Joint Theater Trauma Registry
JTTS	Joint Theater Trauma System
KPP	Key Performance Parameters
LBNP	Lower Body Negative Pressure
LR	Lactated Ringer's
LRMC	Landstuhl Regional Medical Center
MA	Manage the Airway
MACE	Military Acute Concussion Evaluation
MATTERS	Military Application of Tranexamic Acid in Traumatic Emergency and Resuscitative Surgery
MB	Manage Breathing
MBC	Manage Blood Circulation
MBF	Maintain Brain Function
MBP	Myelin Basic Protein
MC	Manage Circulation
MEDEVAC	Medical Evacuation
MHS	Manage Head and Spine
MPFCF	Maintain Psychological Functioning/Cognitive Functioning
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSS	Maintain Sensory Systems
mTBI	Mild Traumatic Brain Injury
MTV	Maintain Tissue Viability
NAMRU-SA	Naval Medical Research Unit – San Antonio
NHC	NeuroHabilitation Corporation
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NIRS	Near Infrared Spectroscopy
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
ONR	Office of Naval Research
PAMPer	Prehospital Air Medical Plasma
PBBI	Penetrating Ballistic-like Brain Injury
PDC	Patient Documentation and Communication
PL	Preserve Life
PLUL	Prevent Loss of Use of Limb(s)
PM	Pain Management
PMI	Patient Movement Instructions

POC	Point of Care
POI	Point of Injury
PoNS	Portable Neuromodulation Stimulator
PPE	Personnel Protective Equipment
PROPPR	Pragmatic, Randomized Optimal Platelet, and Plasma Ratio Study
PRT	Pathogen Reduction Technology
PTSD	Posttraumatic Stress Disorder
PUPTH	Prehospital Use of Plasma for Traumatic Hemorrhage
R&D	Research and Development
RBC	Red Blood Cell
RDT&E	Research, Development, Test, and Evaluation
REBOA	Resuscitative Endovascular Balloon Occlusion of the Aorta
RF	Radiofrequency
RFI	Request for Information
RHBC	Rehabilitative Care
RMI	Reflectance Medical Inc.
ROC	Resuscitations Outcome Consortium
RPI	Repair Physical Injuries
RSPT	Recognize Signs of Psychological Trauma
RTD	Return to Duty
SAM	SAM Junctional Tourniquet
SAMMC	San Antonio Military Medical Center
SBDP	Alpha II-Spectrin Breakdown Products
SBIR	Small Business Innovation Research
SDSD	Solvent Detergent Spray-Dried
SmO_2	Muscle Oxygen Saturation
SOF-T	Special Operation Forces Tactical
SOFT-W	Special Operation Forces Tactical Wide
STTR	Small Business Technology Transfer
TBI	Traumatic Brain Injury
TC3	Theater Combat Casualty Care
TCCC	Tactical Combat Casualty Care
TCNL	University of Wisconsin Tactile Communications and NeuroHabilitation Laboratory
TF	Task Force
TI	Triage Injuries
TS	Treatment for Shock
TTP	Tactics, Techniques, and Procedures
TXA	Tranexamic Acid
UCH-L1	Ubiquitin C-Terminal Hydrolase-L1

U.K.	United Kingdom
U.S.	United States
USAISR	U.S. Army Institute of Surgical Research
USAMMA	U.S. Army Medical Materiel Agency
USAMMDA	U.S. Army Medical Materiel Development Activity
USAMRAA	U.S. Army Medical Research Acquisition Activity
USAMRMC	U.S. Army Medical Research and Materiel Command
USCENTCOM	U.S. Central Command
USSOCOM	U.S. Special Operations Command
UV	Ultraviolet
VA	U.S. Department of Veterans Affairs
VAID	Video Assisted Intubation Devices
WBC	White Blood Cell
WRAIR	Walter Reed Army Institute of Research

Executive Summary

The United States (U.S.) Combat Casualty Care Research Program (CCCRP) at the U.S. Army Medical Research and Materiel Command (USAMRMC) is a requirements-driven medical research and development (R&D) program that is developing knowledge and materiel solutions for the management of combat-related trauma. Through these solutions, the CCCRP seeks to optimize survival and recovery from combat injury in current and future operations.

Successful products and capabilities that have resulted from R&D programmed and overseen by the CCCRP were identified and characterized to illustrate progress toward the goal of advancing and improving hemorrhage control and resuscitation, forward surgical and intensive critical care, casualty transport, and care for traumatic brain injury (TBI) and other neurological trauma. The highlighted successes demonstrate how the work within the CCCRP's portfolios has directly impacted the warfighter and contributed to the closure of capability gaps defined by key requirements sources, including the 2008 Guidance for Development of the Force Assessment, the 2006 Army Theater Combat Casualty Care Initial Capabilities Document (ICD), and the 2015 Defense Health Program Combat Casualty Care ICD.

The *Hemorrhage and Resuscitation Portfolio* chapter highlights seven successes focused on the development of new products and advancement of key clinical practice guidelines (CPGs). These include the stories of bringing new hemostatic devices to the battlefield, as well as advancing improved blood products and damage control resuscitation approaches.

The *Forward Surgical and Intensive Critical Care Portfolio* chapter highlights five successes, illustrating advances that both directly improve prehospital survival and provide enabling capabilities for medical providers including decision support, monitoring, and triage tools.

The *Joint En Route Care Portfolio* chapter highlights three successes in the areas of preparing patients for transport with the use of advanced life support equipment, ensuring patient safety during transport through implementation of new medical technology with associated provider training, and evaluating advanced patient monitoring equipment for en route use.

The *Neurotrauma Portfolio* chapter highlights five successes that are advancing multiple products that may be used to effectively diagnose and treat TBI for the warfighter.

Though the successes highlighted represent only a fraction of the achievements and ongoing efforts of these CCCRP portfolios, they provide concrete illustrations of the impacts of the CCCRP requirements-driven R&D investments for the warfighter on the battlefield. These successes are characterized with respect to the capability gaps they have addressed, CPGs they have influenced, and the peer-reviewed publications that have provided the foundation for these changes.

Introduction

On the battlefield, warfighters are faced with multiple threats and, although significant advances have been made in combat casualty care over the course of recent conflicts, continued research is needed to save lives and improve outcomes for those injured in current and future operations. The Combat Casualty Care Research Program (CCCRP) at the United States Army Medical Research and Materiel Command (USAMRMC) aims to be a leader for trauma care, driving medical innovation to optimize survival and recovery from combat-related injury. The CCCRP plans, programs, budgets, and oversees the execution of efforts focused on reducing morbidity and mortality resulting from combat injuries through collaboration with intramural laboratories and other medical research programs nationwide. To characterize key successes that have been produced by the CCCRP and the impacts of these successes for the warfighter, the Gap Closure Analysis effort was initiated. The goal of the effort was to identify and characterize successful solutions, products, or capabilities for combat casualty care use that resulted from research and development (R&D) efforts under the following CCCRP portfolios:

- Hemorrhage and Resuscitation;
- Forward Surgical and Intensive Critical Care (FSICC);
- Joint En-Route Care (J-ERC); and
- Neurotrauma.

The process of identifying these portfolio successes and characterizing the pathway of their advancement, including identifying the capability gaps addressed by the successes and their impacts on clinical practice, highlights the progress of the CCCRP's requirements-driven research and its impact on the warfighter.

Requirement Sources

The identified successful solutions, products, or capabilities in the CCCRP portfolios align to capability and knowledge gaps identified in Joint Department of Defense (DoD) requirements documents. The portfolios are focused on addressing many capability gaps documented in the 2008 Guidance for Development of the Force (GDF) Assessment, 2006 Army Theater Combat Casualty Care (TC3) Initial Capabilities Document (ICD), and 2015 Defense Health Program (DHP) Combat Casualty Care Medical R&D Capabilities Based Assessment.

Guidance for Development of the Force Assessment

The Joint Force Health Protection (JFHP) concept was developed as a mechanism of incorporating lessons learned from Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) to improve the military health system in a manner that supports the transformation to "more agile, more capable, more versatile, more survivable, more sustainable, and rapidly deployable forces' (Office of the Assistant Secretary of Defense [Health Affairs], 2007). The JFHP focuses on promoting physical and mental health of the warfighter to improve force readiness by addressing the following three pillars: a healthy and fit force, prevention and protection, and medical and rehabilitative care. Further, capability gaps for achieving the JFHP

goal state have been identified and fall into six functional areas: human performance enhancement; health surveillance, intelligence, and preventive medicine; casualty management; patient movement; medical logistics and infrastructure support; and command and control. A GDF working group has assessed capability gaps identified under the JFHP concept of operations to determine those requiring medical R&D for resolution. A list of the subset of these GDF capability gaps that fall within the purview of CCCRP portfolios is provided in Table A-1 of the Appendix.

Army Theater Combat Casualty Care Initial Capabilities Document

The TC3 ICD describes the capabilities encompassed by TC3 and details the critical elements of the associated concept of operations, which are consistent with and supportive of the three JFHP pillars. Within the ICD, improved TC3 capabilities required across the spectrum of present and future conflicts are described, recognizing the need to provide casualty care and evacuation to highly mobile, dispersed forces in logistically austere environments. The anticipated measures of effectiveness of these improved capabilities, which are tracked in part through the Joint Theater Trauma Registry (JTTR) and Clinical Data Repository (CDR), include decreases in:

- percentage of deaths on the battlefield;
- percentage of warfighters who die of wounds;
- morbidity of wounds;
- logistical footprint of deployed medical assets; and
- lift requirements for deployment of equipment and personnel.

A Capability Description table outlining the identified capability gaps, with assigned priority, is provided in Table A-2.

Defense Health Program Medical Research Gaps

The DHP ICD for Combat Casualty Care presents a newly developed set of Medical Research Capability Gaps. These gaps have been developed in support of the Medical Research capabilities based assessment sponsored by the Deputy Assistant Secretary of Defense, Force Health Protection and Readiness. They have been formulated to address needs across five major capability focus areas that span from the point of injury (POI) through definitive care. These focus areas are defined as:

- Prevent – Activities, training, and material that improve warrior resiliency and resistance to physiological and psychological challenges
- Stabilize – Forward resuscitative care activities that mitigate the effects of trauma on morbidity and mortality, and prepare casualties for evacuation
- Preserve – Activities that prevent loss of life and limb, maintain sensory systems, brain function, and psychological functioning, and minimize pain
- Repair – Activities that treat patients for return to duty (RTD) or optimize outcomes (preserve and restore physical and psychological functionality)

- Resolve – Activities that treat and restore a patient's functional health for either RTD or optimal outcomes (maximize physical, physiological, and psychological functionality)

A comprehensive list of the DHP Medical Research Capability Gaps is provided in Table A-3.

References

Office of the Assistant Secretary of Defense [Health Affairs]. (2007). *Joint force health protection concept of operations*.

Initial capabilities document for Theater Combat Casualty Care (TC3). (2006, December 14).

Office of the Assistant Secretary of Defense [Health Affairs]. (2014, May 9). *Support documentation to the Combat Casualty Care Medical Research and Development Joint DOTmLPF-P change recommendation (DCR).*

Under Secretary of Defense for Acquisition, Technology, and Logistics. (2008, June). *Development of the Force FY2010-2015 program and budget assessment A4.16, medical research and development investments.*

Methodology

Identify CCCRP Portfolio Successes

To identify CCCRP portfolio successes that culminated in solutions, products, or capabilities that have been fielded or are poised to be implemented in the near-term to enhance combat casualty care, the portfolio managers of the Hemorrhage and Resuscitation, FSICC, J-ERC, and Neurotrauma portfolios were interviewed. The successes identified for inclusion in this analysis represent only a subset of projects within the CCCRP portfolios, which were selected to demonstrate key impacts and show progress toward the closure of critical capability gaps across a range of strategic focuses.

In collaboration with the CCCRP portfolio managers and using portfolio information that they provided, each identified successful solution, product, or capability was aligned to the existing GDF gaps, TC3 ICD gaps, and DHP ICD gaps.

Data Collection

Project-Specific Information

In coordination with the CCCRP portfolio managers, initial project information was gathered to support documentation of portfolios contributions to the successes. The information gathered included (if available):

- Project name
- Award number
- Principal investigator(s)
- Period of performance
- Funding amount

Changes in Clinical Practice

Clinical practice guidelines (CPGs) and clinical support tools (CSTs) outlining recommendations for use by providers in all roles in the DoD are available through sources such as the Joint Trauma System (JTS) and the Defense Centers of Excellence (DCoE). To identify formal changes in clinical practice resulting from the CCCRP portfolio successes, the JTS and DCoE websites were reviewed. Additional resources were also evaluated to further identify changes to existing CPGs, to understand related changes in civilian trauma practice, to identify supporting publications for all clinical practice changes, and to identify data demonstrating the positive effect of these advances on the battlefield. These included peer-reviewed literature, as well as publically available data in additional forms from researchers and product developers (e.g., websites, project progress reports, clinical trial registrations, and news reports). Searches of the following resources were conducted to identify these data sources:

- PubMed
- Google
- Google Scholar
- Defense Technical Information Center
- ClinicalTrials.gov

Portfolio Successes

The chapters that follow detail successes selected from each of these four portfolios. They include seven Hemorrhage and Resuscitation selections, five selections from FSICC, three J-ERC selections, and five selections from Neurotrauma. Across these 20 successes, alignment of effort to 16 GDF, 13 TC3 ICD, and 50 DHP ICD gaps has been characterized, beginning to demonstrate the breadth of the impact of the CCCRP's advances through medical R&D toward capability gap closure. Many of these selections are mature successes that have been deployed to the battlefield, and whose impacts can be directly supported with data including decreases in morbidity and mortality after implementation. Extremity tourniquets and hemostatic dressings described for the Hemorrhage and Resuscitation portfolio, for example, have proven efficacious in recent conflicts and have already contributed substantially to closure of capability gaps for extremity hemorrhage control. The implementation of a clinical decision support system for burn resuscitation developed through the FSICC portfolio has already yielded improved outcomes in a military hospital burn center, and a mobile version of the system is being deployed to the field. Other successes described for the CCCRP portfolios include critical progress by efforts that are still advancing toward use by the warfighter. Within the J-ERC portfolio, in-flight trials of new noninvasive physiological monitoring tools are underway to enable their use for continuous monitoring during patient transport. In the case of biomarkers for diagnosis of traumatic brain injury (TBI), the identification of strong biomarker candidates under the support of the Neurotrauma portfolio and their successful advance into a large pivotal trial has made tremendous strides toward the challenging goal of enabling fast, objective diagnosis of TBI from a peripheral blood sample. These advances are addressing capability gaps identified by multiple requirements sources that describe the need for rapid diagnosis and monitoring in theater. Together, the successes described in the chapters that follow provide concrete illustrations of the impacts of CCCRP R&D investments on combat casualty care.

Hemorrhage and Resuscitation Portfolio

Hemorrhage is a key driver of combat casualty care, and the top priority of the CCCRP. Hemorrhage is the leading cause of preventable deaths among combat casualties occurring before a medical treatment facility is reached. A study of battlefield fatalities during the period from October 2001 to June 2011, found that of 4,596 fatalities reviewed, 24 percent were potentially survivable (Eastridge et al., 2012). Of these potentially survivable fatalities, the majority (91 percent) were associated with hemorrhage (Figure 1). To improve the outcomes of these casualties, advances in the early management of hemorrhage in the field continue to be necessary. To this end, tremendous strides were made throughout the span of the recent OIF/OEF conflicts, during which concerted R&D efforts enabled the introduction of improved extremity tourniquets, hemostatic dressings, and more effective approaches to resuscitation, all of which have resulted in lives saved. Continued effort remains necessary, however, to improve upon these practices and to fully address remaining capability gaps. Such gaps include the challenges of effectively controlling severe junctional and intracavitary hemorrhage, and the logistics of bringing improved blood products and other optimized interventions into the field for resuscitation and management of the conditions that complicate severe blood loss, including coagulopathy.

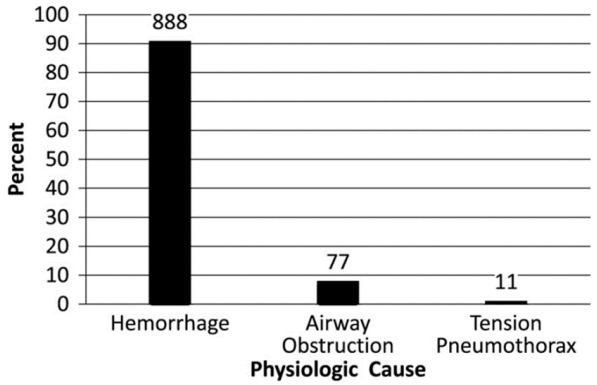


Figure 1. Primary Injuries Associated with Potentially Survivable Battlefield Mortalities (Eastridge et al., 2012)

Solutions to these challenges are sought by the Hemorrhage and Resuscitation portfolio, which supports R&D spanning the areas of hemorrhage control, fluid resuscitation, blood products, transfusion, and pathophysiologic responses to traumatic hemorrhage. The portfolio is driven by a goal state where outcomes for potentially survivable casualties are no longer limited by technology shortfalls related to hemorrhage. The portfolio's focus is also evolving to not only overcome current hurdles, but also to face the potential future needs of U.S. forces in changing combat injury scenarios. Future scenarios involving prolonged evacuation times up to 72 hours will require next generation technologies to maintain casualty survivability (Rasmussen, Baer, Doll, & Caravalho, 2015). The portfolio is being shaped to meet these challenges through development of new approaches for inflammatory modulation, metabolic stabilization, coagulopathy management, and pharmacologic achievement of hemostasis.

Requirement Sources

The current strategic objectives of the portfolio are to: (1) provide technologies to control bleeding in the prehospital environment, (2) provide safer, more effective, and more logistically supportable blood products, (3) provide technologies and knowledge sets for improved damage

control resuscitation, and (4) provide next-generation resuscitation for prolonged prehospital management and casualty survivability. To achieve these objectives, work is being undertaken across six major efforts spanning basic research through clinical development:

- Improved Blood Products
- Damage Control Resuscitation
- Coagulopathy of Trauma
- Immune/Inflammatory Modulation
- Metabolic and Tissue Stabilization
- Hemostatics

The objectives and products of the portfolio align to capability and knowledge gaps identified in Joint DoD requirement documents. The objectives have been developed with Joint input, and reviewed and approved by the Hemorrhage and Resuscitation Steering Committee, the Joint Program Committee (JPC-6), the Commanding General of the USAMRMC, and the Office of the Assistant Secretary for Defense for Health Affairs. The portfolio is addressing many capability gaps documented in the 2008 GDF Assessment, the 2006 Army TC3 ICD, and 2015 DHP ICD (Table 1).

Table 1. Pursued Capability Gaps within the Scope of the CCCRP's Hemorrhage and Resuscitation Portfolio

Requirement Sources	Capability Gaps
GDF	• **Joint Casualty Management (JCM)-1-1** – Inadequate ability to diagnose, resuscitate, and stabilize casualties with survivable wounds • **JCM-1-4** – Inability to stop internal and external bleeding • **JCM-1-5** – Poor ability to stop life-threatening extremity bleeding • **JCM-1-8** – Inadequate therapy for shock and head injury • **JCM-1-11** – Inadequate ability to immediately recognize and correct coagulopathy • **JCM-2-2** – Poor ability to provide tissue oxygenation and compatible shelf-stable blood products • **JCM-2-3** – Poor ability to restore blood volume • **JCM-2-5** – Inability to prevent bleeding problems associated with hypothermia
TC3 ICD	• **Theater Hospitalization, Area Medical Support** – Diagnose, resuscitate and stabilize casualties with survivable wounds • **Hemostatic Agents and Equipment** – Internal bleeding, external bleeding • Capability to Control Extremity Bleeding (e.g., Tourniquets and Other Technologies) – Stop life-threatening extremity bleeding • **Blood Substitutes** – Provide tissue oxygenation, compatible blood types, shelf stable • Rapid Administration of Fluids – Restore blood volume • Adjunctive Medications for Trauma Management – Therapy for shock and head injury • **Coagulopathy Prevention and Treatment Agents** – Immediate recognition and correction of coagulopathy
DHP ICD	• **Triage Injuries (TI)1** – Insufficient current first-responder (medical and non-medical) capacity and capability to initially assess, treat, and maintain severe trauma cases in the pre-hospital environment - Insufficient initial and ongoing training for first responders in the pre-hospital environment overall - Insufficient tools that enable both non-medical and medical first responders. - The technologies do not exist to fulfill some of the needs (e.g., stabilizing the airway or truncal hemorrhage) • **TI3** – No common Tactical Combat Casualty Care (TCC) tactics, techniques, and procedures (TTP) for first responders and medical practitioners across Services and across the continuum of care • **TI8** – Limited ability to properly diagnose and treat seen and unseen non-compressible

Requirement Sources	Capability Gaps
	hemorrhage in the pre-hospital environment • **Manage Circulation (MC)2** – Medical and non-medical first responders frequently misuse medical equipment (i.e., tourniquets) that is provided to control hemorrhage in the TCCC setting • **MC6** – Lack of optimal blood expander with oxygenation capability and fluid resuscitative strategy at POI • **Treatment for Shock (TS)1** – Lack of optimal resuscitation strategies for casualties who have TBI and are in, or at risk for, hemorrhagic shock • **TS2** – Lack of optimal therapies to manage hypo and hyperthermia in the pre-hospital environment • **TS3** – Lack of suitable resuscitative fluids (e.g., blood products or substitutes) appropriate for administration in the pre-hospital environment in order to prevent shock • **TS4** – Lack of ways and means to effectively screen for and diagnose shock throughout continuum of care • **TS5** – Insufficient understanding of the patient's predisposition to outcomes of hemorrhagic shock • **TS6** – Insufficient ways and means to diagnose and manage vascular disruption (with or without hemorrhagic shock) • **Manage Blood Circulation (MBC)1** – Lack of non-surgical means to treat non-compressible truncal/torso hemorrhage in the pre-hospital environment • **MBC2** – Lack of ways and means to manage circulations and control junctional and truncal hemorrhaging in the pre-hospital environment • **Preserve Life (PL)6** – Limited therapies for damage control resuscitation in traumatic injury, to include neuronal damage • **PL8** – Inability to test for the presence of blood pathogens at pre-U.S. hospital (malaria, HIV, hepatitis, etc. for local blood and direct transfusions) in order to reduce morbidity and mortality in the field

Portfolio-managed activities have continued to directly address key gaps outlined in Table 1, as well as complement other R&D efforts for combat care that contribute to advances against additional capability gaps. Hemorrhage and Resuscitation efforts intersect with other CCCRP portfolios and with the work of additional JPCs, and there is close collaborative coordination on these efforts in areas including coagulation monitoring, inflammatory modulation, surgical control of hemorrhage, and others. Interagency cooperative programs have also been an important focus of the portfolio, bringing external investments to bear in areas of specific importance to the DoD. These cooperative programs have varying levels of DoD-supplied funding support (some may be transitioned to advanced developers or other organizations and are no longer DoD funded), but all contribute to advancing the field and have been shaped and/or conducted with the participation of the CCCRP's Hemorrhage and Resuscitation portfolio.

Hemorrhage and Resuscitation Portfolio Successes

The stories of seven select accomplishments begin to illustrate some of the achievements of the Hemorrhage and Resuscitation portfolio to date. These examples highlight not only the development of new technology products, but also the advancement of key CPGs, and critical progress in the coordination of strategic Joint efforts.

Bringing Advanced Hemostatic Products to the Battlefield

The first four portfolio selections feature hemostatic products. The CCCRP and JPC-6 has worked in conjunction with many partners to close gaps in the management of external

hemorrhage through the development and testing of advanced dressings and tourniquets. These have been successfully implemented to save lives in the recent OIF/OEF conflicts.

- **External Hemorrhage Control: Hemostatic Dressings** – Hemostatic agents have been incorporated into gauze or bandages including the HemCon Bandage and QuikClot Combat Gauze for the management of hemorrhage
- **External Hemorrhage Control: Extremity Tourniquets** – Small, light-weight, effective commercial tourniquets have been broadly fielded, preparing service members to quickly control extremity hemorrhage at the scene of a traumatic injury

With technological solutions for external hemorrhage control largely achieved through these efforts, focus was channeled to pursuing additional hemostatic devices to address compressible junctional hemorrhage and noncompressible intracavitary hemorrhage, both of which cannot be appropriately managed with extremity tourniquets or by the use of existing hemostatic dressings alone. The next two portfolio selections, junctional tourniquets and the XStat device for managing intracavitary bleeding, encompass new devices that have recently received U.S. Food and Drug Administration (FDA) clearance for military use, and are in limited fielding as efforts to evaluate and optimize their use continue.

- **Junctional Hemorrhage Control: Development of Junctional Tourniquets including the Combat Ready Clamp** – Focal pressure tourniquet devices to stop blood flow by compressing blood vessels at or proximal to a junctional injury
- **Controlling Intracavitary Noncompressible Bleeding: The XStat** – Syringe-style device to deliver small chitosan-coated sponges into a wound cavity

Improved Blood Products and Damage Control Resuscitation

The final three portfolio selections cover advances to improve and expand the provision of blood, blood products, and other adjunctive measures for transfusion. These efforts together are improving resuscitation outcomes through the development of optimized data-driven protocols and by working to enable whole blood and plasma, more effective resuscitants than the alternative fluids that may also be in use in the field out of necessity, to be made more broadly available in theater.

- **Damage Control Resuscitation** – Optimized protocols have been developed emphasizing resuscitation through the early initiation of blood product transfusions and the overall use of balanced blood components
- **Whole Blood Pathogen Reduction Device** – A transportable pathogen reduction technology is in development to process whole blood in combat environments
- **Logistically Supportable Dried Plasma Products for Transfusion** – Dried plasma products are in development that can be easily maintained both in and outside of hospital settings in theater, and reconstituted quickly for immediate transfusion

References

Eastridge, B. J., Mabry, R. L., Seguin, P., Cantrell, J., Tops, T., Uribe, P., … Blackbourne, L. H. (2012). Death on the battlefield (2001-2011): Implications for the future of combat casualty care. *Journal Trauma Acute Care Surgery, 73*(6 Suppl 5), S431-S437.

Rasmussen, T. E., Baer, D. G., Doll, B. A., & Caravalho, J. (2015). In the golden hour. *Army AL&T Magazine*, 81-85.

External Hemorrhage Control: Hemostatic Dressings

HemCon Bandage and QuikClot Combat Gauze are two FDA-approved hemostatic dressings that have been extensively fielded and used on the battlefield to stanch hemorrhage.

- Developmental Partner Organizations:
  - HemCon Medical Technologies
  - Z-Medica
- Activities supporting the development and evaluation of hemostatic products have been underway since 2001

Key Outcomes and Impact:

- HemCon Bandage and QuikClot granules were developed through USAMRMC grants; additional support enabled development of second-generation QuikClot Combat Gauze
- All have been fielded, recommended in TCCC guidelines, and demonstrated efficacy on the battlefield
- Implementation of these dressings together with additional hemorrhage advances, such as use of modern tourniquets, has proven effective in reducing mortality in U.S. Army regiments that have fully adopted their use (Kotwal et al., 2011)
- The capability gap of external compressible hemorrhage has been assessed as 95 percent closed

QuikClot Combat Gauze was Fielded and TCCC-Recommended in 2008; Evaluation of New Hemostatic Agents Continues (Maxwell, 2008)

Overview

Early and effective hemorrhage control can theoretically save more lives in combat environments than any other measure (Eastridge et al., 2012). It is estimated that of the U.S. military casualties who were designated killed in action while on deployment during the Vietnam War or in OIF/OEF, 38 and 24 percent were caused by uncontrolled hemorrhage, respectively (Eastridge et al., 2012; JTCG/ME, 1970). Furthermore, of these U.S. military casualties killed in action while deployed in OIF/OEF, it has been estimated that 26 percent were potentially survivable from a medical perspective, and that 91 percent of those potentially survivable cases were attributed to uncontrolled hemorrhage (Eastridge et al., 2012). Although these figures successfully underscore the importance of developing strategies and interventions that mitigate and control hemorrhage in combat environments, they fail to account, however, for the U.S. military casualties who survived their severe injuries due to hemostatic agents, dressings, and tourniquets, which have continuously increased in quality, quantity, and use since the beginning of the 21st century.

Because physicians and surgeons are seldom present at the POI, it is critical that lifesaving interventions be readily available and easily employed on the battlefield within minutes of injury. Early intervention is an important aspect of hemorrhage control whereby the physiological processes of the casualty are stabilized before they can be evacuated. Alongside tourniquets, the development of hemostatic agents (i.e., granules, powders) and hemostatic dressings (i.e., an agent incorporated into gauze or bandage) has been an important component of managing hemorrhage on the battlefield. Conceptually simple, hemostatic agents and dressings enable rapid control of hemorrhage at or near the POI and have been vital for controlling extremity and

compressible junctional hemorrhage, particularly for those injuries not amenable to tourniquet application.

Using grants from the USAMRMC, the HemCon Bandage (Figure 2) and the QuikClot granules were developed by HemCon Medical Technologies, Inc., and Z-Medica as first-generation hemostatic products. The HemCon Bandage is a mucoadhesive that is chitosan-based and works by cross-linking cellular blood components to form a barrier. QuikClot granules are a zeolite mineral that is composed of silicon, aluminum, sodium, magnesium, and quartz. It behaves as a molecular sieve by concentrating the platelets and clotting factors in the applied area to promote coagulation. In 2002, both the HemCon Bandage and QuikClot agent were cleared by FDA and immediately put into use by U.S. military forces (HemCon, 2015, QuikClot, 2015).

Figure 2. HemCon Bandage (HemCon, 2015)

With additional support from the USAMRMC, QuikClot developed Combat Gauze, which is a second-generation hemostatic dressing (Figure 3). Like QuikClot granules, QuikClot Combat Gauze is both a factor concentrator, because it absorbs water, and a procoagulant, because it activates the clotting cascade. In 2008, QuikClot Combat Gauze was cleared by FDA for clinical application and distributed very quickly to U.S. military forces. In the Tactical Combat Casualty Care (TCCC) Equipment Evaluation survey, which is based on 2,010 uses of QuikClot Combat Gauze on the battlefield, approximately 89 percent of respondents agreed or strongly agreed that it was "effective at stopping severe external bleeding" (TCCC Equipment Evaluation). Through multiple clinical and preclinical studies, QuikClot Combat Gauze has demonstrated effectiveness against large, open wounds, while also decreasing rate of blood loss (Causey et al., 2012; Gegel et al., 2012; Johnson et al., 2012; Kheirabadi, Scherer, Estep, Dubick, & Holcomb, 2009; Kheirabadi et al., 2010; Pahari, Moliver, Lo, Pinkerton, & Basadonna., 2010; Politi et al., 2011; Satterly et al., 2013; Trabattoni, Gatto, & Bartorelli, 2012).

Figure 3. QuikClot Combat Gauze (QuikClot, 2015)

Similar to most new developments, there is an active debate to determine the best hemostatic agent or dressing for battlefield injuries. Even though no one ideal hemostatic agent or dressing exists, optimal products should meet certain criteria: (1) capable of stopping arterial and venous hemorrhage within two minutes of application, even when applied to sites undergoing massive hemorrhage; (2) suitable for areas not accessible for the application of a tourniquet; (3) instantly available; (4) simple to apply by someone with minimal training; (5) durable and easy to carry; (6) stable in extreme environments; (7) safe to use with minimal risk; and (8) inexpensive (Pusateri, et al., 2006).

Both the HemCon Bandage and QuikClot granules have demonstrated effective hemorrhage control properties in combat (Pusateri et al., 2006). QuikClot granules have been demonstrated to

be effective at controlling hemorrhage in deep jagged wounds, whereas HemCon Bandages have been demonstrated to be more effective when applied to wounds with an even surface (Alam, Burris, DaCorta, & Rhee, 2005). Successful fielding and application of these hemostatic agents has inspired a number of other second- and third-generation hemostatic agents and dressings by additional manufacturers that are now providing improved options for the military (Bennett et al., 2014).

Capability Gap Alignment

Development of the HemCon Bandage, QuikClot Combat Gauze, and related hemostatic agents and dressings directly addresses key capability gaps in hemorrhage control, as defined by multiple requirement sources (Table 2). Following CCCRP-directed and funded research efforts, the capability gap of external compressible hemorrhage is now widely regarded as 95 percent closed within the combat casualty care research community (Pusateri, 2014).

Table 2. Capability Gaps Addressed by Hemostatic Dressings

Requirement Sources	Capability Gaps Addressed
GDF	• **JCM-1-4** – Inability to stop internal and external bleeding • **JCM-1-5** – Poor ability to stop life-threatening extremity bleeding
TC3 ICD	• **Hemostatic Agents and Equipment** – Internal bleeding, external bleeding • **Capability to Control Extremity Bleeding (e.g., Tourniquets and Other Technologies)** – Stop life-threatening extremity bleeding
DHP ICD	• **TI1** – Insufficient current first-responder (medical and non-medical) capacity and capability to initially assess, treat, and maintain severe trauma cases in the pre-hospital environment - Insufficient tools that enable both non-medical and medical first responders - The technologies do not exist to fulfill some of the needs (e.g., stabilizing the airway or truncal hemorrhage) • **MBC1** – Lack of non-surgical means to treat non-compressible truncal/torso hemorrhage in the pre-hospital environment • **MBC2** – Lack of ways and means to manage circulations and control junctional and truncal hemorrhaging in the pre-hospital environment

Impact on the Battlefield/Warfighter

Even though hemorrhage continues to be the leading cause of combat death, aggressive control of hemorrhage on the battlefield has had substantial impact on morbidity and mortality (Cox, Schreiber, McManus, Wade, & Holcomb, 2009; Eastridge et al., 2012). Seven years after hemostatic dressings were introduced, the rate of U.S. military casualties killed in action while deployed in Iraq and Afghanistan decreased approximately 8 and 10 percent, respectively (Kellstrand, 2010). While there are multiple factors affecting this rate, the introduction of hemostatic dressings to help prevent deaths occurring from hemorrhage before reaching a medical treatment facility is an important contributor. In conjunction with updated CPGs supporting their appropriate use, hemostatic dressings have become a key tool for managing compressible external hemorrhage. The implementation of these dressings and related care practices, together with additional hemorrhage advances such as use of modern tourniquets when applicable, has proven to be effective in reducing mortality in U.S. Army regiments that have fully adopted their use (Kotwal et al., 2011).

Clinical Practice

Impact on Clinical Practice Guidelines

The U.S. military's Committee on Tactical Combat Casualty Care (CoTCCC) is responsible for developing guidelines for trauma care on the battlefield. Prior to 2003, the TCCC guidelines recommended that caregivers responding to uncontrolled hemorrhage, equipped with traditional gauze, "consider removing tourniquets and using direct pressure to control bleeding if possible" (Butler, Holcomb, Giebner, McSwain, & Bagian, 2007). In 2003, the CoTCCC considered HemCon Bandages, QuikClot granules, and several recently developed hemostatic agents that were gaining support from ongoing studies as potential options to more effectively control external hemorrhage, including when tourniquet application was not possible or successful (Alam et al., 2003, 2004; Sondeen, Pusateri, Coppes, Gaddy, & Holcomb, 2003; Pusateri et al., 2003, 2004). The HemCon Bandage was assessed to be effective based on the body of available evidence, and did not pose the same concern associated with the similarly effective QuikClot granules' exothermic reaction mechanism (Butler, Holcomb, Giebner, McSwain, & Bagian, 2007). Based on these characteristics, the CoTCCC selected HemCon Bandage as the first non-gauze hemostatic dressing to be recommended in the TCCC guidelines for life-threatening compressible hemorrhage: "For nonextremity wounds, apply pressure and/or a HemCon dressing." In 2005, the U. S. Central Command (USCENTCOM) directed that all combatants entering the USCENTCOM area of responsibility have a HemCon dressing (Butler & Blackbourne, 2012). Later, based on reports of successful use of QuikClot granules on the battlefield by Navy corpsmen, and affirmations by trauma surgeons that the exothermic reaction did not cause substantial tissue damage, the 2006 CoTCCC committee expanded their recommendation to also include QuikClot granules in situations where a HemCon Bandage was not effective or available (Pusateri et al., 2006; Butler et al., 2007). In 2008, QuikClot Combat Gauze was endorsed by the CoTCCC as a first-line treatment for life-threatening compressible hemorrhage, and more recently the CoTCCC has added Celox Gauze by MedTrade Products Ltd. and ChitoGauze by HemCon as additional hemostasis options, citing recent affirmations of their equivalent efficacy to QuikClot Combat Gauze (Bennett et al., 2014) (Figure 4).

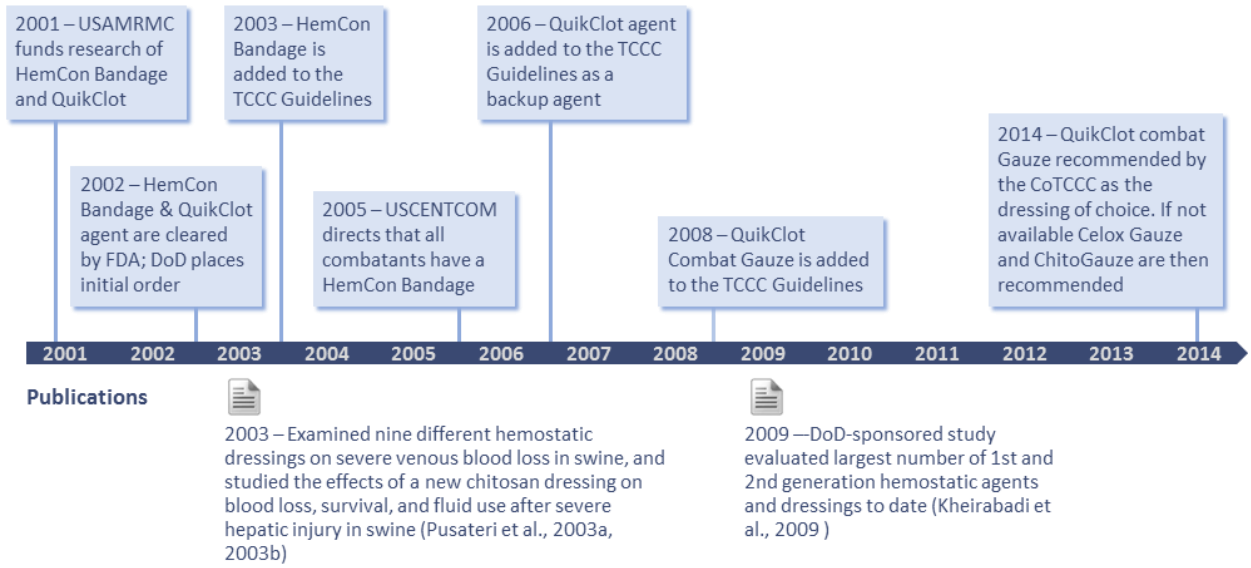


Figure 4. Research, Development, and Fielding Timeline: Hemostatic Agents/Dressings

As R&D has continued, and these recommendations for TCCC have evolved, it has been recognized that the full lifesaving impact of existing hemostatic agents and dressings may also require a different approach to combat casualty care training as exemplified by the Army 75th Ranger Regiment. While deployed in OIF/OEF from 2001 to 2010, the Rangers had a potentially survivable death rate of 3 percent, which is significantly lower than 26 percent for the rest of the DoD (Kotwal et al., 2011). In addition, none of the potentially survivable deaths from the Ranger Regiment was attributed to uncontrolled hemorrhage. The disparity is likely because the Ranger Regiment has institutionalized a casualty response system that integrates (1) TCCC training for all personnel; (2) tactical leader ownership of the casualty response system; and (3) continuous use of theater registry data for updating TCCC Guidelines (Kotwal et al., 2011). By employing similar approaches, it is envisioned that the potentially survivable death rate can continue to be significantly lowered for all U.S. military forces.

Supporting Publications

In most circumstances, medical interventions such as new drugs, devices, and therapies are rigorously tested in randomized clinical trials before gaining approval and going into widespread use. Wartime exigencies presented unique challenges to the approval process, such that the decision to use or not to use hemostatic agents and dressings could not wait for ideal clinical data to become available, and, instead, was made using the best existing data. Thus, when hemostatic dressings and agents were initially supplied to U.S. military forces, no randomized clinical trial involving trauma patients had been conducted. Instead, hemostatic agents and dressings had strong support from animal models (Alam et al., 2003; Alam et al., 2004; Pusateri et al., 2004; Pusateri et al., 2003; Sondeen, Pusateri, Coppes, Gaddy & Holcomb, 2003). In a compelling study of a large-animal model of hemorrhage, use of HemCon Bandage decreased the volume of blood loss, decreased the volume of fluid for resuscitation, and increased survivability (87.5 percent versus 28.6 percent), compared to normal gauze controls (Pusateri et al., 2003b). Continued use of hemostatic agents has support from multiple clinical reports and case studies (Table 3):

Table 3. Supporting Publications for Hemostatic Agents

Reference	Description
Tarpey, 2005	Case study of QuikClot demonstrating its ability to stop femoral hemorrhage
Wedmore, McManus, Pusateri, & Holcomb, 2006	A case report of 64 uses of HemCon demonstrating 97 percent success rate at stopping hemorrhage. For 66 percent of the cases, gauze dressings were tried and failed before HemCon
Cox, Schreiber, McManus, Wade, & Holcomb, 2009	Retrospective cohort review of clinical observations on the efficacy of QuikClot granules and HemCon Bandages
Kheirabadi, Scherer, Estep, Dubick, & Holcomb, 2009	Comparison of multiple hemostatic dressings. QuikClot Combat Gauze resulted in the highest survival rate and lowest amount of hemorrhage
Kheirabadi et al., 2010	Comparison of QuikClot Combat Gauze and WoundStat. QuikClot is as safe as gauze, while WoundStat injured vessels
Ran et al., 2010	Case study of the Israel Defense Force. QuikClot Combat Gauze had a success rate of 79 percent

Furthermore, a comparative study in which Celox Gauze use had the least overall blood loss and highest survival among comparators supports the recent decision in 2014 by the CoTCCC to include Celox Gauze as a recommended alternative hemostatic dressing in the absence of the field-proven Combat Gauze (Rall et al., 2013).

Role of CCCRP-Sponsored Projects

The USAMRMC provided initial support to HemCon Medical Technologies, Inc., and QuikClot for the development and FDA clearance of the HemCon Bandage and QuikClot agent (Figure 4; Table 5). The USAMRMC has also supported efforts to develop a complex groin injury model in swine to test new hemostatic dressings (Table 4). The model simulated battlefield injuries that were inaccessible to tourniquet, including lethal arterial, venous, and soft-tissue injuries.

Table 4. CCCRP-Sponsored Publications of Hemostatic Agent Testing in the Swine Model

Reference	Description
Pusateri et al., 2003a	Examined nine different hemostatic dressings on severe venous blood loss in swine
Pusateri et al., 2003b	Studied the effects of a new chitosan dressing on blood loss, survival, and fluid use after severe hepatic injury in swine

From DoD support of the development of these pioneering hemostatic agent products and the establishment of models and methodologies for testing their efficacy (Table 5), the ongoing development of multiple hemostatic agent products outside of DoD funding has also been encouraged and advanced. Successful outcomes are being reported from new third-generation hemostatic products that continue to seek to improve the functional characteristics to the benefit of the warfighter (Bennett et al., 2014).

Table 5. DoD-Sponsored Projects for Hemostatic Agents

Project Title (Award Number)	Organization/ Principal Investigator	Funding
Hemostatic Control Bandage – *The original aim was to obtain a 510(K) approval for the HemCon Bandage. It was then proposed to extend the scope of this research to include expanding the indications of use to include over-the counter use and temporary internal use for the short term control of internal bleeding. The initial groundwork for application to FDA for permanent implant use of the bandage was also proposed.*	USAMRMC, HemCon Medical Technologies, Inc.	$7,862,085 (2006) $7,862,085 (2007) $7,862,085 (2008) $7,862,085 (2009)
Efficacy of New Hemostatic Agents to Control Lethal Extremity Arterial – *To assess the hemostatic efficacy of new hemostatic granular/powder agents to stop a lethal arterial hemorrhage*	USAMRMC/ U.S. Army Institute of Surgical Research (USAISR)	$120,000 (2007)
Long-term Effects of a New Hemostatic Dressing (Ethicon Dressing, ED) in an Arterial Injury Model of Uncontrolled Hemorrhage in Swine (Sus scrofa)	USAMRMC/USAISR	$457,109 (2006)
Assessment of Efficacy and Safety of New Topical Hemostatic Agents for Stopping Compressible and Noncompressible Bleeding at the Battlefield	Michael A. Dubick and Bijan Kheirabadi, USAMRMC/USAISR	$1,813,000 (2009-2012)

Project Title (Award Number)	Organization/ Principal Investigator	Funding
Effect of Various Hemostatic Dressings on Blood Loss in a Model of Severe Large Venous Hemorrhage and Severe Liver Injury – *Determined the effects of QuikClot on blood loss, time to hemostasis and short-term survival when used to treat severe venous hemorrhage and hepatic injury*	USAMRMC/USAISR	$65,743 (2002)
Comparison of Hemorrhage Control Devices Applied to Lethal Arterial Hemorrhage Using a New Groin Injury Model in Swine – *Evaluate the hemostatic efficacy of QuikClot, Chitosan Dressing, and Fibrin Sealant Dressing, three products in a model of severe extremity arterial hemorrhage that could not be stopped by standard treatment*	USAMRMC/USAISR	$207,000 (2004)
Histologic And Biomechanic Evaluation Of Porcine Skin Incision Healing After Application Of Hemostatic Bandages – *Testing of hemostatic bandages on a porcine skin wound model*	USAMRMC	$44,461 (2008) $44,461 (2009)
Preliminary Safety Assessment of WoundStat and Combat Gauze in Treating Major Vascular Hemorrhage in Swine – *The potential adverse effects of WoundStat or Combat Gauze will be compared with regular surgical gauze*	USAMRMC/USAISR	$84,000 (2009)
Accelerated Clotting with Nanofiber Bandage Technology – *Characterize the impact of nanofiber on clotting mechanisms*	Office of Naval Research (ONR)	$621,367 (2009)
Development of Hemostatic Agents (Grant No. N00014-05-C-0269)	Bob M. Moore II, Ph.D., ONR	(2005 – 2007)
Far Forward Control of Hemorrhage – *Testing and evaluation of hemostatic agents*	ONR	$238,480 (2006) $272,284 (2007) $317,545 (2008) $606,157 (2009)
Evaluation of Zeolite (QuikClot) to Restore Hemostasis – *This study investigated how the product actuates hemostasis in a rat hemorrhage model and how it effects its action through the clotting system.*	ONR	$267,038 (2002) $326,589 (2003)
Hemorrhage Control in a Swine Model: A Comparison of Standard QuikClot Formation, its New Prepackaged Tea-Bag Formulation and a Standard Dressing – *This study compared the standard free granule formulation, the new tea-bag formulation, and a standard dressing, in their effectiveness for controlling venous bleeding in a lethal groin wound in a Swine model of hemorrhage*	Naval Medical Center Portsmouth	$8,100 (2006)
Comparison of Three Hemostatic Agents, CELOX, QuikClot, and HemCon in Controlling Hemorrhage in a Standard Swine Model – This study compared the equivalency of CELOX free granulate formation, QuikClot free granulation formulation, and HemCon wafer formation, in their effectiveness to control venous bleeding in a lethal groin wound in a swine model of hemorrhage	Naval Medical Center Portsmouth	$45,000 (2006) $62,200 (2007) $17,630 (2008) $17,630 (2009)
Bleeding arrest using a modified Zeolite hemostatic dressing, (MZh), in a severe groin injury with uncontrolled hemorrhage in swine – *An improved QuikClot bagged product (MZh) was compared with the original loose granulated powder (PZh) for their effectiveness to control venous bleeding in a lethal groin wound in a swine model of hemorrhage*	Naval Medical Research Center	$20,000 (2005) $42,000 (2006) $42,000 (2007)
Navy Medical Technology Watch: Hemostatic Dressing Products for the Battlefield (Task No. 9T4SJLIS004, Work Unit No. 60316) – Investigated current and developing technologies for hemostatic dressings and reviewed current independently published research evaluating these products	Ted Melcer, Ph.D., Naval Health Research Center, Naval Medical Research Center, Navy Medical Support Command	(2005 – 2006)

Project Title (Award Number)	Organization/ Principal Investigator	Funding
Silica Nanofiber Combat Hemostat (SiNCH) (FA9550-07-1-0563) – Screened a panel of nanomaterials to identify the best promoter of coagulation in vitro	Robert Hugh Daniels, Ph.D., Nanosys Inc., Air Force Office of Scientific Research	(2007 – 2008)
Far Forward Treatment of Hemorrhagic Shock (Contract No. N0001405MP20006/N000140610192, Grant No. MDA905-03-010004) – *Tested various hemostatic agents to identify the best agent for us in the battlefield*	Hasan B. Alam, M.D., Uniformed Services University	(2002 – 2007)

References

Alam, H. B., Uy, G. B., Miller, D., Koustova, E., Hancock, T., Inocencio, R., … Rhee, P. (2003). Comparative analysis of hemostatic agents in a swine model of lethal groin injury. *Journal of Trauma and Acute Care Surgery*, *54*(6), 1077-1082.

Alam, H. B., Chen, Z., Jaskille, A., Querol, R. I. L. C., Koustova, E., Inocencio, R., … Rhee, P. (2004). Application of a zeolite hemostatic agent achieves 100% survival in a lethal model of complex groin injury in swine. *Journal of Trauma and Acute Care Surgery*, *56*(5), 974-983.

Alam, H. B., Burris, D., DaCorta, J. A., & Rhee, P. (2005). Hemorrhage control in the battlefield: Role of new hemostatic agents. *Military medicine*, *170*(1), 63-69.

Bennett, B. L., Littlejohn, L. F., Kheirabadi, B. S., Butler, F. K., Kotawal, R. S., Dubick, M. A., & Bailey, J. A. (2014). Management of external hemorrhage in tactical combat casualty care: Chitosan-based hemostatic gauze dressings – TCCC Guidelines-Change 13-05. *Journal of Special Operations Medicine*, *14*(3), 40-57.

Butler, F. K., & Blackbourne, L. H. (2012). Battlefield trauma care then and now: A decade of Tactical Combat Casualty Care. *Journal of Trauma and Acute Care Surgery*, *73*(6, Suppl5), S395-S402.

Butler, F., Holcomb, J., Giebner, S. D., McSwain, N. E., & Bagian, J. (2007). Tactical combat casualty care 2007: Evolving concepts and battlefield experience. *Military Medicine*, *172*(11), 1.

Causey, M. W., McVay, D. P., Miller, S., Beekley, A., & Martin, M. (2012). The efficacy of Combat Gauze in extreme physiologic conditions. *Journal of Surgical Research*, *177*(2), 301-305.

Cox, E. D., Schreiber, M. A., McManus, J., Wade, C. E., & Holcomb, J. B. (2009). New hemostatic agents in the combat setting. *Transfusion*, *49*(s5), 248S-255S.

Eastridge, B. J., Mabry, R. L., Seguin, P., Cantrell, J., Tops, T., Uribe, P., … Blackbourne, L. H. (2012). Death on the battlefield (2001-2011): Implications for the future of combat casualty care. *Journal Trauma Acute Care Surgery*, *73*(6 Suppl 5), S431-S437.

Gegel, B., Burgert, J., Gasko, J., Campbell, C., Martens, M., Keck, J., … Johnson, D. (2012). The effects of QuikClot Combat Gauze and movement on hemorrhage control in a porcine model. *Military Medicine*, *177*(12), 1543.

HemCon Medical Technologies, Inc. (2015). The hemostatic HemCon Bandage PRO. Retrieved from http://hemcon.com/Products/HemConBandageOverview/HemConBandage2x2.aspx

Initial Capabilities Document for Theater Combat Casualty Care. (2006, December 14). Version 7.0

Johnson, D., Agee, S., Reed, A., Gegel, B., Burgert, J., Gasko, J., & Loughren, M. (2012). The effects of QuikClot Combat Gauze on hemorrhage control in the presence of hemodilution. *U. S. Army Medical Department Journal*, *2012*, 36-39.

Joint Technical Coordinating Group (JTCG) for Evaluation of Wound Data and Munitions Effectiveness in Vietnam (JTCG/ME), Vol I of III. Final report, December 1970, Alexandria, VA, Defense Technical Information Center (AD879516).

Kellstrand, A. A. (2010). *Increasing survivability on the battlefield: Hemorrhage control and the Joint Theater Trauma System.* Marine Corps Command and Staff College. Quantico, VA.

Kheirabadi, B. S., Scherer, M. R., Estep, J. S., Dubick, M. A., & Holcomb, J. B. (2009). Determination of efficacy of new hemostatic dressings in a model of extremity arterial hemorrhage in swine. *Journal of Trauma and Acute Care Surgery*, *67*(3), 450-460.

Kheirabadi, B. S., Mace, J. E., Terrazas, I. B., Fedyk, C. G., Estep, J. S., Dubick, M. A., & Blackbourne, L. H. (2010). Safety evaluation of new hemostatic agents, smectite granules, and kaolin-coated gauze in a vascular injury wound model in swine. *Journal of Trauma and Acute Care Surgery*, *68*(2), 269-278.

Kotwal, R. S., Montgomery, H. R., Kotwal, B. M., Champion, H. R., Butler, F. K., Mabry, R. L., … Holcomb, J. B. (2011). Eliminating preventable death on the battlefield. *Archives of Surgery*, *146*(12), 1350-1358.

Maxwell, S. (2008, December 4). Army fields new equipment to stop bleeding. Retrieved from http://www.army.mil/mobile/article/?p=14824

Pahari, M., Moliver, R., Lo, D., Pinkerton, D., & Basadonna, G. (2010). QuikClot® interventional™ hemostatic bandage (QCI): A novel hemostatic agent for vascular access. *Cath Lab Digest Archive*, *17*.

Politi, L., Aprile, A., Paganelli, C., Amato, A., Zoccai, G. B., Sgura, F., … Sangiorgi, G. M. (2011). Randomized clinical trial on short-time compression with kaolin-filled pad: A new strategy to avoid early bleeding and subacute radial artery occlusion after percutaneous coronary intervention. *Journal of Interventional Cardiology*, *24*(1), 65-72.

Pusateri, A. E. (2014, September 3). Unmet medical needs in prehospital hemorrhage control: DoD perspective. Presentation to the FDA Workshop on Hemostatic Devices. Retrieved from http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM415142.pdf

Pusateri, A. E., Modrow, H. E., Harris, R. A., Holcomb, J. B., Hess, J. R., Mosebar, R. H., … Martinez, R. S. (2003a). Advanced hemostatic dressing development program: Animal model selection criteria and results of a study of nine hemostatic dressings in a model of severe large venous hemorrhage and hepatic injury in Swine. *Journal of Trauma-Injury, Infection, and Critical Care*, *55*(3), 518-526.

Pusateri, A. E., McCarthy, S. J., Gregory, K. W., Harris, R. A., Cardenas, L., McManus, A. T., & Goodwin Jr, C. W. (2003b). Effect of a chitosan-based hemostatic dressing on blood loss and survival in a model of severe venous hemorrhage and hepatic injury in swine. *Journal of Trauma and Acute Care Surgery*, *54*(1), 177-182.

Pusateri, A. E., Delgado, A. V., Dick Jr, E. J., Martinez, R. S., Holcomb, J. B., & Ryan, K. L. (2004). Application of a granular mineral-based hemostatic agent (QuikClot) to reduce blood loss after grade V liver injury in swine. *Journal of Trauma and Acute Care Surgery*, *57*(3), 555-562.

Pusateri, A. E., Holcomb, J. B., Kheirabadi, B. S., Alam, H. B., Wade, C. E., & Ryan, K. L. (2006). Making sense of the preclinical literature on advanced hemostatic products. *Journal of Trauma and Acute Care Surgery*, *60*(3), 674-682.

QuikClot (2015). Retrieved from http://www.quikclot.com/

Rall, J. M., Cox, J. M., Songer, A. G., Cestero, R. F., & Ross, J. D. (2013). Comparison of novel hemostatic dressings with QuikClot combat gauze in a standardized swine model of uncontrolled hemorrhage. *Journal of Trauma-Injury, Infection, and Critical Care*, *75*(2), S150-S156.

Ran, Y., Hadad, E., Daher, S., Ganor, O., Kohn, J., Yegorov, Y., … Hirschhorn, G. (2010). QuikClot Combat Gauze use for hemorrhage control in military trauma: January 2009 Israel Defense Force experience in the Gaza Strip—a preliminary report of 14 cases. *Prehospital and Disaster Medicine*, *25*(06), 584-588.

Satterly, S., Nelson, D., Zwintscher, N., Oguntoye, M., Causey, W., Theis, B., … Rush, R. M. (2013). Hemostasis in a noncompressible hemorrhage model: An end-user evaluation of hemostatic agents in a proximal arterial injury. *Journal of Surgical Education*, *70*(2), 206-211.

Sondeen, J. L., Pusateri, A. E., Coppes, V. G., Gaddy, C. C. E., & Holcomb, J. B. (2003). Comparison of 10 different hemostatic dressings in an aortic injury. *Journal of Trauma and Acute Care Surgery*, *54*(2), 280-285.

Tactical Combat Casualty Care (TCCC) Equipment Evaluation Survey. Retrieved from http://www.usaisr.amedd.army.mil/assets/pdfs/NMLLC_TCCC_Equip_Eval_Summary_120807.pdf

Tarpey, M. (2005). Tactical combat casualty care in Operation Iraqi Freedom. *U.S. Army Medical Department Journal*. April-June, pp 38-41

Trabattoni, D., Gatto, P., & Bartorelli, A. L. (2012). A new kaolin-based hemostatic bandage use after coronary diagnostic and interventional procedures. *International Journal of Cardiology*, *156*(1), 53-54.

Wedmore, I., McManus, J. G., Pusateri, A. E., & Holcomb, J. B. (2006). A special report on the chitosan-based hemostatic dressing: Experience in current combat operations. *Journal of Trauma and Acute Care Surgery*, *60*(3), 655-658.

External Hemorrhage Control: Extremity Tourniquets

The adoption of advanced extremity tourniquets to control hemorrhage in the limbs and prevent exsanguination has reduced casualty deaths on the battlefield from hemorrhage. The three extremity tourniquets that have been fielded and are currently in use are the Combat Application Tourniquet (CAT), Special Operation Forces Tactical Tourniquet (SOF-T Tourniquet), and Emergency Military Tourniquet.

- Manufacturers and Testing Partner Organizations:
  - Phil Durango, LLC
  - Tactical Medical Solutions, LLC
  - Delfi Medical
  - USAISR
  - U.S. Army Medical Materiel Agency (USAMMA)
  - U.S. Army Medical Materiel Development Activity (USAMMDA)

Key Outcomes and Impact:

- USAISR's comparative testing of extremity tourniquets identified through a 2004 Request For Information (RFI) led to the recommendation of these three effective modern tourniquets for use on the battlefield
- 95 percent solution for the overarching capability gap posed by severe extremity hemorrhage has been reached with these extremity tourniquets
- Extremity tourniquets have helped save the lives of 1,000 to 2,000 service members during OIF/OEF since their introduction in 2005 (Andersen et al., 2012)

USAISR testing of the Successful Emergency Military Tourniquet, CAT, and SOF-T (Walters, Baer, Greydanus, & Wenke, 2004)

Overview

Since the beginning of OIF/OEF, advances in TCCC have resulted in lives being saved. Hemorrhage is the leading cause of preventable deaths on the battlefield and, as these conflicts continued, tourniquet use evolved to provide highly effective control of extremity hemorrhage in the battlefield.

A key step in the evolution of tourniquet use during these conflicts was the evaluation of new devices. Faced with the urgent need for effective extremity tourniquets on the battlefield, and faced with shortcomings reported on an early One-Handed Tourniquet device tested in 2000 and 2001 and subsequently fielded for combat evaluation, the Army sought out alternate existing technological solutions (Butler, Holcomb, Giebner, McSwain, & Bagian, 2007; Kragh et al., 2013). USAISR tested seven commercial-off-the-shelf (COTS) extremity tourniquets. USAISR's study noted that an ideal battlefield tourniquet should be light, durable, easily applied in combat environments, and provide reliable occlusion of arterial blood flow (Butler, Holcomb, Giebner, McSwain, & Bagian, 2007). Their study of these COTS devices found three extremity tourniquets were highly effective on both the arm and leg in the laboratory environment. These included the CAT, SOF-T Tourniquet, and Emergency Military Tourniquet. These modern extremity tourniquets were introduced to the battlefield in 2005.

Figure 5. CAT (Composite Resources, 2013)

The CAT, developed by Phil Durango, LLC, is a small and lightweight one-handed windlass tourniquet that completely stops arterial blood flow (Figure 5). The CAT's tightening strap is

placed within a sleeve and is designed to evenly distribute the circumferential force around the limb (Walters, 2005). The SOF-T Tourniquet, developed by Tactical Medical Solutions, LLC, is also a windlass tourniquet and provides high-strength and lightweight alloy components to ensure high-reliability on the largest of limbs. In addition to the SOF-T Tourniquet, Tactical Medical Solutions also developed the slightly modified variant Special Operation Forces Tactical Wide Tourniquet (SOFT-W Tourniquet), which functioned in the same way as the SOF-T, but provided a wider compression pattern for increased comfort and additional arterial compression. Finally, the Emergency Military Tourniquet, developed by Delfi Medical, is a pneumatic tourniquet formed of an inflatable bladder that applies occlusion pressure around an arm or leg. These devices are all COTS available for purchase by both military and civilian personnel, and are the only extremity tourniquets that have received recommendation for use in TCCC (Butler, 2010).

Capability Gap Alignment

The fielding of these advanced tourniquets directly addresses portions of a number of related key capability gaps in extremity hemorrhage control that have been defined by several requirements documents (Table 6):

Table 6. Capability Gaps Addressed by Extremity Tourniquets

Requirement Sources	Capability Gaps Addressed
GDF	• **JCM 1-4 –** Inability to stop internal and external bleeding • **JCM-1-5 –** Poor ability to stop life-threatening extremity bleeding
TC3 ICD	• **Hemostatic Agents and Equipment –** Internal bleeding, external bleeding • **Capability to Control Extremity Bleeding (e.g., Tourniquets and Other Technologies) –** Stop life-threatening extremity bleeding
DHP ICD	• **TI1 –** Insufficient current first-responder (medical and non-medical) capacity and capability to initially assess, treat, and maintain severe trauma cases in the pre-hospital environment - Insufficient tools that enable both non-medical and medical first responders - The technologies do not exist to fulfill some of the needs (e.g., stabilizing the airway or truncal hemorrhage) • **MC2 –** Medical and non-medical first responders frequently misuse medical equipment (i.e., tourniquets) that is provided to control hemorrhage in the TCCC setting

With these extremity tourniquets currently fielded for self and buddy aid, it has been assessed that a 95 percent solution has been reached for the overarching capability gap posed by severe extremity hemorrhage (Pusateri, 2014). Given the technological fill achieved, ongoing efforts in this area are focused on assessing available extremity tourniquets to update inventory and ensure the best value for the DoD. As the threat landscape evolves, however, future scenarios requiring prolonged evacuation times for casualties (up to 72 hours) may necessitate next generation extremity hemorrhage control approaches beyond the effective use of these tourniquets. Such needs are expected to continue to define future capability gaps related to hemorrhage.

Impact on the Battlefield/Warfighter

During the recent OIF/OEF conflicts, the majority (54–82 percent) of casualties in far-forward hospitals suffered from extremity injuries (Kragh, Kirby, & Ficke, 2012). Over the duration of the conflicts, these modern extremity tourniquets were introduced, and combat units trained service members on control techniques for extremity hemorrhage. The tourniquets and related methods achieved wide acceptance among U.S. forces.

Since their introduction in 2005, these advanced prehospital extremity tourniquets have helped save the lives of 1,000 to 2,000 service members during OIF/OEF (Andersen et al., 2012; Dismounted Complex Blast Injury [DCBI] Task Force [TF], 2011). In one analysis, casualty deaths from extremity hemorrhage were found to have occurred at a rate of 23 per year prior to the introduction of modern tourniquets, but decreased to 3.5 per year after they were fully fielded (Eastridge et al., 2012). In addition to reducing deaths, studies of recent prehospital extremity tourniquet use have identified no corresponding threat to the treated limb and no limbs lost to ischemia (Kragh et al., 2011; DCBI TF, 2011).

> "Estimates of tourniquet use have concluded that 1,000 to 2,000 US military service members' lives have been saved by the application of tourniquets during the current conflicts."
>
> Andersen et al., 2012

Clinical Practice

Impact on Clinical Practice Guidelines

In the early 1990's, military combat medics were trained through civilian trauma courses. In regards to tourniquet use to control hemorrhage, combat medics were trained to use extremity tourniquets as a last resort to stop life-threatening bleeding (Butler et al., 2007). Over time, it was determined that prehospital trauma care is performed differently on the battlefield than in the civilian sector, and new recommendations were needed to reflect these differences and capture appropriate guidance for the military. The CoTCCC is responsible for developing guidelines and recommendations for the management of wounded military personnel in the battlefield, and, as the conflict progressed, these TCCC guidelines evolved for a change in tourniquet use from the last resort intervention to the first priority (Kotwal et al., 2013). The TCCC guidelines have advocated for aggressive, immediate use of tourniquets to control life-threatening extremity bleeding.

Following review of USAISR's testing of COTS extremity tourniquets, the TCCC Tactical Field Care guidelines recommended that the CAT be carried by all combatants, and that medics carry the Emergency Medical Tourniquet (Butler et al., 2007). In the most recent update to the TCCC Guidelines, the CoTCCC-recommended tourniquets have remained unchanged. The major update related to the use of extremity tourniquets has been the added recommendation that a second tourniquet should be applied side-by-side with the first, if the first does not control the bleeding (TCCC Guidelines, 2014).

Supporting Publications

The recommendation to implement the use of advanced extremity tourniquets in TCCC is supported by several studies, key among which is USAISR's evaluation (Walters, Wenke, Greydanus, Kauvar, & Baer, 2005). Because of the nature of the devices, the majority of the additional supporting research is based on retrospective studies.

Table 7. Supporting Publications for Extremity Tourniquets

Reference	Description
Lakstein et al., 2003	Evaluated the use of prehospital tourniquets over 4 years in the Israeli Defense Forces and found a total of 78 percent of applications to be effective
King, Filips, Blitz, & Logsetty, 2006	Evaluated tourniquets in a simulated combat environment to make recommendations to the Canadian Forces; found the EMT and latex surgical tubing to be the most effective tourniquets
Beekley et al., 2008	Analyzed the use of prehospital tourniquets in a retrospective review of 1 year during OIF; tourniquet use was associated with improved hemorrhage control and there were no early adverse outcomes related to tourniquet use
Kragh et al., 2008	Evaluated the use of prehospital tourniquets in a prospective study at a combat support hospital in Iraq; morbidity risk was low and there was a positive risk benefit ratio for tourniquet use
Kragh et al., 2009	Evaluated whether the use of emergency tourniquets saved lives among casualties admitted to a combat support hospital. Tourniquet use in the absence of shock was strongly associated with survival, as was prehospital tourniquet use
Tien, Jung, Rizoli, Acharya, & MacDonald, 2009	Evaluated the use of TCCC interventions, including extremity tourniquets, in a combat environment. Appropriate tourniquet use saved lives

Role of CCCRP-Sponsored Projects

Extremity tourniquets have been in use in varying forms since the beginning of OIF/OEF, but research into these devices became a focus when military medical experts made the development of an improved, field-expedient tourniquet able to stop arterial bleeding using one-hand a priority. In response to this recommendation, an expert panel convened as part of the 2003 Advanced Technology Applications for Combat Casualty Care Conference to determine the specifications of the desired extremity tourniquet. Using the consensus developed by the expert panel, USAISR in collaboration with USAMRMC, released an RFI to identify available COTS extremity tourniquets for testing (Walters, Baer, Greydanus, & Wenke, 2005; U.S. Army Medical Research Acquisition Activity [USAMRAA], 2004) (Table 8). USAMRMC and the ONR together provided funding for USAISR's testing of these tourniquets on normal human volunteers (Kragh et al., 2013). Of the seven tourniquets tested, the CAT, SOF-T Tourniquet, and Emergency Military Tourniquet became the CoTCCC-recommended tourniquets for battlefield use (

Table 9).

The release of an RFI in 2004 by USAMRMC and USAISR to identify available extremity tourniquets for comparative testing enabled the identification of three effective modern tourniquets for use on the battlefield.

Casualty deaths from extremity hemorrhage were found to have occurred at a rate of 23 per year prior to the introduction of modern tourniquets, but decreased to 3.5 per year after they were fully fielded (Eastridge et al., 2012).

Table 8. CCCRP-Sponsored Projects for Extremity Tourniquets

Request for Information (RFI)	Date
Sources Sought for Prototype tourniquets for hemorrhage control (W81XWH-TOURNIQUETS)	10 March 2004

Project Title (Award Number)	Organization/ Principal Investigator
Laboratory Evaluation of Battlefield Tourniquets in Human Volunteers (ONR and USAMRMC support)	USAISR

Table 9. CCCRP-Sponsored Publications for Extremity Tourniquets

Reference	Description
Walters, Wenke, Greydanus, Kauvar, & Baer, 2005	Screened the seven COTS tourniquets by trial on the leg and arm in human volunteers, assessing efficacy through elimination of distal Doppler pulse. The EMT, CAT, and SOF-T were all 100 percent effective by this measure on both appendages in the laboratory environment

References

Andersen, R. C., Shawen, S. B., Kragh, J. F., LeBrun, C. T., Ficke, J. R., Bosse, M. J., … Pagenkopf, E. L. (2012). Special topics. *Journal of the American Academy of Orthopaedic Surgeons*, *20*(suppl), S94-S98.

Beekley, A. C., Sebesta, J. A., Blackbourne, L. H., Herbert, G. S., Kauvar, D. S., Baer, D. G., … 31st Combat Support Hospital Research Group. (2008). Prehospital tourniquet use in Operation Iraqi Freedom: Effect on hemorrhage control and outcomes. *Journal of Trauma-Injury, Infection, and Critical Care*, *64*(2), S28-S37.

Butler, F. K. (2010). Tactical combat casualty care: Update 2009. *Journal of Trauma-Injury, Infection, and Critical Care*, *69*(1), S10-S13.

Butler, F., Holcomb, J., Giebner, S. D., McSwain, N. E., & Bagian, J. (2007). Tactical combat casualty care 2007: Evolving concepts and battlefield experience. *Military Medicine*, *172*(11), 1.

Composite Resources. (2013). Combat Application Tourniquet. Retrieved from http://combattourniquet.com/

Dismounted Complex Blast Injury Task Force (DCBI TF). (2011). Dismounted Complex Blast Injury: Report of the Army Dismounted Complex Blast Injury Task Force. Retrieved from http://armymedicine.mil/Documents/DCBI-Task-Force-Report-Redacted-Final.pdf

Eastridge, B. J., Mabry, R. L., Seguin, P., Cantrell, J., Tops, T., Uribe, P., … Blackbourne, L. H. (2012). Death on the battlefield (2001-2011): Implications for the future of combat casualty care. *Journal Trauma Acute Care Surgery*, *73*(6 Suppl 5), S431-S437.

King, R. B., Filips, D., Blitz, S., & Logsetty, S. (2006). Evaluation of possible tourniquet systems for use in the Canadian Forces. *Journal of Trauma*, *60*(5), 1061-1071.

Kotwal, R. S., Butler, F. K., Gross, K. R., Kheirabadi, B. S., Baer, D. G., Dubick, M. A., … Bailey, J. A. (2013). Management of junctional hemorrhage in tactical combat casualty care: TCCC Guidelines-Proposed Change 13-03. *Special Operations Medical Journal*, *13*(4): 85-93.

Kragh Jr, J. F., Kirby, J. M., & Ficke, J. R. (2012). Extremity Injury. In Savitsky, E., & Eastridge, B. (Eds.), *Combat Casualty Care: Lessons Learned from OEF and OIF* (397-469). Fort Detrick, MD: Borden Institute.

Kragh Jr, J. F., O'Neill, M. L., Walters, T. J., Dubick, M. A., Baer, D. G., Wade, C. E., … Blackbourne, L. H. (2011). The military emergency tourniquet program's lessons learned with devices and designs. *Military Medicine*, *176*(10), 1144-1152.

Kragh Jr, J. F., Walters, T. J., Baer, D. G., Fox, C. J., Wade, C. E., Salinas, J., & Holcomb, J. B. (2008). Practical use of emergency tourniquets to stop bleeding in major limb trauma. *Journal of Trauma-Injury, Infection, and Critical Care*, *64*(2), S38-S50.

Kragh Jr, J. F., Walters, T. J., Baer, D. G., Fox, C. J., Wade, C. E., Salinas, J., & Holcomb, J. B. (2009). Survival with emergency tourniquet use to stop bleeding in major limb trauma. *Annals of Surgery*, *249*(1), 1-7.

Kragh Jr, J. F., Walters, T. J., Westmoreland, T., Miller, R. M., Mabry, R. L., Kotwal, R. S., … Butler, F. K. (2013). Tragedy into drama: An American history of tourniquet use in the current war. *Journal of Special Operations Medicine*, *13*(3), 5-25.

Lakstein, D., Blumenfeld, A., Sokolov, T., Lin, G., Bssorai, R., Lynn, M., & Ben-Abraham, R. (2003). Tourniquets for hemorrhage control on the battlefield: A 4-year accumulated experience. *Journal of Trauma-Injury, Infection, and Critical Care*, *54*(5), S221-S225.

Pusateri, A. E. (2014, November 14). Department of Defense Hemorrhage and Resuscitation Research and Development Program. Update Briefing for Health Affairs.

Tactical Combat Casualty Care (TCCC) Guidelines (2014, October). Retrieved from http://usaisr.amedd.army.mil/assets/pdfs/TCCC%20Guidelines%20141028.pdf

Tien, H. C., Jung, V., Rizoli, S. B., Acharya, S. V., & MacDonald, J. C. (2008). An evaluation of tactical combat casualty care interventions in a combat environment. *Journal of the American College of Surgeons*, *207*(2), 174-178.

U.S. Army Medical Research Acquisition Activity (USAMRAA). (2004, March 10). 65--Sources Sought for Prototype tourniquets for hemorrhage control (W81XWH-TOURNIQUETS). Retrieved from https://www.fbo.gov/index?s=opportunity&mode=form&id=d0b7a24e1105eee4bf959ac69027bd1c&tab=core&_cview=0

Walters, T. J., Baer, D. G., Greydanus, D., & Wenke, J. C. (2004). Laboratory evaluation of battlefield tourniquets in human volunteers. Retrieved from http://blog.tacmedsolutions.com/wp-content/uploads/2007/09/cccict12004tk.pdf

Walters, T. J., Wenke, J. C., Greydanus, D. J., Kauvar, D. S., & Baer, D. G. (2005). Laboratory evaluation of battlefield tourniquets in human volunteers (No. USAISR-TR-2005-05). Army Institute of Surgical Research. Fort Sam Houston, TX.

Junctional Hemorrhage Control: Junctional Tourniquets and the Combat Ready Clamp

The Combat Ready Clamp (CRoC) is an FDA-cleared junctional tourniquet that is currently in limited fielding. Through the DoD-supported process of the CRoC's advanced development and testing, the development of other FDA-approved junctional tourniquets by additional medical device manufacturers has been spurred, independent of DoD funds. The resulting collection of solutions is now being evaluated to support a broader acquisition strategy and full fielding of the best device(s).

- Manufacturer and Testing Partner Organizations:
  - Combat Medical Systems
  - Wake Forrest University
  - USAISR
  - Naval Medical Research Unit - San Antonio (NAMRU-SA)

Key Outcomes and Impact:

- FDA-cleared CRoC was identified for testing and initial limited fielding after a 2009 RFI by the CCCRP and USAISR
- Case reports and anecdotal evidence from medics indicate successful performance of the CRoC (Kotawal et al., 2013; Tovmassian, Kragh, Dubick, Baer, & Blackbourne, 2012)
- Junctional Emergency Treatment Tool (JETT), SAM Junctional Tourniquet (SAM), and Abdominal Aortic and Junctional Tourniquet (AAJT) have subsequently achieved FDA clearance
- Development and testing of these devices closes the previously completely open gap in technology to control junctional hemorrhage quickly in the field (Pusateri, 2014)
- TCCC Guidelines have been updated to include the immediate use of CRoC, SAM, or JETT when appropriate

The JETT, CRoC, SAM, and AAJT (top to bottom) are in Early Use by the DoD (Harcke et al., 2014)

Overview

Junctional hemorrhage is bleeding at the interface of the trunk and its appendages or the neck. Damage to areas such as the axilla, groin, neck, and deep pelvic vessels is difficult to manage because of reduced accessibility to apply compression and the presence of major blood vessels. Because of these challenges, junctional bleeding that cannot be controlled before reaching surgical capabilities has remained a cause of potentially preventable death on the battlefield (Eastridge et al., 2012). One approach to manage junctional hemorrhage has been the use of focal pressure tourniquet devices that stop blood flow by compressing damaged vessels against a bony structure. By this approach, blood flow proximal to the injury is occluded, which slows loss from the wound.

The first such device to emerge, leading the pack in the development of junctional hemorrhage tourniquets, has been the CRoC (Figure 6). The CRoC is placed directly over or proximal to the injury and uses a screw mechanism to compress blood vessels to stop blood flow. The CRoC is a product of Combat Medical Systems, and the advanced development and testing of the CRoC for military medical use has been facilitated through partnership with the CCCRP and USAISR.

The CRoC received initial FDA clearance for military use in the case of inguinal and axillary bleeding in 2010, and since has received clearance for expanded indications including unmanageable amputations and pelvic wounds (510(k) numbers K102025 and K130482, 2010 and 2013). The lessons learned from its features and functions during evaluation, and its attainment of FDA clearance for multiple indications, have paved the way for additional junctional hemorrhage control technologies to enter the market from other manufacturers. The CRoC has served as a predicate device for the regulatory clearance of others; in this way, DoD-driven advancement of the CRoC has moved the entire field forward and had even greater returns for the investment in terms of encouraging other new technologies. In addition to the CRoC, the AAJT (Compression Works LLC), JETT (North American Rescue), and SAM (SAM Medical Products) have all subsequently achieved FDA clearance to control junctional bleeding, offering new options to consider hemorrhage management on the battlefield.

Figure 6. The CRoC Junctional Tourniquet (Combat Medical Systems, 2013)

Capability Gap Alignment

Before 2010, there were no technologies available to control junctional hemorrhage quickly in the field (Pusateri, 2014). The development of these devices, and their testing led by the USAISR and NAMRU-SA, has resulted in products that close technology gaps for junctional hemorrhage control.

This work, in conjunction with continued efforts to develop appropriate technologies to facilitate training for the use of these devices, directly addresses portions of several key capability gaps in hemorrhage control that have been defined by multiple requirements sources (Table 10).

Table 10. Capability Gaps Addressed by Junctional Tourniquets

Requirement Source	Capability Gaps Addressed
GDF	• **JCM-1-4** – Inability to stop internal and external bleeding • **JCM-1-5** – Poor ability to stop life-threatening extremity bleeding
TC3 ICD	• **Hemostatic Agents and Equipment** – Internal bleeding, external bleeding • **Capability to Control Extremity Bleeding (e.g., Tourniquets and Other Technologies)** – Stop life-threatening extremity bleeding
DHP ICD	• **TI1** – Insufficient current first-responder (medical and non-medical) capacity and capability to initially assess, treat, and maintain severe trauma cases in the pre-hospital environment - Insufficient initial and ongoing training for first responders in the pre-hospital environment overall - Insufficient tools that enable both non-medical and medical first responders - The technologies do not exist to fulfill some of the needs (e.g., stabilizing the airway or truncal hemorrhage) • **MC2** – Medical and non-medical first responders frequently misuse medical equipment (i.e., tourniquets) that is provided to control hemorrhage in the TCCC setting • **MBC2** – Lack of ways and means to manage circulations and control junctional and truncal hemorrhaging in the pre-hospital environment

In addition to these requirements sources, The Army Surgeon General's DCBI TF has further identified priority research issues for Hemorrhage Control and Resuscitation, one of which is to conduct studies that compare the safety and efficacy of current and future commercially available tourniquets (DCBI TF, 2011). Now that the DoD has several technological solutions available for the management of junctional hemorrhage, its efforts are shifting toward selecting the optimal device for full implementation through comparative evaluations. This will be followed by developing training and expanding acquisition and fielding beyond the current limited availability of junctional devices to U.S. Special Operations Command (USSOCOM) and for field user evaluation.

Impact on the Battlefield/Warfighter

As practices changed over the course of recent conflicts, advanced tourniquets for extremity hemorrhage were brought into widespread use in the U.S. military, and subsequently junctional hemorrhage took the lead to become the most common cause of death from compressible hemorrhage (Kragh et al., 2011). In a retrospective analysis of U.S. service member fatalities from 2001 to 2011, over 90 percent of the potentially survivable deaths that occurred prior to Role of Care 2 treatment facilities were caused by uncontrolled hemorrhage (Eastridge et al., 2012). Within this cohort, junctional hemorrhage accounted for over 17 percent of potentially survivable hemorrhage cases. Addressing this capability gap to enable control of junctional hemorrhage in prehospital settings promises significant improvements in survivability rates of injured U.S. service members. Additionally, as the mission evolves, U.S. forces are faced with changing combat scenarios and injury patterns. These have included an increase in DCBI from improvised explosive devices (IED); the life-threatening bleeding in the groin or very proximal lower extremities that can result from these blast injuries continues to drive the need for junctional tourniquets and to offer a scenario for which these devices can have significant impact (Kragh et al., 2011; DCBI TF, 2011).

Given the recency of their regulatory clearances and their limited use thus far through deployment to Special Operations Forces and U.S. Army Ranger units for combat evaluation, direct measure of the impact of junctional hemorrhage technologies on the battlefield remains to be quantified (Steinbaugh, 2011; Defense Health Board [DHB], 2011). However, current initial case reports and anecdotal reports have begun to indicate successful performance of the CRoC (Kotawal et al., 2013; Tovmassian, Kragh, Dubick, Baer, & Blackbourne, 2012).

Clinical Practice

Impact on Clinical Practice Guidelines

As products to manage severe bleeding from traumatic injuries in a prehospital environment, the impact of junctional tourniquets on clinical practice occurs primarily in far forward TCCC and en route care during tactical evacuation. Following the initial approval of the CRoC in 2010, the CoTCCC, a working group of the DHB Trauma and Injury Subcommittee, reviewed and approved the proposed addition of the recommended use of the CRoC for hemorrhage control to TCCC guidelines (DHB, 2011). This addition amended TCCC Tactical Field Care Guidelines regarding bleeding to recommend that "if a lower extremity wound is not amenable to tourniquet application and cannot be controlled by hemostatics/dressings, consider immediate application of

mechanical direct pressure including CoTCCC-recommended devices such as the Combat Ready Clamp (CRoC)."

> "If the bleeding site is appropriate for use of a junctional tourniquet, immediately apply a CoTCCC-recommended junctional tourniquet. Do not delay in the application of the junctional tourniquet once it is ready for use. Apply hemostatic dressings with direct pressure if a junctional tourniquet is not available or while the junctional tourniquet is being readied for use."
>
> TCCC Guidelines (2014)

As other junctional tourniquets have received FDA clearance and been further studied, the CoTCCC has since recommended three products (CRoC, JETT, and SAM) (Kotawal et al., 2013). With this recommendation, the TCCC Guidelines were updated to include the immediate application of a CoTCCC-recommended junctional tourniquet when appropriate (no longer specifying only the CRoC). These guidelines now recommend the following in both the basic management plan for tactical field care and the basic management plan for tactical evacuation care: "If the bleeding site is appropriate for use of a junctional tourniquet, immediately apply a CoTCCC-recommended junctional tourniquet. Do not delay in the application of the junctional tourniquet once it is ready for use. Apply hemostatic dressings with direct pressure if a junctional tourniquet is not available or while the junctional tourniquet is being readied for use" (TCCC Guidelines, 2014). These recommendations have been based on a total body of evidence graded as Class C (i.e., based on expert opinion, case studies, or standards of care) according to the American College of Cardiology and American Heart Association guidelines (Kotawal et al., 2013). The CoTCCC further recommends that performance improvement data should be gathered on junctional tourniquet use in prehospital environments to assess outcomes and that military personnel conducting research and training should gather feedback from front line military medical personnel on experiences with the devices for continual reevaluation (Kotawal et al., 2013).

The introduction of these junctional tourniquet devices has not yet resulted in widespread, codified change to civilian clinical practice in the U.S., although the manufacturers of the CRoC do state the device has been successful in multiple Life Flight trauma transport cases in the U.S. (Combat Medical Systems, 2013). The use of tourniquets in the civilian emergency medical service (EMS) in general is not widespread (Bulger et al., 2014). Recently the American College of Surgeons Committee on Trauma EMS Committee undertook the development of evidence-based guidelines for the use of tourniquets and hemostatic dressing in the U.S. civilian prehospital setting. In the resulting study, junctional hemorrhage devices were determined to be an important area for further study, but the committee did not yet find sufficient evidence to make a recommendation on their use in civilian trauma contexts (Bulger et al., 2014).

Supporting Publications

The recommendation to adopt junctional tourniquet products and implement their use in TCCC has been supported by several key studies. Further publications on experience with all four FDA-cleared devices for junctional hemorrhage control have continued to emerge since the time of that recommendation, as well. Because of the nature of the devices, available supporting research is not based on prospective trials, but rather mainly on early case reports of product use, cadaver and manikin study data, and data from studies of arterial compression to eliminate blood flow to distal extremities in normal volunteers.

Table 11. Supporting Publications for Junctional Tourniquets

Reference	Description
Case Reports	
Tovmassian, Kragh, Dubick, Baer, & Blackbourne, 2012	Described use of the CRoC on an individual with lower extremity traumatic amputation during helicopter evacuation in Afghanistan
Anonymous, 2013	Described use of the AAJT to treat an individual with bilateral amputation of the lower limbs in Afghanistan
Croushorn, Thomas, & McCord, 2013	Described use of the AAJT to control axillary hemorrhage in a civilian patient
Klotz et al., 2014	Described use of SAM for a battlefield casualty with inguinal junctional hemorrhage
Cadaver and Manikin Studies	
Kragh et al., 2013a	A manikin model of junctional bleeding from the groin was used to assess all four FDA-cleared junctional hemorrhage control devices; all interventions were successful with short times to stop bleeding and low volumes of blood lost
Kragh et al., 2013b	Examined use of the CRoC in a perfused cadaver model of inguinal hemorrhage; when placed on the common iliac artery, the CRoC stopped all ipsilateral distal bleeding
Mann-Salinas, Kragh, Dubick, Baer, & Blackbourne, 2013	Used the CRoC to control simulated bleeding in a manikin model, successfully achieving control 100 percent of the time
Gates, Baer, & Holcomb, 2014	Compared the ability of the CRoC and JETT to control bilateral lower extremity junctional hemorrhage in a perfused cadaver model. Both devices were successful, however, the JETT was faster for bilateral application than the use of two CRoC devices
Johnson, Sims, Hamilton, & Kragh, 2014	Examined the SAM in a perfused cadaver model of inguinal or axillary hemorrhage, providing safety and effectiveness data that supported regulatory clearance of the SAM
Normal Human Controls	
Taylor, Coleman, & Parker, 2013	Blood flow in the common femoral artery was occluded by application of the AAJT in volunteers in a United Kingdom Ministry of Defense study
Kragh et al., 2014a	Assessed use of all four cleared tourniquets on volunteers to examine relative performance characteristics; the CRoC and SAM were the best-performing in this model accounting for effectiveness, tolerability, and speed of use
Kragh et al., 2014b	U.S. military medics tested performance and features of the four cleared junctional tourniquets, also acting as simulated casualties for one another; the CRoC and SAM had the highest effectiveness rates and were preferred by medics
Lyon, Johnson, & Gordon, 2014	The AAJT was used to successfully interrupt blood flow to the proximal femoral artery and the axillary artery in 13 participants, as measured by spectral Doppler

Information from many of these reports, as well as other sources including expert input, informed the proposal from Kotwal et al. (2013) to change TCCC Guidelines to recommended additional junctional devices beyond the CRoC, and to specify the immediate application of these devices in appropriate tactical care scenarios. All four devices are currently being used by the DoD; use is in early stages (Harcke et al., 2014). Ongoing studies of the relative efficacy of the currently approved devices will continue to build the body of knowledge to support and refine clinical practice recommendations.

Role of CCCRP-Sponsored Projects

In 2009, after the CoTCCC made research into junctional tourniquet devices a top priority, the CCCRP and USAISR sought candidate devices for evaluation, publishing RFIs for devices that could stop bleeding at compressible sites where standard tourniquets were ineffective. The characteristics specified in these RFIs, and the resulting conversations with developers, shaped the field by providing initial guidance on the DoD's needs (USAMRAA, 2009, 2012). The CRoC was initially selected for evaluation from a handful of junctional tourniquet prototypes submitted in response to the RFIs for candidate devices, and at the time was the only FDA-cleared option (Kragh et al., 2011; DHB, 2011). This led to the CRoC's early testing and fielding among U.S. Special Operations Forces. With multiple junctional tourniquets since gaining clearance, lead junctional hemostatic device efforts have now proceeded to the test and evaluation phase, with activities being conducted in support of the selection of the best device(s) for full fielding and to develop updated guidance and training for their implementation. Testing is being conducted by USAISR and NAMRU-SA, with support from DHP funds. Additionally, DHP funds have supported related activities to enable the training that will be necessary for widespread junctional tourniquet fielding, including a Small Business Innovation Research award to Charles River Analytics for the development of Tourniquet Master Training, a sensor-based system for use with manikins to provide training and assessment (Tourniquet Master Training, 2014) (Table 12)

- Evaluation of the CRoC under the Hemorrhage and Reusictation portfolio has advanced junctional hemorrhage control, with lessons learned from its features and its attainment of FDA clearance paving the way for multiple new devices
- The capability gap posed by junctional hemorrhage has gone from wide open to having four FDA-cleared devices to enable technological fill of the gap
- Widespread fielding of junctional tourniquets will reduce death on the battlefield from junctional hemorrhage, which previously accounted for 4 percent of deaths

Table 12. CCCRP-Sponsored RFIs and Subsequent DHP-Funded Projects for Junctional Tourniquets

RFIs		Date
REQUEST FOR INFORMATION: Prototype Truncal Tourniquets for the Department of Defense Research On Combat Casualty Care (W81XWH-RFI-003)		3 March 2009
Junctional Tourniquets for the Department of Defense Research On Combat Casualty Care (W81XWH-RFI)		13 April 2012
Project Title (Award Number)	**Organization/ Principal Investigator**	**Funding**
Operational System Management and Postmarket Surveillance of Hemorrhage Control Devices used in Medical Care of U.S. Service Members (DHA; Proposal 201105)	USAISR	
Post-FDA Approval Evaluation of the Abdominal Aortic Junctional Tourniquet (Unknown)	NAMRU-SA	
Tourniquet Master Training (TMT) System for Junctional and Inguinal Hemorrhage Control Devices (W81XWH-13-C-0021)	Peter Weyhrauch (Charles River Analytics, Inc.)	$149,957 (2012) $999,854 (2013)

Key publications resulting from these efforts to date have included the two articles recently published by Kragh and colleagues conducting comparative evaluations of the FDA-cleared junctional tourniquets (Table 13). In one of these studies, normal adult volunteers were recruited in a clinical trial to investigate the performance of the junctional tourniquets to generate data that would aid in the selection of devices for trauma care (NCT01965561; USAISR, 2013). In this population, the CRoC, SAM, and JETT were found to have comparable efficacy for occluding lower extremity blood flow when used at the inguinal junction (Kragh et al., 2014a). All tourniquets could be applied safely and successfully at least once out of several repeated applications in this trial. The CRoC was assessed to be the most tolerable, and the CRoC and SAM were fastest to apply, resulting in the conclusion that the CRoC and SAM were the overall best performers. Similarly, in a study of nine combat-experienced medics who examined the use of all four devices on one another, both the SAM and the CRoC had the highest effectiveness percentages, fastest time to effectiveness, and were preferred by the medics (Kragh et al. 2014b). The strength of these studies was their direct comparison of the four currently FDA-cleared tourniquets for junctional hemorrhage management, filling the specific knowledge gap for junctional tourniquets on their differential performance in the hands of medics. This will contribute to the determination of which devices to provide to medics in the future. As devices are downselected and put into broad use, appropriate training will also be critical to their successful implementation. Work recently published by Weyhrauch et al. (2014) begins to tackle this through the development of advanced manikin technology for tourniquet training.

Table 13. CCCRP-Sponsored Publications for Evaluation of Junctional Tourniquets and Development of Training Technologies

Reference	Description
Mann-Salinas, Kragh, Dubick, Baer, & Blackbourne, 2013	Used the CRoC to control simulated bleeding in a manikin model, successfully achieving control 100 percent of the time
Kragh, Johnson, Henkel, & Dubick, 2013	Demonstrated the technique of CRoC application to control axillary bleeding in a cadaver model, and reported efficacy data used in the CRoC's regulatory application
Kragh et al., 2014a	Assessed use of all four cleared tourniquets on volunteers to examine relative performance characteristics; the CRoC and SAM were the best-performing in this model accounting for effectiveness, tolerability, and speed of use
Kragh et al., 2014b	U.S. military medics tested performance and features of the four cleared junctional tourniquets, also acting as simulated casualties for one another; the CRoC and SAM had the highest effectiveness rates and were preferred by medics
Weyhrauch et al., 2014	To address the training needs associated with new hemorrhage control technologies, a sensor-enabled manikin was design that captured data from the different phases of tourniquet application to enable performance evaluation

References

Anonymous. (2013). Abdominal aortic tourniquet use in Afghanistan. *Special Operations Medical Journal*, *13*, 1-2.

Bulger, E. M., Snyder, D., Schoelles, K., Gotschall, C., Dawson, D., Lang, E. … McSwain, N. (2014). An evidence-based prehospital guideline for external hemorrhage control: American College of Surgeons Committee on Trauma. *Prehospital Emergency Care*, *18*, 163-173.

Combat Medical Systems. (2013, May). Combat Ready Clamp (CRoC) makes tactical medicine history. Retrieved from https://combatmedicalsystems.wordpress.com/2013/05/06/combat-ready-clamp-croctm-makes-tactical-medicine-history/

Combat Ready Clamp 510(k) Summary No. K102025. (2010, August 11). Retrieved from www.accessdata.fda.gov/cdrh_docs/pdf10/K102025.pdf

Combat Ready Clamp 510(k) Summary No. K130482 (2013, April 29). Retrieved from http://www.accessdata.fda.gov/cdrh_docs/pdf13/K130482.pdf

Croushorn, J., Thomas, G., & McCord, S. R. (2013). Abdominal aortic tourniquet controls junctional hemorrhage from a gunshot wound of the axilla. *Journal of Special Operations Medicine*, *13*(3), 1-4.

Defense Health Board (DHB). (2011, September). Combat Ready Clamp addition to the Tactical Combat Casualty Care Guidelines 2011-07. Memo to Assistant Secretary of Defense (Health Affairs). Retrieved from http://www.health.mil/~/media/MHS/Report%20Files/201107.ashx

Dismounted Complex Blast Injury Task Force (DCBI TF). (2011). Dismounted complex blast injury: Report of the Army Dismounted Complex Blast Injury Task Force. Retrieved from http://armymedicine.mil/Documents/DCBI-Task-Force-Report-Redacted-Final.pdf

Eastridge, B. J., Mabry, R. L., Seguin, P., Cantrell, J., Tops, T., Uribe, P., … Blackbourne, L. H. (2012). Death on the battlefield (2001-2011): Implications for the future of combat casualty care. *Journal Trauma Acute Care Surgery*, *73*(6 Suppl 5), S431-S437.

Gates, K. S., Baer, L., & Holcomb, J. B. (2014). Prehospital emergency care: Evaluation of the junctional emergency tourniquet tool with a perfused cadaver model. *Journal of Special Operations Medicine*, *14*(1), 40-44.

Harcke, H. T., Mazuchowski, E., Brunstetter, T., Diaz, G., Burrows, S., Hart, S., & Kragh, J. F. (2014). Feedback to the field (FT2F) #16: Junctional Emergency Treatment Tool (JETT): Observations. Joint Medical Testing & Evaluation Resources. Retrieved from https://www.dmsb.mil/refDocs/F2TF/F2TF_16_Junctional_Emergency_Treatment_Tool.pdf

Johnson, J. E., Sims, R. K., Hamilton, D. J., & Kragh, J. F. (2014). Safety and effectiveness evidence of SAM junctional tourniquet to control inguinal hemorrhage in a perfused cadaver model. *Journal of Special Operations Medicine, 14*(2), 21-25.

Klotz, J. K., Leo, M., Anderson, B. L., Nkodo, A. A., Garcia, G., Wichern, A. M. … Kragh, J. F. (2014). First case report of SAM Junctional Tourniquet use in Afghanistan to control inguinal hemorrhage on the battlefield. *Journal of Special Operations Medicine*, 14(2), 1-5.

Kotwal, R. S., Butler, F. K., Gross, K. R., Kheirabadi, B. S., Baer, D. G., Dubick, M. A., … Bailey, J. A. (2013). Management of junctional hemorrhage in Tactical Combat Casualty Care: TCCC Guidelines-Proposed Change 13-03. *Journal of Special Operations Medicine, 13*(4): 85-93.

Kragh, J. F., Johnson, J. E., Henkel, C. K., & Dubick, M. A. (2013). Technique of axillary use of a Combat Ready Clamp to stop junctional bleeding. *American Journal of Emergency Medicine, 31*(8), 1274-1276.

Kragh, J. F., Kotwal, R. S., Cap, A. P., Aden, J. K., Walters, T. J., Kheirabadi, B. S., Gerhardt, R. T., … Cancio L. C. (2014a). Performance of junctional tourniquets in normal human volunteers. *Prehospital Emergency Care*. Advance online publication. doi:10.3109/10903127.2014.980478.

Kragh, J.F., Mann-Salinas, E. A., Kotwal, R. S., Gross, K. R., Gerhardt, R. T., Kheirabadi, B., … Dubick, M. A. (2013a). Laboratory assessment of out-of-hospital interventions to control junctional bleeding from the groin in a manikin model. *American Journal of Emergency Medicine*, 31(8): 1276-1278.

Kragh, J., Murphy, C., Steinbaugh J., Dubick, M., Baer, D., Johnson, J., Henkelm C., & Blackbourne, L. (2013b). Prehospital emergency inguinal clamp controls hemorrhage in cadaver model. *Military Medicine, 7*, 799-805.

Kragh Jr, J. F., O'Neill, M. L., Walters, T. J., Dubick, M. A., Baer, D. G., Wade, C. E., … Blackbourne, L. H. (2011). The military emergency tourniquet program's lessons learned with devices and designs. *Military Medicine, 176*(10), 1144-1152.

Kragh, J. F., Parsons, D. L., Kotwal, R. S., Kheirabadi, B. S., Aden, J. K., Gerhardt, R. T., Baer, D. G., & Dubick, M. A. (2014b). Testing of Junctional Tourniquets by Military Medics to Control Simulated Groin Hemorrhage. *Journal of Special Operations Medicine, 14*(3), 58-63.

Lyon, M., Johnson, D., & Gordon, R. (2014). Use of a novel Abdominal Aortic and Junctional Tourniquet to reduce or eliminate flow in the brachial and popliteal arteries in human subjects. *Prehospital Emergency Care*. Advance online publication. doi:10.3109/10903127.2014.980479

Mann-Salinas, E., Kragh, J., Dubick, M., Baer, D., & Blackbourne, L. (2013). Assessment of users to control simulated junctional hemorrhage with the combat ready clamp CRoC. *International Journal of Burns and Trauma*, 3: 49-54.

Pusateri, A. E. (2014, November 14). Department of Defense Hemorrhage and Resuscitation Research and Development Program. Update Briefing for Health Affairs.

Steinbaugh, J. (2011). Presentation: Special Operations Medical Research and Development, to the Committee on Tactical Combat Casualty Care.

Tactical Combat Casualty Care (TCCC) Guidelines (2014, October). Retrieved from http://usaisr.amedd.army.mil/assets/pdfs/TCCC%20Guidelines%20141028.pdf

Taylor, D. M., Coleman, M., & Parker, P. J. (2013). The Evaluation of an Abdominal Aortic Tourniquet for the Control of Pelvic and Lower Limb Hemorrhage. *Military Medicine, 178*(11), 1196-1201.

Tourniquet Master Training (TMT) System for Junctional and Inguinal Hemorrhage Control Devices. (2014). Small Business Innovation Research Program. Retrieved from http://www.sbir.gov/sbirsearch/detail/696533

Tovmassian, R., Kragh, J., Dubick, M., Baer, D., & Blackbourne, L. (2012). Combat ready clamp medic technique. *Journal of Special Operations Medicine, 12*: 72-78.

U.S. Army Institute of Surigcal Research (USAISR). (2013, November). Performance of junctional tourniquets in normal human volunteers. Retrieved from https://clinicaltrials.gov/ct2/show/NCT01965561 (Identification No. NCT01965561)

U.S. Army Medical Research Acquisition Activity (USAMRAA). (2009, March 03). REQUEST FOR INFORMATION: Prototype Truncal Tourniquets for the Department of Defense Research On Combat Casualty Care (W81XWH-RFI-003). Retrieved from https://www.fbo.gov/spg/USA/USAMRAA/DAMD17/W81XWH-RFI-003/listing.html

U.S. Army Medical Research Acquisition Activity (USAMRAA). (2012, April 13). A-- Junctional Tourniquets for the Department of Defense Research on Combat Casualty Care (W81XWH-RFI). Retrieved from https://www.fbo.gov/index?s=opportunity&mode=form&id=28ffe6a7b574f823eafb0f13788bef1a&tab=core&_cview=0

Weyhrauch, P. W., Niehaus, J., Metzger, M., Laufer, S., Kwan, C., & Pugh, C. (2014). Tourniquet master training for junctional and inguinal hemorrhage control (TMT). *Studies in Health Technology and Informatics, 196*, 457-461.

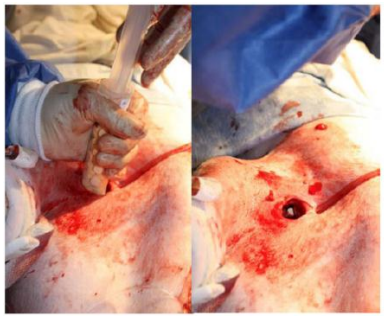
Controlling Intracavitary Noncompressible Bleeding: The XStat

The XStat is a hemostatic device that is rapidly deployable and provides swift hemorrhage control for deep wounds in patients with gunshot or shrapnel injuries. The XStat is cleared by FDA for use in the battlefield, and clearance for broader indications in an expanded population is currently being sought.

- Developmental Partner Organization:
  - RevMedX, Inc.
  - XStat development by RevMedX was funded by USSOCOM and the CCCRP

Key Outcomes and Impact:

- In swine model studies, the XStat use enables a 90 percent survival rate
- It is estimated that the XStat may address approximately 16 percent of potentially survivable cases of mortality on the battlefield due to noncompressible bleeding (Pusateri, 2014)
- The XStat is in initial, limited fielding by USSOCOM



XStat Sponges Applied a Swine Model of Noncompressible Hemorrhage Improved Survival Over the Use of Combat Gauze (Mueller et al., 2012)

Overview

Noncompressible hemorrhage is the leading cause of preventable death in the battlefield and 67 percent of battlefield hemorrhagic injuries are noncompressible (Mueller et al., 2012). To address the challenge of noncompressible hemorrhage, the development of the XStat by RevMedX, Inc., was funded initially by USSOCOM, and the CCCRP provided additional funding to complete development of the product for use in the battlefield (RevMedX, 2014).

The XStat is a hemostatic device used for immediate management of gunshot and shrapnel wounds in the groin or axilla experienced in the battlefield. Each XStat device is comprised of approximately 92 chitosan-coated sponges marked with an x-ray detectable marker (RevMedX, 2015). The sponges are enclosed within a syringe-like applicator and, once injected into the wound, the XStat sponges expand lengthwise and fill the wound capacity within 20 seconds of contact with blood (Figure 7). The XStat is intended for use in the groin or axilla areas, but not the thorax, pleural cavity, mediastinum, abdomen, retroperitoneal space, sacral space above the inguinal ligament, or tissues above the clavicle (RevMedX, 2015). Once injected, the XStat sponges can remain in the wound for up to four hours until surgery is performed.

Figure 7. Image of XStat being used to Stop Hemorrhage, and Before/After Expansion of Pellets (RevMedX, 2015)

As illustrated in Figure 8, RevMedX began the regulatory process for FDA clearance in December 2011, and the XStat received FDA *de novo* 510(k) clearance (K130218) as a Class II device in April 2014 for wounds obtained in battlefield only. FDA has raised concerns in regards to the chitosan purity in the XStat; thus, RevMedX is currently developing a non-chitosan version for broader use (RevMedX, 2015).

Figure 8. Regulatory Timeline for XStat

Capability Gap Alignment

XStat addresses numerous capability gaps with respect to hemorrhage control. The GDF, TC3 ICD, and DHP ICD capability gaps all highlight the inability to stop internal, noncompressible bleeding.

Table 14. Capability Gaps Addressed by the XStat

Requirement Source	Capability Gaps Addressed
GDF	• **JCM 1-4 –** Inability to stop internal bleeding and external bleeding (non-extremity) • **JCM 1-5 –** Poor ability to stop life-threatening extremity bleeding
TC3 ICD	• **Hemostatic Agents and Equipment** – Internal bleeding, external bleeding • **Capability to Control Extremity Bleeding (e.g., Tourniquets and Other Technologies)** – Stop life-threatening extremity bleeding

Requirement Source	Capability Gaps Addressed
DHP ICD	• **TI1 –** Insufficient current first-responder (medical and non-medical) capacity and capability to initially assess, treat, and maintain severe trauma cases in the pre-hospital environment - Insufficient tools that enable both non-medical and medical first responders - The technologies do not exist to fulfill some of the needs (e.g., stabilizing the airway or truncal hemorrhage) • **TI3 –** No common TCCC TTP for first responders and medical practitioners across Services and across the continuum of care • **TI8 –** Limited ability to properly diagnose and treat seen and unseen non-compressible hemorrhage in the pre-hospital environment • **MBC1 –** Lack of non-surgical means to treat non-compressible truncal/torso hemorrhage in the pre-hospital environment • **MBC2 –** Lack of ways and means to manage circulations and control junctional and truncal hemorrhaging in the pre-hospital environment

Impact on the Battlefield/Warfighter

Junctional and noncompressible bleeding that cannot be treated with previously available hemostatic agents account for 79 percent of deaths from hemorrhage on the battlefield. In these cases, surgical intervention at the POI is very difficult, but may be the only option for the medic (Pusateri, 2014). With the introduction of XStat to the battlefield, bleeding can be slowed down or stopped until surgical intervention is available at the next role of care. Given that the XStat has currently only been FDA cleared for battlefield use and not for civilian use, its initial fielding has been limited to the USSOCOM (300 devices) (Pusateri, 2014). Thus, its full impact on the battlefield cannot yet be empirically determined. However, in studies using a swine model of severe hemorrhage, proper use of the XStat results in a 90 percent survival rate. It is estimated that the use of XStat may address approximately 16 percent of the potentially survivable cases of mortality on the battlefield occurring because of noncompressible bleeding (Pusateri, 2014).

Clinical Practice

Impact on Clinical Practice Guidelines

In the recent OIF/OEF conflicts, uncontrolled hemorrhage has accounted for more than 80 percent of deaths on the battlefield, and a majority of these occurs within the first hour of injury (Mueller et al., 2012). The CoTCCC is responsible for developing recommendations for the management of wounded military personnel in the battlefield. These recommendations, known as the TCCC Tactical Field Care Guidelines, are constantly updated as new products, practices, and knowledge emerge (Butler, Holcomb, Giebner, McSwain, & Bagian, 2007). Through the years, there have been updates to the TCCC Guidelines to address hemorrhage on the battlefield; however, the current version of the TCCC Guidelines only includes specific guidelines for extremity and compressible hemorrhage, but does not include guidelines for noncompressible hemorrhage (TCCC Guidelines, 2014). As activities continue toward achieving further FDA clearance of the XStat for commercial use and enabling subsequent broader fielding by the military, the existing TCCC Guidelines would likely be altered to include the use of the XStat to stop noncompressible bleeding in the battlefield.

Supporting Publications

For XStat to achieve FDA *de novo* clearance for battlefield use, animal studies were conducted in swine models to demonstrate safety and effectiveness. In addition, human factors studies validating the device design and labeling for appropriate use by first responders provided strength to the *de novo* submission. A snapshot of these studies and additional supporting publications is provided in Table 15.

Table 15. Supporting Publications and Studies in Support of XStat FDA *de novo* Submission

Reference	Description
Mueller et al., 2012	Evaluated the use of the rapidly expanding mini sponges used in the XStat to stop noncompressible hemorrhage in a pre-clinical swine model; compared to Combat Gauze, the sponges provided significant improvement in hemostasis and survival 60 minutes after injury, as well as a reduction in blood loss
FDA de novo Submission K130218 (FDA, 2014)	Submission package included data from multiple studies supporting the XStat's effective performance: • Good Laboratory Practice (GLP) Evaluation of XStat Device in a Swine Femoral Model: GLP animal study to demonstrate the performance of the XStat device compared to a control article, using the USAISR standard femoral animal injury • Evaluation of XStat Device in a Swine Subclavian Model: Animal study to demonstrate the performance of the XStat device in a swine subclavian injury • User Evaluation of XStat Device and Applicator Use: A user evaluation (human factors) was completed to determine the ability of medics and civilian EMS to understand and execute instructions for using XStat and applying XStat on a simulated casualty • User evaluation of XStat device removal: A user evaluation was completed to assess the ability of surgeons to understand and execute instructions for removing XStat sponges from human cadaver wounds

Role of CCCRP-Sponsored Projects

Initial funding for the XStat device was provided by USSOCOM, with the Hemorrhage and Resuscitation portfolio supporting continued activities by RevMedX to then complete development the device. These projects have been critical to the development and FDA clearance of XStat for use in the battlefield (Table 16). The XStat project is currently ongoing for the device to undergo environmental, operational, and clinical evaluation. The USAMRMC is leading a Joint Advanced Development Integrated Product Team (IPT), which is working to continue to move forward activities for XStat development. The Joint IPT requires that the device be cleared for civilian use, and RevMedX plans to submit a 510(k) application for the chitosan-free version for this broader clearance.

Table 16. CCCRP-Sponsored Projects for XStat

Project Title (Award Number)	Organization/ Principal Investigator	Funding
USSOCOM-sponsored Research and Development (W911NF-11-C-0038)	RevMedX	$5,070,000 (2010-2013)
Junctional Noncompressible Hemorrhage Control Agent – XSTAT Rapidly Self-Expanding Cellulose Sponge (W81XWH-13-C-0080)	RevMedX	$7,055,000 (2013 – 2017)

References

Butler, F., Holcomb, J., Giebner, S. D., McSwain, N. E., & Bagian, J. (2007). Tactical combat casualty care 2007: evolving concepts and battlefield experience. *Military Medicine, 172*(11), 1.

Kragh Jr, J. F., Steinbaugh, J., Parsons, D. L., Mabry, R. L., Kheirabadi, B. S., & Dubick, M. A. (2014). A manikin model for study of wound-packing interventions to control out-of-hospital hemorrhage. *The American Journal of Emergency Medicine, 32*(9), 1130-1131.

Mueller, G. R., Pineda, T. J., Xie, H. X., Teach, J. S., Barofsky, A. D., Schmid, J. R., & Gregory, K. W. (2012). A novel sponge-based wound stasis dressing to treat lethal noncompressible hemorrhage. *Journal of Trauma and Acute Care Surgery, 73*(2), S134-S139.

Pusateri, A. E. (2014). Hemorrhage and resuscitation research program. Pre-Brief to EMC.

RevMedX (2015). RevMedX. Revolutionary medical technologies. Retrieved from http://www.revmedx.com/

RevMedX (September 3, 2014). XSTAT's regulatory journey. Retrieved from http://www.fda.gov/downloads/medicaldevices/newsevents/workshopsconferences/ucm416004.pdf

Tactical Combat Casualty Care (TCCC) Guidelines. (2014, October 28). Retrieved from http://www.usaisr.amedd.army.mil/assets/pdfs/TCCC%20Guidelines%20141028.pdf

U.S. Food and Drug Administration (FDA) (2014). De Novo classification request for XStat. Retrieved from http://www.accessdata.fda.gov/cdrh_docs/reviews/k130218.pdf

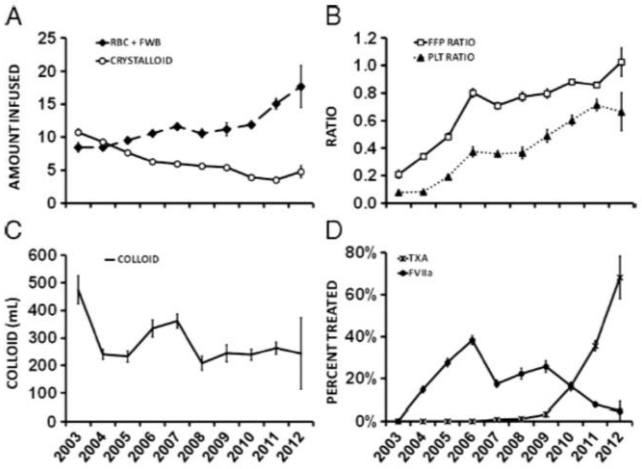
Damage Control Resuscitation

Advances in damage control resuscitation (DCR) have significantly impacted clinical practice. Key among these are the use of blood products in balanced ratios that approximate whole blood, and the adjunctive use of tranexamic acid (TXA) during resuscitation. Continued efforts to optimize resuscitation ratios, prehospital plasma use, and TXA treatment, are ongoing, and yielding additional knowledge to inform clinical practice.

- Partnering Funding Organizations:
  - ONR
  - National Heart Lung and Blood Institute (NHLBI)
- Several performing organizations have been sponsored:
  - NHLBI/Resuscitations Outcome Consortium (ROC; led by the University of Texas Health Sciences Center)
  - University of Colorado, Denver
  - University of Pittsburg
  - University of Washington
  - Virginia Commonwealth University
  - Washington University in St. Louis

Key Outcomes and Impact:

- Supporting evidence has enabled changes in CPGs to recommend close approximation of whole blood during resuscitation, and adjunctive use of TXA
- Improved survival has resulted from increased use of plasma and platelets and the administration of TXA over the course of OIF/OEF (Langan, Eckert, & Martin, 2014; Morrison, DuBose, Rasmussen, & Midwinter, 2012; Pidcoke et al., 2012)
- Ongoing studies to support development of DCR strategies include evaluation of the prehospital use of and clinical research to address specific knowledge gaps in the use of TXA



Transfusion Trends During OIF/OEF. (A) Red cell equivalent transfusion and crystalloid infusion, (B) Fresh frozen plasma and platelet transfusion ratios, (C) Colloid infusion, and (D) Activated factor VII and TXA use (Pidcoke et al., 2012)

Overview

In the intervening decades from the time of the Vietnam War in the 1970's leading up to the advent of recent conflicts in the early 2000's, the immediate treatment of hemorrhagic shock with fluid resuscitation was pursued to increase blood volume and intravascular pressure, and to maintain cardiac-driven blood distribution following traumatic injury and hemorrhage (Miller, 2013). Considerable effort has been devoted to identify the most appropriate fluid for volume expansion and resuscitation. Even though rapid, high-volume fluid resuscitation approaches based on crystalloid and colloid solutions were developed and implemented in trauma care guidelines, basic research and clinical studies have ultimately not provided supporting evidence for these approaches (Butler et al., 2014; DHB, 2011a; Dutton, Mackenzie, & Scalea, 2002; Turner et al., 2000). In contrast, it has become clear that rapid fluid resuscitation can contribute to dangerous secondary events after trauma including coagulopathy, disruption of early thrombus, and accelerated loss of oxygen through hemodilution (Butler et al., 2014; DHB, 2011a).

As this has become better understood, research into more effective approaches has driven not only the use of lower volumes of resuscitation fluids, but also the concept of DCR. Under this concept, crystalloid and colloid solution use is limited and, in a paradigm shift, increased emphasis is placed on blood component-based resuscitation and the adjunctive use of additional hemostatic agents (Glassberg et al., 2013). To enact this approach effectively for trauma care, new products, new approaches to making blood components more broadly available, and new data-backed knowledge have all been necessary.

The CCCRP's strategic activities for resuscitation have ushered in the era of DCR and continue to build upon and shape its practice. Work has progressed from a perspective that the development of individual new technologies is not sufficient to optimally advance casualty survivability. Rather, there must also be an understanding of how to best apply new technologies alone and in combination. In this way, the CCCRP has sought to advance not only new resuscitation products, but also to provide knowledge sets for improved DCR. An iterative approach to improved DCR is being pursued by which the CCCRP works to identify the best ways to use existing and newly developed blood products, drugs, and fluids. Initial phases of this approach have included exploration of the optimal transfusion ratios of blood products. The founding principle of DCR emphases a balanced transfusion of plasma in an equal ratio to red blood cells (RBC), with a minimization of the use of crystalloid solutions. Use of balanced transfusion has now become the standard of care in deployed medical facilities, and as blood products become increasingly accessible outside of fixed medical facilities the same principles are driving modification of prehospital resuscitation protocols (Butler et al. 2014). The CCCRP is now supporting additional studies to further assess prehospital use of plasma to initiate DCR (Table 20). Another aspect of DCR being explored by the CCCRP has been the evaluation of adjunctive measures for use with component resuscitation. One example is the antifibrinolytic compound tranexamic acid (TXA). The CCCRP is sponsoring several clinical trials of the adjunctive use of TXA for traumatic hemorrhage under varying conditions (Table 20). The resulting knowledge products will fill knowledge gaps and continue to influence clinical practice. In the longer term, optimal combinations of technologies for DCR to enable prolonged survivability are being explored, including modulation of inflammatory and metabolic responses in addition to mechanisms of hemostasis.

Capability Gap Alignment

The development of knowledge products such as data-supported transfusion protocols with optimized blood product ratios, and data to inform the use of additional products for DCR such as TXA, has provided significant progress against several capability gaps for hemorrhage resuscitation (Table 17).

Table 17. Capability Gaps Addressed by DCR

Requirement Sources	Capability Gaps Addressed
GDF	• **JCM-1-1** – Inadequate ability to diagnose, resuscitate, and stabilize casualties with survivable wounds • **JCM-1-8** – Inadequate therapy for shock and head injury • **JCM-2-2** – Poor ability to provide tissue oxygenation and compatible shelf-stable blood products • **JCM-2-3** – Poor ability to restore blood volume

Requirement Sources	Capability Gaps Addressed
TC3 ICD	• **Theater Hospitalization, Area Medical Support** – Diagnose, resuscitate and stabilize casualties with survivable wounds • **Blood Substitutes** – Provide tissue oxygenation, compatible blood types, shelf stable • Rapid Administration of Fluids – Restore blood volume • **Coagulopathy Prevention and Treatment Agents** - Immediate recognition and correction of coagulopathy
DHP ICD	• **TI1** – Insufficient current first-responder (medical and non-medical) capacity and capability to initially assess, treat, and maintain severe trauma cases in the pre-hospital environment - Insufficient tools that enable both non-medical and medical first responders. - The technologies do not exist to fulfill some of the needs (e.g., stabilizing the airway or truncal hemorrhage) • **TS1** – Lack of optimal resuscitation strategies for casualties who have TBI and are in, or at risk for, hemorrhagic shock • **TS3** – Lack of suitable resuscitative fluids (e.g., blood products or substitutes) appropriate for administration in the pre-hospital environment in order to prevent shock • **MC6** – Lack of optimal blood expander with oxygenation capability and fluid resuscitative strategy at POI

Impact on the Battlefield/Warfighter

A growing body of data indicates that resuscitation strategies relying on transfusion of large volumes of crystalloids or on the heavy use of RBCs with relatively fewer units of plasma and platelets were potentially exacerbating coagulopathy of trauma. Consequently, civilian trauma centers began to administer DCR using a 1:1:1 ratio of plasma, RBCs, and platelets, which is now the standard of care in the U.S. military for hemorrhagic resuscitation (Butler et al., 2014).

A recent analysis of the effects of DCR practices in forward military treatment facilities on in-hospital deaths determined that patients who died from 2006-2011 (when DCR principles were being employed), were more likely to be severely injured and to have severe brain injury than those who died in hospital before 2006 (Langan, Eckert, & Martin, 2014); these data imply that using DCR improved the mortality rates of severely injured individuals who may otherwise have succumb. An additional analysis of transfusion practices in OIF/OEF over the 10-year span of 2003 through 2012 also supported the impact of DCR, showing that shifting clinical practices toward increased use of plasma and platelets have resulted in improved survival (Pidcoke et al., 2012). Further, when TXA was administered to patients receiving blood transfusion at a Role 3 hospital in Afghanistan, it was found that TXA used in conjunction with component-based resuscitation was associated with improved survival (Morrison, DuBose, Rasmussen, & Midwinter, 2012). All together, the use of DCR practices has already helped to save warfighter lives during the later years of the OIF/OEF conflicts.

Clinical Practices

Impact on Clinical Practice Guidelines

The original 1996 TCCC Tactical Field Care Guidelines for fluid resuscitation on the battlefield called for the use of Hespan (a synthetic starch colloid fluid) as initial treatment for casualties in shock resulting from hemorrhage (Butler, Haymann, & Butler, 1996). During conferences on fluid resuscitation sponsored by USAMRMC and the ONR between 2001 and 2002, new fluid resuscitation guidelines were developed that similarly promoted the use of Hextend, a related starch colloid suspended in Lactated Ringer's (LR) solution, for casualties in shock. The approach of hypotensive resuscitation with Hextend for TCCC was further upheld following a USAMRMC-sponsored conference on fluid resuscitation in 2010 (McSwain et al., 2011). This was followed, however, by changes from a 2011 proposal that shifted recommendations to the use of 1:1 plasma and RBC resuscitation when available in the tactical evacuation phase of care; at the time, it was noted that this approach was already the current theater trauma practice despite the previous guidelines (DHB, 2010). Most recently, TCCC Guidelines have been updated in 2014 to reflect new data supporting the value of most closely approximating whole blood during resuscitation for efficacy and damage control. When whole blood is not available, this means that a 1:1:1 ratio of plasma to RBCs to platelets has been recommended as the next preferred option.

"The preferred fluids for resuscitation of casualties in hemorrhagic shock, in descending order of preference, are:

- Whole blood
- 1:1:1 plasma, RBCs, and platelets
- 1:1 plasma and RBCs
- Reconstituted DP [dried plasma], liquid plasma, or thawed plasma alone or RBCs alone
- Hextend
- LR or Plasma-Lyte A"

In addition to TCCC Guidelines, a current CPG published by the JTS for resuscitation at Role 2b/3 treatment facilities also emphasizes the use of plasma and other blood components at appropriate ratios over crystalloid or colloid solutions (JTS, 2014). The CPG cites strong retrospective evidence that a comparable ratio of plasma and platelets to RBCs improves survival in both civilian and military trauma populations requiring massive transfusion. The guideline also recommends considering TXA as an adjunct to resuscitation, based on its associated survival benefit. The recommendation to add the use of TXA was made in 2011, following the evidence obtained from two large clinical studies, one conducted in civilian trauma patients (the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage [CRASH]-2 Trial) and the other retrospectively analyzing data from military combat casualties (Military Application of Tranexamic Acid in Traumatic Emergency and Resuscitative Surgery [MATTERS] Study) (DHB, 2011b) (Table 18).

"The early use of TXA (i.e., as soon as possible after injury but ideally not later than 3 hours post injury) should be strongly considered for any patient requiring blood products in the treatment of combat related hemorrhage and is most strongly advocated in patients judged likely to require massive transfusion (e.g., significant injury and risk factors of massive transfusion). "

JTS, 2014

As advances continue to be made in blood product availability, such as the anticipated approval of dried plasma products and pathogen reduction technology for whole blood in the near future (both discussed in the sections to follow), DCR strategies will be further adapted and may grow more widely executable in the field.

Supporting Publications

Many studies supported CPGs that advocate the use of balanced blood component ratios and TXA for DCR (Table 18). Optimization of DCR practices continues to be an active area of research, with a growing body of literature. The future results of additional studies, such as targeted clinical trials of TXA designed to address specific knowledge gaps, and a prospective trial randomizing patients to different platelet and plasma ratios for resuscitation, will enable further refinements to these CPGs in the future.

Table 18. Supporting Publications for DCR

Reference	Description
Balanced Blood Component Ratios for Transfusion	
Borgman et al., 2007	The plasma to RBC ratios used in massive transfusions at a combat support hospital were retrospectively assessed; plasma to RBC ratio was associated with survival
Holcomb et al., 2008	Reviewed the records of massive transfusion patients transported to Level 1 trauma centers during 2005-2006. Survival in these civilian patients was associated with increased plasma and platelet ratios, and a 1:1:1 ratio was advocated
Shaz et al., 2010	Evaluated the relationship of transfusion ratios to mortality in massively transfused patients at a Level 1 trauma center; increased levels of plasma, platelets, and cryoprecipitate products relative to RBCs were associated with increased 30-day survival
Holcomb et al., 2013	Prospective multicenter study documenting the timing of transfusions and patient outcomes at ten Level 1 trauma centers. Higher plasma and platelet ratios early in resuscitation were associated with decreased mortality
TXA	
CRASH-2 Trial Collaborators, 2010	A large, international, prospective, randomized trial to examine treatment of adult trauma patients with significant bleeding with TXA. TXA reduced the risk of death in bleeding patients in the study
CRASH-2 Trial Collaborators, 2011	Further examined CRASH-2 data to evaluate the effect of TXA on death due to bleeding; identified strong evidence that the effect varied according to the time from injury to treatment
Morrison, DuBose, Rasmussen, & Midwinter, 2012	Examined the use of TXA in patients receiving blood products at a Role 3 hospital in Afghanistan (MATTERS); there was a decreased mortality with TXA use in this population

Role of CCCRP-Sponsored Projects

The Hemorrhage and Resuscitation portfolio has played an important role DoD-wide in many of the activities related to past, present, and planned future exploration of DCR strategies. The USAMRMC was a sponsor of a number of key conferences bringing together experts to develop consensus-based approaches to fluid resuscitation, on the path to the currently established DCR recommendations (Table 19).

Table 19. Conferences Supporting the Development of Fluid Resuscitation Guidelines

Conference	Outcome
Combat Fluid Resuscitation 2001 **2002 Joint USAMRMC and ONR Fluid Resuscitation Conference**	These conferences yielded the 2003 TCCC fluid resuscitation guidelines which recommended the use of Hextend to resuscitate casualties in hemorrhagic shock (Butler et al., 2014; Champion, 2003; Holcomb, 2003)
2010 USAMRMC Fluid Resuscitation Conference	Consensus was reached during this 2010 conference to leave battlefield fluid resuscitation recommendations unchanged (McSwain et al., 2011)

Those recommendations have further evolved to yield DCR, however, with the support of knowledge products developed from the portfolio-sponsored efforts. DCR remains an active area of investigation for the CCCRP, and a number of additional projects have been undertaken to validate new approaches. These include both direct sponsorship of studies and participation in interagency partnerships (Table 20). One example of such partnerships is DoD's membership on the Executive Committee of the NHLBI/ROC. DoD is a funding partner for the multicenter consortium, and under this relationship the Pragmatic, Randomized Optimal Platelet, and Plasma Ratio Study (PROPPR) has been conducted to examine transfusion ratios.

Table 20. CCCRP-Sponsored Projects for Development of Knowledge Products to Influence DCR Clinical Practice

Project Title (Clinical Trial Identifier and/or Award Number)	Organization/ Principal Investigator	Funding
Optimization of Transfusion Ratios		
Pragmatic, Randomized Optimal Platelet and Plasma Ratio Study (PROPPR) (NCT01545232, ROC oversight funded by DoD via NHLBI)	University of Texas Health Sciences Center	$53,000,000
Prehospital Plasma Trials		
Control of Major Bleeding after Trauma Study (COMBAT) (NCT01838863; W81XWH-12-2-0028)	Ernest E. Moore, M.D. (University of Colorado, Denver)	Three studies were solicited under the 2011 Prehospital Use of Plasma for Traumatic Hemorrhage program announcement. These are 4-year, multi-center trials with an estimated total program funding of $16M.
Prehospital Use of Plasma for Traumatic Hemorrhage (PUPTH) (NCT02303964; W81XWH-12-2-0022)	Bruce D. Spiess, M.D. (Virginia Commonwealth University)	
Prehospital Air Medical Plasma (PAMPer) Trial (NCT01818427; W81XWH-12-2-0023)	Jason L. Sperry, M.D., M.P.H. (University of Pittsburg)	
TXA Clinical Research		
Prehospital Tranexamic Acid Use for Traumatic Brain Injury (NCT01990768; W81XWH-13-2-0090)	Susanne May, Ph.D. (University of Washington)	Three studies were solicited under the 2012 TXA Clinical Research program announcement. These are 3-year studies, with an approximate total program funding of $12M.
Tranexamic Acid Mechanisms and Pharmacokinetics In Traumatic Injury (TAMPITI Trial) (W81XWH-14-1-0373)	Philip C. Spinella, M.D., FCCM (Washington University in St. Louis)	
Study of Tranexamic Acid during Air Medical Prehospital Transport (STAAMP) Trial (NCT02086500)	Jason L. Sperry, M.D., M.P.H. (University of Pittsburgh)	

These CCCRP-sponsored efforts have already resulted in several publications (Table 21), including initial results from the PROPPR study. Results of these efforts will continue to inform the iterative optimization of resuscitation protocols. In addition to these successful projects already completed or in process, the CCCRP is also moving forward several complementary lines of exploration that may revolutionize DCR capabilities in the future. These efforts will inform the next generation of DCR approaches for prolonged prehospital management and casualty survivability by improving our understanding of resuscitation physiology over longer

periods, developing approaches to metabolic stabilization, modulating inflammatory processes, and providing effective oxygenation through synthetic products.

Table 21. CCCRP-Sponsored Publications for Development of Knowledge Products to DCR Clinical Practice

Reference	Description
Optimization of Transfusion Ratios	
Baraniuk et al., 2014	Published the design, rationale, and data on the implementation of the PROPPR trial. Between August 2012 and December 2013, 680 patients were randomized in the trial to receive resuscitation with 1:1:1 or 1:1:2 plasma:platelets:RBCs
Holcomb et al., 2015	Early administration of plasma, platelets, and RBCs in a 1:1:1 ratio compared with a 1:1:2 ratio did not result in significant differences in mortality at 24 hours or at 30 days in patients with severe trauma and major bleeding randomized in the PROPPR trial. Patients in the 1:1:1 group achieved hemostasis and fewer experienced death due to exsanguination by 24 hours
Prehospital Plasma Trials	
Brown et al., 2015a	Published the design and rationale of the PAMPer Trial; the primary objective is to determine the effect of prehospital plasma transfusion during air medical transport on 30-day mortality in patients at risk for traumatic hemorrhage
TXA Clinical Research	
Brown et al., 2015b	Published the design and rationale of the STAAMP Trial; the primary objective is to determine the effect of prehospital TXA infusion during air medical transport on 30-day mortality in patients at risk for traumatic hemorrhage

References

Baraniuk, S., Tilley, B. C., del Junco, D. J., Fox, E. E., van Belle, G., Wade, C. E., … PROPPR Study Group. (2014). Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) Trial: Design, rationale and implementation. *Injury*, *45*(9), 1287-1295.

Borgman, M., Spinella, P. C., Perkins, J. G., Grathwohl, K. W., Repine, T., Beekley, A. C. … Holcomb, J. B. (2007). The Ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *Journal of Trauma, 63*(4), 805-813.

Brown, J. B., Guyette, F. X., Neal, M. D., Claridge, J. A., Daley, B. J., Harbrecht, B. G., … Sperry, J. L. (2015a). Taking the blood bank to the field: The design and rationale of the prehospital air medical plasma (PAMPer) trial. *Prehospital Emergency Care*, doi:10.3109/10903127.2014.995851.

Brown, J. B., Neal, M.D., Guyette, F. X., Peitzman, A. B., Billiar, T. R., Zuckerbraun, B. S., & Sperry, J. L. (2015b). Design of the study of tranexamic acid during air medical prehospital transport (STAAMP) trial: Addressing the knowledge gaps. *Prehospital Emergency Care*, *19*(1), 79-86.

Butler, F. K., Haymann, J., & Butler, E. G. (1996). Tactical Combat Casualty Care in Special Operations. *Military Medicine, 161(*Suppl 1), 3-16.

Butler, F. K., Holcomb, J. B., Schreiber, M. A., Kotwal, R. S., Jenkins, D. A., Champion, H. R., … Bailey, J. A. (2014). Fluid resuscitation for hemorrhagic shock in tactical combat casualty care: TCC Guidelines Change 14-01 – 2 June 2014. *Journal of Special Operations Medicine*, *14*(3), 30-55.

Champion, H. R. (2003). Combat fluid resuscitation: Introduction and overview of Conferences. *J Trauma*, *54*, 7.

Control of Major Bleeding After Trauma Study (COMBAT). (2014). Retrieved from https://clinicaltrials.gov/ct2/show/NCT01838863 (Identification No. NCT01838863)

CRASH-2 Trial Collaborators. (2010). Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): A randomised, placebo-controlled trial. *Lancet, 376*, 23–32

CRASH-2 Trial Collaborators. (2011). The importance of early treatment with tranexamic acid in bleeding trauma patients: An exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet*, *377*(9771), 1096-101.

Defense Health Board (DHB). (2010). Recommendations regarding the Tactical Combat Casualty Care Guidelines on Fluid Resuscitation 2010-07. Retrieved from http://www.health.mil/Reference-Center/Reports/2010/12/10/Tactical-Combat-Casualty-Care-Guidelines-on-Fluid-Resuscitation

Defense Health Board (DHB). (2011a, August 8). Use of dried plasma in prehospital battlefield resuscitation 2011-04. Retrieved from https://www.jsomonline.org/PDFs/DHB%20Memo%20Dried%20Plasma%20110808.pdf

Defense Health Board (DHB). (2011b, September 23). Recommendations regarding the addition of tranexamic acid to the Tactical Combat Casualty Care Guidelines 2011-06. Retrieved from https://www.jsomonline.org/TCCC/07%20TCCC%20Reference%20Documents/DHB%20Memo%20110923%20TXA.pdf

Dutton, R. P., Mackenzie, C. F., & Scalea, T. M. (2002). Hypotensive resuscitation during active hemorrhage: Impact on in-hospital mortality. *Journal of Trauma, 52,* 1141–1146.

Glassberg, E., Nadler, R., Rasmussen, T. E., Abramovich, A., Erlich, T., Blackbourne, L. H., & Kreiss, Y. (2013). Point-of-injury use of reconstituted freeze-dried plasma as a resuscitative fluid: A special report for prehospital trauma care. *Journal of Trauma and Acute Care Surgery, 75*(2, Suppl 2), S111-S114.

Holcomb, J. (2003). Fluid resuscitation in modern combat casualty care: Lessons learned in Somalia. *Journal of Trauma, 54*, S46-S51.

Holcomb, J., del Junco, D. J., Fox, E. E., Wade, C. E., Cohen, M. J., Schreiber, M. A., … PROMMTT Study Group. (2013).The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: Comparative effectiveness of a time-varying treatment with competing risks. *Journal of the American Medical Association Surgery, 148*(2), 127-136.

Holcomb, J. B., Tilley, B. C., Baraniuk, S., Fox, E. E., Wade, C. E., Podbielski, J. M., … PROPPR Study Group. (2015). Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *Journal of the American Medical Association, 313*(5), 471-482.

Holcomb, J. B., Wade, C. E., Michalek, J. E., Chisholm, G. B., Zarzabal, L. A., Schreiber, M. A., … Park, M. S. (2008). Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. *Annals of Surgery, 248*(3), 447-58.

Joint Trauma System (JTS). (2014, December). JTS & CCAT Clinical Practice Guidelines. Retrieved from http://www.usaisr.amedd.army.mil/clinical_practice_guidelines.html

Langan, N. R., Eckert, M., & Martin, M. J. (2014). Changing patterns of in-hospital deaths following implementation of damage control resuscitation practices in US forward military treatment facilities. *Journal of the American Medical Association Surgery, 149*(9), 904-912.

McSwain, N., Champion, H. R., Fabian, T. C., Hoyt, D. B., Wade, C. E., Eastridge, B. J., … Blackbourne, L. H. (2011) State of the art fluid resuscitation 2010: Prehospital and immediate transition to the emergency department. *Journal of Trauma, 70,* S2-S10.

Miller, T. E. (2013). New evidence in trauma resuscitation - is 1:1:1 the answer? *Perioperative Medicine, 2,* 13.

Morrison, J., DuBose, J., Rasmussen, T., & Midwinter, M. (2012). Military application of tranexamic acid in trauma emergency resuscitation (MATTERs) Study. *Archives of Surgery*, *147*(2), 113-9.

Pidcoke, H. F., Aden, J. K., Mora, A. G., Borgman, M. A., Spinella, P. C., Dubick, M. A., … Cap, A. P. (2012). Ten-year analysis of transfusion in Operation Iraqi Freedom and Operation Enduring Freedom: Increased plasma and platelet use correlates with improved survival. *Journal of Trauma and Acute Care Surgery*, *73*(6 Suppl 5), S445-S452.

PreHospital Air Medical Plasma Trial (PAMPer). (2015). Retrieved from https://clinicaltrials.gov/ct2/show/NCT01818427 (Identification No. NCT01818427)

Prehospital Tranexamic Acid Use for Traumatic Brain Injury. (2014). Retrieved from https://clinicaltrials.gov/ct2/show/NCT01990768 (Identification No. NCT01990768)

Safety Study of Spray-Dried Solvent/Detergent-Treated Plasma for Infusion in Healthy Volunteers (2015). Retrieved from https://clinicaltrials.gov/ct2/show/NCT01589666 (Identification No. NCT01589666)

Shaz, B. H., Dente, C. J., Nicholas, J., Macleod, J. B., Young, A. N., Easley, K., … Hillyer, C. D. (2010). Increased number of coagulation products in relationship to red blood cell products transfused improves mortality in trauma patients. *Transfusion, 50*, 493-500.

Study of Tranexamic Acid during Air Medical Prehospital Transport (STAAMP) Trial. (2015). Retrieved from https://clinicaltrials.gov/ct2/show/NCT02086500 (Identification No. NCT02086500).

Turner, J., Nicholl, J., Webber, L., Cox, H., Dixon, S., & Yates, D. (2000). A randomized controlled trial of prehospital intravenous fluid replacement therapy in serious trauma. *Health Technology Assessment, 4,* 1–57.

Whole Blood Pathogen Reduction Device

The Mirasol Pathogen Reduction Technology (PRT) is a whole blood treatment technology for reducing infectious pathogen loads of bacteria, viruses, and parasites. A Phase 2 clinical trial of the technology has been successfully completed, and the device is now moving into a Phase 3 pivotal trial.

- Developmental Partner Organization:
  - Terumo BCT
- Principal Investigator:
  - Raymond Goodrich, Ph.D.

Key Outcomes and Impact:

- Continued funding has extended the technology's capabilities from treatment of blood components to use on fresh whole blood (FWB), and is enabling clinical trials in support of planned FDA submission
- Multiple published studies support the technology as an efficacious method for reducing pathogen load and report that treated FWB maintains resuscitative potential
- Availability of FWB that can be quickly and easily treated to significantly reduce the risk of pathogen transmission can enable increased use and a shift of FWB towards more forward environments

The Mirasol PRT (TerumoBCT, 2015)

Overview

Hemorrhage from injuries sustained in combat is the most common cause of potentially survivable death on the battlefield (Eastridge et al., 2012). In recent military conflicts, more than 28,000 wounded personnel were transfused almost 300,000 blood products; over 9,000 units were FWB (Chandler, Roberts, Sawyer, & Myers, 2012). Although FWB transfusion is associated with improved survival, transmission of infectious agents (e.g., human immunodeficiency virus, hepatitis B/C, and syphilis) in the FWB is a real risk so safeguarding the blood supply is critical.

With DoD funding, Terumo BCT is developing the Mirasol System for Whole Blood, a transportable pathogen reduction technology for processing whole blood in combat environments. The Mirasol systems inactivate pathogens using non-mutagenic, non-toxic agents that do not have to be removed before the treated blood is available for transfusion (Terumo BCT, 2015). The Mirasol System for Whole Blood is based on the Mirasol PRT system, which uses the unique properties of riboflavin (vitamin B2) and ultraviolet (UV) light to reduce the pathogen load (Figure 9). The Mirasol PRT System has been under development since 1999 as a solution for ensuring the safety of the blood supply. With DoD-funding beginning in 2007, Terumo BCT (then Caridian BCT) extended

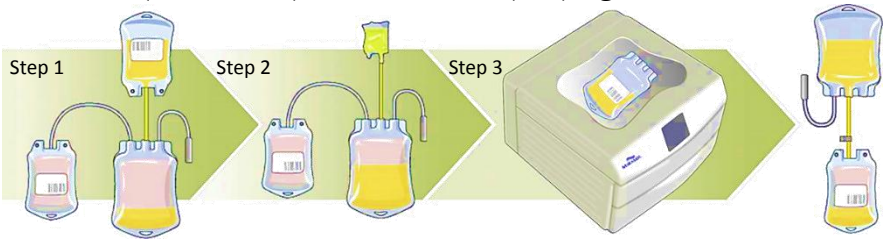


Figure 9.Mirasol Pathogen Reduction Technology Overview.

Step 1 – Fresh whole blood is added to an illumination bag. Step 2 – Riboflavin is added to the illumination bag. Step 3 – Illumination bag is illuminated with UV light, rendering bacteria, viruses, and parasites harmless (Terumo BCT, 2015)

the capability of their technology to reduce pathogenic agents and inactivate white blood cells (WBC) to all three whole blood components (i.e., RBCs, platelets, and plasma) (Figure 10).

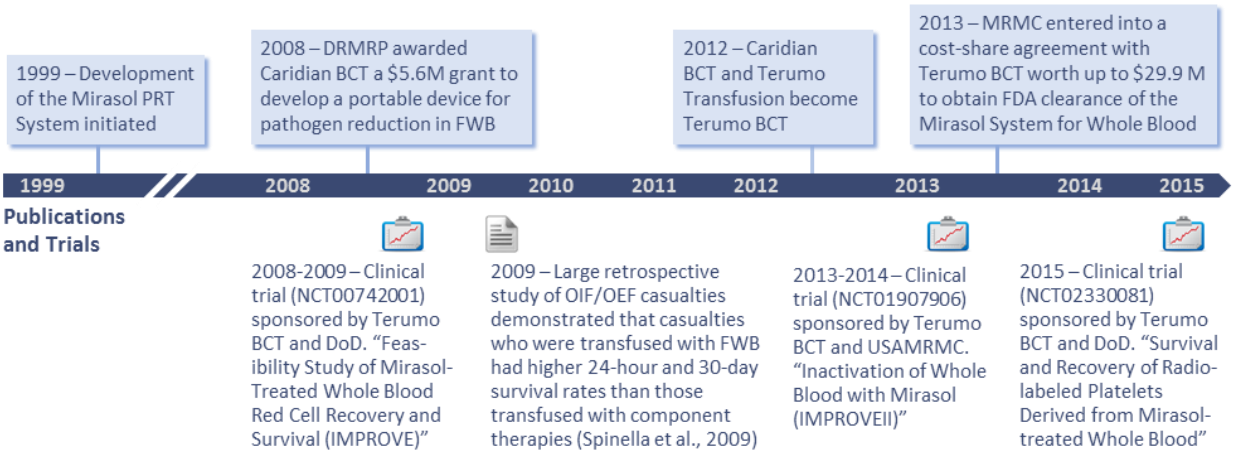


Figure 10. Developmental timeline of Mirasol Pathogen Reduction Technology for Whole Blood

Capability Gap Alignment

When implemented, the Mirasol System for Whole Blood will address several capability gaps with respect to hemorrhage resuscitation (Table 22). Both the GDF and the TC3 ICD capability gaps highlight an inadequate capability to restore blood volume and to resuscitate casualties with potentially survivable injuries. It is anticipated that by allaying concerns about FWB transfusion transmissible diseases, the number of FWB transfusions will increase and contribute to the closure of these gaps. More recently, the DHP ICD specifically identified an inability to test for blood pathogens (prehospital) as a way of reducing morbidity and mortality associated with transfusion. The Mirasol System for Whole Blood directly addresses this capability gap by inactivating blood pathogens, making blood pathogen detection inessential.

Table 22. Capability Gaps Addressed by Whole Blood Pathogen Reduction Technologies

Requirement Sources	Capability Gaps Addressed
GDF	• **JCM1-1** – Inadequate ability to diagnose, resuscitate, and stabilize casualties with survivable wounds • **JCM-1-11** – Inadequate ability to immediately recognize and correct coagulopathy • **JCM-2-2** – Poor ability to provide tissue oxygenation and compatible shelf-stable blood products • **JCM-2-3** – Poor ability to restore blood volume
TC3 ICD	• **Theater Hospitalization, Area Medical Support** – Diagnose, resuscitate and stabilize casualties with survivable wounds • **Blood Substitutes** – Provide tissue oxygenation, compatible blood types, shelf stable • Rapid Administration of Fluids – Restore blood volume
DHP ICD	• **TS3** – Lack of suitable resuscitative fluids (e.g., blood products or substitutes) appropriate for administration in the pre-hospital environment in order to prevent shock • **PL8** – Inability to test for the presence of blood pathogens at pre-U.S. hospital (malaria, HIV, hepatitis, etc. for local blood and direct transfusions) in order to reduce morbidity and mortality in the field • **MC6** – Lack of optimal blood expander with oxygenation capability and fluid resuscitative strategy at POI

Impact on the Battlefield/Warfighter

> "If any single medical program can be credited with the saving of countless lives in World War II and the Korean War, it was the prompt and liberal use of whole blood."
>
> LTG Leonard Heaton,
> Surgeon General U.S. Army 1959—1969

In the U.S. military, blood is first available, albeit in limited supply, from Forward Surgical Teams at Role 2 care. Not until Role 3 care within Combat Support Hospitals are all blood components consistently available, and it is often the case that the supply is inadequate, causing medical providers to resort to FWB (Chandler, Roberts, Sawyer, & Myers, 2012). In Iraq and Afghanistan, the vast majority if FWB transfusions occurred in facilities corresponding to Role 3 or higher when blood components were in short supply (i.e., as a last resort). Considering that about 1 out of 30 blood products transfused in Iraq and Afghanistan was FWB (out of 300,000 total), it becomes clear that FWB is already extensively used to resuscitate casualties and save lives (Chandler, Roberts, Sawyer, & Myers, 2012). It also becomes clear that the current blood-product supply chain does not meet demand. It is expected that FWB that has been treated to significantly reduce the risk of pathogen transmission and is widely available will result in increased use and a shift of FWB towards more forward environments. This would occur, in part, by reducing the screening requirements that are currently used to prevent transfusion-transmitted infections and by diminishing resistance based on perceived risk of the use of FWB in forward environments.

Clinical Practice

Impact on Clinical Practice Guidelines

Current FWB screening methods are labor and time intensive. Using FWB in far forward environments requires prior planning and observance of several precautions. First, because there are no universal donors, a donor pool must be established prior to combat operation that ensures that the donor and recipient have matching blood types. All donors must also be pre-screened to prevent the spread of blood-borne diseases.

Current JTS clinical guidance recommends FWB only in certain situations: (1) When casualties are expected to require massive transfusions (≥ 10 units RBCs in 24 hours), (2) When casualties have clinically significant shock or coagulopathy, (3) When component therapy is unavailable or not adequately resuscitating a casualty with life-threatening injuries, and (4) When (in a Role 3 facility), blood inventory is depleted (JTS, 2012). Use of FWB is not recommended as an alternative to more stringently controlled blood products (i.e., fresh-frozen plasma [FFP], RBCs, platelets), and is ultimately the decision of the attending physician who is cognizant of the clinical situation and availability of blood components (JTS, 2012). It is important that the risks are understood and balanced with potential benefit to the patient.

Much of the clinical guidance on the use of FWB for resuscitation in forward environments attempts to mitigate transfusion-associated risks such as the transmission of blood-borne disease. It is anticipated that a technology, such as the Mirasol system, that can remove the risk of transfusion transmissible diseases will help encourage its use in forward environments.

Supporting Publications

In contrast to component therapies, transfusion with FWB replaces coagulation factors and platelets, restores blood volume and the ability to carry oxygen. Although component therapy has several logistical advantages, multiple studies lend support to the benefit of FWB transfusion. Retrospective studies of OIF/OEF casualties demonstrated there is a significant survival benefit for massively transfused casualties (≥ 10 units RBCs in 24 hours), when RBCs, FFP, and platelets are transfused in a 1:1:1 ratio (Spinella, Perkins, Grathwohl, Beekley, & Holcomb, 2009) (Table 23). Casualties presenting with hemorrhagic shock, and treated using a transfusion strategy that included FWB (with RBCs and plasma), had a greater survival rate than those treated with components only (Spinella, Perkins, Grathwohl, Beekley, & Holcomb, 2009). To make FWB transfusions available and safe, multiple studies have been conducted to further develop and evaluate pathogen reduction technologies (i.e., Mirasol PRT System) (Table 2). Important milestones include validating the PRT as an efficacious method for reducing pathogen load and ensuring that treated FWB maintains resuscitative potential (Table 2).

Table 23. Supporting Publications for Whole Blood Transfusion and Pathogen Reduction Technology

Reference	Description
Transfusion with FWB	
Spinella, Perkins, Grathwohl, Beekley, & Holcomb, 2009	Large retrospective study of OIF/OEF casualties demonstrated that casualties who were transfused with FWB had higher 24-hour and 30-day survival rates than those transfused with component therapies
Nessen et al., 2013	Large retrospective study of OEF casualties from six Forward Surgical Teams demonstrated that resuscitation with FWB in combat environments is safe and independently associated with improved survival compared with RBCs and FFP
Cotton et al., 2013	Single-center randomized controlled trial of patients expected to require large-volume transfusions demonstrated that use of whole blood significantly reduced transfusion volumes
Jones & Frazier, 2014	Logistic regression analysis of the 2009 National Trauma Data Bank showed that transfusion of whole blood was associated with reduced mortality
Development of the Pathogen Reduction Technology	
Goodrich et al., 2009	Evaluation of the immune response of RBCs treated with riboflavin and UV light. Treatment did not stimulate a RBC immunogenic response (Supported by W81XWH-05-2-0001)
Goodrich, Doane, & Reddy, 2010	Overview of developmental efforts for a photochemical pathogen reduction technology that uses riboflavin and UV light (Supported by W81XWH-05-2-0001)
Tonnetti, Proctor, Reddy, Goodrich, & Leiby, 2010	Evaluation of the Mirasol PRT System to inactivate *Babesia microti* in apheresis plasma and platelets. Total log reduction of parasites ranged between 4 and 5, demonstrating proof of principle (Supported by W81XWH-05-2-0001)
Hlavinka, Goodrich, & Hansen, 2011	Patented method for washing multiple units of blood to eliminate prions (Supported by W81XWH-05-2-0001)
Tonnetti et al., 2012	Evaluation of the Mirasol PRT System to inactivate *Trypanosoma cruzi* (causative agent of Chagas disease) in whole blood. The total log reduction (>3.5) indicated that the Mirasol PRT System could be effective at preventing transfusion of *T. cruzi* (Supported by W81XWH-05-2-0001)
Fast et al., 2013	In vitro comparison study demonstrating that treatment of WB with riboflavin plus UV light was as effective as gamma irradiation in the prevention of WBC proliferation, and more effective in the prevention of antigen presentation, cytokine production, and T-cell activation (Supported by W81XWH-09-2-0100)

Reference	Description
Jackman et al., 2013	Demonstration that treatment of WBC-enriched platelet-rich plasma with the Mirasol PRT system effectively blocks alloimmunization and modulates immune responses to subsequent exposures (Supported by W81XWH-09-2-0100)
Keil et al., 2013	Evaluation of the effectiveness of the Mirasol PRT System to inactivate *Plasmodium falciparum* and *Plasmodium yoelii* (causative agents of malaria). The system reduces viable pathogens (>3.2 logs) in plasma and platelet concentrates and plasma products (Supported by W81XWH-05-2-0001)
Pidcoke et al., 2013	Demonstration that in vitro hemostatic function of WB is unaffected by treatment with the Mirasol PRT system and is better preserved by cold storage over 21 days. Results suggest that Mirasol-treated refrigerated WB is suitable for trauma resuscitation (Supported by W81XWH-09-2-0100)
Reddy, Doane, Keil, Marschner, & Goodrich, 2013	Demonstration that the Mirasol PRT system is as effective as gamma-irradiation at inactivating WBCs and reducing pathogen loads in FWB (Supported by W81XWH-09-2-0100 and W81XWH-05-2-0001)
Tonnetti et al., 2013	Demonstration that the Mirasol PRT system can decrease the parasite load in FWB containing *Babesia microti* (Supported by W81XWH-09-2-0100)
Bakkour et al., 2014	Development of a real-time polymerase chain reaction assay to measure the impact of the Mirasol PRT system on pathogen reduction in blood components (Supported by W81XWH-09-2-0100)
Owusu-Ofori et al., 2014	Demonstration that WB treatment with the Mirasol PRT system can inactivate malaria parasites and maintain blood quality during post-treatment cold storage (Supported by W81XWH-09-2-0100)
Tonnetti et al., 2014	Demonstration of the viability of the parasite *Leishmania donovani* in whole blood after treatment with the Mirasol PRT system. Partial reduction of *L. donovani* was achieved suggesting the Mirasol PRT system is useful when donors are exposed to Leishmania sp. during military deployment to an endemic area (Supported by W81XWH-09-2-0100)
Okoye et al., 2015	Comparison of the safety and efficacy of Mirasol-treated FWB to untreated FWB in an in vivo porcine model of surgical bleeding. These data suggest that Mirasol-treated FWB is both safe and efficacious in vivo (Supported by W81XWH-09-2-0100)
Clinical Trials	
Cazenave et al., 2010	Randomized controlled clinical trial that assessed the safety and efficacy of the Mirasol PRT system. Confirmed no increased need for platelet or RBC transfusion in patients receiving Mirasol-treated platelets. The corrected count increments remained stable throughout multiple transfusions
Cancelas et al., 2011	Clinical evaluation of the Mirasol PRT System in the IMPROVE trial; FWB from twelve donors was treated, separated into components, and stored for 42 days, after which RBCs were reinfused into the donors and examined for viability within 24 hours (NCT00742001; Supported by W81XWH-05-2-0001)
Inactivation of Whole Blood With Mirasol (IMPROVEII) (Goodrich, 2014; NCT01907906)	Clinical trial sponsored by Terumo BCT and USAMRMC to evaluate survival of autologous RBCs, derived from Mirasol-treated fresh whole blood stored as leukoreduced packed RBCs and re-infused in healthy adult subjects
Survival and Recovery of Radio-labeled Platelets Derived From Mirasol-treated Whole Blood (Medic) (Goodrich, 2015; NCT02330081)	Clinical trial sponsored by Terumo BCT and DoD to study the survival and recovery of platelets derived from Mirasol-treated whole blood after radiolabeling and re-infusion into the donor

Role of CCCRP-Sponsored Projects

The CCCRP's Hemorrhage and Resuscitation portfolio continues to support and manage various aspects of the Mirasol system, both directly and in coordination as a larger DoD-wide effort. DoD has been instrumental in the advancement of the Mirasol System for Whole Blood (Table 23, Table 24). The Mirasol PRT System has been under development since 1999 and had already been evaluated against a wide range of transfusion transmissible diseases. DoD funded Caridian BCT in 2007 to evaluate blood components such as platelets and plasma following treatment with Mirasol PRT System (Terumo BCT, 2015). Then in 2008, Caridian BCT received a Deployment Related Medical Research Program (DRMRP) award to develop the first transportable Mirasol System for Whole Blood prototype, which is based on the same technology as the benchtop Mirasol PRT System, as well as to conduct numerous validation and optimization studies (Table 23, Table 24). In 2013, DoD awarded Terumo BCT a cost-share contract worth up to $29.9M total to advance the Mirasol System for Whole Blood and obtain FDA clearance (Figure 10). From 2013 to 2016, DoD will fund Terumo BCT $3.46M to prepare for submission of the Mirasol System for Whole Blood to FDA. The grant is supporting two clinical trials of the Mirasol System for Whole Blood that evaluate the system's efficacy at reducing transfusion transmissible diseases and leukocyte-related immunogenic reactions (Table 23). According to the terms of the agreement, DoD has the option of sharing the cost of additional safety and efficacy studies, up to $11.3M, in preparation for a pre-market approval application to FDA.

- Continued funding of the Mirasol System has extended its capabilities from treatment of blood components to use on FWB, and is enabling clinical trials in support of submission for FDA clearance
- The program will give DoD the capability to rapidly perform pathogen reduction on FWB to improve the safety of transfusions in combat environments
- The capability to reduce pathogens in both FWB and blood components quickly and easily with limited resources will not only be a critical adance for combat casualty care, but also provides tremendous value for humanitarian missions and civilian uses

Table 24. DoD-Sponsored Projects for the Mirasol Pathogen Reduction Technology

Project Title (Award Number)	Principal Investigator	Funding
Congressional appropriations (USAMRMC, TATRC; W81XWH-05-2-0001)	Raymond Goodrich, Ph.D. (Caridian BCT)	$5,026,150 (2004–2007)
A Transportable Pathogen Reduction System for Treatment of Whole Blood (CDMRP, DRMRP; W81XWH-09-2-0100)	Raymond Goodrich, Ph.D. (Caridian BCT)	$5,636,779 (2008—2013)
Pathogen-Reduced, Plasmalyte-Extended Stored Platelets (USAMRMC, TATRC; W81XWH-12-1-0441)	Sherrill J. Slichter, M.D. (Puget Sound Blood Center)	$1,393,464 (2011–2014)
Extended Storage of Pathogen-Reduced Platelet Concentrates (USAMRMC; W81XWH-13-2-0089)	Sherrill J. Slichter, M.D. (Puget Sound Blood Center)	$866,326 (2012)
Cost Share Contract to Advance Mirasol System (DoD, USAMMDA; W81XWH-13-C-0160)	Terumo BCT	Up to $11.3M by DoD (2013-2016)

References

Bakkour, S., Chafets, D. M., Wen, L., Meer, P. F., Mundt, J. M., Marschner, S., … Lee, T. H. (2014). Development of a mitochondrial DNA real-time polymerase chain reaction assay for quality control of pathogen reduction with riboflavin and ultraviolet light. *Vox sanguinis*, *107*(4), 351-359.

Cancelas, J. A., Rugg, N., Fletcher, D., Pratt, P. G., Worsham, D. N., Dunn, S. K., … Goodrich, R. P. (2011). In vivo viability of stored red blood cells derived from riboflavin plus ultraviolet light–treated whole blood. *Transfusion*, *51*(7), 1460-1468.

Cazenave, J. P., Folléa, G., Bardiaux, L., Boiron, J. M., Lafeuillade, B., Debost, M., … Stouch, B. (2010). A randomized controlled clinical trial evaluating the performance and safety of platelets treated with MIRASOL pathogen reduction technology. *Transfusion*, *50*(11), 2362-2375.

Chandler, M. H., Roberts, M., Sawyer, M., & Myers, G. (2012, September). The US military experience with fresh whole blood during the conflicts in Iraq and Afghanistan. In *Seminars in cardiothoracic and vascular anesthesia*, *16*(3), 153-159.

Cotton, B. A., Podbielski, J., Camp, E., Welch, T., del Junco, D., Bai, Y., … Holcomb, J. B. (2013). A randomized controlled pilot trial of modified whole blood versus component therapy in severely injured patients requiring large volume transfusions. *Annals of Surgery*, *258*(4), 527-533.

Eastridge, B. J., Hardin, M., Cantrell, J., Oetjen-Gerdes, L., Zubko, T., Mallak, C., … Blackbourne, L. H. (2011). Died of wounds on the battlefield: Causation and implications for improving combat casualty care. *Journal of Trauma and Acute Care Surgery*, *71*(1), S4-S8.

Fast, L. D., Nevola, M., Tavares, J., Reddy, H. L., Goodrich, R. P., & Marschner, S. (2013). Treatment of whole blood with riboflavin plus ultraviolet light, an alternative to gamma irradiation in the prevention of transfusion-associated graft-versus-host disease. *Transfusion*, *53*(2), 373-381.

Feasibility Study of Mirasol-Treated Whole Blood Red Cell Recovery and Survival (IMPROVE). (2008). Retrieved from https://clinicaltrials.gov/ct2/show/NCT00742001 (Identification No. NCT00742001)

Goodrich, R. P. (2013). Inactivation of whole blood with Mirasol (IMPROVEII). Retrieved from https://clinicaltrials.gov/ct2/show/NCT01907906 (Identification No. NCT01907906)

Goodrich, R. P. (2014). Survival and recovery of radio-labeled platelets derived from Mirasol-treated whole blood (Medic). Retrieved from https://clinicaltrials.gov/ct2/show/NCT02330081 (Identification No. NCT02330081)

Goodrich, R. P., Murthy, K. K., Doane, S. K., Fitzpatrick, C. N., Morrow, L. S., Arndt, P. A., … Garratty, G. (2009). Evaluation of potential immune response and in vivo survival of riboflavin-ultraviolet light–treated red blood cells in baboons. *Transfusion*, *49*(1), 64-74.

Goodrich, R. P., Doane, S., & Reddy, H. L. (2010). Design and development of a method for the reduction of infectious pathogen load and inactivation of white blood cells in whole blood products. *Biologicals*, *38*(1), 20-30.

Hlavinka, D. J., Goodrich, R. P., & Hansen, E. T. (2011). *U.S. Patent No. 8,016,736*. Washington, DC: U.S. Patent and Trademark Office.

Jackman, R. P., Muench, M. O., Heitman, J. W., Inglis, H. C., Law, J. P., Marschner, S., … Norris, P. J. (2013). Immune modulation and lack of alloimmunization following transfusion with pathogen-reduced platelets in mice. *Transfusion*, *53*(11), 2697-2709.

Joint Trauma System (JTS). (2012, October). Joint Trauma System Clinical Practice Guidelines. Retrieved from http://www.usaisr.amedd.army.mil/assets/cpgs/fresh_whole_blood_transfusion_24_oct_12.pdf

Jones, A. R., & Frazier, S. K. (2014). Increased mortality in adult trauma patients transfused with blood components compared with whole blood. *Journal of trauma nursing: The official journal of the Society of Trauma Nurses*, *21*(1), 22.

Keil, S. D., Kiser, P., Sullivan, J. J., Kong, A. S., Reddy, H. L., Avery, A., & Goodrich, R. P. (2013). Inactivation of Plasmodium spp. in plasma and platelet concentrates using riboflavin and ultraviolet light. *Transfusion*, *53*(10), 2278-2286.

Mabry, R. L., Holcomb, J. B., Baker, A. M., Cloonan, C. C., Uhorchak, J. M., Perkins, D. E., … & Hagmann, J. H. (2000). United States Army Rangers in Somalia: An analysis of combat casualties on an urban battlefield. *Journal of Trauma and Acute Care Surgery*, *49*(3), 515-529.

Nessen, S. C., Eastridge, B. J., Cronk, D., Craig, R. M., Berséus, O., Ellison, R., … Spinella, P. C. (2013). Fresh whole blood use by forward surgical teams in Afghanistan is associated with improved survival compared to component therapy without platelets. *Transfusion*, *53*(S1), 107S-113S.

Okoye, O. T., Reddy, H., Wong, M. D., Doane, S., Resnick, S., Karamanos, E., … Inaba, K. (2015). Large animal evaluation of riboflavin and ultraviolet light–treated whole blood transfusion in a diffuse, nonsurgical bleeding porcine model. *Transfusion*, *55*(3), 532-543.

Owusu-Ofori, S., Kusi, J., Owusu-Ofori, A., Freimanis, G., Olver, C., Martinez, C. R., … Allain, J. P. (2014) Treatment of whole blood (WB) with riboflavin and UV light: Impact on malaria parasite viability and WB storage. *Shock.* Advance online publication. doi: 10.1097/SHK.0000000000000028

Pidcoke, H. F., McFaul, S. J., Ramasubramanian, A. K., Parida, B. K., Mora, A. G., Fedyk, C. G., … Cap, A. P. (2013). Primary hemostatic capacity of whole blood: A comprehensive analysis of pathogen reduction and refrigeration effects over time. *Transfusion*, *53*(S1), 137S-149S.

Reddy, H. L., Doane, S. K., Keil, S. D., Marschner, S., & Goodrich, R. P. (2013). Development of a riboflavin and ultraviolet light-based device to treat whole blood. *Transfusion*, *53*(S1), 131S-136S.

Spinella, P. C., Perkins, J. G., Grathwohl, K. W., Beekley, A. C., & Holcomb, J. B. (2009). Warm fresh whole blood is independently associated with improved survival for patients with combat-related traumatic injuries. *The Journal of trauma*, *66*(4 Suppl), S69.

Terumo BCT. (2009). A transportable pathogen reduction system for treatment of whole blood (W81XWH-09-2-0100). *Congressionally Directed Medical Research Programs*. Retrieved from http://cdmrp.army.mil/search.aspx?LOG_NO=DR080806

Terumo BCT (2015). Retrieved from https://www.terumobct.com/location/north-america/Pages/home.aspx

Tonnetti, L., Proctor, M. C., Reddy, H. L., Goodrich, R. P., & Leiby, D. A. (2010). Evaluation of the Mirasol platelet reduction technology system against Babesia microti in apheresis platelets and plasma. *Transfusion*, *50*(5), 1019-1027.

Tonnetti, L., Thorp, A. M., Reddy, H. L., Keil, S. D., Goodrich, R. P., & Leiby, D. A. (2012). Evaluating pathogen reduction of Trypanosoma cruzi with riboflavin and ultraviolet light for whole blood. *Transfusion*, *52*(2), 409-416.

Tonnetti, L., Thorp, A. M., Reddy, H. L., Keil, S. D., Goodrich, R. P., & Leiby, D. A. (2013). Riboflavin and ultraviolet light reduce the infectivity of Babesia microti in whole blood. *Transfusion*, *53*(4), 860-867.

Tonnetti, L., Thorp, A. M., Reddy, H. L., Keil, S. D., Doane, S. K., Goodrich, R. P., & Leiby, D. A. (2014). Reduction of Leishmania donovani infectivity in whole blood using riboflavin and ultraviolet light. *Transfusion*, *55*(2), 326-329.

Logistically Supportable Dried Plasma Products for Transfusion

DoD has pursued a two-product strategy for dried plasma, through which both a single-donor freeze-dried plasma (FDP) and a pooled-donor solvent detergent spray-dried (SDSD) plasma product are undergoing clinical trials. Attaining an FDA-approved dried plasma product will fill the critical need for a logistically supportable, effective resuscitation fluid that can be acquired for use by the U.S. military.

- Developmental Partner Organizations:
  - Vascular Solutions, Inc.
  - Entegrion, Inc.
  - USAMMDA
  - ONR
  - DHP-Chartered Joint Advanced Development Program

Key Outcomes and Impact:

- Army-led studies funding development and testing of Vascular Solutions' FDP are ongoing to support submission of a Biologics License Application
- Following initial sponsorship by ONR, development of Entegrion's SDSD plasma product Resusix is continuing under the first DHA-chartered medical Joint Development Program. A Phase 1 trial was conducted and Entegrion is funded to develop Resusix through Phase 3 trials
- U.S. military casualties have been treated effectively by coalition forces with German FDP (Glassberg et al., 2013a; Hervig et al., 2014; Pennardt, 2010)
- Pending an FDA-approved dried plasma, U.S. Special Operations Forces were granted access to French FDP through an Expanded Access Investigational New Drug (IND) protocol in 2011

French Dried Plasma Has Been Used by U.S. Special Forces (Rasmussen, Baer, Doll, & Caravalho)

Overview

Hemorrhage remains the leading cause of potentially survivable death among combat casualties (Eastridge et al., 2012). Consequently, many advances have been made for the care of hemorrhaging trauma patients, such as improved control of bleeding with devices like modern tourniquets and hemostatic dressings, and resuscitation strategies with blood components including plasma. However, initial resuscitation of hemorrhagic shock by ground medics has often been limited to replacement of circulating volume using crystalloid or colloid solutions (DHB, 2011). Large-volume transfusions of these solutions can be a contributing factor to the development of a condition of impaired blood clotting, or coagulopathy, in trauma patients (DHB, 2011). Coagulopathy is common among combat casualties requiring transfusion who arrive at emergency rooms, and has been associated with a five- to six-fold increase in mortality (Glassberg et al., 2013b; DHB, 2011; Schreiber, 2010). Coagulopathy induced by trauma develops in 20–30 percent of combat casualties requiring blood transfusion, with a rise in prevalence with increasing injury severity (Maegele et al., 2012). Given these complications, emphasis on increasing plasma volumes for in-hospital transfusions has become a standard of care at medical treatment facilities in theater in Iraq and Afghanistan, and is being adopted by civilian trauma centers (DHB, 2011). Plasma infusion is also the standard of care for treating coagulopathy, and medical centers around the world are shifting toward administering plasma as the initial resuscitation for trauma victims (Glassberg et al., 2013b). The capabilities of plasma to both provide coagulation factors and appropriately buffered, sustained intravascular volume have made it an invaluable resuscitation fluid and early and aggressive plasma infusion is associated

with increased survival in patients with coagulopathy and life-threatening hemorrhage (Glassberg et al., 2013b, DHB, 2011).

As U.S. forces are active in austere environments and are faced with potential future theaters of operation from which evacuation times will be lengthy, access to consistently available and effective resuscitation resources remains an important consideration, and has spurred efforts to identify new means for managing hemorrhage. One approach is making plasma more accessible as a primary resuscitation fluid in the field. Though the use of plasma for prehopital resuscitation may have significant benefits, there are substantial logistical challenges to this approach when using currently available FFP sources.

The logistics of current plasma sources create limitations both at prehospital and at higher roles of care in theater. FFP requires freezer storage and must be used relatively quickly once thawed, with most protocols calling for use within 4–5 days (Inaba, 2011). Consequently, plasma is often thawed on demand for use, which delays the time to first transfusion. FFP is typically not suitable for use at lower roles of care because of the cold-chain requirements and associated equipment for temperature maintenance and thawing that make it infeasible. The logistical burden of getting FFP products to theater is also high, and in the past there has been significant waste from units breaking during shipment from the continental U.S. (DHB, 2011; USAMRMC, 2009).

Dried plasma sources offer several logistical benefits over FFP for treatment of trauma patients prehospital. These benefits include ease of transport because of reduced weight and size, stability at room temperature, and rapid reconstitution for infusion. To bring these benefits to standard practice for U.S. forces, the DoD has supported the development of two different dried plasma sources that are now in clinical trials: a single-donor FDP being produced in partnership with Vascular Solutions, Inc., and a pooled-donor SDSD plasma product called Resusix, developed by Entegrion (Figure 11).

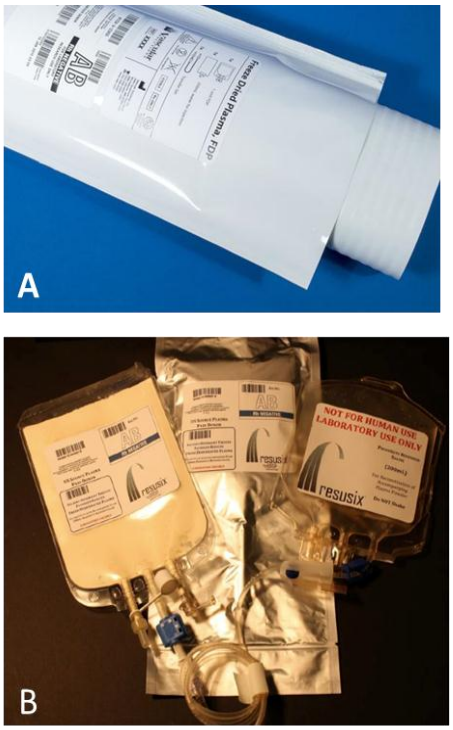


Figure 11. (A) Vascular Solutions' FDP (Grayson, 2014), (B) Resusix's SDSD Plasma (Entegrion 2012)

Capability Gap Alignment

Developing logistically supportable, dried plasma products and successfully guiding them through the FDA-approval process will enable their use by U.S. forces in theater and addresses multiple capability gaps that have been outlined by key requirement sources for combat casualty care (Table 25).

Table 25. Capability Gaps Addressed by Dried Plasma

Requirement Sources	Capability Gaps Addressed
GDF	• **JCM-1-1** – Inadequate ability to diagnose, resuscitate, and stabilize casualties with survivable wounds • **JCM-1-8** – Inadequate therapy for shock and head injury • **JCM-2-2** – Poor ability to provide tissue oxygenation and compatible shelf-stable blood products • **JCM-2-3** – Poor ability to restore blood volume
TC3 ICD	• **Theater Hospitalization, Area Medical Support** – Diagnose, resuscitate and stabilize casualties with survivable wounds • **Blood Substitutes** – Provide tissue oxygenation, compatible blood types, shelf stable • Rapid Administration of Fluids – Restore blood volume • **Coagulopathy Prevention and Treatment Agents** – Immediate recognition and correction of coagulopathy
DHP ICD	• **TI1** – Insufficient current first-responder (medical and non-medical) capacity and capability to initially assess, treat, and maintain severe trauma cases in the pre-hospital environment - Insufficient tools that enable both non-medical and medical first responders - The technologies do not exist to fulfill some of the needs (e.g., stabilizing the airway or truncal hemorrhage) • **MC6** – Lack of optimal blood expander with oxygenation capability and fluid resuscitative strategy at POI • **TS3** – Lack of suitable resuscitative fluids (e.g., blood products or substitutes) appropriate for administration in the pre-hospital environment in order to prevent shock

In addition to these requirements sources, the DCBI TF identified priority research issues in the area of Hemorrhage Control and Resuscitation that included the early use of blood products for battlefield trauma care (DCBI TF, 2011). Indeed, the top priority materiel recommendation of the TF was facilitating the fielding of an FDA-approved FDP product for use by medics.

Impact on the Battlefield/Warfighter

Implementation of dried plasma products will have several substantial impacts for U.S. forces. In the past, simply transporting FFP from the U.S. to a distant theater of operations has resulted in a substantial loss of plasma because of breakage of as many as 40 percent of FFP units in transport, and because of further fracture of FFP bags upon thawing (DHB, 2011; USAMRMC, 2009). Dried plasma sources will offer greater flexibility and reliability through their reduced size and weight, and ability to be handled outside of cold chain requirements. Together these factors not only provide greater robustness and ease of use, but also reduce requirements on resources including power supply. The ability to quickly reconstitute a dried plasma source when needed will enable faster responses to casualties without the waste that is often associated with thawing fresh frozen blood products with limited shelf lives in anticipation of potential use that does not occur.

Beyond the logistical improvements, there can be improvements in outcome for trauma casualties by enabling resuscitation faster and increasingly closer to the POI. Transitioning to the earlier use of plasma during resuscitative care as a part of new and evolving DCR strategies has already shown the ability to improve outcomes for combat casualties. This has been demonstrated with the use of available, approved FFP sources by U.S. forces and in civilian contexts. Early use of plasma has increased survival in the hospital setting (Glassberg et al.,

2013a). Evidence gained from both military and civilian experience has driven the administration of plasma as the initial resuscitation fluid by some medical centers, and studies have shown that early and aggressive plasma infusion is associated with increased survival (DHB, 2011; Glassberg et al., 2013b, Holcomb et al., 2013; Gonzalez et al., 2007; Pidcoke et al., 2012). An analysis of transfusion practices for U.S. service members admitted to a military hospital in OIF/OEF over the 10-year span of 2003-2012 has shown that shifting clinical practices toward inclusion of high transfusion ratios of FFP have resulted in improved survival (Pidcoke et al., 2012). As these results have emerged, evaluation of the prehospital use of plasma has also received increasing attention. Although the approach remains to be fully evaluated, initial reports have suggested a positive impact, and prehospital plasma for resuscitation is being advocated by many experts (DHB, 2011; Glassberg et al., 2013a; Glassberg et al., 2013b; Lee, et al., 2013b; Pennardt, A., 2010; Sailliol et al., 2013).

Although there is not yet an FDA-approved dried plasma product available, dried plasma products have been effectively used by allied forces including German, French, and Norwegian militaries, as well as the Norwegian civilian emergency aeromedical services (Glassberg et al., 2013a; Hervig et al., 2014). U.S. military casualties have already been treated effectively by coalition forces with German FDP; German forces have administered over 500,000 units without significant adverse events (Pennardt, 2010). Use of the French product to support military operations has been ongoing since 2003, with the use of more than 1,100 units monitored without adverse events (Sailliol et al., 2013). The French product has improved responsiveness in the treatment of military casualties during combat operations primarily because it is shelf stable at room temperature, available in less than 6 minutes, and blood type universal. Together, these foreign products have demonstrated the efficacy and advantages of dried plasma in modern theaters.

Clinical Practice

Impact on Clinical Practice Guidelines

Dried plasma was identified by expert consensus during a 2011 USAISR-USAMRMC Fluid Resuscitation Conference to be the most promising agent for DCR, and the DHB recommended that support for the development and fielding of an FDA-approved dried plasma product be increased (DHB, 2011). The push for dried plasma is due in part to changing DCR CPGs over the last decade. Current TCCC Guidelines do not support the use of large volumes of crystalloids in fluid resuscitation, and give preference to the use of balanced blood products including plasma (Butler, Giebner, McSwain, Salomone, & Pons, 2010; DHB, 2011; TCCC, 2014). While guidelines for DCR have been developed primarily taking into account the use of FFP as a plasma source when available, the availability of a dried plasma source will provide a substitute in the future and may enable more extensive recommendation of plasma use based on its

> "The preferred fluids for resuscitation of casualties in hemorrhagic shock, in descending order of preference, are:
>
> - Whole blood
> - 1:1:1 plasma, RBCs, and platelets
> - 1:1 plasma and RBCs
> - Reconstituted DP [dried plasma], liquid plasma, or thawed plasma alone or RBCs alone
> - Hextend
> - LR or Plasma-Lyte A"
>
> TCCC Guidelines Change 14-01
> Butler et al., 2014

improved accessibility to all roles of care. Indeed, in the most recent change to guidelines for fluid resuscitation for hemorrhagic shock in TCCC, dried plasma has been recommended among the preferred fluids for resuscitation of casualties in hemorrhagic shock when other blood components or whole blood are not available. The publication implementing this guideline change cites dried plasma as offering opportunities for both volume replacement and the replacement of clotting factors, while having a good safety record (Butler et al., 2014). The report also notes, however, that without an FDA-approved product, the option of dried plasma is not yet available to most U.S. combat medics. In conjunction with continued research into prehospital plasma use, FDA-approved dried plasma products can make plasma more accessible at all roles of care, including for medics in the field. This will certainly further impact CPGs for resuscitation during tactical care.

In addition to tactical care guidelines, a current CPG published by JTS for resuscitation at Role 2b/3 treatment facilities recommended the use of plasma and other blood components at appropriate ratios over crystalloids (JTS, 2014). It also emphasizes the need to quickly obtain a casualty's blood type to enable the provision of type-specific plasma transfusion as quickly as possible. With the advent of dried plasma, the requirement of thawing is removed and time to prepare type-specific plasma can be shortened. A pooled dried plasma approach may also enable a universal product that can be sustainably available and used without the delay of typing.

The use of FDP has already influenced the modern practices of many U.S. allies, including in the prehospital environment. The prehospital use of FDP was approved by the Israeli Surgeon General in November 2012 and presented to the Advisory Transfusion Committee to the Ministry of Health, with procurement and distribution of FDP beginning in December 2012 (Glassberg et al., 2013a). The Israel Defense Forces (IDF) has chosen to use the German FDP product, LyoPlas. The IDF Medical Corps (IDF-MC) policy has named plasma as the resuscitation fluid of choice for trauma casualties, rather than crystalloid solutions, and states it should be transfused as near to POI as practicable (Glassberg et al. 2013a). The protocol for plasma use was developed by the Trauma and Combat Medicine Branch of the IDF-MC, with support from trauma and hematology experts in both Israel and the U.S. The protocol sets the resuscitation goal at a systolic blood pressure of greater than 80 mmHg or the return of palpable radial pulse; after transfusion of three units of FDP, providers are instructed to carefully consider further FDP administration (Glassberg et al., 2013a) (Figure 12).

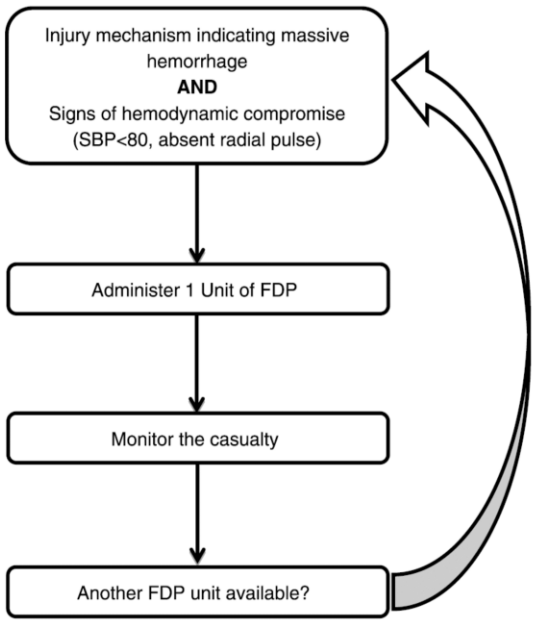


Figure 12. The IDF Dried Plasma Transfusion Protocol (Glassberg et al., 2013a).

The French FDP product has been routinely used in strategic air evacuation to France from theaters of operation. The French Military Blood Institute (CTSA) has assessed the clinical and biological efficacy and safety of FDP, and found support for the early transfusion of FDP combined with RBCs to improve survival through prevention or correction of coagulopathy without adverse effects (Sailliol et al., 2013). The CTSA now recommends early use of FDP to prevent coagulopathy in treatment of severe hemorrhage at remote Role 1 facilities and in the tactical medical evacuation by helicopter of bleeding casualties from Role of Care 1 to Role 2 or 3, before administration of FWB or other blood products (Sailliol et al., 2013). The CTSA additionally proposed the use of FDP in civilian settings when thawed FFP is not yet available and when conditions prohibit an effective cold chain, such as emergency services in isolated locations and in prehospital settings (Sailliol et al., 2013). Pending the availability of an FDA-approved source of dried plasma, U.S. Special Operations Forces were granted access to the French product through an Expanded Access IND protocol in 2011 (USAISR, 2014). The Assistant Secretary of Defense for Health Affairs approved the use of FDP under the protocol in November 2011 (Swann, 2012). Purchasing arrangements were established to enable contracting of the French FDP, and initial units for training were received in 2012 (Swann, 2012). This IND has enabled an initial, limited change in clinical practice by U.S. forces with respect to modern use of FDP.

Supporting Publications

A long history of research and clinical use already support dried plasma products. FDP itself is not a recent invention; it was introduced in 1941 and was used sporadically by the U.S. in World War II and Korea (Glassberg et al., 2013b; Schmidt, 2012). These early products, however, were pooled from many donors without protocols and technologies yet available to properly control the risk of spreading blood-born infection. Because of the infectious danger, FDP use was abandoned by the U.S. blood bank, accompanied by the logic that the introduction of helicopters would bring shorter evacuation times to modern warfare and that the resulting diminished need for field resuscitation would mean the risks of plasma administration were no longer justified (Glassberg et al., 2013b). Since that time, the use of FDP by other countries has continued, and the U.S. has returned the development of a safe, effective dried plasma source to priority, given the current and envisioned future needs for such a product for operations in austere conditions and during extended evacuation times.

Published modern data on the use of dried plasma includes supporting data on the functional equivalence of FDP to FFP from animal models and in vitro studies of plasma activity (Inaba, 2011; Glassberg et al., 2013b; Lee et al., 2013a; Martinaud et al., 2012; Shuja et al., 2008; Spoerke et al., 2009). Additionally, many key clinical publications have supported the ongoing use of dried plasma in the casualty care practices of allied forces (Table 26).

Table 26. Supporting Publications for Dried Plasma

Reference	Description
Clinical Use by Allied Forces	
Martinaud et al., 2012	Summarizes French experience with FDP at a Role 3 medical treatment facility in Afghanistan during 2010-2011. Eighty-seven casualties received FDP; clinicians reported ease of use, efficacy equivalent to FFP, and no significant adverse events
Bux, Dickhorner, & Scheel, 2013	Assessed German Red Cross single-donor FDP. Coagulation factor activity was only slightly reduced with freeze drying when assessed in vitro, and there were no reports of clinical ineffectiveness for more than 230,000 units delivered for clinical use from 2007 to 2011
Recent Advancement of Prehospital Dried Plasma Use	
Glassberg et al., 2013b	Case report of the first use of single-donor FDP at the POI by IDF paramedic responding to a motor vehicle crash
Glassberg et al., 2013a	Reports on the first 10 casualties treated by FDP transfusion at the POI by the IDF

Many studies continue to evaluate the role of plasma specifically in prehospital trauma care, and will enable continued development and optimization of CPGs through their results. These include a number of clinical trials of prehospital plasma administration currently being sponsored by the CCCRP, discussed below.

Role of CCCRP-Sponsored Projects

The CCCRP has played key roles in DoD's comprehensive approach towards plasma product development and use. These include sponsoring a number of efforts for the development of plasma products, and the study of the prehospital use of plasma for traumatic hemorrhage, largely through the support of DHP funding. Other efforts studied the lyophilization of plasma and explored its use in animal models, including a swine model of multiple trauma and severe hemorrhage (Spoerke et al., 2009). Several additional projects are in process (Table 27), with the CCCRP playing an integral role in moving forward the DoD's strategy for advancing a modern FDA-approved dried plasma source. This strategy has pursued two different products in parallel. Ongoing Army-led studies have funded the development and testing of a FDP product, begun initially through efforts in partnership with HemCon Medical Technologies, Inc., and now with Vascular Solutions, Inc., as a manufacturing partner. USAMMDA has entered into a cooperative research and development agreement (CRADA) with Vascular Solutions in which the Army will sponsor, conduct, and fund all FDA required pre-clinical and clinical studies to support a Biologics License Application for the FDP product. This Army development program is expected to deliver a single-donor, pathogen tested, FDP product. This work has also been complemented by additional CCCRP-sponsored studies of the optimized reconstitution and use of FDP, performed by researchers at academic organizations (Table 27).

In the second arm of the strategy, DoD has provided funding to Entegrion to develop a SDSD plasma product, Resusix, which is derived from pooled plasma. The product is treated by solvent detergent protein inactivation to reduce pathogens, and has a shelf life of

The first DHA-chartered medical Joint Development Program has been formed for the advancement of Entegrion's Resusix SDSD plasma product, setting a precedent for success in partnership of organizations across the services.

2–5 years (DHB, 2011). Development of Resusix was initially sponsored by the ONR, and published studies have shown the ability of Resusix to confer comparable protective effects to FFP for the correction of coagulopathy and reduction of bleeding (Wataha et al., 2013). As Resusix has successfully progressed, the first DHA-chartered medical Joint Development Program has now been formed for the product. This achievement, driven with the contribution of the CCCRP's leadership, represents a tremendous success in partnership of organizations across the services. Entegrion has conducted a Phase 1 trial to test the safety of Resusix in healthy volunteers (NCT01589666), and has received funding to develop Resusix through Phase 3 clinical trials.

Together, these two approaches are expected to deliver dried plasma products that will ultimately reduce logistical constraints and enable the administration of plasma quickly under a range of circumstances and environments.

Table 27. CCCRP-Sponsored Projects for Development of Dried Plasma Products and Clinical Evaluation of Prehospital Plasma Use

Project Title (Clinical Trial Identifier and/or Award Number)	Organization/ Principal Investigator	Funding
Dried Plasma Development and Clinical Testing		
Pooled SDSD Plasma (NCT01589666; CRADA with Entegrion)	Entegrion	Funding of the development of Resusix through Phase 3 clinical trials and Biological License Application (up to $43.7M)
Single Donor FDP (CRADA with Vascular Solutions, Inc.)	Vascular Solutions, Inc.	Funding of all studies required by FDA for regulatory approval; sponsor and fund a post-approval clinical study to broaden the approved indication if required by FDA
Optimization of Lyophilized Plasma for use in Combat Casualties (W81XWH-11-2-0084)	Martin Schreiber (Oregon Health & Science University)	$1,539,756 (2010-2013)
Evaluation of Lyophilized Plasma (LP) in Models of Vascular Injury and Hemorrhagic Shock (W81XWH11-2-0068)	Bryan A. Cotton, M.D., M.P.H. (University of Texas Health Science Center at Houston)	$330,068 (2010-2013)
Prehospital Plasma Trials		
Prehospital Air Medical Plasma (PAMPer) Trial (NCT01818427; W81XWH-12-2-0023)	Jason L. Sperry, M.D., M.P.H. (University of Pittsburg)	Three studies were solicited under the 2011 Prehospital Use of Plasma for Traumatic Hemorrhage program announcement. These are 4-year, multi-center trials. Estimated total program funding of $16M
Prehospital Use of Plasma for Traumatic Hemorrhage (PUPTH) (NCT02303964; W81XWH-12-2-0022)	Bruce D. Spiess, M.D. (Virginia Commonwealth University)	
Control of Major Bleeding after Trauma Study (COMBAT) (NCT01838863; W81XWH-12-2-0028)	Ernest E. Moore, M.D. (University of Colorado, Denver)	

The CCCRP continues to fund additional clinical studies of the prehospital use of plasma to determine optimal therapeutic approaches to managing coagulopathy in hemorrhaging trauma patients. These include three recently initiated trials administered by the Telemedicine and Advanced Technology Research Center (Table 27). The PAMPer trial is examining the administration of two units of thawed AB plasma to trauma patients during air transport, the PUPTH trial is examining the impact of the administration of thawed plasma by emergency medical service personnel in ground ambulance on mortality and coagulopathy, and the COMBAT trial is also assessing coagulopathy, transfusion requirements, metabolic recovery, organ failure, and mortality following plasma administration in ground ambulance (Brown et al., 2015).

These various CCCRP-sponsored efforts have resulted in multiple publications (Table 28). These continue to build the foundation for further results to come as plasma use advances.

Table 28. CCCRP-Sponsored Publications of Prehospital Plasma Use and Development of Dried Plasma

Reference	Description
Prehospital Plasma Trials	
Brown et al., 2015	Published the design and rationale of the PAMPer Trial; the primary objective is to determine the effect of prehospital plasma transfusion during air medical transport on 30-day mortality in patients at risk for traumatic hemorrhage
Development of Dried Plasma	
Spoerke et al., 2009	Examined the use of FDP for resuscitation in a swine model of multiple trauma; determined that coagulation factor activity in plasma was reduced by 14% with lyophilization, but the FDP could be used successfully for resuscitation and there were not acute differences in blood loss compared with FFP
Lee et al., 2013a	Evaluated FDP in the swine model, demonstrating that minimized volume and buffering during reconstitution may improve the safety and logistical feasibility of its use for hemostatic resuscitation
Lee et al., 2013b	Sought to optimize FDP reconstitution into a minimal volume fluid that provides effective hemostatic resuscitation for trauma while minimizing logistical limitations. Reconstitution to 50 percent volume was tolerated and effective for resuscitation in a swine model
Lee et al., 2014	Examined reconstitution of FDP with water, lactated Ringer's solution, saline, and Hextend solutions for resuscitation in a swine model of polytrauma and hemorrhagic shock; low-volume reconstitution with sterile water was safe and presents an available, cost-effective option

References

Brown, J. B., Guyette, F. X., Neal, M. D., Claridge, J. A., Daley, B. J., Harbrecht, B. G., … Sperry, J. L. (2015a). Taking the blood bank to the field: The design and rationale of the prehospital air medical plasma (PAMPer) trial. *Prehospital Emergency Care*, doi:10.3109/10903127.2014.995851.

Butler, F. K., Giebner, S. D., McSwain, N., Salomone, J., & Ponos, P. (Eds). (2010). *Prehospital Trauma Life Support Manual, Military Edition, Seventh Edition*. St. Louis, Missouri: Mosby, Inc.

Butler, F. K., Holcomb, J. B., Schreiber, M. A., Kotwal, R. S., Jenkins, D. A., Champion, H. R., … Bailey, J. A. (2014). Fluid resuscitation for hemorrhagic shock in Tactical Combat Casualty Care: TCC Guidelines Change 14-01 – 2 June 2014. *Journal of Special Operations Medicine*, *14*(3), 30-55.

Bux, J., Dickhorner, D., & Scheel, E. (2013). Quality of freeze-dried (lyophilized) quarantined single-donor plasma. *Transfusion, 53*, 3203-3209.

Control of Major Bleeding After Trauma Study (COMBAT). (2014). Retrieved from https://clinicaltrials.gov/ct2/show/NCT01838863 (Identification No. NCT01838863)

Defense Health Board (DHB). (2011, August 8). Use of dried plasma in prehospital battlefield resuscitation 2011-04. Retrieved from https://www.jsomonline.org/PDFs/DHB%20Memo%20Dried%20Plasma%20110808.pdf

Dismounted Complex Blast Injury Task Force (DCBI TF). (2011). Dismounted complex blast injury: Report of the Army Dismounted Complex Blast Injury Task Force. Retrieved from http://armymedicine.mil/Documents/DCBI-Task-Force-Report-Redacted-Final.pdf

Eastridge, B. J., Mabry, R. L., Seguin, P., Cantrell, J., Tops, T., Uribe, P., … Blackbourne, L. H. (2012). Death on the battlefield (2001-2011): Implications for the future of combat casualty care. *Journal of Trauma Acute Care Surgery, 73*(6 Suppl 5), S431-S437.

Entegrion. (2012). Product spotlight: Resusix. Retrieved from http://www.entegrion.com/

Entegrion. (2011). Safety study of spray-dried solvent/detergent-treated plasma for infusion in health volunteers. Retrieved from https://clinicaltrials.gov/ct2/show/NCT01589666. (Identification No. NCT01589666)

Glassberg, E., Nadler, R., Gendler, S., Abramovich, A., Spinella, P. C., Gerhardt, R. T., Holcomb, J. B., & Kreiss, Y. (2013a). Freeze-dried plasma at the point of injury: From concept to doctrine. *Shock, 40*(6): 444-450.

Glassberg, E., Nadler, R., Rasmussen, T. E., Abramovich, A., Erlich, T., Blackbourne, L. H., & Kreiss, Y. (2013b). Point-of-injury use of reconstituted freeze-dried plasma as a resuscitative fluid: A special report for prehospital trauma care. *Journal of Trauma and Acute Care Surgery, 75*(2, Suppl 2), S111-S114.

Gonzalez, E. A., Moore, F. A., Holcomb, J. B., Miller, C. C., Kozar, R. A., Todd SR, … McKinley, B. A. (2007). Fresh frozen plasma should be given earlier to patients requiring massive transfusion. *Journal of Trauma, 62*, 112-119.

Grayson, K. (2014, April 23). U.S. Army backs Vascular Solutions' freeze-dried plasma push. Retrieved from http://www.bizjournals.com/twincities/blog/in_private/2014/04/u-s-army-backs-vascular-solutions-freeze-dried.html.

Hervig, T., Doughty, H., Ness, P., Badloe, J. F., Berseus, O., Glassberg, E., Heier, H. E. (2014). Prehospital use of plasma: The blood bankers' perspective. *Shock, 41*(Suppl 1), 39-43.

Holcomb, J. B., Del Junco, D. J., Fox, E. E., Wade, C. E., Cohen, M. J., Schreiber, M. A., … PROMMTT Study Group. (2013). The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) Study: Comparative effectiveness of a time-varying treatment with competing risks. *Journal of the American Medical Association Surgery, 148*(3):127-136.

Inaba, K. (2011). Freeze-dried plasma. *Journal of Trauma*, *70* (Suppl 5), S57-S58.

Joint Trauma System (JTS). (2014, December). JTS & CCAT Clinical Practice Guidelines. Retrieved from http://www.usaisr.amedd.army.mil/clinical_practice_guidelines.html

Lee, T. H., McCully, S. P., McCully, B. H., Sands, C., Hampton, D. A., Louis, S. G., … Schreiber, M. A. (2014). Comparison of the hemostatic efficacy of low-volume lyophilized plasma reconstituted using sterile water, lactated Ringer's, normal saline, and Hextend solutions. *Journal of Trauma and Acute Care Surgery*, *76*(2), 264-272.

Lee, T. H., Van, P. Y., Spoerke, N. J., Hamilton, G., J., Cho, S. D., Watson, K., … Schreiber, M. A. (2013a). The use of lyophilized plasma in a severe multi-injury pig model. *Transfusion*, *53*(Suppl 1), S72-S79.

Lee, T. H., Watson, K.,Fabricant, L., Barton, J., Differding, J., Kremenevskiy, I., … Schreiber, M. A. (2013b). Hyperosmolar reconstituted lyophilized plasma is an effective low-volume hemostatic resuscitation fluid for trauma. *Journal of Trauma and Acute Care Surgery*, *75*(3), 369-75.

Martinaud, C., Civadier, C., Ausset, S., Verret, C., Deshayes, A. V., & Sailliol, A. (2012). In vitro hemostatic properties of French lyophilized plasma. *Anesthesiology, 117*, 339-346.

Pennardt A. (2010). The time to field freeze dried plasma is now. *Journal of Special Operations Medicine*, *10*, 49.

Pidcoke, H. F., Aden, J. K., Mora, A. G., Borgman, M. A., Spinella, P. C., Dubick, M. A., … Cap, A. P. (2012). Ten-year analysis of transfusion in Operation Iraqi Freedom and Operation Enduring Freedom: Increased plasma and platelet use correlates with improved survival. *Journal of Trauma and Acute Care Surgery*, *73*(6 Suppl 5), S445-S452.

PreHospital Air Medical Plasma Trial (PAMPer). (2015). Retrieved from https://clinicaltrials.gov/ct2/show/NCT01818427 (Identification No. NCT01818427)

Safety Study of Spray-Dried Solvent/Detergent-Treated Plasma for Infusion in Healthy Volunteers (2015). Retrieved from https://clinicaltrials.gov/ct2/show/NCT01589666 (Identification No. NCT01589666)

Schmidt, P. J. (2012). The plasma wars: A history. *Transfusion*, 52, 2S-4S.

Schreiber, M. (2010, November 16). Observations on prehospital trauma care from the deployed director of the JTTS. Presentation to the Committee on Tactical Combat Casualty Care.

Shuja, F., Shults, C., Duggan, M., Tabbara, M., Butt, M. U., Fischer, T. H., … Alam, H. B. (2008). Development and testing of freeze-dried plasma for the treatment of trauma-associated coagulopathy. *Journal of Trauma, 65*, 975-985.

Sailliol, A., Martinaud, C., Cap, A. P., Civadier, C., Clavier, B., Deshayes, A.-V., … Ausset, S. (2013). The evolving role of lyophilized plasma in remote damage control resuscitation in the French Armed Forces Health Service. *Transfusion, 53* (Suppl), 65S-71S.

Spoerke, N., Zink, K., Cho, D., Differding, J., Muller, P., Karahan, A., … Schreiber, M. (2009). Lyophilized plasma for resuscitation in a swine model of severe injury. *Archives of Surgery*, *144*(9), 829-834.

Swann, S. W. (2012, May 10). USSOCOM Command Surgeon. Presentation at the Medical Technology, Training and Treatment Conference (MT3) 2012 Conference, Orlando, Florida.

Tactical Combat Casualty Care (TCCC) Guidelines (2014, October). Retrieved from http://usaisr.amedd.army.mil/assets/pdfs/TCCC%20Guidelines%20141028.pdf

U.S. Army Medical Research and Materiel Command (USAMRMC). (2009). Freeze dried plasma. Retrieved from http://www.usammda.army.mil/documents/FDP%20Brochure.pdf

U.S. Army Institute of Surgical Research (USAISR). (2014, October 23). Coagulation and blood research program. Retrieved from http://www.usaisr.amedd.army.mil/blood_research.html.

Wataha, K., Menge, T., Deng, X., Sha, A., Bode, A., Holcomb, J. B., … Pati, S. (2013). Spray-dried plasma and fresh frozen plasma modulate permeability and inflammation in vitro in vascular endothelial cells. *Transfusion*, *53*, 80S-90S.

Forward Surgical and Intensive Critical Care Portfolio

The FSICC portfolio works in areas spanning prehospital, emergency, surgical, intensive, and nursing care, with emphases on advanced monitoring and battlefield medical equipment. The portfolio seeks to decrease morbidity and mortality across all roles of care through R&D that expands knowledge, and through the development of new algorithms, devices, and procedures that advance medical decision-making and promote earlier intervention.

In doing so, the FSICC portfolio is accounting for the changing environments of modern combat. In future conflicts with U.S. military involvement, theater characteristics (both with regard to geographic and threat landscapes) may restrict the ability to quickly evacuate casualties to military treatment facilities. The previous concept of the "golden hour," or the period immediately after trauma during which intervention by first responders and transport to a higher role of care is critical for reducing morbidity and mortality, has been reappraised for 2015 and beyond (Rasmussen, Baer, Doll, & Caravalho, 2015). In the new context, bringing advanced resuscitative and intensive care capabilities far forward toward the POI is considered the key to reducing mortality and is increasingly the focus of the FSICC portfolio (Figure 13). This also calls for the continued development of automated systems linking patient movement and medical providers at all roles of care with medical reach back. This reappraisal places emphasis on closing capability gaps related to in-field care, and presents emerging capability gaps that are driving the direction of the portfolio, such as the need for effective decision support technologies to assist providers and closed-loop medical systems to autonomously manage aspects of care (Hatzfeld and Cardin, 2014).

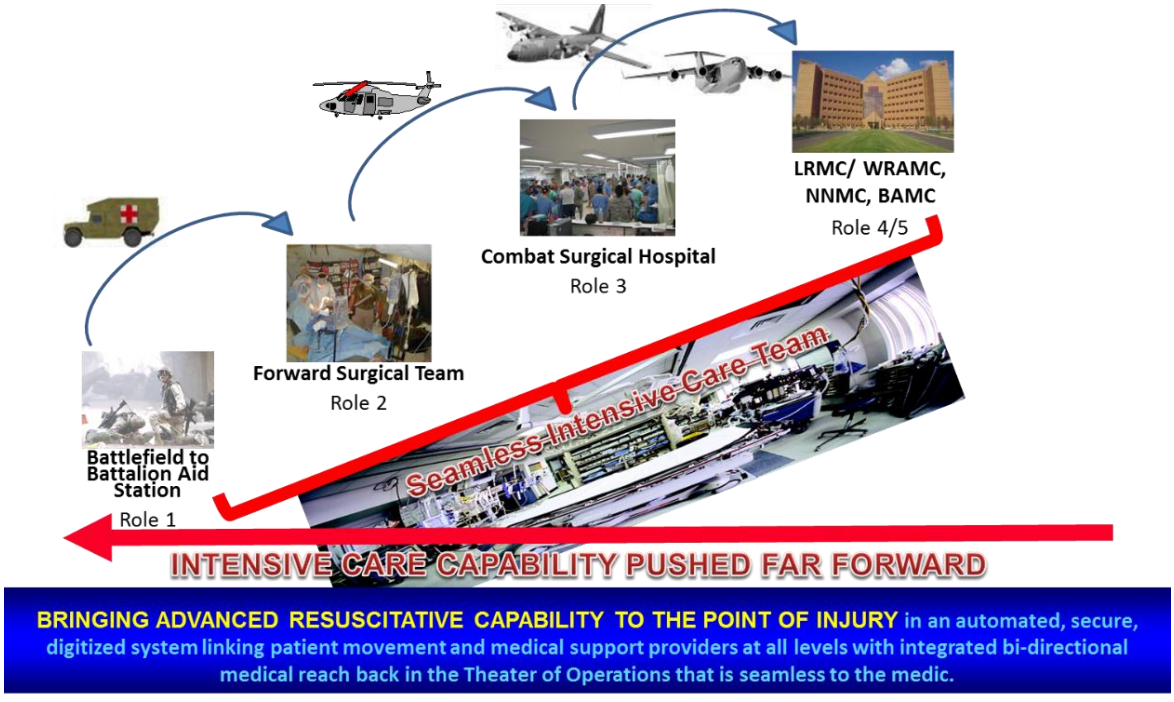


Figure 13. With the Reappraised Golden Hour Concept, Capabilities must be Pushed Far Forward (Cardin, 2014)

Requirement Sources

The activities of the FSICC portfolio have been reviewed and approved by the FSICC Steering Committee, JCP-6, Commanding General USAMRMC, and DHA. Management of the FSICC portfolio is guided by capability requirements that are outlined in Joint capability documents (JCD), ICDs, and guiding frameworks such as the JFHP concept. Gaps and shortfalls applicable to the FSICC portfolio documented in these capability requirements are described by multiple sources (Table 29).

- The 2008 GDF Assessment 4.16 Working Group's JCD identified 69 capability gaps that require medical R&D. Twenty-nine of these capability gaps are in areas under the purview of the CCCRP. Nine gaps within the area of JCM have been specifically prioritized by the FSICC portfolio, though the portfolio's activities also intersect with additional GDF gaps.
- The 2006 TC3 ICD identified 24 capability gaps, several of which are being addressed by work within the scope of the FSICC portfolio.
- Moving forward, newly defined gaps that further account for the challenges of advancing resuscitative capability to the POI and stabilizing trauma patients for greater periods before evacuation are increasingly being used to guide the work of the portfolio. Such FSICC-relevant gaps have been outlined in the DHP ICD for Combat Casualty Care Medical R&D.

Table 29. Capability Gaps Pursued within the Scope of the CCCRP's FSICC Portfolio

Requirement Sources	Capability Gaps
GDF	• **JCM-1-1** – Inadequate ability to diagnose, resuscitate, and stabilize casualties with survivable wounds • **JCM-1-2** – Inadequate initial emergent resuscitative surgery coupled with life and limb saving actions • **JCM-1-3** – Inadequate ability to locate and evaluate casualties • **JCM-1-4** – Inability to stop internal and external bleeding • **JCM-1-5** – Poor ability to stop life-threatening extremity bleeding • **JCM-1-6** – Poor ability to ensure casualty airway • **JCM-1-7** – Inability to monitor, evaluate, and triage casualties by combat medical personnel for early identification of life-saving interventions • **JCM-1-8** – Inadequate therapy for shock and head injury • **JCM-1-10** – Inadequate integrated medical information systems across the taxonomy of casualty care • **JCM-1-11** – Inadequate ability to immediately recognize and correct coagulopathy • **JCM-2-1** – Inadequate stabilization of injuries and ability to monitor response to treatment
TC3 ICD	• **Theater Hospitalization, Area Medical Support** – Diagnose, resuscitate and stabilize casualties with survivable wounds • **Damage Control Surgery** – Initial emergent resuscitative surgery coupled with life- and limb-saving actions • **En Route Care** – Locate and evaluate casualties • **First Response Medical Care** – Stabilize injuries, monitor response to treatment • **Airway Management Technology** – Ensure casualty airway • **Advanced Casualty Locating and Remote Physiologic Monitoring** – Monitor, evaluate, triage casualties by combat medical personnel for early identification of life-saving interventions • **Pain Management Medications** – Battlefield analgesia with minimal side effects

Requirement Sources	Capability Gaps
	• **Casualty Movement** – Medical evacuation (MEDEVAC) by organic or supporting attended medical evacuation platforms with en-route care • **Casualty Movement** – Casualty evacuation (CASEVAC) by non-standard platforms, attended by combat lifesaver en-route • **Medical Situational Awareness** – Integrated medical information system • **Coagulopathy Prevention and Treatment Agents** – Immediate recognition and correction of coagulopathy
DHP ICD	• **Develop Knowledge (DK)2** – Lead-times for new technology are very long and hindered by the current processes (requirements, funding, development, etc.) • **DK3** – Lack a decision support mechanism that enables timely, accurate decisions and diagnosis at all levels of care • **DK4** – Lack of evidence-based clinical data to support decision-making regarding the protocol (all levels) and timing (particularly for strategic movement) of post-surgical patients • **TI1** – Insufficient current first-responder (medical and non-medical) capacity and capability to initially assess, treat, and maintain severe trauma cases in the pre-hospital environment - Insufficient initial and ongoing training for first responders in the pre-hospital environment overall - Insufficient tools that enable both non-medical and medical first responders - The technologies do not exist to fulfill some of the needs (e.g. stabilizing the airway or truncal hemorrhage) - Incorrect alignment of trained skill sets and operational needs - Inconsistent integration of recurrent medical training into overall unit training • **TI4** – Lack an understanding of the effectiveness of the current pre-hospital triage system to determine if it is valid and correctly performed • **TI6** – First responders lack interoperable ways and means to understand and provide rapid, reliable, and actionable information about a casualty's physiological/psychological status in the pre-hospital environment (for information technology [IT] devices there are no defined key performance parameter [KPP] requirements; no clearly defined MILSPECS for non-IT) • **TI7** – Current ways and means of documentation at POI hinder ability to capture rapid, reliable and actionable information about a casualty's physiological status in the pre-hospital environment and subsequently transmit it for follow on analysis • **TI8** – Limited ability to properly diagnose and treat seen and unseen non-compressible hemorrhage in the pre-hospital environment • **TI11** – Lack of computational algorithms and predictive tools for physiological status that use available information and can predict necessary statuses in an expedient manner • **TI12** – In pre-hospital environment, lack ways and means to enable clinical decision support and have inadequate ways and means to enable clinical decision support at Level III and higher • **Manage Breathing (MB)1** – Inability to provide analgesia without depressing respiration and circulation in the pre-hospital environment • **MB2** – Lack of treatment strategies in the pre-hospital environment for severe/acute respiratory injuries (e.g. inhalation injuries) including but not limited to extracorporeal life support • **MB4** – In the pre-hospital environment there is a lack of understanding of the optimal oxygen requirements for casualties • **MB5** – First responders do not have a means to provide supplemental oxygen • **MB6** – Limited capability to identify and treat lung function problems and respiratory failure in the pre-hospital environment • **Manage the Airway (MA)3** – Lack of adequate tools for first responders to establish and maintain the airway in a pre-hospital environment • **MA5** – Insufficient capability to diagnose and manage tension pneumothorax in a POI and pre-hospital environment • **MA6** – Lack of ability to identify arterial oxygen and CO_2 levels • **MA7** – Lack of ability to maintain optimal arterial oxygen and CO_2 levels in the pre-hospital environment

Requirement Sources	Capability Gaps
	• **Identify and Manage Fractures/Wounds** (**IMFW)3** – Lack of ability to rapidly detect and treat internal non-compressible bleeding caused by complex pelvic fracture in the pre-hospital environment • **IMFW4** – Lack of ability to identify and monitor internal injuries in extended time in the pre-hospital environment • **TS1** – Lack of optimal resuscitation strategies for casualties who have TBI and are in, or at risk for, hemorrhagic shock • **TS2** – Lack of optimal therapies to manage hypo and hyperthermia in the pre-hospital environment • **TS4** – Lack of ways and means to effectively screen for and diagnose shock throughout continuum of care • **TS6** – Insufficient ways and means to diagnose and manage vascular disruption (with or without hemorrhagic shock) • **MBC1** – Lack of non-surgical means to treat non-compressible truncal/torso hemorrhage in the pre-hospital environment • **MBC2** – Lack of ways and means to manage circulations and control junctional and truncal hemorrhaging in the pre-hospital environment • **Maintain Tissue Viability (MTV)1** – Insufficient understanding of the acute inflammatory response to combat injury and its consequences • **MTV2** – Lack of a comprehensive burn management strategy in the pre-hospital environment • **MTV3** – Lack of knowledge, skills, and tools to provide extracorporeal support in the setting of single and multi-system organ failure across the continuum of care • **MTV5** – Lack knowledge, skills, and tools to prevent negative impacts of shock from burns during lengthy transports in the pre-hospital environment • **MTV7** – At POI, lack adequate ways and means to address pain control related to complex soft tissue wounds • **Patient Documentation and Communication** (**PDC)1** – Lack the suitable, interoperable ways and means to capture, transmit, and store TC3 data in the pre-hospital environment • **PDC3** – Lack of electronic medical record spanning the spectrum of combat casualty care architecture integrated into the Joint Trauma System (DODTR) • **PL1** – Lack of evidence-based data and metrics to assess the effectiveness of training methodologies, specifically TC3, to include both technical skills such as establishing surgical airways, and cognitive skills, such as decision-making in a complex tactical casualty scenario • **PL2** – Lack of evidence-based clinical data to support decision-making regarding the protocol (all levels) and timing (particularly for strategic movement) of post-surgical patients • **PL3** – Insufficient surgical capability to manage torso hemorrhage, junctional hemorrhage, airway compromise, and tension pneumothorax in a pre-hospital environment due to insufficient tools, techniques, therapies, and trainings • **PL7** – insufficient knowledge of the use and effects of regional anesthesia/analgesia modalities for complex war time injuries

FSICC-managed activities are contributing directly to the closure of gaps outlined in Table 29, and the portfolio is supporting closure of gaps in additional areas through collaboration. Many efforts under FSICC management are interrelated to the J-ERC and Hemorrhage and Resuscitation portfolios. There are also key collaborative interactions between the FSICC portfolio and JPCs 1 (Medical Training and Health Information Sciences) and 8 (Clinical and Rehabilitative Medicine), increasing the breadth of the portfolio's impact in areas including pain management, and communication and health information technology.

Forward Surgical and Intensive Critical Care Portfolio Successes

The stories of five select accomplishments illustrate achievements of the FSICC portfolio in closing capability gaps. These examples highlight advances toward several of the portfolio's seven major lines of effort, each grouped under an overarching strategic objective of either directly improving prehospital survival or developing enabling capability for medical providers.

Improving Survival

The first portfolio selection falls under the major effort of forward surgical and intensive care interventions. Under this effort, new life-saving strategies for combat medical personnel are being developed by refining surgical techniques and field medicine devices.

- **Use of Vented Chest Seals for Prevention of Tension Pneumothorax** – Recommends vented rather than unvented chest seals for treatment of penetrating chest wounds in the field

Providers implementing this recommendation eliminate a potentially deadly risk arising in the management of chest wounds in the field. The second selection is aligned with the major effort of endovascular hemostasis, under which new acute endovascular procedures and techniques to control intracavitary and junctional vascular injury and shock are being sought. By bringing endovascular approaches out of the hospital and closer to the POI, prehospital deaths from severe hemorrhage will be reduced.

- **Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) to Control Severe Hemorrhage –** A new endovascular balloon catheter system called the ER-REBOA is in development to enable far forward performance of REBOA, buying time for further life-saving interventions in the most severe cases of hemorrhage

Enabling Capabilities: Decision Support, Monitoring and Triage

The last three portfolio selections are focused on developing enabling capabilities for medical providers. They are aligned to two major efforts: decision support/automated technologies, and battlefield monitoring and triage. Together, these technologies are allowing for continuous and dynamic casualty monitoring, in conjunction with advanced approaches to interpret the resulting raw physiological data to support earlier and more effective clinical decision making.

- **Burn Resuscitation Decision Support System** – An algorithm automatically generating patient-specific fluid rate recommendations for resuscitation has been implemented for use in hospital settings and in the field

- **The CareGuide Oximeter: Noninvasive and Continuous Casualty Monitoring –** Oximeter monitors tissue oxygen saturation and pH, facilitating detection of internal hemorrhage, prediction of shock, and determination of adequacy of resuscitation

- **Compensatory Reserve Index Algorithm: Next Generation Monitoring for Evaluating and Treating Hemorrhage –** Algorithm analyzes physiological waveform data to identify warning indicators in advance of shock, assisting providers with diagnosis and implementing treatment

References

Cardin, S. (2014, December). Forward Surgical and Intensive Critical Care. Presentation for Defense Health Program Review and Analysis.

Hatzfeld, J., & Cardin, S. (2014). Medical Research to Support the Future of Patient Evacuation. *Aviation Digest*, 33-34.

Rasmussen, T. E., Baer, D. G., Doll, B. A., & Caravalho, J. (2015). In the golden hour. *Army AL&T Magazine*, 81-85.

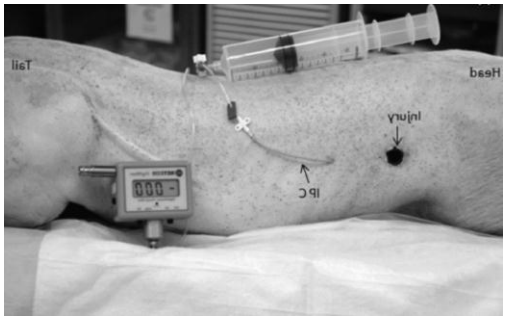
Use of Vented Chest Seals for Prevention of Tension Pneumothorax

The efficacy of vented versus unvented chest seals was compared, leading to the recommendation to use unvented chest seals for treatment of chest wounds to prevent the risk of tension pneumothorax.

- Research Partner:
  - USAISR

Key Outcomes and Impact:

- USAISR's examination of chest seals in a swine model of pneumothorax found that tension pneumothorax could result when an unvented chest seal was used and air was introduced into the pleural cavity by injection (Kheirabadi et al., 2013)
- The study directly supported a change in TCCC Guidelines in 2013 to recommend use of vented chest seals to prevent the risk of development of tension pneumothorax (Butler et al., 2013)



The Reproducible Swine Model of Open Pneumothorax Established for Chest Seal Testing (Kheirabadi et al., 2013)

Overview

Penetrating chest trauma with damage to the lung has been reported to account for 5–6 percent of battlefield injuries (Peoples, Gerlinger, Craig, & Burlingame, 2005). Penetrating trauma can allow air to enter the chest with a breath, yielding a sucking chest wound, or open pneumothorax. Pneumothorax can also occur when the lung is directly damaged and air leaks internally from the lung. If air continues to fill the chest and cannot exit, the potentially deadly secondary condition of tension pneumothorax can occur in which pressure is significantly altered and lung function is compromised.

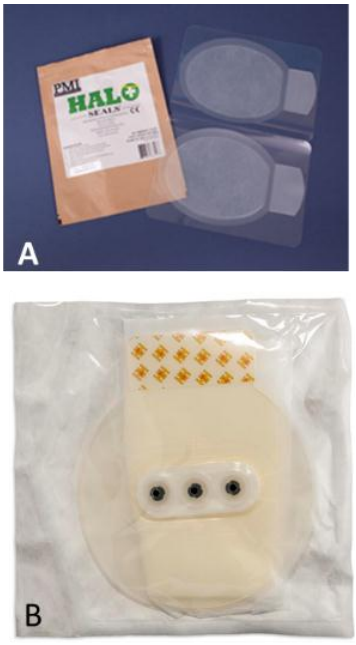


Figure 14. Chest Seals Evaluated by USAISR. (A) Halo Occlusive (Pantel Tactical 2014), (B) Bolin Vented (Chinook Medical, 2015)

Medical manufacturers have developed a range of disposable adhesive chest seals, or self-adhering coverings, that have been applied for the management of open chest wounds in the field. Chest seals are designed to cover the wound and prevent entry of air. While many are occlusive, some possess a one-way venting valve that allows air to escape from the chest cavity.

The recommendation of the CoTCCC leading into 2013 had been to apply an occlusive chest seal to an open pneumothorax. During a USCENTCOM and JTS assessment of prehospital trauma care in Afghanistan, the deployed director of the Joint Theater Trauma System (JTTS) questioned, "Why do we treat a nonlethal condition [open pneumothorax] with an intervention [a nonvented chest seal] that may result in a lethal condition [tension pneumothorax]?" (Kotwal et al., 2013). This potential

risk of converting an open pneumothorax to a tension pneumothorax through occlusion had long ago been recognized by clinicians, but had not been adequately experimentally examined in the context of modern practices and chest shields to support pursuing an alternate clinical recommendation (Butler et al., 2013; Haynes, 1952; Sellors, 1957).

Addressing this question, the FSICC portfolio directed U.S. Army core funding to the TCCC task area at USAISR to examine this potential risk. USAISR developed a swine model to directly examine treatment of open pneumothorax with vented versus occlusive chest seals (Kheirabadi et al., 2013) (Figure 14). This study provided animal model evidence that use of an unvented chest seal in the presence of an ongoing air leak from an injured lung can cause accumulation of air in the pleural space and the possible development of tension pneumothorax. The study provided direct support for a change in practice; it is now recommended that vented chest seals be used (Butler et al., 2013).

Capability Gap Alignment

Research to evaluate the use of vented chest seals has made a small but significant advance toward closure of several broad gaps related to the stabilization and treatment of casualties (Table 30). The DHP ICD specifically highlights the inability to diagnose and manage tension pneumothorax in the prehospital environment as a capability gap; the consistent use of vented chest seals aims to preempt this challenge in the possible case of tension pneumothorax occurring with the use of occlusive chest seal for chest wound management.

Table 30. Capability Gaps Addressed by the use of Vented Chest Seals

Requirement Sources	Capability Gaps Addressed
GDF	• **JCM-1-1 –** Inadequate ability to diagnose, resuscitate, and stabilize casualties with survivable wounds • **JCM-2-1 –** Inadequate stabilization of injuries and ability to monitor response to treatment
TC3 ICD	• **Theater Hospitalization, Area Medical Support –** Diagnose, resuscitate and stabilize casualties with survivable wounds • **Damage Control Surgery –** Initial emergent resuscitative surgery coupled with life- and limb-saving actions • **First Response Medical Care –** Stabilize injuries, monitor response to treatment
DHP ICD	• **TI1 –** Insufficient current first-responder (medical and non-medical) capacity and capability to initially assess, treat, and maintain severe trauma cases in the pre-hospital environment - Insufficient tools that enable both non-medical and medical first responders • **MB6 –** Limited capability to identify and treat lung function problems and respiratory failure in the pre-hospital environment • **MA5 –** Insufficient capability to diagnose and manage tension pneumothorax in a POI and pre-hospital environment

Impact on the Battlefield/Warfighter

As there have been no reports of fatalities during OIF or OEF attributed directly to isolated open pneumothorax in the absence of significant injury to underlying thoracic structures or secondary infection, it is difficult to determine whether discontinuing the treatment of open pneumothoraces with occlusive chest seals will prevent fatalities (Eastridge et al., 2012; Butler et al., 2013). The shift to the standard use of vented chest seals, however, ensures that this potential risk is accounted for, erring on the side of caution in treating open pneumothorax. The data

suggest the use of vented chest seals may confer a safety advantage, and there is no apparent downside (Butler et al., 2013). Finally, on the battlefield when a medic's attention is taxed in multiple casualty situations, it may be challenging to carefully monitor for a developing tension pneumothorax in an individual treated with an occlusive seal (Butler et al., 2013). Removing this concern benefits both casualties and medics in stressful scenarios where resources are limited and every second counts.

Clinical Practice

Impact on Clinical Practice Guidelines

Similar to the goals of instituting vented chest seals, previous CoTCCC recommendations for combat casualty care have suggested the use of an improvised "3-sided dressing" to enable venting of air from the pleural space by leaving one side open to allow air to escape (Butler et al., 2013). However, constructing a 3-sided dressing takes more time for the medic than simply applying a commercial chest seal. Variations in medic skill, available materials, and technique may introduce inconsistent clinical results when this option is used in battlefield conditions (Butler et al., 2013). In a 2008 review of the TCCC guideline, it was noted that there was no evidence to show that improvised 3-sided dressings are reliably effective in preventing the conversion of an open pneumothorax to a tension pneumothorax. Given this lack of support, and the time and skill necessary to construct and apply a dressing by a medic in the absence of commercial chest seals designed to vent to one side, the prevailing recommendation for TCCC became to use a completely occlusive (unvented) chest seal with close monitoring of casualties for development of tension physiology (Butler et al., 2013; Kheirabadi et al., 2013). This recommendation remained in place until 2013 when TCCC guidelines with respect to penetrating chest trauma were once again revisited, following USAISR's comparative study of vented versus unvented chest seals in a swine model of pneumothorax. TCCC guidelines were updated to recommend the use of vented chest seals during both tactical field care and tactical evacuation. When using chest seals, the vented design presents no additional risk, and has potential safety benefits with respect to development of tension pneumothorax (Butler et al., 2013).

> Based on USAISR research in a model of open pneumothorax, TCCC guidelines have been updated to recommend use of vented chest seals in prehospital trauma care to prevent the development of tension pneumothorax:
>
> "All open and/or sucking chest wounds should be treated by immediately applying a vented chest seal to cover the defect. If a vented chest seal is not available, use a non-vented chest seal. Monitor the casualty for the potential development of a subsequent tension pneumothorax."
>
> Butler et al., 2013

Supporting Publications

USAISR's study of chest seals by Kheirabadi et al. (2013) has provided the primary impetus for the change in TCCC recommendation for the use of vented chest seals. Additional studies of chest seals in dog and swine models, as well as examination of chest seal adherence in simulated injury studies with human volunteers have also supported the development of the new guidelines (Table 31).

Table 31. Supporting Publications for Vented Chest Seals

Reference	Description
Ruiz, Lueders, & Petersen, 1993	Compared the use of a vented dressing with conventional occlusive gauze dressing in a dog model of penetrating chest wounds. In the absence of positive pressure ventilation, the vented dressing improved pulmonary functioning in comparison with the occlusive dressing
Arnaud et al., 2008	Compared the performance of Asherman and Bolin chest seals in a swine model of open pneumothorax; both prevented the development of a tension pneumothorax, though the Bolin seal had better adherence
Kotora, Henao, Littlejohn, & Kircher, 2013	Three commercial vented chest seals were compared in a swine model of open pneumothorax. HyFin, Sam, and Sentinel vented chest seal were equally effective in evacuating blood and air, and all prevented tension pneumothorax formation after penetrating thoracic trauma in the model
Kheirabadi et al., 2013	Compared the efficacies of unvented and vented chest seals were in a swine model of pneumothorax. When air was introduced into the pleural cavity by injection, the unvented chest shield led to tension pneumothorax whereas the vented chest shield did not

Role of CCCRP-Sponsored Projects

Through the FSICC portfolio, USAMRMC core funding was directed to the TCCC task area for USAISR to conduct this key comparative evaluation (Table 32). The reproducible open pneumothorax swine model developed by USAISR enabled the direct comparison of vented and unvented chest seals. Based on the results obtained in this model, the investigators at USAISR recommended that vented chest seals be used during combat casualty care.

Table 32. CCCRP-Sponsored Publications of Chest Seal Evaluation in the Swine Model

Reference	Description
Kheirabadi et al., 2013	Compared the efficacy of unvented and vented chest seals in a swine model of pneumothorax. When air was introduced into the pleural cavity by injection, the unvented chest shield led to tension pneumothorax whereas the vented chest shield did not

References

Arnaud, F., Tomori, T., Teranishi, K., Yun, J., McCarron, R., & Mahon, R. (2008). Evaluation of chest seal performance in a swine model: comparison of Asherman vs. Bolin seal. *Injury, 39*(9), 1082-1088.

Butler, F. K., Dubose, J. J., Otten, E. J., Bennett, D. R., Gerhardt, R. T., Kheirabadi, B. S., … Bailey, J. A. (2013). Management of open pneumothorax in Tactical Combat Casualty Care: TCCC Guidelines change 13-02. *Journal of Special Operations Medicine, 13*(3), 81-86.

Chinook Medical. (2015). Bolin chest seal. Retrieved from http://www.chinookmed.com/cgi-bin/item/12101/s-chest_thoracic/-Bolin-Chest-Seal-

Eastridge, B. J., Mabry, R. L., Seguin, P., Cantrell, J., Tops, T., Uribe, P., … Blackbourne, L. H. (2012). Death on the battlefield (2001-2011): Implications for the future of combat casualty care. *Journal Trauma Acute Care Surgery, 73,* S431-7.

Haynes B. (1952). Dangers of emergency occlusive dressing in sucking wounds of the chest. *Journal of the American Medical Association, 150,* 1404.

Kheirabadi, B. S., Terrazas, I. B., Koller, A., Allen, P. B., Klemcke, H. G., Convertino, V. A., … Blackbourne, L. H. (2013). Vented versus unvented chest seals for treatment of pneumothorax and prevention of tension pneumothorax in a swine model. *Journal of Trauma Acute Care Surgery, 75*(1), 150-156.

Kotora, J. G., Henao, J., Littlejohn, L. F., & Kircher, S. (2013). Vented chest seals for prevention of tension pneumothorax in a communicating pneumothorax. *Journal of Emergency Medicine, 45*(5), 686-694.

Kotwal, R. S., Butler, F. K., Edgar, E. P., Shackelford, S. A., Bennett, D. R., & Bailey, J. A. (2013, January 30). Saving Lives on the Battlefield: A Joint Trauma System Review of Pre-Hospital Trauma Care in Combined Joint Operating Area – Afghanistan (CJOA-A). Final Report. Retrieved from http://rdcr.org/wp-content/uploads/2013/02/CENTCOM-Prehospital-Final-Report-130130.pdf

Pantel Tactical. (2014). Progressive Medical Int. Halo chest seal. Retrieved from http://www.panteltactical.com/pd-progressive-medical-int-halo-chest-seal---2-pack.cfm

Peoples, G. E., Gerlinger, T., Craig, R., & Burlingame, B. (2005). Combat casualties in Afghanistan cared for by a single team during the initial phase of operation enduring freedom. *Military Medicine, 170*(6), 462-468.

Ruiz, E., Lueders, J., & Petersen, C. (1993). A one-way valve chest wound dressing: evaluation in a canine model of open chest wounds. *Annals of Emergency Medicine, 22,* 922.

Sellors, T. (1957). Chest injuries. *British Medical Journal, 2,* 1097.

Resuscitative Endovascular Balloon Occlusion of the Aorta to Control Severe Hemorrhage

Resuscitative endovascular balloon occlusion of the aorta (REBOA) is an adjunctive procedure to control life-threatening hemorrhage. Fielding a catheter system designed specifically for this application may save lives by enabling early, prehospital use before the onset of profound shock or traumatic arrest.

- Partnering Development Organization:
  - Pryor Medical Devices, Inc.

Key Outcomes and Impact:

- Advances in endovascular surgery have led to reappraisal of REBOA
- Modern clinical experience has enabled REBOA to be recommended for consideration in the setting of uncontrolled truncal and extremity bleeding in surgically capable theater facilities (JTS, 2014)
- Pryor Medical is developing the ER-REBOA catheter system specifically for emergent use in trauma and insertion without the aid of imaging
- Support of ongoing ER-REBOA development and testing is expected to enable FDA-clearance and deployment

The ER-REBOA in Development by Pryor Medical is Designed for Hemorrhage Control and Resuscitation for Trauma (Pryor Medical, 2014)

Overview

Truncal hemorrhage is the leading cause of potentially survivable death on the battlefield. In a study of 15,209 battle injuries reported within the JTTS from 2002 to 2010, 13 percent of casualties sustained an anatomic injury pattern that is at risk for noncompressible truncal hemorrhage and, of these, 17 percent had evidence of ongoing hemorrhage (Stannard et al., 2013a). Given the significant threat of noncompressible truncal hemorrhage to the warfighter, the CCCRP has prioritized focus on devices and techniques to address this challenge and reduce morbidity and mortality. One such approach is aortic occlusion, which increases central aortic pressure during severe shock, enabling perfusion of the heart and brain to be maintained. In this way, the approach not only halts hemorrhage in other areas of the body, but also contributes to damage control for these key vital organs. This temporary, life-saving approach can be applied while surgical hemostasis is achieved and other resuscitation approaches are begun. The use of REBOA as an adjunct for resuscitation is not an entirely recent intervention. Early use of the technique was described by Hughes (1954) in a review of combat injury cases. In the decades that followed, the use of REBOA as an adjunct in the setting of hemorrhagic shock has been described in animal models and in some clinical cases, though it has not yet been widely used. However, in light of the modern transformation of endovascular surgery, and the dire need for improved hemorrhage control methods adaptable to forward environments to prolong military casualty survival until further life-saving hemostatic and resuscitative interventions are accessible, the approach has received recent reappraisal.

As currently performed for trauma care, the procedure relies on available catheter systems developed for other applications; there are no FDA-cleared catheter systems designed specifically for the use of REBOA in a trauma care environment. There continues to be a need to better understand the physiology of occlusion, to gain clinical experience with the approach, and to develop a new catheter system optimized for this purpose. Using current endovascular technologies has required that REBOA be performed with a large-caliber balloon catheter passed over a wire through a large sheath. In addition, existing REBOA technology requires fluoroscopy for wire guidance and balloon positioning, which significantly limits the setting under which it can be conducted (Scott et al., 2013).

The FSICC portfolio, in close collaboration with the Hemorrhage and Resuscitation portfolio, is seeking to increase the clinical study of REBOA and is collaborating with Pryor Medical Devices, Inc. to advance the technology for a trauma-specific REBOA catheter. Pryor Medical is currently developing the ER-REBOA for this purpose; the catheter system is designed to be field-deployable with the potential for prehospital use at the POI in austere combat environments (Pryor Medical, 2014). The ER-REBOA is being developed to enable fast, fluoroscopy-independent placement, using a low-profile catheter that does not require the use of a guidewire for placement and which employs controls to protect against balloon overinflation (Scott et al., 2013, Pryor Medical, 2014).

> "The most important characteristic of this and future technologies for REBOA in trauma is liberation from radiographic imaging. Although a lower insertion profile is imperative, the ability to accurately introduce, position, and inflate REBOA devices without fluoroscopy represents the paradigm shift, which would allow this maneuver to be performed in urgent settings. If REBOA devices also included the ability to monitor central aortic pressure before, during, and following inflation of the balloon, one could envision proactive access and control of the aorta in patients prone to cardiovascular collapse. In this context, resuscitative aortic occlusion could move from a reactive and terminal operation to a proactive, less invasive maneuver."
>
> Scott et al., 2013

Capability Gap Alignment

Control of noncompressible truncal hemorrhage remains a critical gap that has been emphasized by all three of the requirements sources examined (Table 33). Because 70 percent of deaths on the battlefield result from truncal hemorrhage, and 9 out of every 10 of these deaths occur before hospitalization, identification of technologies and procedures that can be effectively implemented earlier is critical (Eastridge et al., 2012; Scott et al., 2013). Improving REBOA capabilities through the development of the ER-REBOA system that can be fielded for use in emergent settings has significant potential to address gaps in truncal hemorrhage control for the most severe incidences of hemorrhagic shock.

Table 33. Capability Gaps Addressed by REBOA

Requirement Sources	Capability Gaps Addressed
GDF	• **JCM-1-1** – Inadequate ability to diagnose, resuscitate, and stabilize casualties with survivable wounds • **JCM-1-2** – Inadequate initial emergent resuscitative surgery coupled with life and limb saving actions • **JCM-1-4** – Inability to stop internal bleeding (non-extremity)

Requirement Sources	Capability Gaps Addressed
TC3 ICD	• **Theater Hospitalization, Area Medical Support** – Diagnose, resuscitate and stabilize casualties with survivable wounds • **Damage Control Surgery** – Initial emergent resuscitative surgery coupled with life- and limb-saving actions • **Hemostatic Agents and Equipment** – Internal bleeding, external bleeding
DHP ICD	• **TI1** – Insufficient current first-responder (medical and non-medical) capacity and capability to initially assess, treat, and maintain severe trauma cases in the pre-hospital environment - Insufficient tools that enable both non-medical and medical first responders. - The technologies do not exist to fulfill some of the needs (e.g. stabilizing the airway or truncal hemorrhage) • **TI8** – Limited ability to properly diagnose and treat seen and unseen non-compressible hemorrhage in the pre-hospital environment • **IMFW3** – Lack of ability to rapidly detect and treat internal non-compressible bleeding caused by complex pelvic fracture in the pre-hospital environment • **MBC2** – Lack of ways and means to manage circulations and control junctional and truncal hemorrhaging in the pre-hospital environment • **PL2** – Insufficient surgical capability to manage torso hemorrhage, junctional hemorrhage, airway compromise, and tension pneumothorax in a pre-hospital environment due to insufficient tools, techniques, therapies, and trainings

Impact on the Battlefield/Warfighter

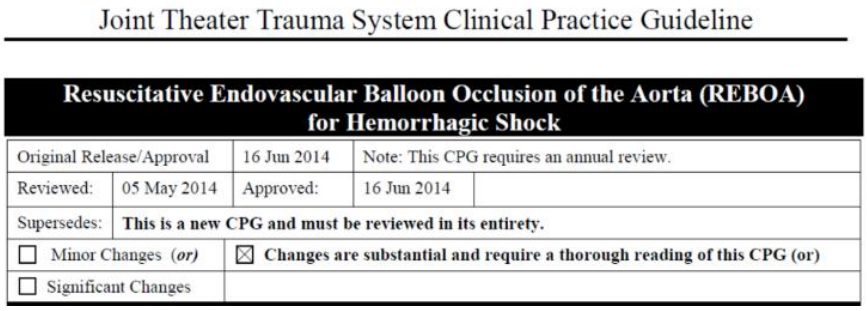
The development of REBOA methods using existing catheter systems has already enabled the performance of REBOA in severely hemorrhaging trauma patients, though the approach has not yet been extensively adopted (Brenner et al., 2013; Martinelli et al., 2010; Stannard, Eliason, & Rasmussen, 2011). In a retrospective examination of data from the United Kingdom (U.K.) Joint Theatre Trauma Registry spanning 2002–2012, one in five severely injured U.K. combat casualties had a focus of hemorrhage potentially amenable to REBOA (Morrison et al., 2014a). These cases were associated with a high burden of mortality. Within the group with indications for REBOA, there were 174 deaths: 79 at the point of wounding, 66 en route to hospital, and 29 in-hospital deaths. Similarly, it is estimated that more than 2,000 U.S. service members had comparable indications for REBOA over 13 years of OIF/OEF (Rasmussen, 2014). The introduction of a REBOA catheter system specifically for use in traumatic hemorrhage will provide a new intervention that can benefit future casualties with these indications. Deployment of the ER-REBOA system prehosptial during the en route phase of evacuation, for example, may become possible (Morrison et al., 2014a). This capability in transit would enable earlier steps to be taken in the case of severe hemorrhage, before the onset of profound shock further compounds the threat to a wounded patient's life. Perhaps a glimpse of this promise has already been viewed in the civilian context, when the first prehospital REBOA procedure was recently performed by London's Air Ambulance helicopter emergency medical system (EMS World, 2014).

> One in five severely injured U.K. combat casualties had a hemorrhagic injury potentially amenable to REBOA.
>
> Morrison et al., 2014a
>
> Over 13 years of OIF/OEF, it is estimated that more than 2,000 U.S. casualties had injuries meeting indications for REBOA.
>
> Rasmussen, 2014

Clinical Practices

Impact on Clinical Practice Guidelines

In June 2014, a new CPG for REBOA for Hemorrhagic Shock was published by the JTS (JTS, 2014) (Figure 15). This CPG outlines information pertaining to the use of REBOA as an interventional capability for control of hemorrhagic shock in the setting of uncontrolled truncal and extremity bleeding in surgically capable theater facilities. The CPG was guided substantially by a publication of current REBOA procedure by Stannard, Eliason, and Rasmussen (2011).



Joint Theater Trauma System Clinical Practice Guideline

Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) for Hemorrhagic Shock

Original Release/Approval		16 Jun 2014	Note: This CPG requires an annual review.
Reviewed:	05 May 2014	Approved:	16 Jun 2014
Supersedes:	**This is a new CPG and must be reviewed in its entirety.**		
☐ Minor Changes *(or)*	☒ **Changes are substantial and require a thorough reading of this CPG (or)**		
☐ Significant Changes			

Figure 15. REBOA CPG Approved in 2014 (JTS, 2014)

As new catheter technology such as the ER-REBOA specifically designed for trauma care is tested and achieves regulatory clearance, this CPG will likely undergo additional adaptation to account for changes in the technology and process.

Supporting Publications

As modern advances in endovascular surgery and the tremendous effects of hemorrhage during ongoing military conflicts have spurred the reappraisal of REBOA, several of key publications have resulted. These have documented the modern REBOA technique with existing catheter technologies approved for endovascular surgeries, described its use in traumatic hemorrhage cases, examined catheter placement, and explored the use and physiological impacts of current and emerging REBOA devices in animal models of hemorrhage (Table 34). These studies have provided key support for the development of the new JTS CPG for REBOA use in hemorrhagic shock, and continue to support the development of the advanced ER-REBOA for use in trauma.

Table 34. Supporting Publications for REBOA

Reference	Description
Procedure	
Stannard, Eliason, & Rasmussen, 2011	Reported a technical description of the REBOA procedure, providing the foundation for the JTS CPG
Case Reports and Clinical Studies	
Martinelli et al., 2010	Described the use of REBOA in 13 patients treated for pelvic fractures. All balloons were successfully placed and 12 of 13 patients became transferable to enable angiography. Survival was inversely related to the length of inflation and injury severity
Brenner et al., 2013	Descriptive case series of REBOA use in trauma centers. There were no REBOA-related complications or hemorrhage-related mortality reported in the cases
Stannard et al., 2013b	Characterized aortic morphometry in 88 males undergoing computed tomography (CT); findings suggested that center line aortic distances correlate with external measure of the torso

Reference	Description
Morrison et al., 2014b	Conducted a prospective study of adult males undergoing CT at a Combat Support Hospital to model the relationship between externally measured torso height and intra-arterial distance. Resulting linear regression models demonstrated high accuracy (99.3–100 percent) for predicting the insertion distance required to place a catheter within the middle of each aortic zone
Translational Research Animal Studies	
Avaro et al., 2011	Balloon occlusion for 40 minutes followed by surgical damage control improved survival in a swine model of uncontrolled hemorrhagic shock caused by abdominal trauma
White et al., 2011	REBOA was compared with invasive thoracotomy with aortic clamping for resuscitation in a swine model of hemorrhagic shock. REBOA increased central perfusion pressures with less physiologic disturbance than the thoracotomy method
Morrison et al., 2012	REBOA was effective for controlling pelvic arterial bleeding in a swine model of noncompressible pelvic hemorrhage
Markov et al., 2013	Characterized the burden of reperfusion and organ dysfunction incurred during 30 or 90 minutes of REBOA in a swine model of hemorrhagic shock; prolonged REBOA was survivable and enabled greater mean central aortic pressure during shock
Scott et al., 2013	Examined fluoroscopy-free placement of a prototype balloon system by Pryor Medical in a swine model of hemorrhagic shock. Placement of the prototype was feasible, and occlusion for 60 minutes prior to resuscitation was tolerated and recoverable
Park et al., 2014	Examined fluoroscopy-free placement of the ER-REBOA for 30-60 minutes prior to transfusion in a swine model of hemorrhagic shock; ER-REBOA was successfully placed in 100 percent of cases. Groups treated with ER-REBOA had significantly higher survival rates than positive controls who did not undergo occlusion before being transfused

Role of CCCRP-Sponsored Projects

Efforts to develop the trauma-specific ER-REBOA catheter system for treatment of severe hemorrhage as experienced in combat have been funded through the FSICC portfolio (Table 35). Following the release of a request for information (RFI) in late 2014, planning is now underway for continued support of the clinical development and testing of the ER-REBOA, with the goal of enabling its submission for FDA clearance (USAMRMC, 2014).

Table 35. CCCRP-Sponsored Projects for Development of ER-REBOA

RFI		Date
Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) as a Field Expedient System for Patients with Severe Torso Hemorrhage-Research and Development (W911QY-15-R-REBO)		19 December 2014
Project Title (Award Number)	**Organization/Principal Investigator**	**Funding**
Advanced Fluoroscopy Free Endovascular Aortic Occlusion System for Non-Compressible Hemorrhage (W81XWH-12-1-0558)	Christopher Banas (Pryor Medical Devices, Inc.)	$1.5M (2013–2014)

References

Avaro, J. P., Mardelle, V., Roch, A., Gil, C., de Biasi, C., Oliver, M., … Thomas, P. (2011). Forty-minute endovascular aortic occlusion increases survival in an experimental model of uncontrolled hemorrhagic shock caused by abdominal trauma. *Journal of Trauma, 71*(3), 720-725.

Brenner, M. L., Moore, L. J., DuBose, J. J., Tyson, G. H., McNutt, M. K., Albarado, R. P., … Rasmussen, T. E. (2013). A clinical series of resuscitative endovascular balloon occlusion of the aorta for hemorrhage control and resuscitation. *The Journal of Trauma and Acute Care Surgery, 75*(3), 506-511.

Eastridge, B. J., Mabry, R. L., Seguin, P., Cantrell, J., Tops, T., Uribe, P., … Blackbourne, L. H. (2012). Death on the battlefield (2001-2011): implications for the future of combat casualty care. *Journal Trauma Acute Care Surgery, 73*, S431-7.

EMSWorld. (2014, July 2). London's Air Ambulance performs world's first prehospital REBOA. Retrieved from http://www.emsworld.com/news/11545597/londons-air-ambulance-performs-worlds-first-prehospital-reboa

Hughes, C. W. (1954). Use of an intra-aortic balloon catheter tamponade for controlling intra-abdominal hemorrhage in man. *Surgery, 36*(1), 65-68.

Joint Trauma System (JTS). (2014, June). Joint Trauma System Clinical Practice Guidelines. Retrieved from http://www.usaisr.amedd.army.mil/pdfs/TCCC_Guidelines_140602.pdf

Markov, N. P., Percival, T. J., Morrison, J. J., Ross, J. D., Scott, D. J., Spencer, J. R., & Rasmussen, T. E. (2013). Physiologic tolerance of descending thoracic aortic balloon occlusion in a swine model of hemorrhagic shock. *Surgery, 153*, 848-856.

Martinelli, T., Thony, F., Declety, P., Sengel, C., Broux, C., Tonetti, J., … Ferretti, G. (2010). Intra-aortic balloon occlusion to salvage patients with life-threatening hemorrhagic shocks from pelvic fractures. *The Journal of Trauma, 68*(4), 942-948.

Morrison, J. J., Percival, T. J., Markov, N. P., Villamaria, C., Scott, D. J., Saches, K. A., … Rasmussen, T. E. (2012). Aortic balloon occlusion is effective in controlling pelvic hemorrhage. *Journal of Surgical Research, 177*(2), 341-347.

Morrison, J. J., Ross, J. D., Rasmussen, T. E., Midwinter, M. J., & Jansen, J. O. (2014a). Resuscitative endovascular balloon occlusion of the aorta: a gap analysis of severely injured UK combat casualties. *Shock, 41*(5), 388-393.

Morrison, J. J., Stannard, A., Midwinter, M. J., Sharon, D. J., Eliason, J. L., & Rasmussen, T. E. (2014b). Prospective evaluation of the correlation between torso height and aortic anatomy in respect of a fluoroscopy free aortic balloon occlusion system. *Surgery, 155*(6):1044-1051.

Park, T., Batchinsky, A., Baker, W., Belenkiy, S., Jordan, B., Dubick, M, … Cancio, L. (2014). 248: Resuscitative endovascular balloon occlusion of the aorta improves survival in lethal hemorrhage. *Critical Care Medicine, 42*(12), A1420.

Pryor Medical, Inc. (2014). Technology: REBOA. Retrieved from http://www.pryormedical.com/technology/

Rasmussen, T. E. (2014). AAST grand rounds April 2014: Catheter-based control of shock and reappraisal of resuscitative endovascular balloon occlusion of the aorta (REBOA). Retrieved from http://www.pryormedical.com/PDFS/Rasmussen%20Evolution%20of%20REBOA%20for%20Shock%20AAST%20GR.pdf

Scott, D. J., Eliason, J. L., Villamaria, C., Morrison, J. J., Houston, R., Spencer, J. R., & Rasmussen, T. E. (2013). A novel fluoroscopy-free, resuscitative endovascular aortic balloon occlusion system in a model of hemorrhagic shock. *The Journal of Trauma and Acute Care Surgery*, *75*(3), 122-128.

Stannard, A., Eliason, J. L., & Rasmussen, T. E. (2011). Resuscitative endovascular balloon occlusion of the aorta (REBOA) as an adjunct for hemorrhagic shock. *The Journal of Trauma*, *71*(6), 1869-1872.

Stannard, A., Morrison, J. J., Scott, D. J., Ivatury, R. A., Ross, J. D. & Rasmussen, T. E. (2013a). The epidemiology of noncompressible torso hemorrhage in the wars in Iraq and Afghanistan. *Journal of Trauma and Acute Care Surgery*, *74*(3), 830-834.

Stannard, A., Morrison, J. J., Sharon, D. J., Eliason, J. L., & Rasmussen, T. E. (2013b). Morphometric analysis of torso arterial anatomy with implications for resuscitative aortic occlusion. *The Journal of Trauma and Acute Care Surgery*, *75*(2, Suppl 2), S169-S172.

U.S. Army Medical Research and Materiel Command (USAMRMC). (2014, December 19). A--Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) as a Field Expedient System for Patients with Severe Torso Hemorrhage-Research and Development. Retrieved from https://www.fbo.gov/index?s=opportunity&mode=form&tab=core&id=09d7d05b1b44aefdf32fce6fbadc33a8

White, J. M., Cannon, J. W., Stannard, A., Markov, N. P., Spencer, J. R., & Rasmussen, T. E. (2011). Endovascular balloon occlusion of the aorta is superior to resuscitative thoracotomy with aortic clamping in a porcine model of hemorrhagic shock. *Surgery*, *150*, 400–409

Burn Resuscitation Decision Support System

The Burn Resuscitation Decision Support System (BRDSS) can enable providers to accurately resuscitate burn patients from the POI to definitive care. By assessing urine output levels hourly and employing an algorithm to automatically generate a fluid rate recommendation, the BRDSS decreases the chance of over- or under-resuscitation of combat casualties.

- Research, Development, and Manufacturing Partner Organizations:
  - USAISR, Comprehensive Intensive Care Research (CICR) Task Area
  - University of Texas Medical Branch
  - Arcos Medical, Inc.

Key Outcomes and Impact:

- Versions of the BRDSS for clinical use in hospital (BRDSS-C) and for mobile use (BRDSS-M) have both achieved FDA clearance
- First medical devices to start as a research project within the USAMRMC, go through advanced development, FDA clearance, and exit the decision gate process into fielding
- BRDSS-C has been successfully implemented in the USAISR Burn Center
- BRDSS-M devices were first delivered for deployed use in 2014 (marketed commercially as the Burn Navigator; Arcos, 2014)

Demonstration of the BRDSS-M to Combat Support Hospital Staff during a Training Exercise (Galvan, 2014)

Overview

One of the most challenging parts of the initial management of severe burn casualties is achieving appropriate fluid resuscitation to prevent shock and organ failure (Chung, Salinas, & Renz, 2011). Though recommendations of the American Burn Association have long provided an initial guideline for fluid resuscitation, they are intended to help predict fluid needs over a 24-hour period, and cannot guide patient care hour by hour. Resuscitation requires an attentive provider who is adjusting fluid therapy based on a number of factors, with the goal of maintaining an appropriate urinary output. This can be a challenging process, and requires multiple calculations to be performed. This process is not always appropriately executed by civilian pre-burn center providers in the U.S. and it can be even more difficult to ensure that fluid resuscitation can be initiated consistently by combat providers in theater who may have limited burn experience and be faced with additional stresses and demands, including triaging multiple casualties (Chung, Salinas, & Renz, 2011).

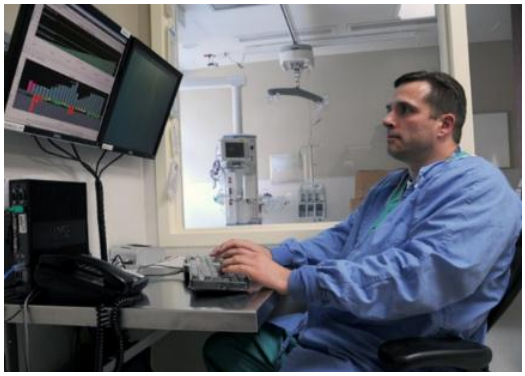


Figure 16. The FDA-Cleared BRDSS-C Software is in use at the USAISR Burn Center (Galvan, 2015)

The USAISR has made a number of advances to address the challenges of fluid resuscitation, working toward standardized processes to ensure improved outcomes. These have included the development of a simplified formula to calculate initial fluid resuscitation rate based on estimated burn size, and the development of burn resuscitation CPGs and flow sheets that have been disseminated through the JTS (Chung, Salinas, & Renz, 2011). In addition to these advances, USAISR has now developed a computer-based decision support algorithm for fluid resuscitation to further guide and optimize care. This has been achieved with the support of the CCCRP's FSICC portfolio to USAISR's CICR Task Area. This effort has yielded clinical and mobile algorithms designed to support care providers during burn patient resuscitation. The clinical version (BRDSS-C) has been developed for use by experienced burn providers and includes recommendations tailored for burn experts. The mobile version (BRDSS-M) is intended for field deployment and use by providers with limited or no burn resuscitation expertise.

The BRDSS-C has been implemented in the USAISR Burn Center, where it is integrated with the hospital electronic medical record (Figure 16). The system has improved outcomes with respect to mortality, length of intensive care unit stay, and ventilator days (Salinas et al., 2011, Schmidt & Mann-Salinas, 2014). The BRDSS-C achieved FDA clearance in 2014 and is currently undergoing U.S. Army network certification for future deployment (K140387, 2014; Galvan, 2015). To pursue development and manufacture of the BRDSS-M in a rugged, transportable platform that can travel with burn care providers and patients in deployed and en route settings, the technology was licensed to Arcos Medical, Inc. Arcos has collaborated with USAISR to integrate the BRDSS algorithm in a tablet-based device, which achieved FDA clearance and Army airworthiness certification in 2013 (K121659, 2013; Meador, 2014) (Figure 17). Arcos is manufacturing the BRDSS-M device under the commercial name of Burn Navigator. The Burn Navigator is now in full rate production and is being deployed to the field (Meador, 2014).

Figure 17. The FDA-Cleared BRDSS-M has Achieved Army Airworthiness Certification and has been introduced for Deployed Use (USAISR, 2015)

Capability Gap Alignment

The development and implementation of both the BRDSS-C and BRDSS-M have contributed to the closure of several capability gaps, both by directly improving capabilities for monitoring

burn resuscitation, and more generally by contributing to the advancement of decision support tools that can be used throughout the continuum of care, including in theater and en route environments (Table 36). Because the BRDSS-C was the first medical device to go from concept to full FDA clearance using USAISR's internal quality system, its success represents a development model that is also enabling progress against gaps defined by the DHP ICD related to the difficulties of advancing medical products (Galvan, 2015).

Table 36. Capability Gaps Addressed by BRDSS

Requirement Sources	Capability Gaps Addressed
GDF	• **JCM 1-1** – Inadequate ability to diagnose, resuscitate, and stabilize casualties with survivable wounds • **JCM 1-7** – Inability to monitor, evaluate, and triage casualties by combat medical personnel for early identification of life-saving interventions • **JCM 2-1** – Inadequate stabilization of injuries and ability to monitor response to treatment
TC3 ICD	• **Theater Hospitalization, Area Medical Support** – Diagnose, resuscitate and stabilize casualties with survivable wounds
DHP ICD	• **DK2** – Lead-times for new technology are very long and hindered by the current processes (requirements, funding, development, etc.) • **DK3** – Lack a decision support mechanism that enables timely, accurate decisions and diagnosis at all levels of care • **DK4** – Lack of evidence-based clinical data to support decision-making regarding the protocol (all levels) and timing (particularly for strategic movement) of post-surgical patients • **TI11** – Lack of computational algorithms and predictive tools for physiological status that use available information and can predict necessary statuses in an expedient manner • **TI12** – In pre-hospital environment, lack ways and means to enable clinical decision support and have inadequate ways and means to enable clinical decision support at Level III and higher • **MTV2** – Lack of a comprehensive burn management strategy in the pre-hospital environment • **MTV5** – Lack knowledge, skills, and tools to prevent negative impacts of shock from burns during lengthy transports in the pre-hospital environment • **PL3** – Lack of evidence-based clinical data to support decision-making regarding the protocol (all levels) and timing (particularly for strategic movement) of post-surgical patients

Impact on the Battlefield/Warfighter

Ten percent of casualties during military conflicts have suffered from burns, with a significant portion of these (nearly 20 percent) categorized as severe (Chung et al., 2006). In a study of OIF/OEF burn casualties treated by the USAISR Burn Center between 2003 and 2006, 36 percent of those with severe burns over greater than 30 percent of their body surface area developed abdominal compartment syndrome and died of their injuries (Ennis et al., 2008). After the implementation of new resuscitation guidelines and burn flow sheets by USAISR, however, the incidence of compartment syndrome and mortality for individuals with comparable injuries treated between 2006 and 2007 was decreased to 18 percent. This was indicative, in part, of the effectiveness of guidelines implemented to improve documentation and standardization of burn care. However, room for improvement remained since these guidelines could not actively assist providers in determining how resuscitation should be performed. The need for more dynamic tools that assist resuscitation decisions was recognized, leading to the development of the BRDSS.

Use of the BRDSS-C software in the USAISR Burn Center has already improved care for severely burned warfighters. The system has enabled better fluid management during resuscitation, leading to improved outcomes with respect to mortality, length of intensive care unit stay, and ventilator days (Salinas et al., 2011, Schmidt & Mann-Salinas, 2014).

Outside of continental U.S. burn centers, the deployment of the BRDSS-M now has the potential to tremendously impact early burn care of the warfighter. In theater, burn resuscitation within the first 24 to 48 hours is often performed by providers with varying levels of experience, and may involve multiple handoffs of the patient across four or more provider teams during transport to definitive care (Chung, Salinas, & Renz, 2011). The BRDSS-M offers the opportunity to guide resuscitation by less experienced providers and standardize care during this early, critical period. By providing individual patient trend-based recommendations, it is believed that the implementation of the BRDSS can reduce the incidence of compartment syndrome and other complications of over or under-resuscitation (Meador, 2014).

Clinical Practice

Impact on Clinical Practice Guidelines

Prior to the advances spurred by military patient care and research over the last decade, burn resuscitation capabilities and knowledge have been relatively stagnant since the 1970's (Alvarado, Chung, Cancio & Wolf, 2009). Through U.S. Army research, guidelines for burn resuscitation have now advanced significantly throughout the course of the OIF/OEF conflicts, with the initial development of burn resuscitation CPGs and a burn resuscitation flow sheet in 2005 leading to improvements in care (Ennis et al., 2008; Chung, Salinas, & Renz, 2011). These tools have continued to be reviewed and updated, and currently a 2013 revision of the associated Burn Care CPG is available from the JTS (JTS, 2013). Building on this, the development of the BRDSS has now provided a new tool that has changed clinical practice, ushering in a shift to a more dynamic resuscitation guidance that is responsive to an individual patient's parameters over time (Figure 18).

The USAISR Burn Center's adoption of the BRDSS-C as part of an ongoing internal clinical performance improvement program and continued use of the system for several years has represented a substantial shift in clinical practice. Following studies of the performance of the system, and surveys of users, strategies have been continually developed and implemented to improve acceptance of the technology, which is now a standard feature in the Burn Center (Mann, Allen, Serio-Melvin, Wolf, & Salinas, 2012). The BRDSS-C is poised to continue to impact civilian burn resuscitation practice, as the commercial software has achieved FDA clearance and is being adopted by additional burn centers.

As the BRDSS-M is now being deployed and providers at combat support hospitals are receiving training in its use, its implementation will continue to affect clinical practice in theater. It will enable patient specific fluid resuscitation history and guidance to be passed with a patient across different roles of care. A future aim is to enable the data from the BRDSS-M to be seamlessly imported into the BRDSS-C when a patient reaches a burn center (Galvan, 2015). Ultimately, the BRDSS technologies may also provide the basis for greater impacts on clinical practice in the future as the USAISR continues to seek ways to advance the approaches used in decision support

algorithms into closed-loop burn resuscitation systems that could be used to automatically resuscitate burn patients without human intervention (Salinas et al., 2008).

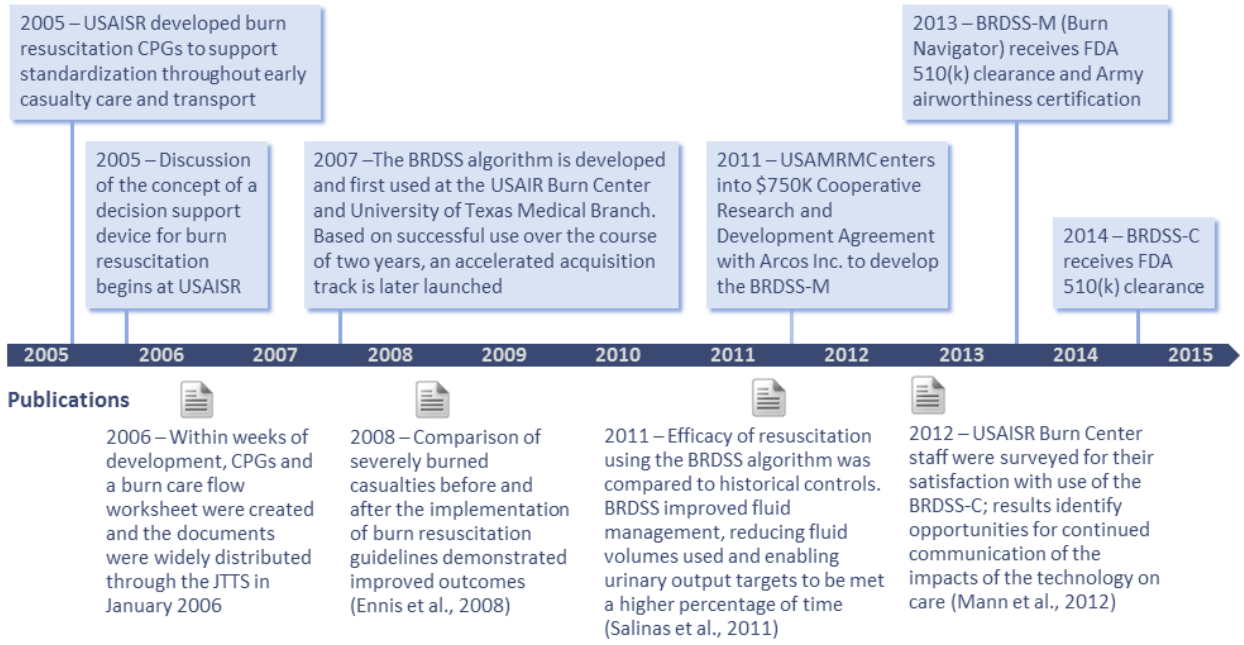


Figure 18. Research, Development, and Fielding timeline: BRDSS

Supporting Publications

A growing body of literature has supported the need for carefully managed fluid resuscitation for burns, initiated at an appropriate rate and managed hour to hour to ensure adequate urinary output. This data has laid a foundation for updates to the military CPGs for burn resuscitation and for the development of the algorithm at the heart of the BRDSS systems (Table 37).

Table 37. Supporting Publications for Burn Resuscitation Guidelines

Reference	Description
Ennis et al., 2008	Comparison of severely burned casualties before and after the initial implementation of burn resuscitation guidelines and flow sheets demonstrated improved outcomes following these changes. The composite endpoint of abdominal compartment syndrome and mortality was significantly lower following implementation
Alvarado, Chung, Cancio, & Wolf, 2009	Reviewed the evolution of burn resuscitation and analyzed guidelines and adjuncts to resuscitation; underscored the need for continued advances to prevent the complication of over- or under-resuscitation
Chung et al., 2009	Retrospectively examined severely burned military casualties treated at the USAISR Burn Center during 2005-2008 for whom burn flow sheets had been completed. Resuscitation with a higher initial fluid rate resulted in a significantly larger fluid volume load in the first 24 hours. Starting at a lower initial rate resulted in less fluids being given in the first 24 hours without any detectible difference in outcome
Markwell, et al., 2009	Retrospectively examined all severely burned military and civilian patients with abdominal pathology at the USAISR Burn Center during 2003-2008. Review of the data by a panel of surgeons experienced in abdominal catastrophes led to the recommendation of more aggressive monitoring of abdominal compartment pressures

Reference	Description
Chung et al., 2010	Developed a simplified formula to derive initial burn resuscitation fluid rate, called the "rule of 10." For the majority of adult patients, the rule approximated initial fluid rate within acceptable ranges
Salinas et al., 2011	Examined the efficacy of the computerized decision support system for burn resuscitation compared to historical controls. Implementation of the system improved fluid management of severely burned patients, reducing resuscitation fluid volumes used and enabling urinary output targets to be met a higher percentage of time

Role of CCCRP-Sponsored Projects

The USAISR's CICR Task Area is linked to the FSICC portfolio, and the CCCRP has supported the development of the BRDSS algorithm and related activities through this task area. Additionally, USAMRMC entered into a cooperative agreement with Arcos, Inc., to collaborate on the production of the BRDSS-M device, including the production of a prototype system and activities for FDA clearance and airworthiness certification (Table 38).

With the support of the CCCRP, the BRDSS has become the first medical device to start as a research project within the USAMRMC, go through advanced development and FDA clearance, and exit the decision gate process into fielding.

Table 38. CCCRP-Sponsored Projects for BRDSS

Project Title (Award Number)	Organization/ Principal Investigator	Funding
CCCRP funding to CICR Task Area	USAISR CICR	$5M (2005–2014)
Burn Resuscitation Decision Support System (BRDSS) (W81XWH-11-2-0157)	Christopher Meador, MBA (Arcos, Inc.)	$750,000 (2011–2014)

Through support of this work, the BRDSS-C and BRDSS-M have both successfully gained regulatory clearance and are already in use to improve burn resuscitation outcomes for the warfighter, as well as a for civilians. On this path, several key publications have documented the development of the BRDSS algorithm, improvement in burn care outcomes through its implementation in the USAISR Burn Center, analysis of user acceptance, and opportunities for continued improvements (Table 39).

Table 39. CCCRP-Sponsored Publications for BRDSS

Reference	Description
Salinas et al., 2008	Review of contemporary burn resuscitation approaches, including a metaanalysis of 26 years. Reviewed engineering efforts, animal studies, and algorithm development for decision support and autonomous systems for burn resuscitation
Salinas et al., 2011	Examined the efficacy of the computerized decision support system for burn resuscitation compared to historical controls. Implementation of the system improved fluid management of severely burned patients, reducing resuscitation fluid volumes used and enabling urinary output targets to be met a higher percentage of time
Mann, Allen, Serio-Melvin, Wolf, & Salinas, 2012	Staff members at the USAISR Burn Center intensive care unit were surveyed about their satisfaction with use of the BRDSS-C software; results indicated opportunities for continued communication to emphasize the impacts that consistent use of the technology can have on outcomes

Reference	Description
Serio-Melvin, Meador, & Garcia, 2013	Poster presentation detailing the human factor study conducted with the participation of 30 nurses to support FDA clearance of the BRDSS-M. Several training, user manual, and software changes were made to the BRDSS-M prior to its clearance, based on the study findings
Meador, 2014	Final report of Arcos activities for BRDSS-M development under the cooperative agreement with USAMRMC. Detailed development of the device, human factors validation, FDA clearance, and airworthiness certification
Schmidt & Mann-Salinas, 2014	Reviewed advancements supporting treatment of combat burns, including the implementation of the BRDSS-C

References

Alvarado, R., Chung, K. K., Cancio, L. C., & Wolf, S. E. (2009). Burn resuscitation. *Burns*, *35*, 4-14.

Burn Resuscitation Decision Support system – Clinical (BRDSS-C), v. 1.0 510(k) Summary No. K130482 (2014, December 23). Retrieved from http://www.accessdata.fda.gov/cdrh_docs/pdf14/K140387.pdf

Burn Resuscitation Decision Support system (BRDSS) 510(k) Summary No. K121658 (2013, April 18). Retrieved from http://www.accessdata.fda.gov/cdrh_docs/pdf12/K121659.pdf

Chung, K. K., Blackbourne, L. H., Wolf, S. E., White, C. E., Renz, E. M., Cancio, L. C., … Barillo, D. J. (2006). Evolution of burn resuscitation in operation Iraqi freedom. *Journal of Burn Care & Research*, *27* (5), 606-611.

Chung, K. K., Salinas, J., & Renz, E. M. (2011). Advances in prehospital burn resuscitation for the combat injured. *The United States Army Medical Department Journal*, *April-June*, 55-60.

Chung, K. K., Salinas, J., Renz, E. M, Alvarado, R. A., King, B. T., Barillo, D. J., … Blackbourne, L. H. (2010). Simple derivation of the initial fluid rate for resuscitation of severely burned adult combat casualties: in silico validation of the rule of 10. *Journal of Trauma & Acute Care Surgery*, *69*(Suppl 1), S49-S54.

Chung, K. K., Wolf, S. E., Cancio, L. C., Alvarado, R., Jones, J. A., McCorcle, J., … Blackbourne, L. H. (2009). Resuscitation of severely burned military casualties: Fluid begets more fluid. *The Journal of Trauma, Injury, Infection, and Critical Care, 67*(2), 231-237.

Ennis, J. L., Chung, K. K., Renz, E. M., Barillo, D. J., Albrecht, M. C., Jones, J. A., … Holcomb, J. B. (2008). Joint Theater Trauma System implementation of burn resuscitation guidelines improves outcomes in severely burned military casualties. *The Journal of Trauma, Injury, Infection, and Critical Care, 64*, S146-S152.

Galvan, S. (2014, April 10). Burn flight team instructs CSH staff on burn patient care. Retrieved from https://mrmc.amedd.army.mil/index.cfm?pageid=media_resources.articles.CSH_staff_instructed_on_burn_patient_care

Galvan, S. (2015, March 4). BRDSS-C. Retrieved from http://www.army.mil/media/384008/

Joint Trauma System (JTS). (2013, November). Joint Theater Trauma System Clinical Practice Guideline: Burn Care. Retrieved from http://usaisr.amedd.army.mil/cpgs.html

Mann, E. A., Allen, D. A., Serio-Melvin, M. L., Wolf, S. E., & Salinas, J. (2012). Clinician satisfaction with computer decision support in the intensive care unit. *Dimensions of Critical Care Nursing*, *31*(1), 31-36.

Markwell, K. W., Renz, E. M., White, C. E., Albrecht, M. E., Blackbourne, L. H., Park, M. S., … Wolf, S. E. (2009). Abdominal complications after severe burns. *Journal of the American College of Surgeons, 208*(5), 940-947.

Meador, C. (2014). Burn Resuscitation Decision Support System (BRDSS). Final Report (Award Number: W81XWH-11-2-0157). Retrieved from http://www.dtic.mil/dtic/tr/fulltext/u2/a608762.pdf

Salinas, J., Chung, K. K., Mann, E. A., Cancio, L. C., Kramer, G., C., Serio-Melvin, M. L., … Wolf, S. E. (2011). Computerized decision support system improves fluid resuscitation following severe burns: An original study. *Critical Care Medicine*, *39*(9), 2031-2038.

Salinas, J., Drew, G., Gallagher, J., Cancio, L. C., Wolf, S. E., Wade, C. E., … Kramer, G. C. (2008). Closed-loop and decision-assist resuscitation of burn patients. *The Journal of Trauma Injury, Infection, and Critical Care, 64(4)*, S321-S332.

Schmidt, P., & Mann-Salinas, E. A. (2014). Evolution of burn management in the U.S. military. *Annual Review of Nursing Research, 32*, 25-39.

Serio-Melvin, M. L., Meador, C., & Garcia, A. (2013, August). Conducting a FDA human factors study on a burn resuscitation decision support system. Poster presented at the 2013 Military Health System Research Symposium, Ft. Lauderdale, FL.

U.S. Army Institute of Surgical Research (USAISR). (2015, January 5). Comprehensive Intensive Care Research. Retrieved from http://usaisr.amedd.army.mil/beta/08_cicr.html

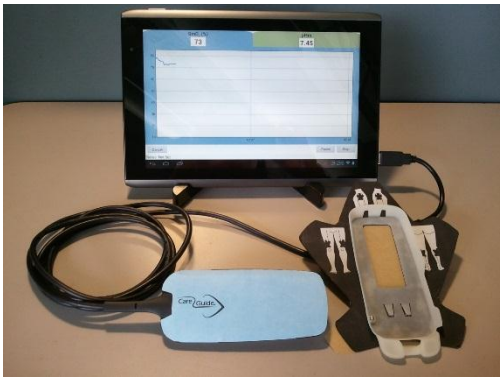
The CareGuide Oximeter: Noninvasive and Continuous Casualty Monitoring

Noninvasive physiological monitors hold the potential to decrease morbidity and mortality across the continuum of care by providing caregivers with accurate and predictive real-time casualty data.

- Developmental Partner Organization:
  - Reflectance Medical Inc. (RMI)

Key Outcomes and Impact:

- All CareGuide Oximeters have been developed with support from the USAMRMC and have FDA clearance
- CareGuide Oximeters use near infrared spectroscopy (NIRS) to noninvasively and continuously monitor muscle oxygen saturation (SmO_2) and pH (pHm)
- Measurements from the CareGuide Oximeter can be used to detect internal hemorrhage, predict risk of shock, and track the adequacy of resuscitation



Multi-parameter Mobile CareGuide 4100 Oximeter (RMI, 2015)

Overview

Hemorrhage and subsequent cardiovascular collapse represent major causes of death on the battlefield (Eastridge et al., 2012). Delays in the identification and control of hemorrhage in the prehospital phase of treatment resulted in a large percentage (26 percent) of the potentially survivable deaths in Operation Iraqi Freedom (Eastridge et al., 2012; Martin et al., 2009)

In forward combat environments, uncontrolled hemorrhage and ensuing hypovolemic shock lead to organ dysfunction and damage, and possibly death. In reaction to hypovolemic shock, the sympathetic nervous system is activated and peripheral blood is redistributed to the central compartment. This compensatory mechanism masks the hemorrhage by attempting to maintain heart rate, blood pressure, and other vital signs within normal clinical ranges even after up to a 30 percent reduction in blood volume (Convertino et al., 2011; Cottingham, 2006). Masking of the underlying hemorrhage will often lead to situations where the first clear clinical sign of life-threatening hemorrhage is hypovolemic shock including precipitous cardiovascular collapse and a sudden and substantial drop in blood pressure (Cottingham, 2006).

Compensatory physiological mechanisms limit the caregiver's ability to detect internal hemorrhage and prevent shock.

The key to the successful management of critically injured casualties is currently vigilance. Frequent monitoring is imperative for the early detection of life-threatening internal hemorrhage. Rapid detection and treatment of traumatic injuries and shock saves lives and reduces complications (Pinsky, 2007). Even so, being aware of multiple casualties is difficult, especially in battlefield settings where capabilities are constrained and the medic's time and attention are limited. Thus, it has become increasingly clear that as casualties enter and progress along the continuum of care, there is a need for continuous monitoring technologies that enhance the caregiver's ability to, for example, detect internal hemorrhage and the beginning of hypoperfusion, and guide therapies such as damage control resuscitation.

Figure 19. The Mobile CareGuide Oximeter Noninvasively Measures Oxygen Saturation and pH of Regional Tissues (RMI, 2015)

The CCCRP is supporting several emerging technologies that collectively represent the new generation of smart sensors and fully integrated transport monitors. These technologies will enable medics in forward environments to rapidly identify critically injured casualties and correctly triage casualties to the most appropriate level of care.

Table 40. Development of the CareGuide Oximeter

Model	Details
CareGuide 1100 Oximeter (1st generation)	• Noninvasively measures SmO_2 using NIRS • First FDA-cleared device for the continuous monitoring of SmO_2 • First FDA-cleared device for measuring tissue perfusion independent of skin pigmentation
Mobile CareGuide 2100 Oximeter (2nd generation)	• Battery-powered • Interfaces with smart devices or patient monitors to display measurements and trends
Multi-parameter Mobile CareGuide 3100 Oximeter (3rd generation)	• First device to continuously and noninvasively measure patient acid-base status (pHm), an indicator of tissue acidosis • Simultaneously and continually measures SmO_2 and pHm
Multi-parameter Mobile CareGuide 4100 Oximeter (4th generation)	• Performs SmO_2 and pHm measurements automatically every 30 seconds • Ready to use. Sensor automatically detects placement and does not require calibration • Accurately measures SmO_2 and pHm independent of skin pigmentation • Ruggedized and reusable sensor • Attaches to the patient with a disposable peal and stick clip • Operation is plug'n play. Interfaces with other monitors and displays through a USB connection

The FSICC portfolio initiated a collaboration with RMI to develop a noninvasive sensor for accurate continuous monitoring of tissue oxygenation (Table 40). The CareGuide sensors can continuously, and noninvasively, measure oxygen saturation, pH, and hematocrit from a region of skeletal muscle tissue below the oximeter sensor. The body-worn sensor is applied to the muscle in the arm or the leg and the sensor collects a NIRS absorbance spectrum (Figure 19). At the core of the CareGuide Oximeters are

RMI's CareGuide Oximeters provide noninvasive, continuous measurements of tissue metabolism, and can be used to determine if a casualty is hemorrhaging internally and at risk for hypovolemic shock.

The early detection of hemorrhage and shock will alert medics to intervene before cardiovascular collapse.

proprietary algorithms that calculate medical parameters by NIRS. In contrast to pulse oximetry, which is a measure of the oxygen carrying capacity of the blood, SmO_2 measurements provide information about whether or not enough oxygen is being delivered to the muscles to meet metabolic demands. The CareGuide Oximeter was designed to interface with other vital sign monitors or be used with a dedicated Android tablet to display SmO_2 and pHm values (RMI, 2015).

The USAMRMC supported the development of CareGuide Oximeters 1100, 2100, and 3100, and is currently providing funding for the CareGuide 4100, a ruggedized version of the 3100 Mobile CareGuide that meets military specifications (Table 40). Similarly, in 2013, RMI entered into an agreement with ZOLL Medical Corporation, a manufacturer of resuscitation devices and related software solutions (ZOLL, 2013) (Figure 20). A goal of the collaboration is to develop a ruggedized version of the CareGuide Oximeter for detecting the onset of shock in military casualties during air and ground transport.

In a related collaborative effort from the CCCRP, the J-ERC portfolio has also provided funding for a collaboration between RMI and Sotera Wireless to integrate the CareGuide Oximeter with ViSi Wireless, Sotera's monitoring technology platform. The integrated use of these two FDA-cleared devices is currently in clinical trials with healthy flight crews to assess monitoring functionality and accuracy, and to gauge the devices' potential impact on en route care.

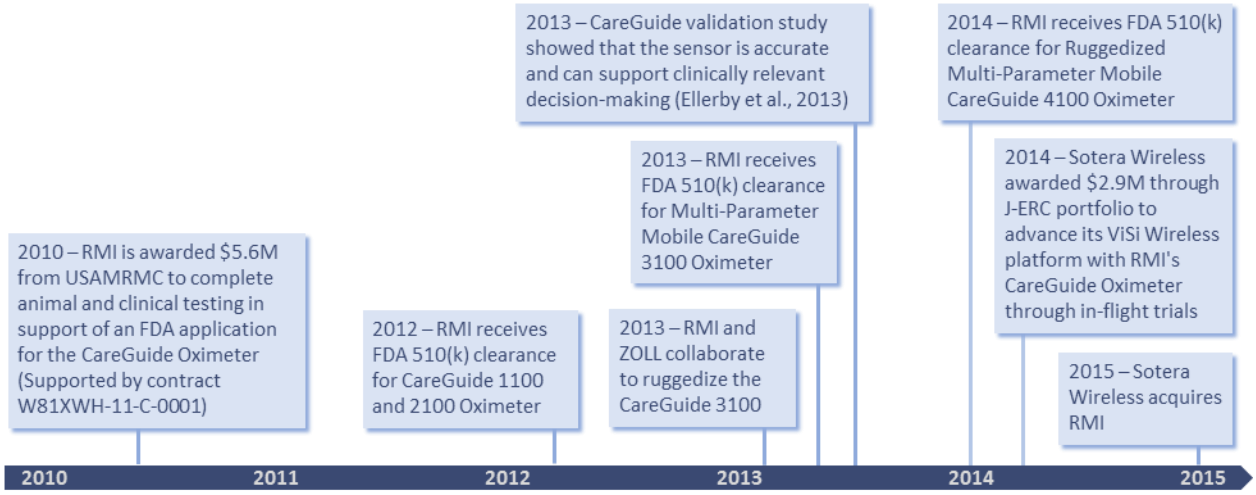


Figure 20. Key Milestones and Developmental Timeline of the CareGuide Oximeter

Capability Gap Alignment

As part of its strategic approach, the FSICC portfolio has focused on battlefield monitoring, which includes enhancing the capability to detect hemorrhage and perform life-saving interventions through forward monitoring and predictive device capabilities across the continuum of care. These efforts will introduce the next generation of monitors, which will be tightly integrated into clinical support and communication systems.

The development and implementation of the CareGuide Oximeter, standalone or in conjunction with other sensor technologies, will directly contribute to the closure of multiple different gaps

and provide enabling capability for the closure of others across the continuum of care (Table 41). All three requirement sources listed in Table 41 identify a need for monitoring capabilities to enhance activities including triage and resuscitation.

Table 41. Capability Gaps Addressed by the CareGuide Oximeter

Requirement Sources	Capability Gaps Addressed
GDF	• **JCM-1-1** – Inadequate ability to diagnose, resuscitate, and stabilize casualties with survivable wounds • **JCM-1-3** – Inadequate ability to locate and evaluate casualties • **JCM-1-7** – Inability to monitor, evaluate, and triage casualties by combat medical personnel for early identification of life-saving interventions • **JCM-1-11** – Inadequate ability to immediately recognize and correct coagulopathy • **JCM-2-1** – Inadequate stabilization of injuries and ability to monitor response to treatment
TC3 ICD	• **Theater Hospitalization, Area Medical Support** – Diagnose, resuscitate and stabilize casualties with survivable wounds • **En Route Care** – Locate and evaluate casualties • **First Response Medical Care** – Stabilize injuries, monitor response to treatment • **Advanced Casualty Locating and Remote Physiologic Monitoring** – Monitor, evaluate, triage casualties by combat medical personnel for early identification of life-saving interventions
DHP ICD	• **DK3** – Lack a decision support mechanism that enables timely, accurate decisions and diagnosis at all levels of care • **TI1** – Insufficient current first-responder (medical and non-medical) capacity and capability to initially assess, treat, and maintain severe trauma cases in the pre-hospital environment - Insufficient tools that enable both non-medical and medical first responders - The technologies do not exist to fulfill some of the needs (e.g. stabilizing the airway or truncal hemorrhage) • **TI6** – First responders lack interoperable ways and means to understand and provide rapid, reliable, and actionable information about a casualty's physiological/psychological status in the pre-hospital environment (for IT devices there are no defined KPP requirements; no clearly defined MILSPECS for non-IT) • **TI7** – Current ways and means of document POI hinder ability to capture rapid, reliable, and actionable information about a casualty's physiological status in the pre-hospital environment and subsequently transmit it for follow on analysis • **TI11** – Lack of computational algorithms and predictive tools for physiological status that use available information and can predict necessary statuses in an expedient manner • **TI12** – In pre-hospital environment, lack ways and means to enable clinical decision support and have inadequate ways and means to enable clinical decision support at Level III and higher • **MB4** – In the pre-hospital environment, there is a lack of understanding of the optimal oxygen requirements for casualties • **MB6** – Limited capability to identify and treat lung function problems and respiratory failure in the pre-hospital environment • **MA6** – Lack of ability to identify arterial oxygen and CO_2 levels • **TS1** – Lack of optimal resuscitation strategies for casualties who have TBI and are in, or at risk for, hemorrhagic shock • **TS4** – Lack of ways and means to effectively screen for and diagnose shock throughout continuum of care • **TS6** – Insufficient ways and means to diagnose and manage vascular disruption (with or without hemorrhagic shock)

Impact on the Battlefield/Warfighter

Although CareGuide Oximeters have not yet been fielded, their broad clinical utility and connectivity will have a significant impact on military personnel in various combat casualty care settings.

Probably most anticipated is the CareGuide Oximeter's impact on hemorrhage mortality and morbidity across the continuum of care. For hemorrhaging casualties that require treatment, the continuous feedback capability of the CareGuide Oximeter enables the medic to deliver resuscitative intervention with greater accuracy and responsiveness. Resuscitation that is more accurate would, for example, reduce the incidence and impact of over-resuscitation (i.e., rapid increase in systolic blood pressure and dilution of clotting factors). Tissue acidosis occurs because of inadequate oxygen, and causes a dangerous buildup of lactic acid. To avoid serious complications of acidosis, including organ dysfunction and death, it is important that acidosis be quickly reversed by resuscitation. Progress is currently assessed by repeated blood draws and laboratory analyses to verify the blood pH. The Mobile CareGuide Oximeter is expected to eliminate serial blood samples by providing noninvasive continuous monitoring of pHm.

It is envisioned that the CareGuide Oximeter integrated and operating on the ViSi Wireless platform will benefit casualties and medics during air transport. The integrated device will enable medics to continuously monitor and capture physiological information during taxi, takeoff, and the flight. In conjunction with additional sensors, the CareGuide Oximeter can be used to identify and explore the risks of air transport on the health of casualties. Current evidence obtained from pulse oximeters indicates that even during normal flights, passengers experience minor hypoxia, which, for critically injured patients may have profound impacts (Bendrick, Nicholas, Krause, & Castillo, 1995; Cottrell, Lebovitz, Fennell & Kohn, 1995; Humphreys, Dyermond, Bali, Stevenson & Fee, 2005; Smith et al., 2012). Because of hypoxia's impact on the aircrew and flight safety, the Navy has also identified the need for an oxygen monitoring system in flight, beyond patient transport (Phillips, 2010). Rapid depressurization events are obvious and infrequent, but most hypoxia-related incidents involve moderate hypoxia caused by, for example, faulty oxygen delivery systems. Aircrew must recognize that a hypoxic event is happening while they are conscious and have the cognitive reserve to initiate emergency procedures. This is key because there are currently no means to continuously monitor the physiological status of aircrew in military aircraft. It is envisioned, however, that future monitoring systems based on the CareGuide Oximeter and connected through the ViSi Wireless platform will provide this capability.

Clinical Practice

Impact on Clinical Practice Guidelines

Combat medics employ pulse oximeters to monitor arterial blood oxygen in casualties who have sustained a variety of injuries across different environments. The 2014 TCCC Guidelines recommend that casualties with moderate to severe TBI should be monitored by pulse oximetry (in addition to vital signs monitoring); with the caveat that readings may be misleading if the casualty has marked hypothermia or is in shock (JTS, 2014). The TCCC Guidelines also recommend that oxygen saturation be closely monitored in casualties with burn and inhalation injuries (JTS, 2014). For many of these situations, CareGuide Oximeters are expected to replace

standard pulse oximeters. Besides simply replacing pulse oximeters, CareGuide Oximeters will also likely usher in multiple changes to CPGs that are rooted in their expanded capabilities.

The primary reason for the CCCRP's involvement in developing a continuous physiological monitor was to increase the capability of first-responders in prehospital environments to assess, treat, and maintain severe trauma cases, particularly those involving hemorrhage. This is because rapid management and treatment of traumatic injuries and shock has been shown to help save lives and reduce medical complications. It is expected that when implemented the CareGuide's monitoring capabilities will significantly decrease the burden on combat medics. Because muscle SmO_2 can be easily monitored in emergencies, it may represent an improved method to gauge the severity of shock or the adequacy of fluid resuscitation after trauma.

During air transport, the JTTS CPG recommends that all patients be monitored with a cardiac monitor, pulse oximeter, and an automatic blood pressure monitor (JTS, 2007). Aircrew medics are encouraged to carry a Nonin Onyx mini-pulse oximeter or similar device for spot-checks during the flight (JTS, 2007). In addition, because alarms are typically inaudible during flight, medics are advised to visually monitor for alarming equipment (JTS, 2007). Implementation of the CareGuide, in conjunction with related noninvasive monitoring technologies, may enable all of these needs to be met with continuous monitoring, making it easier for healthcare providers to evaluate casualty status.

Supporting Publications

The concept and technology behind NIRS has existed for decades but monitoring oxygen levels, as recommended by multiple CPGs, is currently performed largely with pulse oximeters. Nonetheless, multiple articles have highlighted the underlying technology (i.e., NIRS) in the CareGuide Oximeter as an effective measure to predict hemodynamic instability (Table 42).

Table 42. Supporting Publications for the CareGuide Oximeter

Reference	Description
Cairns et al., 1997	Used a NIRS probe to measure oxygen utilization in trauma patients during resuscitation. Impaired oxygen utilization was observed early in resuscitation and suggested NIRS could predict multiple organ dysfunction
McKinley, Marvin, Cocanour, & Moore., 2000	Evaluated hemoglobin oxygen levels from tissues using noninvasive NIRS. Results indicate skeletal muscle SmO_2 levels, measured by NIRS, can be an effective guide for resuscitation
Crookes, Cohn, Burton, Nelson, & Proctor, 2004	In a porcine model, noninvasive muscle SmO_2 levels determined by NIRS were more reliable than invasive oxygenation measurements as a predictor of hemorrhagic shock. Because muscle SmO_2 can be easily monitored in emergencies, it may represent an improved method to gauge the severity of shock or the adequacy of fluid resuscitation after trauma
Crookes et al., 2005	Prospective study found that decreased oxygen levels (as measured by NIRS) in the thenar muscle reflect the existence of severe hypoperfusion
Cohn et al., 2007	Prospective study that investigated the association between SmO_2 levels (measured by NIRS) and hemorrhagic shock. SmO_2 measurements collected from patients within an hour of their arrival at a trauma center could be used to discriminate those patients who died from those who developed multiple organ dysfunction syndrome. SmO_2 measurements were equivalent in predictive power to measurements of arterial base deficit and systolic blood pressure

Role of CCCRP-Sponsored Projects

The CCCRP's FSICC portfolio supported the development and validation of the CareGuide Oximeter beginning in 2008. With this support, RMI obtained FDA clearance for the first and three subsequent models of the CareGuide Oximeter (i.e., models 1100, 2100, 3100, and 4100) (Table 40). In addition, the CCCRP funded multiple projects that were focused on validating NIRS as a way to measure oxygen saturation and to explore CareGuide's utility overall (Table 43).

Table 43. CCCRP-Sponsored Projects for the CareGuide Oximeter

Project Title (Award Number)	Principal Investigator	Funding
A Real-Time, Portable Non-Invasive Monitoring System of Muscle Oxygen and pH in Trauma Patients (Small Business Technology Transfer [STTR]; W81XWH-08-C-0114)	RMI	$848,915 (2008–2010)
Noninvasive, Body-Worn Device for Providing Real-Time Cardio-Pulmonary and Metabolic Status for Triage and Resuscitation Feedback (W81XWH-11-2-0085)	Sotera-RMI Collaboration	$5,146,722 (2010–2013)
CareGuide Non Invasive Trauma Patient Monitor (W81XWH-11-C-0001)	RMI	$5,619,630 (2010–2013)

Table 44. CCCRP-Sponsored Publications for the CareGuide Oximeter

Reference	Description
Zou, Jin, Ross, & Soller, 2010	Evaluated SmO_2 prediction accuracy of an algorithm that employed the simulated annealing method. The study demonstrated the method to be highly repeatable
Soller, Ryan, & Convertino, 2010	Used an NIRS device to monitor SmO_2, pHm, and whole blood volume in volunteers subjected to lower body negative pressure (LBNP), a model for central hypovolemia. Results demonstrate significant decreases in SmO_2 that are similar to progressive reductions in central blood volume
Convertino et al., 2011	Used LBNP as a model of hemorrhage to evaluate continuous, noninvasive monitoring of hemodynamic signals in 28 healthy volunteers. Used machine-learning algorithms to analyze hemodynamic signals. Machine modeling accurately identified loss of central blood volume and predicted when hemodynamic decompensation occurs
Grudic, Moulton, & Mulligan, 2012	U.S. Patent claiming tools and techniques to estimate if patient has internal bleeding or has sustained intravascular volume loss
Ellerby, Smith, Zou, Scott, & Soller, 2013	Used an isolated perfused swine limb model to evaluate the CareGuide Oximeter for its ability to simultaneously and continuously measure SmO_2 and pHm. The oximeter was accurate enough to support clinically relevant decision-making
Soller et al., 2014a	Evaluated the CareGuide Oximeter by measuring pHm and SmO_2 in a swine shock model of uncontrolled hemorrhage and restricted volume resuscitation. Results suggested that an evaluation of the CareGuide Oximeter in trauma patients is warranted
Soller et al., 2014b	Demonstrated the utility of NIRS measurements of SmO_2 to continuously detect plasma leakage in children with suspected dengue infection

References

Bendrick, G. A., Nicolas, D. K., Krause, B. A., & Castillo, C. Y. (1995). Inflight oxygen saturation decrements in aeromedical evacuation patients. *Aviation, Space, and Environmental Medicine, 66*(1), 40-44.

Cairns, C. B., Moore, F. A., Haenel, J. B., Gallea, B. L., Ortner, J. P., Rose, S. J., & Moore, E. E. (1997). Evidence for early supply independent mitochondrial dysfunction in patients developing multiple organ failure after trauma. *Journal of Trauma and Acute Care Surgery*, *42*(3), 532-536.

Cohn, S. M., Nathens, A. B., Moore, F. A., Rhee, P., Puyana, J. C., Moore, E. E., … StO_2 in Trauma Patients Trial Investigators. (2007). Tissue oxygen saturation predicts the development of organ dysfunction during traumatic shock resuscitation. *Journal of Trauma and Acute Care Surgery*, *62*(1), 44-55.

Convertino, V. A., Moulton, S. L., Grudic, G. Z., Rickards, C. A., Hinojosa-Laborde, C., Gerhardt, R. T., … Ryan, K. L. (2011). Use of advanced machine-learning techniques for noninvasive monitoring of hemorrhage. *Journal of Trauma and Acute Care Surgery*, *71*(1), S25-S32.

Cottingham, C. A. (2006). Resuscitation of traumatic shock: a hemodynamic review. *AACN advanced critical care*, *17*(3), 317-326.

Cottrell, J. J., Lebovitz, B. L., Fennell, R. G., & Kohn, G. M. (1995). Inflight arterial saturation: continuous monitoring by pulse oximetry. *Aviation, Space, and Environmental Medicine*, *66*(2), 126-130.

Crookes, B. A., Cohn, S. M., Burton, E. A., Nelson, J., & Proctor, K. G. (2004). Noninvasive muscle oxygenation to guide fluid resuscitation after traumatic shock. *Surgery*, *135*(6), 662-670.

Crookes, B. A., Cohn, S. M., Bloch, S., Amortegui, J., Manning, R., Li, P., … Proctor, K. G. (2005). Can near-infrared spectroscopy identify the severity of shock in trauma patients? *Journal of Trauma and Acute Care Surgery*, *58*(4), 806-816.

Eastridge, B. J., Mabry, R. L., Seguin, P., Cantrell, J., Tops, T., Uribe, P., … Blackbourne, L. H. (2012). Death on the battlefield (2001–2011): implications for the future of combat casualty care. *Journal of Trauma and Acute Care Surgery*, *73*(6), S431-S437.

Ellerby, G. E. C., Smith, C. P., Zou, F., Scott, P., & Soller, B. R. (2013). Validation of a spectroscopic sensor for the continuous, noninvasive measurement of muscle oxygen saturation and pH. *Physiological measurement*, *34*(8), 859.

Grudic, G. Z., Moulton, S. L., & Mulligan, I. J. (2012). *U.S. Patent Application 13/554,483*.

Humphreys, S., Deyermond, R., Bali, L, Stevenson, M., & Fee, J. P. (2005). The effect of high altitude commercial air travel on oxygen saturation. *Anaesthesia, 60*(5), 458-460.

Joint Trauma System (JTS). (2014, June). Joint Trauma System Clinical Practice Guidelines. Retrieved from http://www.usaisr.amedd.army.mil/pdfs/TCCC_Guidelines_140602.pdf

Joint Trauma System (JTS). (2007, Sept). JTTS Clinical Practice Guideline for Intratheater Transfer and Transport of Level II and III Critical Care Trauma Patients. Retrieved from: http://www.dmrti.army.mil/documents/Intratheater%20Transfer%20Transport%20CPG%20Sep%2007.pdf

Martin, M., Oh, J., Currier, H., Tai, N., Beekley, A., Eckert, M., & Holcomb, J. (2009). An analysis of in-hospital deaths at a modern combat support hospital. *Journal of Trauma and Acute Care Surgery*, *66*(4), S51-S61.

McKinley, B. A., Marvin, R. G., Cocanour, C. S., & Moore, F. A. (2000). Tissue hemoglobin O2 saturation during resuscitation of traumatic shock monitored using near infrared spectrometry. *The Journal of Trauma*, *48*(4), 637-642.

Phillips, J. B. (2010). A Comparison of near-infrared spectroscopy and reflectance sensors to traditional pulse oximetry under conditions of low blood oxygen saturation. *Naval Aerospace Medical Research Laboratory Research Information Bulletin*, No-10-27

Pinsky, M. R. (2007). Hemodynamic evaluation and monitoring in the ICU. *CHEST Journal*, *132*(6), 2020-2029.

Reflectance Medical Inc. (2015). Products. Retrieved from http://www.reflectancemedical.com/Company.html

Smith, T. G., Talbot, N. P., Chang, R. W., Wilkinson, E., Nickol, A. H., Newman, D. G., Robins, P. A., & Dorrington, K. L. (2012). Pulmonary artery pressure increases during commercial air travel in healthy passengers. *Aviation, Space and Environmental Medicine*, *66*(2), 126-130.

Soller, B. R., Ryan, K. L., & Convertino, V. A. (2010). *Lightweight Noninvasive Trauma Monitor for Early Indication of Central Hypovolemia and Tissue Acidosis*. ARMY INST OF SURGICAL RESEARCH FORT SAM HOUSTON TX.

Soller, B. R., Zou, F., Ryan, K. L., Rickards, C. A., Ward, K., & Convertino, V. A. (2012). Lightweight noninvasive trauma monitor for early indication of central hypovolemia and tissue acidosis: a review. *Journal of Trauma and Acute Care Surgery*, *73*(2), S106-S111.

Soller, B., Smith, C., Zou, F., Ellerby, G. E., Prince, M. D., & Sondeen, J. L. (2014a). Investigation of noninvasive muscle pH and oxygen saturation during uncontrolled hemorrhage and resuscitation in swine. *Shock*, *42*(1), 44-51.

Soller, B., Srikiatkachorn, A., Zou, F., Rothman, A. L., Yoon, I. K., Gibbons, R. V., … Green, S. (2014b). Preliminary evaluation of near infrared spectroscopy as a method to detect plasma leakage in children with dengue hemorrhagic fever. *BMC infectious diseases*, *14*(1), 396.

Zoll. (2013, April 18). ZOLL and Reflectance Medical form development agreement to incorporate mobile CareGuide sensor into ZOLL monitor/defibrillators. Retrieved from http://www.zoll.com/news-releases/2013/04/18/mobile-careguide-sensor-monitor-defibrillators/

Zou, F., Jin, C., Ross, R. R., & Soller, B. (2010). Investigation of spectral interferences on the accuracy of broadband CW-NIRS tissue SO_2 determination. *Biomedical Optics Express*, *1*(3), 748-761.

Compensatory Reserve Index Algorithm: Next Generation Monitoring for Evaluating and Treating Hemorrhage

With their machine-learning software platform, Flashback Technologies has developed an algorithm for the early diagnosis and treatment of hemorrhage.

- Developmental Partner Organizations:
  - Flashback Technologies

Key Outcomes and Impact:

- Flashback Technologies has developed an algorithm that estimates compensatory reserve indices (CRI) from raw physiological vital sign data
- The CRI algorithm can differentiate between hypovolemia and rigorous exercise, and predict which casualties are on the brink of shock
- The CRI algorithm is pending 510(k) clearance, which is being sought on multiple monitoring platforms

Flashback Technologies' CRI monitor estimates compensatory reserve values noninvasively from arterial waveforms (Flashback Technologies, 2015)

Overview

Hemorrhage represents the leading cause of death on the battlefield (Eastridge et al., 2012). Because one quarter of battlefield deaths caused by hemorrhage are deemed potentially survivable if the hemorrhage had been detected and treated sooner, survival rates increase when casualties at risk for hemorrhagic shock are identified early and provided the appropriate treatment (Eastridge et al., 2012). This finding has shed light on the need to equip Role 1 medical practitioners with advanced prehospital monitoring capabilities, which would enable them to accurately identify and treat those casualties who are most at risk for developing hemorrhagic shock. Detection of hemorrhage and its intervention is limited not only by the availability of vital sign monitoring equipment available to forward medical providers, but also by the efficacy of standard vital signs to predict which casualty will develop hemorrhagic shock. This is because physiological compensatory mechanisms mask the underlying hemorrhage by working to maintain heart rate, blood pressure, and other vital signs all within normal clinical ranges (Convertino et al., 2011; Cottingham, 2006). Critical casualties who are physiologically compensated will appear normal, with the first clear clinical sign of life-threatening hemorrhage marked by a sudden and substantial drop in blood pressure and cardiovascular collapse (Figure 21) (Cottingham, 2006). Thus, it has becoming increasingly clear that as casualties progress along the continuum of care, there is a need for advanced monitoring technologies that can enhance the caregiver's ability to, for example, detect occult hemorrhage and the beginning of hypoperfusion, or to help guide interventions such as fluid volume resuscitation.

Casualties with compensated internal hemorrhage may appear normal based on standard vital sign monitors. When symptoms of hypovolemic shock finally appear, it is often too late to pursue life-saving interventions.

The USAMRMC is supporting the development of several sensor/monitoring technologies. One example is a partnership with Flashback Technologies, which initiated in 2008, to close capability gaps related to the monitoring and evaluation of casualties in forward environments. Most physiological sensors in use are designed to generate raw vital sign data, rather than generate interpreted information about the raw data. The goal of the partnership with Flashback is to develop physiological algorithms that increase medical providers' ability to diagnose and treat. Flashback Technologies relied on its proprietary software, CipherSensor, which uses feature extraction and machine-learning methods to analyze physiological waveform data, to create the CRI algorithm for the prediction of hemorrhagic shock (Figure 21). The idea is that subtle changes in physiological waveforms are predictive of acute blood loss, regardless of physiological compensatory mechanisms, and can be leveraged to enhance real-time decision support, guide intervention, monitor resuscitation efficacy, and reduce incidence of cardiovascular collapse (Figure 21).

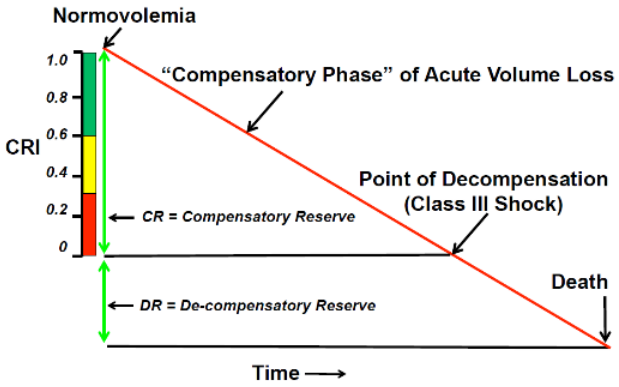


Figure 21. Flashback's CRI Reflects a Casualty's Compensatory Reserve (Moulton, 2013)

When implemented in a monitoring device, the CRI algorithm continuously analyzes and compares the entirety of waveform data in a window of time to identify features indicative of intravascular volume loss due to hemorrhage. In a prototype device, measuring CRI from an individual, the CRI algorithm generates a number from zero to one (Figure 21). If the number is one, it means the body has full ability to compensate and no blood loss has occurred. If the number is zero, however, it means the body has lost all ability to compensate for severe blood loss, and shock is imminent (Figure 21).

The CRI is not a measure of absolute volume loss; rather it is a measure of compensation for volume loss.

Capability Gap Alignment

Further development and fielding of the CRI algorithm in medical monitoring devices is expected to directly or indirectly contribute to the closure of multiple different gaps from all three requirement sources across the continuum of care (Table 45). All three sources mention the need for monitoring capabilities to enhance a variety of activities including triage, resuscitation, and accurate assessment of internal hemorrhage at all levels of care. It is expected that the CRI algorithm in a fielded sensor device will make triage of mass casualties more efficient (i.e., only those casualties who require resuscitation receive treatment). The CRI algorithm may help bring into reality decision-support systems that can assess the severity of blood loss and/or guide resuscitation in combat casualties throughout the continuum of care.

Table 45. Capability Gaps Addressed by Flashback Technologies' CRI Algorithm

Requirement Sources	Capability Gaps Addressed
GDF	• **JCM-1-1** – Inadequate ability to diagnose, resuscitate, and stabilize casualties with survivable wounds • **JCM-1-3** – Inadequate ability to locate and evaluate casualties • **JCM-1-7** – Inability to monitor, evaluate, and triage casualties by combat medical personnel for early identification of life-saving interventions • **JCM-1-11** – Inadequate ability to immediately recognize and correct coagulopathy • **JCM-2-1** – Inadequate stabilization of injuries and ability to monitor response to treatment
TC3 ICD	• **Theater Hospitalization, Area Medical Support** – Diagnose, resuscitate and stabilize casualties with survivable wounds • **En Route Care** – Locate and evaluate casualties • **First Response Medical Care** – Stabilize injuries, monitor response to treatment • **Advanced Casualty Locating and Remote Physiologic Monitoring** – Monitor, evaluate, triage casualties by combat medical personnel for early identification of life-saving interventions
DHP ICD	• **DK3** – Lack a decision support mechanism that enables timely, accurate decisions and diagnosis at all levels of care • **TI1** – Insufficient current first-responder (medical and non-medical) capacity and capability to initially assess, treat, and maintain severe trauma cases in the pre-hospital environment - Insufficient initial and ongoing training for first responders in the pre-hospital environment overall - Insufficient tools that enable both non-medical and medical first responders - The technologies do not exist to fulfill some of the needs (e.g. stabilizing the airway or truncal hemorrhage) • **TI6** – First responders lack interoperable ways and means to understand and provide rapid, reliable, and actionable information about a casualty's physiological/psychological status in the pre-hospital environment (for IT devices there are no defined KPP requirements; no clearly defined MILSPECS for non-IT) • **TI7** – Current ways and means of document POI hinder ability to capture rapid, reliable and actionable information about a casualty's physiological status in the pre-hospital environment and subsequently transmit it for follow on analysis • **TI11** – Lack of computational algorithms and predictive tools for physiological status that use available information and can predict necessary statuses in an expedient manner • **TI12** – In pre-hospital environment, lack ways and means to enable clinical decision support and have inadequate ways and means to enable clinical decision support at Level III and higher • **MB4** – In the pre-hospital environment there is a lack of understanding of the optimal oxygen requirements for casualties • **MB6** – Limited capability to identify and treat lung function problems and respiratory failure in the pre-hospital environment • **MA6** – Lack of ability to identify arterial oxygen and CO_2 levels • **TS1** – Lack of optimal resuscitation strategies for casualties who have TBI and are in, or at risk for, hemorrhagic shock • **TS4** – Lack of ways and means to effectively screen for and diagnose shock throughout continuum of care • **TS6** – Insufficient ways and means to diagnose and manage vascular disruption (with or without hemorrhagic shock)

Impact on the Battlefield/Warfighter

Medical monitoring technologies can be designed for use at all roles of care, including at the POI, during transport from the field to the hospital, and within the hospital.

When implemented, Flashback's CRI algorithm is expected to have a considerable impact across all roles of care. First, by making the prediction of hemodynamic instability (i.e., shock) more accurate overall in hemorrhaging casualties, and by pushing up the start of appropriate interventions to a time when the casualty is more likely to respond. It can also be envisioned that the CRI algorithm may impact casualty triage by giving first-responders the ability to differentiate those casualties requiring immediate care from those that do not, and by making resuscitation more efficient and effective, leading to fewer medical complications. The CRI algorithm is expected to significantly reduce the 26 percent of potentially survivable deaths from hemorrhage that now occur on the battlefield (Eastridge et al., 2012). In addition, during air transport, a monitoring device running the CRI algorithm will enable caregivers to receive clinically relevant information on a hemorrhage patient's status from the continuous monitoring and capture of vital sign information, including during taxi and takeoff.

Clinical Practice

Impact on Clinical Practice Guidelines

Continual awareness of a casualty's condition and response to interventions will profoundly affect how medical providers deliver combat casualty care to the warfighter. Currently, medical providers are simply unable to monitor multiple vital signs from multiple patients continuously throughout the day. Instead, medical providers examine casualties for short intermittent periods and make medical decisions based on limited data points. Consequently, decisions about care may represent snap shots (or snap judgments) rather than a deliberate determination based on long-term trends and dynamics.

The CRI algorithm has already affected clinical practices of allied military forces. Although a monitor using the CRI algorithm has not yet been fielded for use by the U.S. military, prototype versions are currently being used by the Israeli Defense Force (Cook, 2014). Because the CRI algorithm measures the body's compensation to fluid loss, it is envisioned that CRI monitors will have multiple uses beyond the detection of hemorrhage, including, for example, the assessment of dehydration in athletes during vigorous exercise.

Supporting Publications

Pending 510(k) clearance from the FDA, a monitoring system incorporating the CRI algorithm is not yet in clinical use by the U.S. military. In support of several FDA applications, Flashback Technologies is conducting clinical trials (Table 46). One study is designed to validate implementation of the CRI algorithm in a monitoring system, by comparing CRI to intravascular volume change and stroke volume from human subjects undergoing progressive reduction in central blood volume (Convertino et al., 2015). In a second related validation study, the CRI algorithm is tested in human subjects by comparing CRI to intravascular volume change and stroke volume from human subjects donating blood (Moulton, 2015). Phase 2 clinical trials have also initiated as part of the MERIT study involving emergency room patients. Eligible patients are being assessed with the CipherOx monitor, and the resulting CRI is being used to guide decisions.

Table 46. Supporting Publications for the CRI Algorithm

Reference	Description
Convertino et al., 2015	Clinical trial: Assessed sensitivity and specificity of the CRI versus vital signs in the detection of blood loss from individuals undergoing voluntary hemorrhage. Only CRI decreased commensurately with blood loss
Stewart et al., 2014 **Moulton, 2015**	Clinical trial: Determined if the CRI provided greater sensitivity and specificity in the detection of low-volume blood loss compared with standard vital signs. The CRI algorithm detected low-volume blood loss with significantly more specificity than standard physiological measurements
MERIT Research Study, 2015	Clinical trial: Emergency room trauma patients with suspected blood loss are being assessed with the CipherOx monitor to determine their CRI. Healthcare providers will use the CRI to guide decisions regarding blood transfusion, fluids, or surgery

Role of CCCRP-Sponsored Projects

The CCCRP's FSICC portfolio played a key role in many of the past and present activities related to the development of the CRI algorithm and its advanced development. One example was their support and development of a human model of hemorrhage that used lower body negative pressure LBNP, for the evaluation of predictive medical algorithms on volunteers (Convertino et al., 2011). In a recent effort, USAMRMC has funded Phase 2 trials for a prototype device, the CipherOx Resuscitation Monitor, which is built around the CRI algorithm (Table 47). USAMRMC is funding ongoing efforts with Flashback Technologies to seek the regulatory clearance of the CRI, through which us of the algorithm is expected to be evaluated on several devices including Sotera Wireless' ViSi Mobile wireless platform (Table 47).

CRI can provide more accurate resuscitation by monitoring compensatory reserve in real-time

Table 47. CCCRP-Sponsored Projects Conducted by Flashback Technologies, Inc.

Project Title (Award Number)	Organization/ Principal Investigator	Funding
Early and Reliable Detection of Hypovolemia (USAMRMC, W81XWH-09-1-0750)	Flashback Technologies, Inc.	$250,000 (2009)
A Portable, Real-Time, Non-Invasive Resuscitation Monitoring Device with Built-In Decision Support (USAMRMC, W81XWH-11-2-0091)	Flashback Technologies, Inc.	$750,000 (2011)
Regulation of Cerebral and Systemic Perfusion Following Traumatic Brain Injury (USAMRMC, W81XWH-11-2-0094)	Flashback Technologies, Inc.	$238,864 (2011)
A Real-Time, Non-Invasive Monitoring System of Combat Casualties for Early Detection of Hemorrhagic Shock During Transport and Higher Echelon Medical Care (USAMRMC, USAMRAA, STTR Phase III, W81XWH-09-C-0160)	Flashback Technologies, Inc.	$950,000 (2011–2013)
Non-invasive Physiological Monitoring, Machine Learning Algorithms, Estimation of Blood Loss Volume, Fluid Resuscitation, Prediction of Cardiovascular Collapse, Triage (USAMRMC, W81XWH-12-2-0112)	Flashback Technologies, Inc.	$2,118,687 (2012-2015)

Project Title (Award Number)	Organization/ Principal Investigator	Funding
Noninvasive, Body-Worn Device for Providing Real-Time Cardio-Pulmonary and Metabolic Status for Triage and Resuscitation Feedback (Subaward - Sotera) (U.S. Army, W81XWH-11-2-0085)	Flashback Technologies, Inc. (Subaward – Sotera)	$735,469
A Real-Time, Non-Invasive Monitoring system to Guide Accurate Fluid Resuscitation of Combat Casualties During Pre-Hospital and Transport Medical Care (USAMRMC, Small Business Innovation Research [SBIR] Phase I, II, and III, W81XWH-13-C-0121)	Flashback Technologies, Inc.	$1,889,205 (2013–2014)
A Universal Pulse Oximeter Compensatory Reserve (POCR) Monitor for Decision Support and Physiological Recording during Transport (TATRC; DoD Forward Surgical and En Route Care grant, W81XWH-15-2-0007)	Flashback Technologies, Inc.	$1,988,683 (2014)

Support from multiple USAMRMC awards has led to numerous publications related to the CRI algorithm (Table 48). Collectively, they have contributed to the validation of the CRI algorithm within various contexts.

Table 48. CCCRP-Sponsored Publications for the CRI

Reference	Description
Moulton, Haley-Andrews, & Mulligan, 2010	Review article highlighting emerging technologies in trauma care and the need for advanced machine-learning techniques to leverage data available on current medical monitoring technologies
Convertino et al., 2011	Used LBNP as a model of hemorrhage to evaluate continuous, noninvasive monitoring of hemodynamic signals in 28 healthy volunteers for the development of machine-learning algorithms. Machine modeling accurately identified loss of central blood volume and predicted when hemodynamic decompensation occurs
Grudic, Moulton, & Mulligan, 2012	U.S. Patent for tools and techniques for estimating if a patient is bleeding or has sustained intravascular volume loss
Convertino, Grudic, Mulligan, & Moulton, 2013	Determined how well the machine-learning CRI model differentiated individuals based on their reaction to volume loss
Moulton, Mulligan, Grudic, & Convertino, 2013	Determined whether machine-learning techniques could be leveraged to detect beat-to-beat changes in arterial pulse waveforms associated with hemodynamic decompensation. Machine modeling quickly and accurately detected reductions in central blood volume during the compensatory phase of hemorrhage
Muniz et al., 2013	Tested the hypothesis that the use of a decision-assist machine-learning algorithm by emergency medical personnel could shorten the time required to identify hemodynamic instability. Use was associated with early identification of impending hemodynamic instability
Van Sickle et al., 2013	Tested the hypothesis that the CRI would provide an earlier indicator of cardiovascular instability than the common shock index. CRI provided a significantly earlier indicator of impending hemodynamic decompensation than the shock index
Rickards et al., 2014	Evaluated a machine-learning algorithm based on physiological signals and reliably distinguished central hypovolemia from exercise
Nadler et al., 2014	Compared a noninvasive CRI device with available vital signs to detect mild hemorrhage. The CRI was better than standard indices in detecting mild hemorrhage

Reference	Description
Convertino et al., 2015	Comparison of CRI versus blood pressure, heart rate, SpO_2, cardiac output, and stroke volume to detect blood loss in 20 human subjects after voluntary hemorrhage of 1.2 liters. CRI detected hemorrhage and restoration with significantly greater specificity than traditional physiologic measures
Stewart, Mulligan, Grudic, Pyle, & Moulton, 2015	Evaluated the association of the CRI with percent total body surface area and fluid administration in children suffering burn injuries. Results suggest that the CRI may be a useful guide for fluid resuscitation

References

Convertino, V. A. (2013). Comparison of compensatory reserve index to intravascular volume change and stroke volume. Retrieved from https://clinicaltrials.gov/ct2/show/study/NCT01935427 (Identification No. NCT01935427)

Convertino, V. A., Grudic, G., Mulligan, J., & Moulton, S. (2013). Estimation of individual-specific progression to impending cardiovascular instability using arterial waveforms. *Journal of Applied Physiology*, *115*(8), 1196-1202.

Convertino, V. A., Howard, J. T., Hinojosa-Laborde, C., Cardin, S., Batchelder, P., Mulligan, J., … MacLeod, D. B. (2015). Individual-specific, beat-to-beat trending of significant human blood loss: The compensatory reserve. *Shock*, [Epub ahead of print]

Convertino, V. A., Moulton, S. L., Grudic, G. Z., Rickards, C. A., Hinojosa-Laborde, C., Gerhardt, R. T., … Ryan, K. L. (2011). Use of advanced machine-learning techniques for noninvasive monitoring of hemorrhage. *Journal of Trauma and Acute Care Surgery*, *71*(1), S25-S32.

Cook, (2014). Army Device Developed in San Antonio Could Save Lives in Combat. *San Antonio Express*, Retrieved from http://www.mysanantonio.com/news/local/article/New-army-technology-could-revel-problems-missed-5638251.php#photo-6632137

Cottingham, C. A. (2006). Resuscitation of traumatic shock: a hemodynamic review. *AACN advanced critical care*, *17*(3), 317-326.

Eastridge, B. J., Mabry, R. L., Seguin, P., Cantrell, J., Tops, T., Uribe, P., … Blackbourne, L. H. (2012). Death on the battlefield (2001–2011): implications for the future of combat casualty care. *Journal of trauma and acute care surgery*, *73*(6), S431-S437.

Flashback Technologies. (2015). CRI – Not for sale pending 510(k) clearance. Retrieved from http://www.flashbacktechnologies.com/technology/cri

Grudic, G. Z., Moulton, S. L., & Mulligan, I. J. (2012). *U.S. Patent Application 13/554,483*.

MERIT Research Study (2015). Retrieved from: https://meritresearchstudy.wordpress.com/

Moulton, S. (2015). Comparison of compensatory reserve index to intravascular volume change and stroke volume during blood donation. Retrieved from https://clinicaltrials.gov/ct2/show/NCT02029807 (Identification No. NCT02029807)

Moulton, S. L., Haley-Andrews, S., & Mulligan, J. (2010). Emerging technologies for pediatric and adult trauma care. *Current opinion in pediatrics*, *22*(3), 332.

Moulton, S. L., Mulligan, J., Grudic, G. Z., & Convertino, V. A. (2013). Running on empty? The compensatory reserve index. *Journal of Trauma and Acute Care Surgery*, *75*(6), 1053-1059.

Muniz, G. W., Wampler, D. A., Manifold, C. A., Grudic, G. Z., Mulligan, J., Moulton, S., … Convertino, V. A. (2013). Promoting early diagnosis of hemodynamic instability during

simulated hemorrhage with the use of a real-time decision-assist algorithm. *Journal of Trauma and Acute Care Surgery*, *75*(2), S184-S189.

Nadler, R., Convertino, V. A., Gendler, S., Lending, G., Lipsky, A. M., Cardin, S., … Glassberg, E. (2014). The value of noninvasive measurement of the compensatory reserve index in monitoring and triage of patients experiencing minimal blood loss. *Shock*, *42*(2), 93-98.

Rickards, C. A., Vyas, N., Ryan, K. L., Ward, K. R., Andre, D., Hurst, G. M., … Convertino, V. A. (2014). Are you bleeding? Validation of a machine-learning algorithm for determination of blood volume status: application to remote triage. *Journal of Applied Physiology*, *116*(5), 486-494.

Soller, B., Smith, C., Zou, F., Ellerby, G. E., Prince, M. D., & Sondeen, J. L. (2014). Investigation of noninvasive muscle pH and oxygen saturation during uncontrolled hemorrhage and resuscitation in swine. *Shock, 42*(1), 44-51.

Stewart, C. L., Mulligan, J., Grudic, G. Z., Convertino, V. A., & Moulton, S. L. (2014). Detection of low-volume blood loss: Compensatory reserve versus traditional vital signs. *Journal of Trauma and Acute Care Surgery*, *77*(6), 892-898.

Stewart, C. L., Mulligan, J., Grudic, G. Z., Pyle, L., & Moulton, S. L. (2015). A Noninvasive Computational Method for Fluid Resuscitation Monitoring in Pediatric Burns: A Preliminary Report. *Journal of Burn Care & Research*, *36*(1), 145-150.

Van Sickle, C., Schafer, K., Mulligan, J., Grudic, G. Z., Moulton, S. L., & Convertino, V. A. (2013). A sensitive shock index for real-time patient assessment during simulated hemorrhage. *Aviation, space, and environmental medicine*, *84*(9), 907-912.

Joint En Route Care Portfolio

Patient movement is conducted at points across a continuum of care by all of the Services, using various vehicles, to position patients for treatment (Figure 22). En route care in these unique environments is an essential part of combat casualty care. Over the course of the OIF/OEF conflicts, as surgical capabilities have been increasingly pushed further forward, phased evacuation approaches have been developed with the goal of enabling a seamless continuum of care from POI to definitive care. The improvements that these and other combat casualty care advances have yielded are clearly visible in studies of casualty outcomes. For example, the percentage of deaths among all combat injuries in Afghanistan decreased from 17 percent in late 2005 to 8 percent in 2013, despite an increase in the mean injury severity score over that same time; the tremendous advances in the military medical system for combat casualty care that enabled this feat include significant innovations in en route care to ensure the outcomes of evacuated casualties (Hatzfeld, Dukes, & Bridges, 2014; Rasmussen, Gross, & Baer, 2013). These innovations have included systems adaptations such as the development of specialized teams, and also specific care advances for spinal immobilization, pain management, and patient monitoring that have improved outcomes and increased casualty survival (Hatzfeld, Dukes, & Bridges, 2014). Innovations to en route care are continuing as refinements and new capabilities are sought throughout the process. The challenges of supporting and transporting critically injured casualties whose initial survival on the battlefield has increasingly been enabled by life-saving advances in hemorrhage control is also now a crucial charge for en route care (Neff et al., 2013).

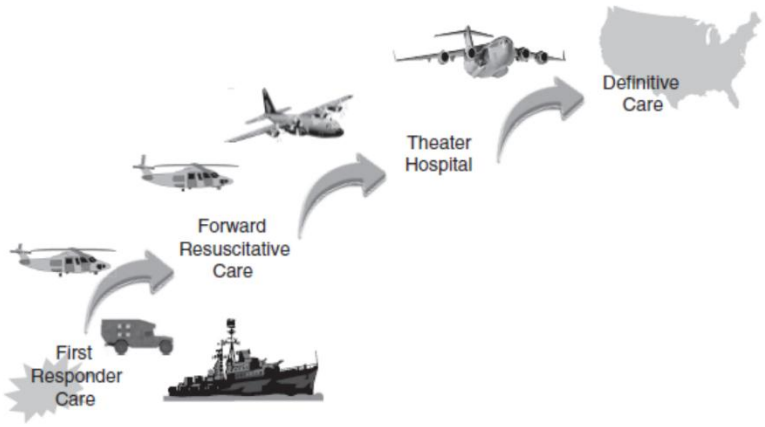


Figure 22. The En Route Care System (Hatzfeld, Dukes, & Bridges, 2014)

As the threats faced by U.S. forces change, future combat scenarios may place significant new demands on en route care. Future theaters of operations may have less mature medical infrastructures, dictate longer evacuation times by their geographies, and require new modes of casualty transport (Fitzgerald, 2012; Rasmussen, Baer, Doll, & Caravalho, 2015). These circumstances in conjunction with the push of advanced resuscitative capabilities closer to the POI, will impact en route care. Together these factors are demanding the reappraisal of the "golden hour" standard of time between injury and life-sustaining medical treatment, and may require that new innovations be made to allow field care to be prolonged and higher levels of care to be performed en route on transport vehicles (Rasmussen, Baer, Doll, & Caravalho, 2015).

The J-ERC portfolio is working to address these challenges. The relatively young portfolio is currently being actively shaped with consideration for present and future challenges of patient

movement. A key part of the portfolio management is the input of a 44-person steering committee composed of clinical subject matter experts from each of the Services. Efforts under the J-ERC portfolio seek to advance the understanding of patient physiology and the effects of the transportation environment on patient treatment and outcomes. Research to minimize negative effects and improve outcomes during evacuation across the continuum of care is supported. To this end, J-ERC research priorities have been established in the focus areas of:

- Impact of transport,
- Patient safety, and
- Equipment.

Within these areas, patient physiology, lifesaving interventions, and noninvasive methods for monitoring have been prioritized in the near term.

Requirement Sources

The J-ERC portfolio's activities are aligned to capability gaps defined by multiple capabilities-based assessments and functional needs analyses including Aeromedical Evacuation, Ground Contingency Medical Support Systems, and TC3 ICD. The identified gaps span the en route care mission from clinical to operational, including attributes such as training, interoperability, process/materiel standardization, and doctrine. With respect to clinical care, many capability gaps driving en route care are highly similar and complementary to those identified within other functional areas of combat casualty care. Given this, many J-ERC focuses are closely matched with other CCCRP portfolios through integrative efforts; one example is collaboration with the FSICC portfolio on approaches for passive medical data capture and transmission. Other capability gaps addressed by the portfolio, however, are unique to patient movement. Effort to close these gaps is focused both on research activities related to the transport environment and on operational solutions.

The work of the J-ERC portfolio can be aligned against a broad range of the capability gaps identified by the 2008 GDF Assessment, the 2006 TC3 ICD, and 2015 DHP ICD (a selection of salient gaps is presented in Table 49). These are not solely the charge of en route care, but as en route care intersects so many aspects of combat casualty care, J-ERC activities are contributing to aspects of their closure.

Table 49. Pursued Capability Gaps within the Scope of the CCCRP's Joint En Route Care Portfolio

Requirement Sources	Capability Gaps
GDF	• **JCM-1-1** – Inadequate ability to diagnose, resuscitate, and stabilize casualties with survivable wounds • **JCM-1-2** – Inadequate initial emergent resuscitative surgery coupled with life and limb saving actions • **JCM-1-3** – Inadequate ability to locate and evaluate casualties • **JCM-1-6** – Poor ability to ensure casualty airway • **JCM-1-7** – Inability to monitor, evaluate, and triage casualties by combat medical personnel for early identification of life saving interventions • **JCM-1-9** – Inadequate battlefield analgesia with minimal side effects • **JCM-1-10** – Inadequate integrated medical information systems across the taxonomy of casualty care • **JCM-1-11** – Inadequate ability to immediately recognize and correct coagulopathy

Requirement Sources	Capability Gaps
	• **JCM-2-1** – Inadequate stabilization of injuries and ability to monitor response to treatment • **JCM-2-8** – Inadequate CASEVAC by non-standard platforms, attended by combat lifesaver en route • **Joint Patient Movement (JPM)-TER-ER2** – Interoperability between C4 systems in support of reception/staging operations is lacking. A single joint medical C4 system does not exist. Joint medical C4 systems do not provide operational and clinical situational awareness to nonmedical C4 systems. PM and personnel tracking systems do not interact and are labor intensive • **JPM-TRA-AE2** – En route care lacks standardization. Standardized joint medical equipment for transport of critical patients is lacking. Joint critical care transport capability and training platforms do not exist. There is no joint directive/ authority to ensure standardized Patient Movement Instructions (PMI) program compliance • **JPM-TER-EC3** – JPM training platforms and skill-identification tracking systems are lacking. Models to replicate medical processes in joint exercise are lacking. Programs to establish JPM leadership development and education are inadequate
TC3 ICD	• **Theater Hospitalization, Area Medical Support** – Diagnose, resuscitate, and stabilize casualties with survivable wounds • **Damage Control Surgery** – Initial emergent resuscitative surgery coupled with life- and limb-saving actions • **En Route Care** – Locate and evaluate casualties • **First Response Medical Care** – Stabilize injuries, monitor response to treatment • **Airway Management Technology** – Ensure casualty airway • **Advanced Casualty Locating and Remote Physiologic Monitoring** – Monitor, evaluate, triage casualties by combat medical personnel for early identification of life-saving Interventions • **Pain Management Medications** – Battlefield analgesia with minimal side effects • **Casualty Movement** – MEDEVAC by organic or supporting attended medical evacuation platforms with en-route care • **Casualty Movement** – CASEVAC by non-standard platforms, attended by combat lifesaver en-route • **Medical Situational Awareness** – Integrated medical information system • **Coagulopathy Prevention and Treatment Agents** – Immediate recognition and correction of coagulopathy
DHP ICD	• **DK3** – Lack a decision support mechanism that enables timely, accurate decisions and diagnosis at all levels of care • **DK4** – Lack of evidence-based clinical data to support decision-making regarding the protocol (all levels) and timing (particularly for strategic movement) of post-surgical patients • **TI1** – Insufficient current first-responder (medical and non-medical) capacity and capability to initially assess, treat, and maintain severe trauma cases in the pre-hospital environment • Insufficient initial and ongoing training for first responders in the pre-hospital environment overall - Insufficient tools that enable both non-medical and medical first responders - The technologies do not exist to fulfill some of the needs (e.g., stabilizing the airway or truncal hemorrhage) - Incorrect alignment of trained skill sets and operational needs - Inconsistent integration of recurrent medical training into overall unit training • **TI3** – No common TCCC TTP for first responders and medical practitioners across Services and across the continuum of care • **TI5** – Inability to allocate optimal resources for patient movement - Lack sufficient situational awareness (patient, transport, medical resources) - Lack command and control to direct operational elements • **TI6** – First responders lack interoperable ways and means to understand and provide rapid, reliable, and actionable information about a casualty's physiological/psychological status in the pre-hospital environment (for IT devices there are no defined KPP requirements; no clearly defined MILSPECS for non-IT)

Requirement Sources	Capability Gaps
	• **TI7** – Current ways and means of documentation at POI hinder ability to capture rapid, reliable and actionable information about a casualty's physiological status in the pre-hospital environment and subsequently transmit it for follow on analysis • **TI9** – Current ways and means of training medical and non-medical providers for treating trauma are inadequate to maintain proficiency • **TI11** – Lack of computational algorithms and predictive tools for physiological status that use available information and can predict necessary statuses in an expedient manner • **TI12** – In pre-hospital environment, lack ways and means to enable clinical decision support and have inadequate ways and means to enable clinical decision support at Level III and higher • **MB1** – Inability to provide analgesia without depressing respiration and circulation in the pre-hospital environment • **MB2** – Lack of treatment strategies in the pre-hospital environment for severe/acute respiratory injuries (e.g., inhalation injuries) including but not limited to extracorporeal life support (ECLS) • **MB4** – In the pre-hospital environment there is a lack of understanding of the optimal oxygen requirements for casualties • **MB6** – Limited capability to identify and treat lung function problems and respiratory failure in the pre-hospital environment • **MA3** – Lack of adequate tools for first responders to establish and maintain the airway in a pre-hospital environment • **MA4** – Lack of authorities and/or skillsets to establish and maintain the airway in a pre-hospital environment • **MA6** – Lack of ability to identify arterial oxygen and CO_2 levels • **TS4** – Lack of ways and means to effectively screen for and diagnose shock throughout continuum of care • **TS5 –** Insufficient understanding of the patient's predisposition to outcomes of hemorrhagic shock (Related to genomics/OMICS, immune-modulation or inflammatory response mentioned above) • **TS6** – Insufficient ways and means to diagnose and manage vascular disruption (with or without hemorrhagic shock) • **Manage Head and Spine (MHS)4** – Insufficient non-invasive techniques to continuously monitor intra-cranial pressure • **MHS6** – Lack of suitable ways and means to detect and manage the spinal cord in casualties with suspected spinal cord injuries in the pre-hospital environment • **MTV1** – Insufficient understanding of the acute inflammatory response to combat injury and its consequences • **MTV3** – Lack of knowledge, skills, and tools to provide extracorporeal support in the setting of single and multi-system organ failure across the continuum of care • **MTV5** – Lack knowledge, skills, and tools to prevent negative impacts of shock from burns during lengthy transports in the pre-hospital environment • **PDC1** – Lack the suitable, interoperable ways and means to capture, transmit, and store TC3 data in the pre-hospital environment • **PDC2** – Ineffective and inconsistent patient regulating paradigms across Roles and components • **PDC3** – Lack of electronic medical record spanning the spectrum of combat casualty care architecture integrated into the JTS DoD Trauma Registry • **PL1** – Lack of evidence-based data and metrics to assess the effectiveness of training methodologies, specifically TC3, to include both technical skills such as establishing surgical airways, and cognitive skills, such as decision-making in a complex tactical casualty scenario • **PL3** – Lack of evidence-based clinical data to support decision-making regarding the protocol (all levels) and timing (particularly for strategic movement) of post-surgical patients • **PL5 –** Lack of evidence based data to improve overall combat-related injury infection care • **PL7 –** Insufficient knowledge of the use and effects of regional anesthesia/analgesia

Requirement Sources	Capability Gaps
	modalities for complex war time injuries • **Repair Physical Injuries (RPI)1 –** Lack ability to conduct non-invasive physiological monitoring (intra-cranial, compartment syndrome, intra-abdominal pressure, etc.) • **RPI2 –** Insufficient understanding of how to mitigate the negative impact of long flights on a critically injured patient (altitude, temperature, duration)

Joint En Route Care Portfolio Successes

Though the J-ERC portfolio's history is relatively short and many projects underway are still maturing, three emerging success stories highlight the advances already being made within the task areas pursued by the portfolio.

Impact of Transport: Preparation/Transition for Patient Movement

The first selection describes the ongoing development of new capabilities for life saving support in the case of organ failure, through the study of how to best implement complex extracorporeal support technologies before and during transport, and the capture of clinical data on their use.

- **Comprehensive Adult Extracorporeal Life Support Program** – Expertise was developed for the extracorporeal support of adult patients both in medical treatment facilities and during transport

Patient Safety: Skill Level/Training of En Route Medical Personnel

The second selection details an effort to evaluate new technologies for intubation in the context of air transport that may improve outcomes in difficult intubations and also offer benefits for the training and skill sustainment of providers.

- **Comparative Evaluation of Qualities of Video Assisted Intubation Devices** – Use of multiple commercial devices by both novice and experienced air transport providers was examined to evaluate the relative features of these devices as they pertain to use in flight, and to airway training and instruction

Equipment: Noninvasive Methods for Patient Monitoring During Transport

The third selection describes efforts to advance continuous, noninvasive physiological monitoring technologies that can provide accurate real-time data that can be used to monitor treatment and identify early indicators of impending degradation.

- **Noninvasive Monitors for Casualty Triage, Resuscitation, and Transport** – Sensors for noninvasive tissue metabolic status monitoring integrated with a body-worn vital sign monitor are currently being evaluated for in-flight use during patient transport

References

Hatzfeld, J. J., Dukes, S., & Bridges, E. (2014). Innovations in the En Route Care of Combat Casualties. *Annual Review of Nursing Research*, *32*(1), 41-62.

Neff, L. P., Cannon, J. W., Stewart, I. J., Batchinsky, A. I., Zonies, D. H., Pamplin, J. C., & Chung, K. K. (2013). Extracorporeal organ support following trauma: The dawn of a new era in combat casualty critical care. *Journal of Trauma and Acute Care Surgery, 75*(2), S120-S129.

Rasmussen, T. E., Baer, D. G., Doll, B. A., & Caravalho, J. (2015). In the golden hour. *Army AL&T Magazine*, 81-85.

Rasmussen, T. E., Gross, K. R., & Baer, D. G. (2013). Where do we go from here? Preface. US Military Health System Research Symposium, August 2013. *The Journal of Trauma and Acute Care Surgery, 75*(2 Suppl 2), S105-S106.

Comprehensive Adult Extracorporeal Life Support Program

Extracorporeal membrane oxygenation (ECMO) is a form of extracorporeal life support (ECLS) historically used in the pediatric population to support patients in respiratory distress. The Comprehensive Adult ECLS Program has been funded to develop this capability for the transport and care of adults with acute respiratory distress syndrome (ARDS).

- Research Organization:
  - Wilford Hall Ambulatory Surgical Center, San Antonio Military Medical Center (SAMMC)
- Principal Investigator:
  - Lt Col Jeremy Cannon, MD, SM, FACS

Key Outcomes and Impact:

- SAMMC successfully treated their first ECMO patient in 2012 (Sine et al., 2014)
- Achieved a favorable 83 percent survival rate in the first six patients treated (Belenkiy et al., 2014)
- Program will complement Acute Lung Injury Rescue Team (ALIRT) evacuation capabilities, completing the transport chain for combat casualties with critical illness by enabling long-range transport with ECMO
- SAMMC recognized as DoD ECMO Center of Excellence in 2013; program development is continuing with support of additional funding streams

ECMO use by ALIRT (Cannon et al., 2011)

Overview

As advances have been made in the ability to prevent acute combat deaths from causes such as massive hemorrhage, improved initial survivability results in an increase in physiologically compromised patients who may later face respiratory failure (Neff et al., 2013). Respiratory failure following severe traumatic injury poses a significant critical care challenge in deployed forces in combat zones. A 2008 study of JTTR data found that approximately 6 percent of combat casualties requiring mechanical ventilation developed acute respiratory distress syndrome (ARDS) (Allan, Osborn, Bloom, Wanek, & Cannon, 2011; Park et al., 2009). Outside of the deployed context, other genetic, immune, and infectious factors can also cause acute respiratory distress more rarely in non-deployed units and their dependents. Across these contexts, capabilities for advanced organ support are important, as well as the ability to transport patients requiring this type of support to appropriate care facilities. Technologies for long-term extracorporeal support for patients in respiratory failure have advanced, and are known as ECLS (Allan, Osborn, Bloom, Wanek, & Cannon, 2011; Santullo, 2012). The continued development of the use of ECLS to treat adult patients with ARDS has been funded by the J-ERC portfolio.

Figure 23. ECMO Unit in use at Bagram Air Force Base (Neff, 2013)

ECMO, a form of ECLS which uses an external artificial lung to oxygenate and circulate blood back into the patient's bloodstream, works as a heart-lung bypass system for patients not improving on a ventilator alone (Figure 23) (Sanchez, 2012; Sanchez, 2013). The use of ECMO dates back to the 1970's, but it was not until relatively recently that ECMO has been effectively adapted and increasingly considered for use in the adult population (Neff et al., 2013; Sanchez, 2012). Recent case studies and trials have increasingly indicated that ECMO can be safely and successfully used to support adults with severe respiratory failure (Allan, Osborn, Bloom, Wanek, & Cannon, 2011; Brodie & Bacchetta, 2011). As instances of combat casualties treated in forward facilities developing ARDS were increasingly identified in the mid 2000's, the concept of specialized transport capabilities to enable their evacuation was developed, and the ALIRT was created in 2005 from specialists based at the Landstuhl Regional Medical Center (LRMC) in Germany. Through partnership with ECMO experts at the University Hospital of Regensberg, the ALIRT has initiated ECMO as an additional rescue measure for these patients.

To further advance the use of ECMO and create a center for ECMO knowledge and transport capabilities in the U.S., Lt Col Jeremy Cannon at SAMMC was funded by the J-ERC portfolio to develop a team of experts provide ECLS to adult patients with ARDS (Santullo, 2012). The program has studied multiple aspects of how to best implement ECLS technologies, and to gather clinical data on their use. Data from patients is being prospectively collected and compared to the Extracorporeal Life Support Organization (ELSO) registry and to historic controls in the JTTR (Santullo, 2012). In addition, new applications for ECLS and the development of new ECMO equipment for use during transport from remote theaters to the continental U.S. (CONUS) is being explored. Through these activities, the team is positioning itself to complement the ALIRT capabilities and complete the transport chain for combat casualties with critical illness by enabling ECMO use in long-range transport. This is being accomplished through the benefit of the longstanding ECMO transport expertise at Wilford Hall Medical Center and the long-range transport expertise of the USAISR adult burn transport team (Allan, Osborn, Bloom, Wanek, & Cannon, 2011). As shown in Figure 24, significant milestones for the use of ECMO at SAMMC under the direction of Lt Col Cannon have been achieved. Activities of this program are ongoing, and in addition to funding under the J-ERC portfolio, SAMMC has brought in funding from other streams to continue to support these efforts.

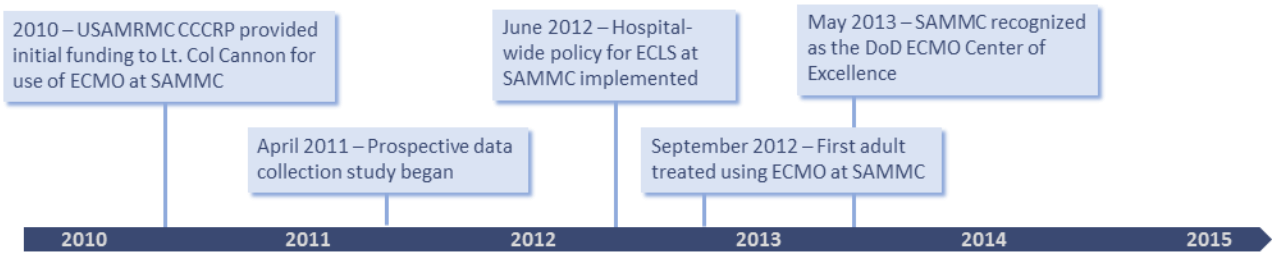


Figure 24. Timeline for Adult ECLS Program at SAMMC

Capability Gap Alignment

The Comprehensive Adult ECLS Program is developing a team of experts with the capabilities to use ECLS for ARDS patients both in medical treatment facilities and during transport, and which can provide education and training to other ECLS users in the DoD. These activities ultimately will address portions of several capability gaps (Table 50).

Table 50. Capability Gaps Addressed by the Comprehensive Adult ECLS Program

Requirement Sources	Capability Gaps Addressed
GDF	• **JCM-1-1** – Inadequate ability to diagnose, resuscitate, and stabilize casualties with survivable wounds • **JCM-1-2** – Inadequate initial emergent resuscitative surgery coupled with life and limb saving actions • **JCM-2-1** – Inadequate stabilization of injuries and ability to monitor response to treatment • **JPM-TRA-AE2** – En-route care lacks standardization. Standardized joint medical equipment for transport of critical patients is lacking. Joint critical care transport capability and training platforms do not exist. There is no joint directive/ authority to ensure standardized PMI program compliance
TC3 ICD	• **Theater Hospitalization, Area Medical Support** – Diagnose, resuscitate and stabilize casualties with survivable wounds • **Damage Control Surgery** – Initial emergent resuscitative surgery coupled with life- and limb-saving actions • **Casualty Movement** – MEDEVAC by organic or supporting attended medical evacuation platforms with en-route care
DHP ICD	• **DK4** – Lack of evidence-based clinical data to support decision-making regarding the protocol (all levels) and timing (particularly for strategic movement) of post-surgical patients • **MB2** – Lack of treatment strategies in the pre-hospital environment for severe/acute respiratory injuries (e.g., inhalation injuries) including but not limited to ECLS • **MB6** – Limited capability to identify and treat lung function problems and respiratory failure in the pre-hospital environment • **MTV3** – Lack of knowledge, skills, and tools to provide extracorporeal support in the setting of single and multi-system organ failure across the continuum of care • **PL3** – Lack of evidence-based clinical data to support decision-making regarding the protocol (all levels) and timing (particularly for strategic movement) of post-surgical patients

Impact on the Battlefield/Warfighter

With the introduction of ECMO to support adults in respiratory distress, mortality can be decreased for this unique group of patients. The Comprehensive Adult ECLS program aims to support all forms of adult extracorporeal therapy in military medical treatment facilities. Through

this program, education and training to all ECLS physicians and support staff within the DoD will be provided to ensure mortality for ARDS patients is reduced. Over time, the SAMMC Adult ECLS Program will support long-range transport of combat casualties requiring ECLS. Though the full potential for impact on the battlefield is not seen until this is implemented, several initial successes using ECMO in deployed settings and while transporting adult patients provide insight into what is possible. In the recent OIF/OEF conflicts, multiple combat casualties required the use of ECMO to support respiratory distress in the deployed setting. The first clinical experiences with ECMO in combat causalities requiring transport occurred in 2005 with use of an initial portable pumpless technology (Neff et al., 2013). This was followed by the introduction of a more advanced and efficient centrifugal pump-driven ECMO technology, which was first used to support a combat casualty in 2010, after the service member sustained a severe penetrating wound requiring pneumonectomy (Neff et al., 2013). Ten cases were identified in a study of the use of ECMO in casualties between 2005 and 2011, with four of these initially treated in the war zone before evacuation and six placed on support at LRMC after evacuation by ALIRT to Germany (Bein et al., 2012). Support was successfully maintained in those evacuated, and there was an overall 90 percent 1-year survival rate in these cases (Bein et al., 2012). In addition to these examples in the deployed setting, the successful use of ECMO by SAMMC in the U.S. has been reported for a civilian patient diagnosed with severe toxic epidermal necrolysis and a cystic fibrosis patient who developed viral and bacterial pneumonia (Sanchez, 2012; Sanchez, 2013; Sine et al., 2014). The patient with cystic fibrosis brings a unique element for the use of ECMO as the first patient in military medicine to be successfully transported from one location to another stateside under the support of ECMO, traveling from San Antonio to New York City (Sanchez, 2013).

Clinical Practice

Impact on Clinical Practice Guidelines

As the SAMMC program has established and implemented clinical policy for adult ECLS and been recognized as the DoD ECMO Center of Excellence, new CPGs for ECMO use have been developed and optimized. The recent success stories supporting the use of ECMO have also continued to lead to increased interest in transporting critical combat casualties to CONUS while still on ECMO (Neff et al., 2013). As the experience of the Adult Comprehensive ECLS Program continues to grow, the resulting knowledge will be a key contributor to the development of additional CPGs for the use of ECMO and other forms of ECLS, both in military medical treatment facilities and en route. In addition to the civilian lives the SAMMC team has already helped to save through its initial uses of ECMO, the program's efforts may also contribute more broadly to support and refine current civilian CPGs, such as the comprehensive guidelines on ECMO published by the ELSO (Brodie & Bacchetta, 2011; ELSO, 2015). This guidance from the ELSO includes a CPG for adult respiratory failure, and ELSO guidelines have served as the framework for iniation of ECMO by the SAMMC program (Belenkiy et al., 2014). Finally, a recently published position paper on the optimal approach to structuring ECMO programs for acute respiratory failure has also provided overarching recommendations on ECMO practice. This included the organization of mobile ECMO teams, for which the position paper cited the precedent of highly successful transportation of ECMO patients by ambulance, helicopter, and airplane (Combes et al., 2014). This position paper received concurrence from physicians practicing ECMO internationally, including individuals affiliated with the SAMMC program.

Supporting Publications

There is a growing body of publications supporting the successful use of ECMO for adults with ARDS. This knowledge base informs and supports the continued efforts of the Comprehensive Adult Extracorporeal Support Program at SAMMC, and the development of new practice recommendations (Table 51).

Table 51. Supporting Publications for Adult ECMO

Reference	Description
Use of ECMO for ARDS in Adults	
Guirand et al., 2014	Retrospectively evaluated data from two Level 1 trauma centers that have employed ECLS between 2001 and 2009. Twenty-six ECLS patients and 76 mechanically ventilated patients were compared; survival was greater in the ECLS group
Brodie & Bacchetta, 2011	Presented a case vignette of adult ARDS and provided a discussion of the mechanisms and benefits of ECMO. Reviewed major clinical studies and current ELSO guidelines, providing a recommendation for the use of ECMO
Davies et al., 2009	Examined the use of ECMO in patients with the 2009 influenza A(H1N1)-associated ARDS; a survival rate of 75 percent was achieved
Peek et al., 2009	Conducted a controlled clinical trial using modern ECMO in adults with severe but potentially reversible respiratory failure. Death or severe disability at 6 months, occurred in 37 percent of the patients referred for ECMO, as compared with 53% of those assigned to conventional management
ECMO for Combat Casualty Care	
Bein et al., 2012	Examined cases of U.S. casualties placed on ECLS both in theater and at LRMC; of 10 cases treated from 2005 to 2011, there was a 1-year survival rate of 90 percent
Neff et al., 2013	Reviewed experiences with ECLS including ECMO for combat casualty care in the deployed setting and during transport

- With DoD support for supplies, training, and equipment to explore the use of ECMO on adults, the team of specialists at SAMMC treated their first ECMO patient in 2012
- The patient, suffering from severe toxic epidermal necrolysis, was successfully transitioned off ECMO after 23 days, and later discharged to outpatient care

Sanchez, 2012; Sine et al., 2014

Role of CCCRP-Sponsored Projects

The J-ERC portfolio has included intramural funding to Lt Col Jeremy Cannon at Wilford Hall Ambulatory Surgical Center, SAMMC to conduct a full range of activities for the use of ECLS to support adult patients with ARDS (Table 52). Under this project, knowledge and capabilities

related to adult ECLS have been built, and these efforts are now continuing with the ongoing support of additional funders. The goals and activities of the program have been detailed in review publications (Allan, Osborn, Bloom, Wanek, & Cannon, 2011), and from this program several additional publications have already resulted detailing the successful use of extracorporeal support for patients at SAMMC, and conducting analyses of existing data from other organizations on clinical use of ECLS (Table 53).

Table 52. CCCRP-Sponsored Projects for the Comprehensive Adult ECLS Program

Project Title	Principal Investigator	Funding
Comprehensive Adult Extracorporeal Support Program	Lt Col Jeremy Cannon, M.D., SM, FACS (SAMMC)	$951,000 (2010 – 2014)
Comprehensive Adult Extracorporeal Support Program - Nurse Researcher Support	Lt Col Jeremy Cannon, M.D., SM, FACS (SAMMC)	$580,000 (2010 – 2014)

Table 53. CCCRP-Sponsored Publications for the Comprehensive Adult ECLS Program

Reference	Description
Belenkiy et al., 2014	Described the early experiences of the SAMMC program in using inhaled nitric oxide as an indicator of potential need for ECMO in critically ill patients, and the clinical course of six initial patients managed in the ECMO program. Survival to hospital discharge was 83 percent in patients managed with ECMO
Guirand et al., 2014	Retrospectively evaluated data from two Level 1 trauma centers that have employed ECLS between 2001 and 2009. Twenty-six ECLS patients and 76 mechanically ventilated patients were compared; survival was greater in the ECLS group
Sine et al., 2014	Case report of successful ECLS use by the SAMMC program to support a patient suffering from ARDS secondary to severe toxic epidermal necrolysis

- Published data on the initial experience of the program presented outcomes of ECMO at SAMMC that compare favorably to current adult survival rates for severe respiratory failure, and provided preliminary evidence for the utility of inhaled nitric oxide use alerts for identification of candidate ECMO patients (Belenkiy et al., 2014)
- A retrospective cohort study of patients receiving ECLS for respiratory failure at Level 1 trauma centers was coauthored by SAMMC physicians. The study identified an independent association of ECLS with survival, and provided support for the recommendation of ECLS use in trauma patients when conventional therapies prove ineffective, with transfer to ECLS centers recommended when the capability is not locally available (Guirand et al., 2014)

References

Allan, P. F., Osborn, E. C., Bloom, B. B., Wanek, S., & Cannon, J. W. (2011). The introduction of extracorporeal membrane oxygenation to aeromedical evacuation. *Military Medicine, 176* (8), 932-937.

Bein, T., Zonies, D., Philipp, A., Zimmermann, M., Osborn, E. C., Allan, P. F., … Fang, R. (2012). Transportable extracorporeal lung support for rescue of severe respiratory failure in combat casualties. *Journal of Trauma and Acute Care Surgery, 73*(6), 1450-1456.

Belenkiy, S. M., Batchinsky, A. I., Park, T. S., Luellen, D. E., Serio-Melvin, M. L., Cancio, L. C., … Cannon, J. W. (2014). Automated inhaled nitric oxide alerts for adult extracorporeal membrane oxygenation patient identification. *Journal of Trauma and Acute Care Surgery, 77*, S184-S189.

Brodie, D., & Bacchetta, M. (2011). Extracorporeal membrane oxygenation for ARDS in adults. *New England Journal of Medicine, 365*(20), 1905-1914.

Cannon, J. W., Zonies, D. H., Benfield, R. J., Elster, E. A., & Wanek, S. M. (2011). Advanced en-route critical care during combat operations. *Bulletin of the American College of Surgeons, 96*(5), 21-29.

Combes, A., Brodie, D., Bartlett, R., Brochard, L., Brower, R., Conrad, S., … Vuylsteke, A. (2014). Position paper for the organization of extracorporeal membrane oxygenation programs for acute respiratory failure in adult patients. *American Journal of Respiratory and Critical Care Medicine, 190*(5), 488-496.

Davies, A., Jones, D., Bailey, M., Beca, J., Bellomo, R., Blackwell, N., … Ziegenfuss, M. (2009). Extracorporeal membrane oxygenation for 2009 influenza A (H1N1) acute respiratory distress syndrome. *The Journal of the American Medical Association, 302*(17), 1888-1895.

Extracoporeal Life Support Organization (ELSO). (2015). ELSO Guidelines. Retrieved from http://www.elso.org/Resources/Guidelines.aspx

Guirand, D. M., Okoye, O. T., Schmidt, B. S., Mansfield, N. J., Aden, J. K., Martin, R. S., Cestero, R. F., … Cannon, J. W. (2014). Venovenous extracorporeal life support improves survival in adult trauma patients with acute hypoxemic respiratory failure: A multicenter retrospective cohort study. *Journal of Trauma and Acute Care Surgery, 76*, 1275-1281.

Neff, L. P., Cannon, J. W., Stewart, I. J., Batchinsky, A. I., Zonies, D. H., Pamplin, J. C., & Chung, K. K. (2013). Extracorporeal organ support following trauma: The dawn of a new era in combat casualty critical care. *Journal of Trauma and Acute Care Surgery, 75*(2), S120-S129.

Peek, G. J., Mugford, M., Tiruvoipati, R., Wilson, A., Allen, E., Thalanany, M. M., … Elbourne, D. (2009). Efficacy and economic assessment of conventional ventilatory support versus

extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): A multicentre randomised controlled trial. *Lancet, 374*(9698), 1351-1363.

Sanchez, E. (2012, November 29). Military docs use cutting-edge device to save patient. Defense.gov. Retrieved from http://www.defense.gov/news/newsarticle.aspx?id=118660

Sanchez, E. (2013, February 20). ECMO medical team achieves cutting-edge patient transfer. Brooke Army Medical Center Public Affairs. Retrieved from http://www.jbsa.af.mil/news/story.asp?id=123336928

Santullo, R. F. (2012, September 6). Joint en-route care research. Portfolio brief.

Sine, C. R., Chung, K. K., Pamplin, J. C., Batchinsky, A. I., Hull, J. E., King, B. T., … Cannon, J. W. (2014). Extracorporeal membrane oxygenation in a patient with refractory acute respiratory distress syndrome secondary to toxic epidermal necrolysis. *Journal of Burn Care & Research, 35*(6), e428-e430.

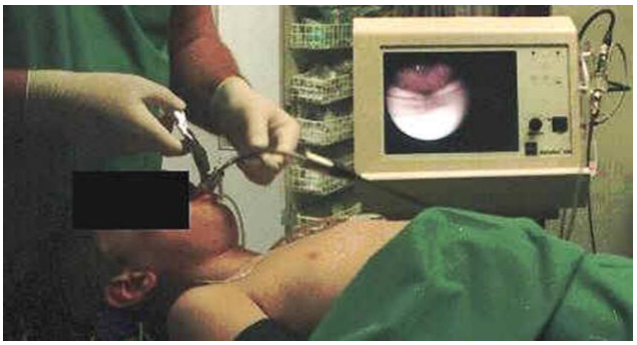
Comparative Evaluation of Qualities of Video Assisted Intubation Devices

A comparative study of FDA-approved video assisted intubation devices (VAID) has evaluated which devices allow for successful intubation under the constrained conditions of en route care environments by novices and experienced care providers alike.

- Research Organization:
  - 711 Human Performance Wing, U.S. Air Force School of Aerospace Medicine, Air Force Expeditionary Medical Skills Institute, Center for the Sustainment of Trauma & Readiness Skills
- Principal Investigator:
  - Col Todd Carter, M.D.

Key Outcomes and Impact:

- Assessment of six different VAIDs helped identify optimal devices for training and use in military casualties, particularly by Critical Care Air Transport Teams (CCATT)
- GlideScope Ranger by Verathon Inc. has been identified as an effective tool; it has been used in Afghanistan and Iraq in en route care environments including CCATT, and has since been selected as the Joint Product of Choice for VAID
- Increased rates of successful intubation in simulations of standard and difficult airway conditions have been demonstrated in complementing studies of military medics, nurses, and physicians trained with VAID (Boedeker, Barak-Bernhagen, Boedeker, & Murray, 2011)



VAID in use (Carter, 2011)

Overview

Compromise of the airway is a small but significant cause of military casualties, with a 1–2 percent incidence of fatal airway obstruction in the battlefield, and obstructed airway responsible for 8 percent of potentially survivable deaths occurring before reaching a medical treatment facility (Eastridge et al., 2012; Niven, 2013). Effective airway management is a critical part of successfully resuscitating seriously injured casualties, and a challenge in both tactical and en route care environments. Operational conditions and patterns of injury can make the lifesaving procedure of intubation difficult to successfully perform. In the case of en route care, characteristics dictated by the transport platforms including available space and safety concerns while in motion mean care must be delivered within bounded resources. Improved airway devices and training and maintenance for related provider skills are needed to enable optimal airway management under such conditions (Eastridge et al., 2012).

The emergence of VAID technology, beginning with the introduction of the first commercial instrument in 2001, has offered a new and advantageous option for facilitating intubation (Pacey, 2015). The use of a video laryngoscope allows for a real-time view of the airway to aid in the navigation of difficult airways and to help ensure proper tube placement. Research has indicated that VAID can improve intubation success in the operating room and emergency department, and the devices are now undergoing increasing evaluation both by the military and civilian

organizations in prehospital and en route care environments that present unique demands (Mcintosh, Swanson, McKeone & Barton, 2008; Wayne and McDonnell, 2010).

As the market for this technology has grown, several FDA-approved VAID are now available with varying characteristics. Understanding how the available technologies can best be used for en route care, and how to evaluate these technologies in ways that move toward validated, standardized equipment and training across the services is important. To this end, a study for the comparative evaluation of the characteristics of several VAID for use by CCATT was sponsored under the J-ERC portfolio. CCATT Teams operate in an austere environment, with limited lighting and cramped conditions that can impact the ability of the team to successfully intubate patients. This study aimed to compare the dynamic properties of ease of use during flight, time needed for light to be emitted from the device during boot up, and the amount of light emitted during blackout conditions, for six different VAID units and make recommendations for future acquisitions to improve patient care and outcomes. A key aspect of this study was to also apply these results also to inform training through the use of appropriate VAID. Under this study, VAID units were tested by novices in a hospital simulation environment, and by both novice and experienced CCATT individuals in standard flight environment and under blackout conditions. The results of this study have contributed to efforts to determine optimal devices for the CCATT and broader aeromedical evacuation community, and to building a body of knowledge to support the ongoing integration of VAID technology into combat casualty care use.

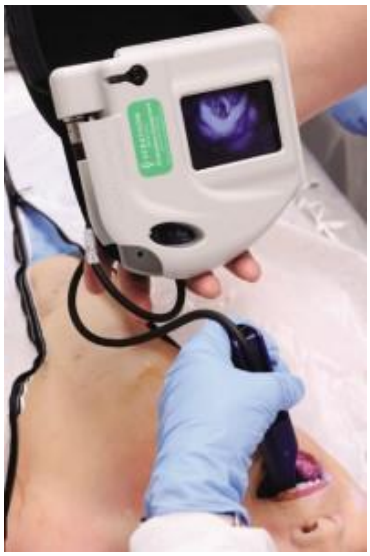


Figure 25. Verathon's GlideScope Ranger Has Been Used En Route by U.S. Forces and Has Been Selected as the Joint Product of Choice for VAID (Eisele, 2008)

Among the devices examined in this study and in other military evaluations of VAID technology, the GlideScope Ranger by Verathon Inc. has been identified as an effective tool (Figure 25). It has been designed for prehospital intubation, and has received airworthiness certification from both the U.S. Army and Air Force (Pacey, 2012; Wayne and McDonnell, 2010). The GlideScope has seen initial use in both Afghanistan and Iraq by U.S. and allied forces in multiple en route care environments including CCATT; it has since been selected as the Joint Product of Choice for VAID (Hawkins, 2008; Pacey, 2012).

Capability Gap Alignment

The identification of an optimal VAID and implementation of its standardized use to facilitate challenging intubation during en route care, in conjunction with the use of VAID in provider training, is contributing to the fill of a number of capability gaps (Table 54).

Table 54. Capability Gaps Addressed by VAID Implementation and Training

Requirement Sources	Capability Gaps Addressed
GDF	• **JCM-1-1** – Inadequate ability to diagnose, resuscitate, and stabilize casualties with survivable wounds • **JCM-1-6** – Poor ability to ensure casualty airway • **JPM-TRA-AE2** – En route care lacks standardization. Standardized joint medical equipment for transport of critical patients is lacking. Joint critical care transport capability and training platforms do not exist. There is no joint directive/ authority to ensure standardized PMI program compliance • **JPM-TER-EC3** – JPM training platforms and skill-identification tracking systems are lacking. Models to replicate medical processes in joint exercise are lacking. Programs to establish JPM leadership development and education are inadequate
TC3 ICD	• **Theater Hospitalization, Area Medical Support** – Diagnose, resuscitate, and stabilize casualties with survivable wounds • **En Route Care** – Locate and evaluate casualties • **Airway Management Technology** – Ensure casualty airway
DHP ICD	• **TI1** – Insufficient current first-responder (medical and non-medical) capacity and capability to initially assess, treat, and maintain severe trauma cases in the pre-hospital environment - Insufficient initial and ongoing training for first responders in the pre-hospital environment overall - Insufficient tools that enable both non-medical and medical first responders - The technologies do not exist to fulfill some of the needs (e.g., stabilizing the airway or truncal hemorrhage) - Incorrect alignment of trained skill sets and operational needs - Inconsistent integration of recurrent medical training into overall unit training • **TI3** – No common TCCC TTP for first responders and medical practitioners across Services and across the continuum of care • **TI9** – Current ways and means of training medical and non-medical providers for treating trauma are inadequate to maintain proficiency • **MA3** – Lack of adequate tools for first responders to establish and maintain the airway in a pre-hospital environment • **MA4** – Lack of authorities and/or skillsets to establish and maintain the airway in a pre-hospital environment • **PL1** – Lack of evidence-based data and metrics to assess the effectiveness of training methodologies, specifically TC3, to include both technical skills such as establishing surgical airways, and cognitive skills, such as decision-making in a complex tactical casualty scenario

Requirements sources such as the TC3 ICD have highlighted that advances in evacuation equipment will continue to reduce morbidity and mortality, calling for equipment that is compatible with, and standardized across, evacuation assets from all services. To this end, lightweight, portable, airworthy devices for emergency intervention are among the recommended medical material approaches.

Impact on the Battlefield/Warfighter

The patients of CCATT and other aeromedical evacuation teams have the potential to greatly benefit from a VAID that is easily used by the novice, easy to use during flight, and that provides adequate lighting abilities during blackout conditions. Though clinical data from performance in the CCATT environment have not been published, studies of VAID use in civilian air transport have demonstrated a reduced number of attempts to achieve successful intubation (Wayne and McDonnell, 2010). Outside of the aeromedical evacuation context but within the military,

however, use of the GlideScope Ranger as the primary adjunct for difficult airway management was examined over 6 months by an Army anesthesia team in a combat support hospital in Iraq. During that time there were no reported cases of obstructed view of the vocal folds, or the glottis, and providers with infrequent use of laryngoscopy skills reported it enhanced their ability to obtain a glottic view (Hawkins, 2008). Details provided for select cases further highlighted the utility of the GlideScope Ranger for intubation, including the unique intubation in the field of a patient impaled by unexploded ordinance, who required sedation and surgical removal of the ordinance with extreme caution to avoid disturbance (Hawkins, 2008).

- **Combat Casualty Care:** Use of the GlideScope Ranger for combat casualty care enables unobstructed tracheal views and enhanced visualization for providers with infrequent use of laryngoscopy skills (Hawkins, 2008)
- **Training:** Military medics, nurses, and physicians trained with VAID had an increased rate of successful intubation in simulations of standard and difficult airway conditions (Boedeker, Barak-Bernhagen, Boedeker, & Murray, 2011)
- **Patient Safety and Improvement:** VAID recordings of helicopter emergency service intubations could be used to measure multiple components of performance that were useful to define successful intubation attempts (Carlson, Quintero, Guyette, Callaway, & Menegazzi, 2012)

Beyond the impact of the use of new VAID technology during intubation, the equipping of en route care platforms based on rigorous supporting data with considerations for their unique requirements, and supporting the optimal training of those attending evacuations, are critical high-level impacts of the funded study that are in line with the goals of the J-ERC portfolio. The use of VAID can improve patient safety not only directly by enabling successful airway management in patients en route from the battlefield, but also by offering improvements in skill training and sustainment in military simulation centers (Boedeker, Boedeker, Bernhagen, Miller, & Lacy, 2011). In a recent operational assessment of VAID technology for medical training and airway management conducted by the Center for Advanced Technology and Telemedicine, users rated the value of the technology highly (Boedeker, Boedeker, Bernhagen, Miller, & Lacy, 2011). Military medics, nurses, and physicians being deployed to Afghanistan were trained on the use of VAID and conducted a series of intubations either through standard direct laryngoscopy or VAID; trainees also achieve an increased rate of successful intubation in both standard and difficult airway conditions (Boedeker, Barak-Bernhagen, Boedeker, & Murray, 2011). Training with VAID improved the view of the airway, enhanced performance, and increased trainee confidence in intubation. Additional studies have also suggested that VAID users become proficient more quickly and maintain competency with fewer annual intubations than users of direct intubation (Bauer, 2012; Wayne, 2008). The use of VAID in the training of deploying medical personnel, and supplying VAID as standard military issue, can improve airway management and save lives in combat trauma situations (Boedeker, Barak-Bernhagen, Boedeker, & Murray, 2011; Niven, 2013).

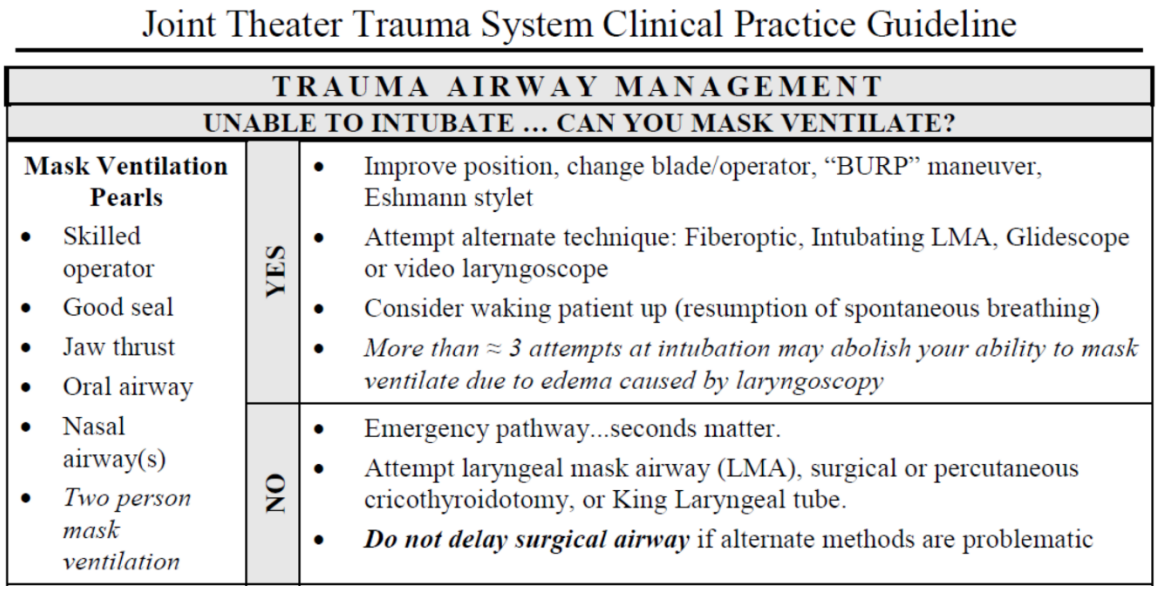
Finally, recent studies have suggested that VAID can serve as important research and training tools through the recording of procedures for later analysis. A study of VAID use in a helicopter emergency service examined recordings of intubations as captured by VAID. The recordings could be used to measure multiple components of performance that defined successful intubation attempts (Carlson, Quintero, Guyette, Callaway, & Menegazzi, 2012). VAID recordings provided details with the potential to help providers improve proficiency and patient safety.

Clinical Practice

Impact on Clinical Practice Guidelines

In general, expert opinion currently supports significant advantages of VAID in the management of difficult and failed airways, though further study remains necessary to continue to understand under what additional clinical situations and practice settings VAID should be regularly used (Niven, 2013; Gerhardt, Mabry, De Lorenzo, & Butler, 2012). Though it has not supplanted existing tools and methods for airway management, VAID use by military care providers in several contexts has already had an impact on CPGs. Current TCCC guidelines and the JTS CPGs on trauma airway management continue to emphasize standard intubation with rapid sequence induction as the primary approach to airway management (Gerhardt, Mabry, De Lorenzo, & Butler, 2012; JTS, 2014; Niven, 2014). In the absence of the necessary equipment, pharmaceuticals, or training to perform rapid sequence intubation, cricothyroidotomy is a preferred method for establishing definitive airway during tactical care or tactical evacuation (Gerhardt, Mabry, De Lorenzo, & Butler, 2012). However, the recent advent of VAID, including the GlideScope Ranger, provides a viable option for intubation in field and transport settings (Gerhardt, Mabry, De Lorenzo, & Butler, 2012). The Trauma Airway Management CPG now suggests that, in the event that intubation is not successful, an alternate technique can be attempted including GlideScope or other video laryngoscope (Figure 26) (JTS, 2012). Additionally, the CPG for Trauma Anesthesia published by the JTS has been adapted to cite video laryngoscopy among the airway adjuncts available that can potentially provide an improved view of the vocal cords during intubation (JTS, 2014). This CPG emphasizes, however, that this may not necessarily improve successful first pass intubation or result in faster time to intubation, and it remains prudent to have a limited number of immediately available airway adjuncts familiar to the provider rather than a larger selection of less familiar equipment (Griesdale, Liu, McKinney & Choi, 2012; JTS, 2014).

The Glidescope has now been made a part of the approved allowance standard for CCATT, and as such is brought on board every CCATT flight. Thus its use is integrated into CCATT practice guidelines and training. In the civilian context, some air medical transport programs have also already gone so far as to adopt the use of VAIDs as a first-line intubation tool (Bauer, 2012). The American Society of Anesthesiologists Task Force on Management of the Difficult Airway has also suggested VAID be considered as a technique for difficult airway management, citing higher frequencies of successful intubations overall and on the first attempt, as evidenced by meta-analyses of randomized clinical trials (Apfelbaum et al., 2013).



Joint Theater Trauma System Clinical Practice Guideline

TRAUMA AIRWAY MANAGEMENT		
UNABLE TO INTUBATE … CAN YOU MASK VENTILATE?		
Mask Ventilation Pearls • Skilled operator • Good seal • Jaw thrust • Oral airway • Nasal airway(s) • *Two person mask ventilation*	YES	• Improve position, change blade/operator, "BURP" maneuver, Eshmann stylet • Attempt alternate technique: Fiberoptic, Intubating LMA, Glidescope or video laryngoscope • Consider waking patient up (resumption of spontaneous breathing) • *More than ≈ 3 attempts at intubation may abolish your ability to mask ventilate due to edema caused by laryngoscopy*
	NO	• Emergency pathway...seconds matter. • Attempt laryngeal mask airway (LMA), surgical or percutaneous cricothyroidotomy, or King Laryngeal tube. • ***Do not delay surgical airway*** if alternate methods are problematic

Figure 26. Trauma Airway Management CPG (JTS, 2012)

Supporting Publications

Many clinical studies have evaluated VAID, and support use in difficult airway management, and also in environments outside of the hospital (Table 55). Several small studies have also examined the use of VAID in military provider training, identifying improved performance.

Table 55. Supporting Publications for VAID

Reference	Description
Emergent and Difficult Airway Management	
Mosier, Stolz, Chiu, & Sakles, 2012	Compared emergency department intubation success rates with GlideScope and direct laryngoscopy; GlideScope had a higher success rate at first attempt for difficult airways
Sakles, Mosier, Chiu, & Keim, 2011	Compared the success rates of GlideScope with direct laryngoscopy in emergency department intubations; both techniques worked equivalently overall, with a lower number of esophageal complications occurring with VAID use
Koh, Lee, Lee, & Chang, 2010	Examined use of VAID versus direct laryngoscopy in patients with cervical spine immobilization; VAID enabled a better laryngeal view and higher first attempt intubation success
Malik, Subramaniam, Maharaj, Harte, & Laffey, 2009	Conducted a randomized controlled trial comparing VAID (GlideScope and Pentax AWS) with direct laryngoscopy for difficult intubations; VAID significantly reduced intubation difficulty score and the rate of successful intubations
Stroumpoulis et al., 2009	Examined direct laryngoscopy versus VAID in a study of 112 patients with an estimated difficult intubation; VAID significantly improved laryngeal exposure, facilitating intubation
Prehospital and En Route Use	
Bjoernsen, Parquette, & Lindsay, 2008	Case report of GlideScope Ranger use by an air medical crew in the prehospital setting

Reference	Description
Wayne & McDonnell, 2010	Compared direct laryngoscopy with VAID in prehospital intubations performed by paramedics; the number of attempts to achieve intubation was significantly reduced in the VAID group
Struck, Wittrock, & Nowak, 2011	Evaluated the experience of anesthetists using GlideScope for difficult airway management in a helicopter rescue program over a 3-year period; the prehospital use of GlideScope in 23 cases was effective and successful
Bauer, 2012	Describes the development of a structured, standardized approach to airway management in training and prehospital settings by air medical organization Airlift Northwest, including the use of GlideScope as a first-line intubation tool. Since implementation in May 2011, the organization has had a continued rise in overall intubation success rates in each quarter
Grover, Lubin, Finney, & Tietjen, 2013	Simulated intubation with direct laryngoscopy or the GlideScope Ranger in a standard manikin under various conditions in a medical helicopter. In nondifficult airways, both modalities may be comparable
Silverberg, Li, Acquah, & Kory, 2015	A randomized controlled trial comparing intubation with the GlideScope to direct laryngoscopy during urgent endotracheal intubation by pulmonary and critical care medicine fellows; first-attempt success was achieved more frequently with GlideScope (74 versus 40 percent). All unsuccessful direct laryngoscopy patients were successfully intubated with GlideScope video laryngoscopy
Military Use and Training	
Boedeker, Barak-Bernhagen, Boedeker, & Murray, 2011	Examined the performance and training of military healthcare providers in a brief intubation training course using both direct laryngoscopy VAID. Airway visualization and intubation performance were improved by VAID training, promoting increased trainee confidence
Boedeker, Boedeker, Bernhagen, Miller, & Lacy, 2011	Conducted an Operational Assessment of VAID technology for medical training; deploying medical providers participating in training rated the value of VAID for intubation and the value of training as high
Walker, Underwood, Bernhagen, Markin, & Boedeker, 2012	Demonstrated the use of video conferencing technology in conjunction with VAID in the virtual laryngoscopy training of deployed military medical personnel

Role of CCCRP-Sponsored Projects

The CCCRP's J-ERC portfolio funded the comparative study of VAID devices to provide the acquisition community with a recommendation on which VAID unit best meets the needs of en route care providers, and to help inform the training of providers through the use of these devices to ensure competency and, in turn, maximize patient safety (Table 56).

Table 56. CCCRP-Sponsored Project for VAID Evaluation

Project Title (Award Number)	Principal Investigator	Funding
Comparative Study Evaluating Specific Qualities of the Video Assisted Intubation Devices (VAID) as it applies to Airway Training and Instruction (FA8650-11-2-6B03 Task 3; D10_I_AR_J6_1011)	Col Todd Carter, M.D. (711 Human Performance Wing)	$133,000 (2010-2013)

Knowledge to ensure available technologies can best be applied to en route care is critical as the services work to achieve validated, standardized, and effective equipment and practices for current and future casualty care needs. Work performed under this study to assess several different VAIDs has helped to identify optimal devices for use in military casualties in the restrictive environment of air transport.

References

Apfelbaum, J. L., Hagberg, C. A., Caplan, R. A., Blitt, C. D., Connis, R. T., Nickinovich, D. G., … American Society of Anesthesiologists Task Force on management of the Difficult Airway. (2013). Practice guidelines for management of the difficult airway: An updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology*, *118*(2), 251-270.

Bauer, K. (2012). Prehospital airway management: High tech meets trauma. *Critical Care Nursing Quarterly*, *35*(3), 281-291.

Bjoernsen, L. P., Parquette, B. T., & Lindsay, M. B. (2008). Prehospital use of video laryngoscope by an air medical crew. *Air Medical journal*, *27*(5), 242-244.

Boedeker, B. H., Barak-Bernhagen, M. A., Boedeker, K. A., & Murray, W. B. (2011a). Intubation success rates and perceived user satisfaction using the video laryngoscope to train deploying far forward combat medical personnel. *Studies in Health Technology and Informatics*, *163*, 77-79.

Boedeker, B. H., Boedeker, K. A., Bernhagen, M. A., Miller, D. J., & Lacy, T. (2011b). Battlefield tracheal intubation training using virtual simulation: A multi center operational assessment of video laryngoscope technology. *Studies in Health Technology and Informatics*, *163*, 74-76.

Carlson, J. N., Quintero, J., Guyette, F. X., Callaway, C. W., & Menegazzi, J. J. (2012). Variables associated with successful intubation attempts using video laryngoscopy: a preliminary report in a helicopter emergency medical service. *Prehospital Emergency Care*, *16*(2): 293-298.

Eastridge, B. J., Mabry, R. L., Seguin, P., Cantrell, J., Tops, T., Uribe, P., … Blackbourne, L. H. (2012). Death on the battlefield (2001-2011): Implications for the future of combat casualty care. *Journal Trauma Acute Care Surgery*, *73* (6 Suppl 5), S431-S437.

Gerhardt, R. T., Mabry, R. L., De Lorenzo, R. A., & Butler, F. K. (2012). Fundamentals of Combat Casualty Care. In Savitsky, E., & Eastridge, B. (Eds.), *Combat Casualty Care: Lessons Learned from OEF and OIF* (397-469). Fort Detrick, MD: Borden Institute.

Griesdale, D. E., Liu, D., McKinney, J., & Choi, P. T. (2012). Glidescope video-laryngoscopy versus direct laryngoscopy for endotracheal intubation: A systematic review and meta-analysis. *Canadian Journal of Anesthesia*, *59*(1), 41-52.

Grover, J. M., Lubin, J. S., Finney, A. L., & Tietjen, K. (2013). The use of video laryngoscopy during air medical transport: A manikin study. *Simulation in Healthcare*, *8*(4), 229-233.

Hawkins, M. R. (2008). The military experience: The GlideScope Ranger improves visualization in the combat setting. *Journal of Emergency Medical Services*, Supplement, 16-18.

Joint Trauma System (JTS). (2008, Nov). Joint Trauma System Clinical Practice Guidelines. http://usaisr.amedd.army.mil/beta/cpgs/Intratheater_Transfer_and_Transport_19_Nov_2008.pdf

Joint Trauma System (JTS). (2012, June). Joint Trauma System Clinical Practice Guidelines. Retrieved from http://usaisr.amedd.army.mil/beta/cpgs/Trauma_Airway_Management_11_Jun_12.pdf

Joint Trauma System (JTS). (2014, June). Joint Trauma System Clinical Practice Guidelines. Retrieved from http://usaisr.amedd.army.mil/beta/cpgs/Trauma_Anesthesia_16Jun2014.pdf

Koh, J. C., Lee, J. S., Lee, Y. W., & Chang, C. H. (2010). Comparison of the laryngeal view during intubation using Airtraq and Macintosh laryngoscopes in patients with cervical spine immobilization and mouth opening limitation. *Korean Journal of Anesthesiology*, *59*(5), 314-318.

Malik, M. A., Subramaniam, R., Maharaj, C. H., Harte, B. H., & Laffey, J. G. (2009). Randomized controlled trial of the Pentax AWS, Glidescope, and Macintosh laryngoscopes in predicted difficult intubation. *British Journal of Anaesthesia*, *103*(5), 761-768.

McIntosh, S. E., Swanson, E. R., McKeone, A. F., & Barton, E. D. (2008). Location of airway managmenet in air medical transport. *Prehospital Emergency Care*, *12*, 438-442.

Mosier, J., Stolz, U., Chiu, S., & Sakles, J. (2012). Difficult airway management in the emergency department: GlideScope videolaryngoscopy compared to direct laryngoscopy. *Journal of Emergency Medicine, 42*, 629-634.

Niven, A. S. (2013, October 24). Controversies in airway management. *Military Medical and Veterans Affairs Forum, 17*(5). Retrieved from http://www.kmimediagroup.com/military-medical-veterans-affairs-forum/442-articles-m2va/controversies-in-airway-management

Pacey, J. A. (2013). GlideScope video laryngoscope in military medicine and veterans administration healthcare. *The Year in Veterans Affairs & Military Medicine*, 58-60.

Pacey, J. A. (2015). The video laryngoscopy movement. Retrieved from http://www.jems.com/article/patient-care/video-laryngoscopy-movement

Sakles, J. C., Mosier, J. M., Chiu, S., & Keim, S. M. (2011). Tracheal Intubation in the Emergency Department: A Comparison of GlideScope(®) Video Laryngoscopy to Direct Laryngoscopy in 822 Intubations. *Journal of Emergency Medicine, 42*(6), 629-634.

Stroumpoulis, K., Pagoulatou, A., Violari, M., Ikonomou, I., Kalantzi, N., Kastrinaki, K., …Michaloliakou, C. (2009). Videolaryngoscopy in the management of the difficult airway: A comparison with the Macintosh blade. *European Journal of Anaesthesiology*, *26*(3), 218-222.

Struck, M. F., Wittrock, M., & Nowak, A. (2011). Prehospital Glidescope video laryngoscopy for difficult airway management in a helicopter rescue program with anaesthetists. *European Journal of Emergency Medicine, 18*, 282-284.

U.S. Army Institute of Surgical Research (USAISR). (2015, January 30). Clinical Practice Guidelines. Retrieved from http://usaisr.amedd.army.mil/cpgs.html.

Walker, R. B., Underwood, P. K., Bernhagen, M., Markin, N., & Boedeker, B. H. (2012). Virtual intubation training at a remote military site. *Studies in Health Technology and Informatics, 173,* 540-542.

Wayne, M. A. (2008). Use of video laryngoscopy in a ground EMS system. *Journal of Emergency Medical Services, 33,* (9, Suppl), 11-14.

Wayne, M. A., & McDonnell, M. (2010). Comparison of traditional versus video laryngoscopy in out-of-hospital tracheal intubation. *Prehospital Emergency Care, 14,* 278-282.

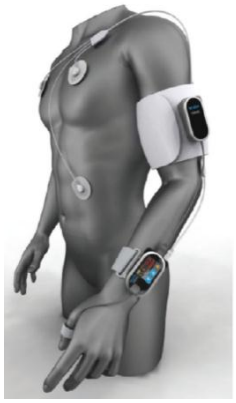
Noninvasive Monitors for Casualty Triage, Resuscitation, and Transport

Noninvasive physiological monitors hold the potential to decrease morbidity and mortality across the continuum of care by providing caregivers with accurate and predictive real-time casualty data. The use of the Multi-Parameter CareGuide 4100 sensor for noninvasive tissue metabolic status monitoring in conjunction with the body-worn, vital sign, ViSi Mobile Monitoring System is currently being evaluated for in-flight use during patient transport.

- Development and Testing Partners:
  - Sotera Wireless, Inc.
  - RMI
  - USAMMA
- Principal Investigator:
  - Mr. James Welch

Key Outcomes and Impact:

- Progress has been enabled through collaboration between the FSICC and J-ERC portfolios
- The CareGuide + ViSi Mobile integrated device has been FDA cleared with support from the FSICC portfolio. Project is now entering two phases of air trials: the first in healthy flight crews during transport, and the second in the transport of trauma patients
- Noninvasive continuous monitoring of vital sign information during air transport (including taxi and takeoff), has the potential to improve casualty care
- Continuous blood pressure measurements from these trials will be provided to a committee of the Association for the Advancement of Medical Instrumentation to inform the establishment of medical equipment standards



Components of the ViSi, Including Continuous Blood Pressure Monitoring (Welch et al., 2012)

Overview

Hemorrhage and subsequent cardiovascular collapse represent a major cause of death on the battlefield (Eastridge et al., 2012). About 26 percent of these deaths are deemed potentially survivable given early detection, intervention, and treatment of hemorrhage (Eastridge et al., 2012). However, early detection and rapid intervention to prevent hemorrhagic shock is confounded by physiological compensatory mechanisms, which attempt to maintain heart rate, blood pressure and other vital signs within normal clinical ranges during hemorrhage of up to 30 percent of total blood volume (Convertino et al., 2011; Cottingham, 2006). Thus, compensatory mechanisms can potentially mask the underlying hemorrhage and lead to a situation where the first clear clinical sign of life-threatening hemorrhage is a precipitous cardiovascular collapse marked by a sudden and substantial drop in blood pressure (Cottingham, 2006). Although compensatory mechanisms are critical, they limit the caregiver's ability to detect imminent cardiovascular collapse based on traditional vital signs. Thus, it has become increasingly clear that when casualties progress along the continuum of care, there is a need for continuous monitoring technologies that can enhance the caregiver's ability to, for example, detect occult hemorrhage and the beginning of hypoperfusion, and guide resuscitation. In addition to the scenario of hemorrhagic shock, advanced monitoring technologies can be similarly beneficial for the continuous monitoring of a range of parameters to enable the clinically meaningful detection

of early signs of deterioration in the care of critically injured patients (Welch, Moon & McCombie, 2012).

In USAMRMC led efforts, DoD has provided funding for three companies developing complementary noninvasive, body-worn devices and related algorithms that provide metabolic status and resuscitation feedback. This work has been shaped and sponsored through close collaboration between both the FSICC portfolio and the J-ERC portfolio. One of these companies, Sotera Wireless, has developed the ViSi Mobile technology platform, which is a comprehensive vital sign-monitoring platform that can be paired with auxiliary sensors to allow caregivers to monitor their patients continuously, even during transport (Figure 27).

Figure 27. Sotera's ViSi Mobile System is the First FDA-Cleared Body-Worn Monitor (ViSi Mobile, 2015)

Figure 28. The Mobile CareGuide Sensor Enables Caregivers to Obtain Tissue Measurements of Oxygen and pH (RMI, 2015)

The ViSi monitoring device can be used with a proprietary optical sensor developed by RMI, called the CareGuide sensor (Figure 28). RMI has been funded through multiple DoD awards to further develop its CareGuide sensors for the noninvasive and continuous monitoring of tissue metabolic status through the measurement of muscle oxygen saturation (SmO_2), acidosis (pH_m), and hematocrit (Figure 29, Table 59). The sensor is worn on the body and uses near infrared absorbance spectra from muscle tissue to provide real-time feedback. The USAMRMC funded development of the CareGuides 1100, 2100, and 3100, and is currently providing funding for the CareGuide 4100, a ruggedized version of the 3100 Mobile CareGuide that meets military specifications (Figure 29).

In the future, a CRI algorithm developed by Flashback Technologies may also be cleared for integration onto the ViSi monitoring device and other similar devices. Development of the CRI has been supported through multiple awards by the USAMRMC (Table 59). The CRI algorithm, which can be integrated into any standard monitor that creates an arterial waveform, will enhance the caregiver's capability to anticipate hemodynamic instability and initiate intervention at an earlier stage when the patient is more likely to respond. Flashback Technologies is using feature extraction and machine-learning methods to analyze physiological waveform data to identify subtle changes in human physiology that are predictive of acute blood loss. This information can be leveraged to enhance real-time decision support, guide intervention, monitor resuscitation efficacy, and reduce incidence of cardiovascular collapse.

In a current project managed under the J-ERC portfolio, the use of the CareGuide sensor with the ViSi Mobile monitoring platform for continuous data monitoring in flight is being examined by Sotera in early air trials (Table 59). This effort is continuing to move forward these two technologies whose development and regulatory clearance have been previously supported under CCCRP sponsorship through the FSICC portfolio.

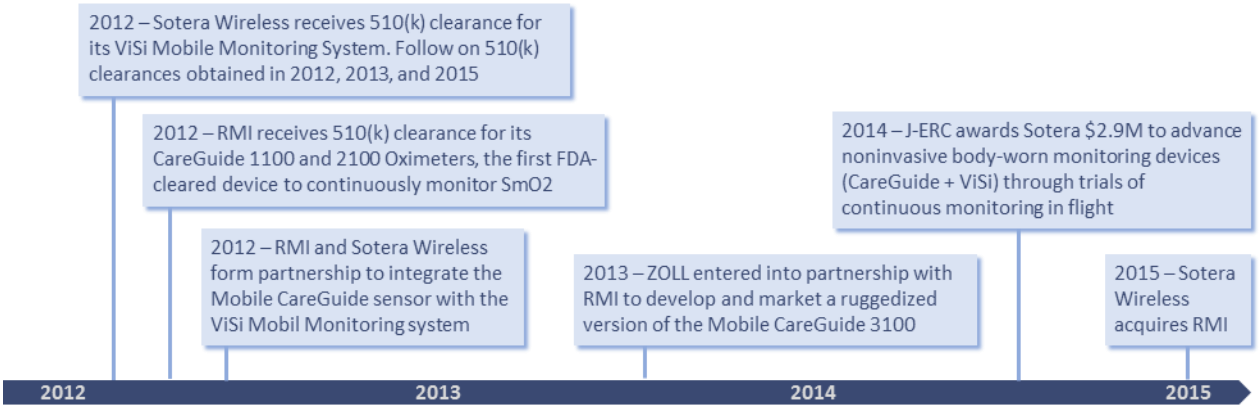


Figure 29. Timeline of Progress for the Noninvasive ViSi + CareGuide Monitoring Device

Capability Gap Alignment

The implementation of the noninvasive ViSi monitoring device integrated with sensors including the CareGuide can directly contribute to the closure of multiple gaps across the continuum of care. Each requirement source mentions the need for monitoring capabilities to enhance a variety of activities including triage and resuscitation (Table 57).

Table 57. Capability Gaps Addressed by Noninvasive Monitors for Casualty Triage, Resuscitation, and Transport

Requirement Sources	Capability Gaps Addressed
GDF	• **JCM-1-1** – Inadequate ability to diagnose, resuscitate, and stabilize casualties with survivable wounds • **JCM-1-3** – Inadequate ability to locate and evaluate casualties • **JCM-1-7** – Inability to monitor, evaluate, and triage casualties by combat medical personnel for early identification of life saving interventions • **JCM-1-11** – Inadequate ability to immediately recognize and correct coagulopathy • **JCM-2-1** – Inadequate stabilization of injuries and ability to monitor response to treatment
TC3 ICD	• **Theater Hospitalization, Area Medical Support** – Diagnose, resuscitate and stabilize casualties with survivable wounds • **En Route Care** – Locate and evaluate casualties • **First Response Medical Care** – Stabilize injuries, monitor response to treatment • **Advanced Casualty Locating and Remote Physiologic Monitoring** – Monitor, evaluate, triage casualties by combat medical personnel for early identification of life-saving Interventions • **Coagulopathy Prevention and treatment Agents** – Immediate recognition and correction of coagulopathy
DHP ICD	• **DK3** – Lack a decision support mechanism that enables timely, accurate decisions and diagnosis at all levels of care • **TI1** – Insufficient current first-responder (medical and non-medical) capacity and capability to initially assess, treat, and maintain severe trauma cases in the pre-hospital environment - Insufficient tools that enable both non-medical and medical first responders • **TI6** – First responders lack interoperable ways and means to understand and provide rapid, reliable, and actionable information about a casualty's physiological/psychological status in the pre-hospital environment (for IT devices there are no defined KPP requirements; no clearly defined MILSPECS for non-IT) • **TI7** – Current ways and means of document POI hinder ability to capture rapid, reliable, and actionable information about a casualty's physiological status in the pre-hospital environment and subsequently transmit it for follow on analysis

Requirement Sources	Capability Gaps Addressed
	• **TI11** – Lack of computational algorithms and predictive tools for physiological status that use available information and can predict necessary statuses in an expedient manner • **TI12** – In pre-hospital environment, lack ways and means to enable clinical decision support and have inadequate ways and means to enable clinical decision support at Level III and higher • **MB4** – In the pre-hospital environment there is a lack of understanding of the optimal oxygen requirements for casualties • **MB6** – Limited capability to identify and treat lung function problems and respiratory failure in the pre-hospital environment • **MA6** – Lack of ability to identify arterial oxygen and CO_2 levels • **TS1** – Lack of optimal resuscitation strategies for casualties who have TBI and are in, or at risk for, hemorrhagic shock • **TS4** – Lack of ways and means to effectively screen for and diagnose shock throughout continuum of care • **TS6** – Insufficient ways and means to diagnose and manage vascular disruption (with or without hemorrhagic shock) • **RPI1** – Lack ability to conduct non-invasive physiological monitoring (intra-cranial, compartment syndrome, intra-abdominal pressure, etc.)

Impact on the Battlefield/Warfighter

Even though these devices are not yet in clinical use by the U.S. military during transport, they are expected to make considerable impact on en route care. At the very least, during air transport the monitoring device will enable caregivers to continuously monitor and capture vital sign information throughout transport, including during periods of restricted mobility such as taxi and takeoff. The device may also inform the impact and risks of air transport on casualty physiology. For example, multiple studies have reported that arterial oxygen saturation may be reduced during flight, even in healthy volunteers, and this may trigger additional physiological effects (Bendrick, Nicholas, Krause, & Castillo, 1995; Cottrell, Lebovitz, Fennell & Kohn, 1995; Humphreys, Dyermond, Bali, Stevenson & Fee, 2005; Smith et al., 2012). While such impacts of flight may not be manifest in obvious clinical changes under many conditions, they may have profound impacts for critical patients. This suggests that continuous monitoring of multiple clinical parameters, including oxygen saturation, may be important for safe air transport of patients.

Once implemented, the monitoring devices would offer continuous, noninvasive measurement of vital signs and provide feedback on conditions including uncontrolled hemorrhage that could be used to guide and improve treatment. For instance, by accurately monitoring resuscitation, the incidence and effects of over-resuscitation (e.g., rapid increase in systolic blood pressure and dilution of clotting factors) are reduced.

Clinical Practice

Impact on Clinical Practice Guidelines

The CareGuide and the ViSi have both achieved FDA clearance (FDA, 2015). Although they are not yet fielded for en route care, they have been deemed airworthy (i.e., the devices operate properly in flight conditions) and are now entering into testing for continuous data monitoring capabilities in two phases of air trials: the first in healthy flight crews during transport, and the

second in the transport of trauma patients. These trials, which are funded by the J-ERC portfolio and managed by USAMMA, are intended to assess the functionality and accuracy of the devices, and gauge their potential impact on en route care (Table 59).

During transport, non-ICU level patients are accompanied by nurses and/or medics who periodically take vital signs. This is accomplished through the use of a traditional vital signs monitor shared between patients. En route care clinicians must carefully monitor these parameters for departure from pre-flight recommended criteria, often visually, as alarms are inaudible during flight. The ViSi + CareGuide system gives en route care clinicians the ability to measure and monitor these patients continuously throughout transport. It also provides a greater awareness of patients' status and enables more timely and effective care by expanding the monitored clinical parameters and by centralizing the monitoring systems. It is also anticipated that this personal monitor system will automatically capture the clinical data into the Electronic Health Record and DoD Trauma Registry, significantly decreasing the workload demands for en route care clinicians.

Supporting Publications

Multiple publications highlight the need to enhance continuous vital sign monitoring capabilities (Convertino et al., 2008; Moulton, Haley-Andrews, & Mulligan, 2010; Welch, Moon, & McCombie, 2012). As such, many publications have emerged from the development and test of the ViSi Mobile Monitoring system and the CareGuide sensor that support their use, and that may provide a foundation in conjunction with the outcomes of the currently in-process air trials to support the implementation of these devices for en route care (Table 58).

Table 58. Supporting Publications for Noninvasive Monitors for Casualty Triage, Resuscitation, and Transport

Reference	Description
Moulton, Haley-Andrews, & Mulligan 2010	A review of the next generation of transport monitors (supported by DoD Small Business Technology Transfer Research [STTR] funding from contract W81XWH-09-C-0610)
Henry et al., 2011	Demonstration and implementation of three cardiovascular parameters on a small, noninvasive body-worn device that connects wirelessly to a central monitoring system (supported by USAMRMC contract W81XWH-11-2-0085)
Soller et al., 2012	Monitored parameters including SmO_2 and pH_m in healthy volunteers placed under lower body negative pressure; SmO2 and SV preceded other vital signs as indicators of impending cardiovascular collapse (Supported by USAMRMC CCCRP, and STTR funding)
Grudic, Moulton, & Mulligan, 2012	U.S. Patent for tools and techniques for estimating whether a patient is bleeding or has sustained intravascular volume loss
Ellerby, Smith, Zou, Scott, & Soller 2013	Using an isolated perfused swine limb model, the CareGuide sensor was evaluated for its ability to simultaneously and continuously determine SmO_2 and pH_m. The sensor was accurate enough to support clinically relevant decision-making (supported by USAMRMC contract W81XWH-11-C-001)
Soller et al., 2014	Evaluated pH_m and SmO_2 using the CareGuide in a swine shock model that used uncontrolled hemorrhage and restricted volume resuscitation. Results suggest an evaluation in trauma patients is warranted

Reference	Description
Bernstein et al., 2015	Compared stroke volume and cardiac output obtained via electrical interrogation of the brachial artery versus cardiac magnetic resonance imaging. Despite being a potential source of error, the noninvasive electrical method was in good agreement with magnetic resonance imaging and may be clinically acceptable (supported by funds from USAMRMC contract W81XWH-11-2-0085)

Role of CCCRP-Sponsored Projects

The CCCRP has played an important role in many of the past and present activities related to the development of a fully integrated monitoring device. The current effort to flight test these devices under the J-ERC portfolio is building upon previously funded work through the CCCRP's FSICC portfolio for the clearance of the ViSi and development of the CareGuide sensor. Beginning in 2008, the USAMRMC has made multiple awards to each of the contributing companies to develop their respective technology (Table 59).

Table 59. CCCRP-Sponsored Projects for Noninvasive Monitors for Casualty Triage, Resuscitation, and Transport

Project Title (Award Number)	Organization/ Principal Investigator	Funding
A Real-Time, Portable Non-Invasive Monitoring System of Muscle Oxygen and pH in Trauma Patients (STTR; W81XWH-08-C-0114)	RMI	$848,915 (2008 – 2010)
CareGuide Noninvasive Trauma Patient Monitor (USAMRMC; W81XWH-11-C-0001)	RMI	$5,619,630 (2010 – 2013)
Noninvasive, Body-Worn Device for Providing Real-Time Cardio-Pulmonary and Metabolic Status for Triage and Resuscitation Feedback (USAMRMC; W81XWH-11-2-0085)	Mr. James Welch (Sotera Wireless)	$5,146,722 (2010 – 2013)
Non-Invasive, Body-Worn Device for Characterizing a Patient's Cardio-Pulmonary and Metabolic Status During Triage, Resuscitation and Transport Efforts (W81XWH-14-C-1417)	Mr. James Welch (Sotera Wireless)	$2,911,964 (2014 – current)

Funding from these awards has led to multiple publications that together build support for the ViSi + CareGuide monitoring device. Table 58 highlighted crucial publications for the development of the ViSi + CareGuide monitoring device; these publications have all resulted from these DoD-funded awards. The results from the ongoing J-ERC project examining the ViSi + CareGuide monitoring device during flight will add to this body of knowledge in the near future. Through this J-ERC project, Sotera is also working with a committee of the Association for the Advancement of Medical Instrumentation to inform the establishment of medical equipment standards by providing raw data from continuous blood pressure measurements obtained during in flight trials. This provides an additional valuable outcome from the funded work.

> "The U.S. military is currently the major driver for developing the next generation of transport monitors."
>
> Moulton, Haley-Andrews, & Mulligan, 2010

References

Bendrick, G. A., Nicolas, D. K., Krause, B. A., & Castillo, C. Y. (1995). Inflight oxygen saturation decrements in aeromedical evacuation patients. *Aviation, Space, and Environmental Medicine, 66*(1), 40-44.

Bernstein, D. P., Henry, I. C., Lemmens, H. J., Chaltas, J. L., DeMaria, A. N., Moon, J. B., & Kahn, A. M. (2015). Validation of stroke volume and cardiac output by electrical interrogation of the brachial artery in normals: Assessment of strengths, limitations, and sources of error. *Journal of Clinical Monitoring and Computing*, 1-12.

Convertino, V. A., Ryan, K. L., Rickards, C. A., Salinas, J., McManus, J. G., Cooke, W. H., & Holcomb, J. B. (2008). Physiological and medical monitoring for en route care of combat casualties. *Journal of Trauma, 64*(Suppl 4), S342-S353.

Convertino, V. A., Moulton, S. L., Grudic, G. Z., Rickards, C. A., Hinojosa-Laborde, C., Gerhardt, R. T., … Ryan, K. L. (2011). Use of advanced machine-learning techniques for noninvasive monitoring of hemorrhage. *Journal of Trauma and Acute Care Surgery, 71*(1), S25-S32.

Cottingham, C. A. (2006). Resuscitation of traumatic shock: A hemodynamic review. *AACN Advanced Critical Care, 17*(3), 317-326.

Cottrell, J. J., Lebovitz, B. L., Fennell, R. G., & Kohn, G. M. (1995). Inflight arterial saturation: continuous monitoring by pulse oximetry. *Aviation, Space, and Environmental Medicine, 66*(2), 126-130.

Eastridge, B. J., Mabry, R. L., Seguin, P., Cantrell, J., Tops, T., Uribe, P., … Blackbourne, L. H. (2012). Death on the battlefield (2001–2011): Implications for the future of combat casualty care. *Journal of Trauma and Acute Care Surgery, 73* (6 Suppl 5), S431-S437.

Ellerby, G. E. C., Smith, C. P., Zou, F., Scott, P., & Soller, B. R. (2013). Validation of a spectroscopic sensor for the continuous, noninvasive measurement of muscle oxygen saturation and pH. *Physiological Measurement, 34*(8), 859.

Grudic, G. Z., Moulton, S. L., & Mulligan, I. J. (2012). *U.S. Patent Application 13/554,483*.

Henry, I., Bernstein, D., Banet, M., Mulligan, J., Moulton, S., Grudic, G., & Convertino, V. (2011, October). Body-worn, non-invasive sensor for monitoring stroke volume, cardiac output and cardiovascular reserve. In *Proceedings of the 2nd Conference on Wireless Health* (p. 26). ACM.

Humphreys, S., Deyermond, R., Bali, L, Stevenson, M., & Fee, J. P. (2005). The effect of high altitude commercial air travel on oxygen saturation. *Anaesthesia, 60*(5), 458-460.

Joint Trauma System (JTS). (2008, Nov). Joint Trauma System Clinical Practice Guidelines. http://usaisr.amedd.army.mil/beta/cpgs/Intratheater_Transfer_and_Transport_19_Nov_2008.pdf

Moulton, S. L., Haley-Andrews, S., & Mulligan, J. (2010). Emerging technologies for pediatric and adult trauma care. *Current Opinion in Pediatrics, 22*(3), 332.

Reflectance Medical Inc. (2015). Retrieved from http://www.reflectancemedical.com/

Rickards, C. A., Vyas, N., Ryan, K. L., Ward, K. R., Andre, D., Hurst, G. M., … Convertino, V. A. (2014). Are you bleeding? Validation of a machine-learning algorithm for determination of blood volume status: Application to remote triage. *Journal of Applied Physiology, 116*(5), 486-494.

Smith, T. G., Talbot, N. P., Chang, R. W., Wilkinson, E., Nickol, A. H., Newman, D. G., Robins, P. A., & Dorrington, K. L. (2012). Pulmonary artery pressure increases during commercial air travel in healthy passengers. *Aviation, Space and Environmental Medicine, 66*(2), 126-130.

Soller, B., Smith, C., Zou, F., Ellerby, G. E., Prince, M. D., & Sondeen, J. L. (2014). Investigation of noninvasive muscle pH and oxygen saturation during uncontrolled hemorrhage and resuscitation in swine. *Shock, 42*(1), 44-51.

Soller, B. R., Zou, F., Ryan, K. L., Rickards, C. A., Ward, K., & Convertino, V. A. (2012). Lightweight noninvasive trauma monitor for early indication of central hypovolemia and tissue acidosis: A review. *Journal of Trauma and Acute Care Surgery, 73*, S106-S111.

U.S. Food and Drug Administration (FDA). (2015). 510(k) Premarket Notification. Retrieved from http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm

ViSi Mobile. (2015). Retrieved from http://www.visimobile.com/

Welch, J., Moon, J, & McCombie, S. (2012). Early detection of the deteriorating patient: The case for a multi-parameter patient-worn monitor. *Biomedical Instrumentation & Technology, 46*(s2), 57-64.

Neurotrauma Portfolio

The Neurotrauma portfolio supports research activities that are advancing care for service members who have sustained a TBI, with major efforts focused in the areas of basic science, screening and diagnostics, therapeutics, and initial and en route care for TBI.

TBI can be defined as "a traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force" (The Management of Concussion/Mild TBI [mTBI] Working Group, 2009). TBI is further categorized as severe, moderate, or mild, based on acute clinical signs such as length of loss of consciousness, amnesia, and alteration in mental state (The Management of Concussion/mTBI Working Group, 2009).

Historically, head injury has been identified in 15 to 25 percent of combat-related injuries (Bellamy, 1992; Shear & Tortella, 2013). The recent combat missions of OEF and OIF have placed an increased awareness on TBI, as the landscape of head injury has evolved during these conflicts to bring the ramifications of exposure to blasts into the spotlight). The Defense and Veterans Brain Injury Center (DVBIC) has tracked statistics on the incidence of TBI in U.S. military populations since 2000 (Figure 30), with over 80 percent of these recorded TBIs diagnosed in military personnel in non-deployed settings, resulting from events such as car crashes, sports injuries, and training. As evidenced by the large portion of service member TBIs occurring in non-deployed settings, TBI is also a significant health issue beyond the battlefield. Every year in the U.S., approximately 1.7 million civilians sustain a TBI, and 52,000 die from this injury, while many who survive continue to have chronic neurological deficits that reduce quality of life (Faul, Xu, Wald & Coronado, 2010).

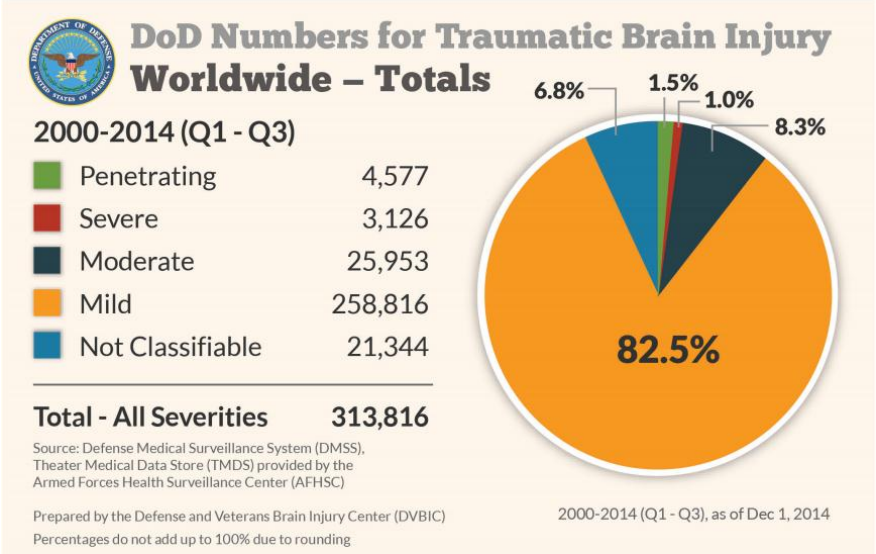


Figure 30. Department of Defense (DoD) TBI Statistics (DVBIC, 2015)

Requirement Sources

The management framework for the Neurotrauma portfolio is guided by input from capability requirements that are defined in JCDs, ICDs, and such guiding frameworks as the JFHP concept. Gaps that are documented in these capability requirements and applicable to the Neurotrauma portfolio are described by multiple sources (Table 60).

- The 2008 GDF Assessment 4.16 Working Group's JCD identified 69 capability gaps that require medical R&D. Twenty-nine of these capability gaps are in areas under the purview of the CCCRP, and four gaps, within the areas of JCM and Joint Human Performance Enhancement (JHPE), are directly within the scope of the Neurotrauma portfolio.
- The 2006 TC3 ICD identified 24 capability gaps that are under the purview of the CCCRP. Work within the scope of the Neurotrauma portfolio is contributing to closure of three of these capability gaps.
- DHP Combat Casualty Care ICD Medical Research Capability Gaps include multiple gaps across 29 different task areas, more than 60 of which are being addressed by research within the CCCRP's portfolios. Several of these overlap with the scope of the Neurotrauma portfolio.

Table 60. Capability Gaps pursued under the Scope of the CCCRP's Neurotrauma Portfolio

Requirement Sources	Capability Gaps
GDF	• **JCM-1-1** – Inadequate ability to diagnose, resuscitate, and stabilize casualties with survivable wounds • **JCM-1-8** – Inadequate therapy for shock and head injury • **JCM-1-8.1** – Inadequate definitive, restorative, and rehabilitative therapy for head injury and shock • **JHPE-EPC-PN1** – Provide neuroprotection to decrease brain injury. Inability to provide, in advance or on site, countermeasures to prevent morbidity/mortality directly related to TBI
TC3 ICD	• **Theater Hospitalization, Area Medical Support** – Diagnose, resuscitate, and stabilize casualties with survivable wounds • **First Response Medical Care** – Stabilize injuries, monitor response to treatment • Adjunctive Medications for Trauma Management – Therapy for shock and head injury
DHP ICD	• **Enhance Psychological Abilities (EPA)1** – Insufficient understanding of the effects of a blast event on neurologic tissue to develop immediate therapeutics and mitigation strategies for long-term negative effects • **TI1** – Insufficient current first-responder (medical and non-medical) capacity and capability to initially assess, treat, and maintain severe trauma cases in the prehospital environment: - Insufficient tools that enable both non-medical and medical first responders - The technologies do not exist to fulfill some of the needs (e.g., stabilizing the airway or truncal hemorrhage) • **TI14** – Lack the ability to use modern imaging or emerging biomarkers in the diagnosis of TBI • **MHS5** – Inability to objectively and definitively identify or treat TBI (or make return to duty [RTD] determination) in the prehospital environment where there are no visible external indications (across the spectrum from mild, moderate, to severe) • **MHS9** – Lack of capability to objectively and definitively identify and treat TBI/concussion immediately following traumatic event • **RTD1** – Lack of objective assessment tools to determine fitness for duty in the case of sub-acute injury in the prehospital environment • **Maintain Sensory Systems (MSS)2** – Insufficient hearing and vestibular rehabilitation research for: - Regenerative medicine-based approaches - Technologies supporting restoration to Service member-level capabilities - Hearing loss and tinnitus • **MSS3** – Lack of assessment or rehabilitation ability for balance issues • **Maintain Brain Function (MBF)1** – Lack of understanding of TBI (combat and non-combat related):

Requirement Sources	Capability Gaps
	- Reliance upon self-reporting (over self-reporting and under self-reporting are both common) Relationship of the wartime injury (including TBI) and psychiatric morbidity - Neuroplasticity (brain recovery) following traumatic combat-related TBI - Pathobiology and body responses of long-term and acute TBIs - Relationship between TBIs and psychological reactions to combat stress - Insufficient data that ties blast exposure to injury in order to establish correlation - Insufficient full-spectrum treatment options for TBI (e.g., pharmaceuticals, neuro-protectives, etc.) - Reliance upon self-reporting (over self-reporting and under self-reporting are both common) - Lack of coherent strategy for development of improved neurocognitive assessment tool • **MBF2** – Inability to diagnose on the battlefield • **Regenerative Care** – Lack of ability to regenerate or restore certain tissues and/or functions (e.g., large bone, vision, genitourinary (GU), over 40 percent burn patients, upper extremity function, spinal cord, peripheral nerves, brain function) • **Regenerative Care** – Lack of evidence-based understanding and knowledge of benchmarks for regenerative medicine (e.g., relevant animal models, regulatory guidelines, and technology) • **Restorative Care** – Insufficient understanding of the healing process associated with physical injuries to the brain, versus healing process associated with brain's response to other body-wide injuries • **Restorative Care** – Insufficient understanding of the short-term and long-term effects of mTBI on cognitive and behavioral abilities • **Restorative Care** – Lack understanding of long-term data pertaining to functional patient outcomes of initial and long-term mTBI therapies • **Rehabilitative Care (RHBC)1** – Lack the understanding of the short-term and long-term effects of TBI (combat and non-combat related) on individuals: - Relationship between mTBI and posttraumatic stress disorder (PTSD) - Effectiveness of current and emerging mTBI therapies - Effectiveness of current mTBI screening criteria - Objective screening capability to detect and measure suspected mTBI - Co-morbidities associated with TBI - Lack of evidence-based data to indicate effectiveness of current therapies • **RHBC2** – Inadequate sustained neuromusculoskeletal rehabilitation clinical research capabilities at local military treatment facilities (only available at major installations)

Neurotrauma Portfolio Successes

The following five accomplishments were selected to provide a glimpse into the Neurotrauma portfolio and highlight how the coordinated efforts of the portfolio are contributing to capability gap closure for the care of TBI.

Diagnostics for TBI

The first three Neurotrauma portfolio selections feature advances for detection and diagnosis of TBI. The goal of these approaches under evaluation is to identify the unique molecular and biological features of TBI and to then exploit this information to develop objective tools that can determine the presence and severity of injury. Each of the diagnostics highlighted here is based on different biological effects of TBI.

- **Biomarker Assessment for Neurotrauma Diagnosis and Improved Triage System** – TBI diagnostic assays based on blood biomarkers of neuronal and glial damage

- **Eye-Tracking Rapid Attention Computation for Neurological Assessment** – Smooth pursuit eye-tracking goggles that examine the relationship between eye-tracking, attention, and predicitive motor planning networks within the brain to measure attention pathways affected by mTBI

- **Miniature Field Deployable System for Rapid TBI Assessment** – Portable electroencephalography (EEG) device that quantifies and analyzes the brain's electrical activity patterns unique to TBI to aid in the early, rapid, effective, and objective assessment of TBI severity and also determine the need for medical imaging

Pharmacotherapy for TBI

The next portfolio selection is a pharmacotherapy for TBI. Despite a growing body of promising preclinical data, the majority of clinical trials of TBI therapies to date have not resulted in significant improvements in outcomes, and no therapy has yet reached approval by the U.S. Food and Drug Administration (FDA; The CDC, NIH, DoD, and VA Leadership Panel, 2013). However, the benefit of a treatment that could successfully halt or counter the damaging mechanisms occurring secondary to TBI would be remarkable, and this remains an important focus of research. One compound pursued within the Neurotrauma portfolio, NNZ-2566, is currently being evaluated in Phase 2 trials for the treatment of TBI across the spectrum of injury – mild and moderate to severe. The unique use of more than 15 biomarkers and neurocognitive tests to assess functional outcomes in these trials is providing critical data not only on NNZ-2566, but also for continuing to better understand the pathophysiology of TBI.

- **Treatment of TBI with the Neuroprotective Compound NNZ-2566** – Compound that inhibits inflammatory cytokines, pathological microglial activation, apoptosis, and necrosis

Cranial Nerve Non-Invasive Neuromodulation Treatment for TBI

The final selection is a device for the treatment of patients who have chronic neurological symptoms from their TBI. One approach to such treatment is the use of neurostimulation, including indirect stimulation via nerves. The electrical stimulation of cranial nerves sends signals to the brain stem and throughout the brain and central nervous system.

- **Portable Neuromodulation Stimulator for TBI Treatment** – Device that treats TBI-associated vestibular dysfunction and augments the benefits of physical therapy

References

Bellamy, R.F. (1992). The medical effects of conventional weapons. *World Journal of Surgery, 16*(5), 888-892.

Defense and Veterans Brain Injury Center (DVBIC). (2015, January). DoD worldwide numbers for TBI. Retrieved from http://dvbic.dcoe.mil/dod-worldwide-numbers-tbi

Faul, M., Xu, L., Wald, M. M., & Coronado, V. G. (2010). Traumatic brain injury in the United States: Emergency department visits, hospitalizations and deaths 2002-2006. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Retrieved from http://www.cdc.gov/traumaticbraininjury/pdf/blue_book.pdf.

Shear, D. A., & Tortella, F. C. (2013). A military-centered approach to neuroprotection for traumatic brain injury. *Frontiers in Neurology*, *4*, 73.

The Management of Concussion/mTBI Working Group. (2009, April). Management of Concussion/mild traumatic Brain Injury: VA/DoD Evidence Based Practice. Retrieved from http://www.dcoe.mil/Content/navigation/documents/VA%20Dod%20Management%20of%20Concussion%20mild%20Traumatic%20Brain%20Injury%20Summary.pdf

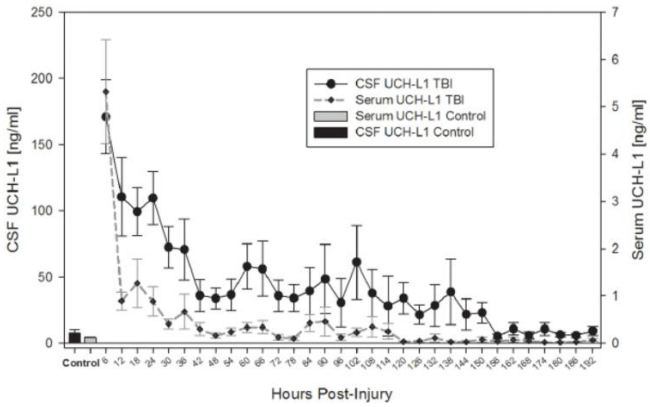
Biomarker Assessment for Neurotrauma Diagnosis and Improved Triage System

The Biomarker Assessment for Neurotrauma Diagnosis and Improved Triage System (BANDITS) program is developing a blood test for brain cell damage that can be used to diagnose mild, moderate, and severe TBI. The program is progressing toward an end goal of validating biomarkers for implementation in a range of diagnostic system configurations appropriate for fast and sensitive assessment of TBI in theater.

- R&D Partner Organization:
  - Banyan Biomarkers, Inc.
- Principal Investigators:
  - Ronald Hayes, Ph.D.
  - Stanislav Svetlov, M.D., Ph.D.
- Banyan Biomarkers has been funded through multiple awards starting in 2003 for their ongoing work on TBI biomarkers

Key Outcomes and Impact:

- Specific, sensitive assays for lead candidates ubiquitin C-terminal hydrolase-LI (UCH-L1) and glial fibrillary acidic protein (GFAP) have been developed
- Clinical studies support ability to identify TBI, differentiate TBI severity, and predict mortality and unfavorable outcomes from GFAP and UCH-L1 serum levels
- ALERT-TBI pivotal clinical study is evaluating correlation of these biomarkers with acute intracranial pathology identified by imaging; results expected in 2015 (NCT01426919)
- BANDITS program has entered device phase for continued development



Temporal Profile of UCH-L1 in Severe TBI Patients (Mondello et al., 2012b)

Overview

Identifying sensitive and specific biomarkers that can be used clinically to assess TBI has long been an urgent need. To date, there are no FDA-approved biomarkers to objectively diagnose or classify TBI, and discerning mTBI form other confounding conditions with similar symptoms, in particular, remains a challenge (Mondello et al., 2011b). The BANDITS program conducted by Banyan Biomarkers, Inc. (Banyan), however, has made significant progress in identifying strong candidate markers and bringing them to clinical trials for validation.

With the support of USAMRMC, Banyan Biomarkers has completed the enrollment of 2,000 patients in the ALERT-TBI pivotal trial. The trial is examining the utility of Banyan's UCH-L1 and GFAP biomarkers for the evaluation of suspected TBI and determination of the need for CT imaging.

The BANDITS program has identified circulating biomarkers that are associated with TBI. They are developing a testing platform to measure these biomarkers that is expected to have a major impact on the diagnosis, management, and prognosis of TBI in combat environments. A small volume of blood is analyzed to determine levels of brain injury-specific biomarkers and the results of this bioassay, combined with a preliminary medical evaluation, could be used to provide a diagnosis of injury severity, determine casualty triage status, and make recommendations for treatment specific to the casualty's condition. The CCCRP's Neurotrauma portfolio has funded Banyan's exploration of biomarkers under the BANDITS program, and the company has developed assays for lead biomarkers that have been demonstrated to be specific and sensitive for TBI. Banyan has conducted many clinical trials examining levels of candidate biomarkers across a range of TBI severities to include a pilot study and feasibility study in severe TBI, and both a pilot study and feasibility study in mild/moderate TBI (Hayes, Wang, & Mondello, 2011). Among the candidate biomarkers evaluated, Ubiquitin C-Terminal Hydrolase-L1 (UCH-L1) and glial fibrillary acidic protein (GFAP) have emerged as key targets in the blood, both of which can be detected in increased quantities shortly after injury (Banyan Biomarkers, Inc., 2015). Most recently, a large pivotal study to support application for FDA approval or clearance of these markers for TBI diagnosis has been conducted with support from USAMRMC. The company has just completed enrollment of 2,000 patients in this pivotal study, titled ALERT-TBI, and expects results in mid-2015 (NCT01426919; Banyan Biomarkers, Inc., 2015; Banyan Biomarkers, Inc., 2014).

With the successful identification of two candidate markers that have provided diagnostic power in initial clinical trials, the BANDITS program has now entered into the device phase for further development of its assays in conjunction with diagnostic instrument hardware. This includes pursuing automated systems available across the roles of care, from an open bench top system to a handheld device (Figure 31).[1]

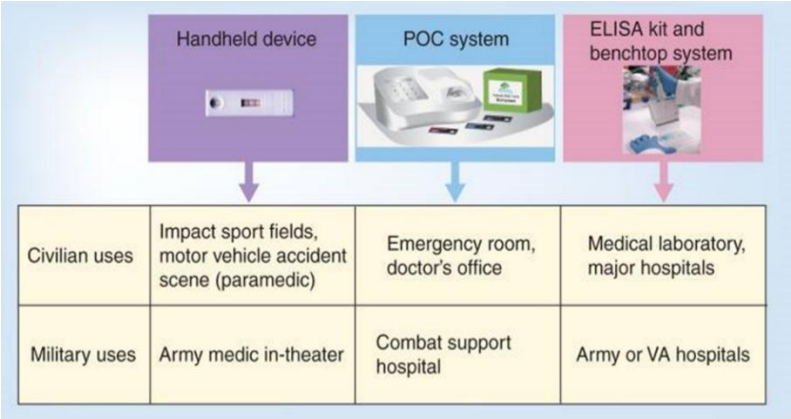


Figure 31. Biomarker Assay Device Options for Different Applications (Mondello et al., 2011b)

[1] The program is also currently referred to within the DoD as the "TBI Diagnostic Assay System," with a planned Increment I benchtop system for use at Role 3 or 4 medical treatment facilities, Increment II being a POC device for use further forward, and Increment III being a handheld device.

The ability to test for biomarkers of TBI in the far forward environment will have a significant impact on diagnosis and treatment of injured service members. Additionally, this BANDITS biomarker technology will have utility in the civilian sector particularly in the trauma care and sports medicine settings.

Capability Gap Alignment

The BANDITS effort is developing biomarkers whose implementation in validated diagnostic assays can ultimately address several capability gaps for diagnosis with respect to TBI (Table 61). The newly developed DHP gaps, in specific, directly highlight the need to implement emerging biomarkers in the diagnosis of TBI.

Table 61. Capability Gaps Addressed by TBI Biomarker Development

Requirement Sources	Capability Gaps Addressed
GDF	• **JCM-1-1 –** Inadequate ability to diagnose, resuscitate, and stabilize casualties with survivable wounds
TC3 ICD	• **Theater Hospitalization, Area Medical Support –** Diagnose, resuscitate, and stabilize casualties with survivable wounds • **First Response Medical Care –** Stabilize injuries, monitor response to treatment
DHP ICD	• **EPA1 –** Insufficient understanding of the effects of a blast event on neurologic tissue to develop immediate therapeutics and mitigation strategies for long-term negative effects • **TI1 –** Insufficient current first-responder (medical and non-medical) capacity and capability to initially assess, treat, and maintain severe trauma cases in the prehospital environment - Insufficient tools that enable both non-medical and medical first responders - The technologies do not exist to fulfill some of the needs (e.g., stabilizing the airway or truncal hemorrhage) • **TI14 –** Lack the ability to use modern imaging or emerging biomarkers in the diagnosis of TBI • **MHS5 –** Inability to objectively and definitively identify or treat TBI (or make RTD determination) in the prehospital environment where there are no visible external indications (across the spectrum from mild, moderate, to severe) • **MHS9 –** Lack of capability to objectively and definitively identify and treat TBI/concussion immediately following traumatic event • **RTD1 –** Lack of objective assessment tools to determine fitness for duty in the case of sub-acute injury in the prehospital environment • **MBF1 –** Lack of understanding of TBI (combat and non-combat related): - Reliance upon self-reporting (over self-reporting and under self-reporting are both common) • **MBF2 –** Inability to diagnose on the battlefield • **RHBC1 –** Lack the understanding of the short-term and long-term effects of TBI (combat and non-combat related) on individuals: - Effectiveness of current mTBI screening criteria - Objective screening capability to detect and measure suspected mTBI

Beyond these defined gaps, the TC3 ICD also specifically outlines ideas for materiel approaches to achieve capability gap closure, which included a combat casualty care roadmap highlighting the need to identify brain trauma biomarkers for diagnostics. Also among the materiel approaches recommended for further analysis under the TC3 process was the general development of minimally invasive or noninvasive instruments for diagnosis and treatment of internal injuries. The development of blood-based biomarkers for TBI under the BANDITS

program has proceeded in alignment with these approaches, and has made great progress with respect to TBI toward the goal states defined by the TC3 ICD.

Impact on the Battlefield/Warfighter

The potential impact of BANDITS biomarkers on the battlefield is significant. In the years preceding 2008, the majority (approximately 57 percent) of U.S. veterans of OIF/OEF who sustained mTBIs are estimated to have gone untreated, in part due to the frequency of closed brain injury occurring secondary to blast, which may not be promptly diagnosed (Tanielian & Jaycox, 2008). Mild and moderate TBI represent the greatest challenge to accurately diagnose, with neurological criteria such as duration of loss of consciousness often used to attempt to infer severity and predict outcome (Mondello et al., 2011b). Neurological examinations such as the Glasgow Coma Scale (GCS) for acute assessment, imaging by CT scans, and more extensive neuropsychological testing over the longer term have been relied on as the key tools for TBI assessment. These measures have limitations in sensitivity, and may not always be readily available in theater. There are no rapid, definitive, blood-based diagnostic tests for TBI. The availability of blood biomarker diagnostics that are indicative of TBI status and that can be easily performed and analyzed not only in hospital environments, but also at lower roles of care in the field during deployment, would provide unprecedented diagnostic capabilities and pave the way for new interventions. The diagnostic tools being developed in the BANDITS program will facilitate injury management, and in doing so may reduce residual disability and long-term care demands (USAMRMC, 2007).

Clinical Practice

Impact on Clinical Practice Guidelines

In general, current approaches to TBI identification and severity determination rely on the use of neurological evaluations such as the GCS, and neuroimaging modalities including CT scan and/or magnetic resonance imaging (MRI; Mondello et al., 2011b). Many experts and working groups have suggested these methods are limiting, and the development of effective biomarkers would be an important improvement to clinical practice (Saatman et al., 2008; Jagoda, 2008). Biomarker assays may replace some current clinical assessments, and can be complementary to current imaging and observational/neuropsychological testing approaches. Data from clinical trials under the BANDITS effort, and the diagnostic devices that are expected to result from this work, have the potential to impact current CPGs and clinical recommendations (CRs) pertaining to TBI management both in the deployed and non-deployed setting.

Existing CPGs and CRs for the diagnosis and management of TBI do not include the use of biomarkers. BANDITS has the potential to changes this, and if so, clinical tools will need modification. Examples of current clinical tools used within the DoD with the potential to be impacted by BANDITS and the other successful advances in development under the Neurotrauma portofolio are provided in Table B-1.

The establishment of biomarkers for TBI through BANDITS could also impact civilian TBI practices. Civilians are treated for brain injuries in emergency rooms each year at a rate of 715.7 per 100,000 in the U.S. population (CDC, 2014). As with military populations, diagnosis and assessment of the severity of these individuals' injuries through biomarkers may help to ensure that they receive palliative care for symptoms where indicated, are counseled appropriately on

decisions about returning to activities, and receive rehabilitative care when necessary. Ultimately, it is hoped that biomarker-based assays will also guide administration of therapeutics when approved pharmacologic or biologic treatments for TBI become available. The CDC and American College of Emergency Physicians have developed clinical policy on neuroimaging and decision making for adult mTBI in the acute setting (Jagoda et al., 2008). Currently, this policy advises that serum biomarkers for assessing acute traumatic intracranial injury are not yet an FDA-approved clinical diagnostic. The policy grades the use of one candidate biomarker – S100 calcium-binding protein B – as a Level C recommendation (e.g., characterized as a strategy for patient management based on preliminary, inconclusive, or conflicting evidence, or in the absence of any published literature, based on panel consensus). Advancement and approval of BANDITS biomarkers UCH-L1 and GFAP would enable a new recommendation of biomarker use to be made for these markers at a stronger level.

Supporting Publications

Numerous clinical studies under the BANDITS program have been published to date that provide support for the continued development of the blood-based biomarker approach, and that may contribute to the body of evidence for future changes in CPGs if BANDITS diagnostic assays achieve regulatory clearance and are implemented (Table 62). These clinical studies have measured the levels of BANDITS biomarkers in serum and cerebrospinal fluid (CSF) at various times after injury in multiple civilian cohorts, and have provided support for the ability of levels of GFAP and UCH-L1 in serum to distinguish between the presence and absence of TBI, differentiate TBI severity, and predict mortality and unfavorable outcomes.

Table 62. Supporting Publications for BANDITS TBI Biomarkers

Reference	Description
Pineda et al., 2007	Examined the relationship of levels of alpha II-spectrin breakdown products (SBDP) in CSF) to severity of injury and clinical outcome in individuals with TBI
Papa et al., 2010	Compared CSF levels of UCH-L1 from adult patients with severe TBI to uninjured controls; overall mean levels of UCH-LI were significantly greater in TBI patients than controls. Amongst patients, UCH-L1 levels were significantly elevated in groups with lower GCS scores at 24 hours, post-injury complications, or 6-week mortality
Brophy et al., 2011	Examined UCH-L1 in serum and CSF of individuals with severe TBI. There was a significant correlation of UCH-L1 levels with mortality at 3 months
Mondello et al., 2011a	Examined relationships of UCH-L1 and GFAP levels in serum to neuroradiological findings and outcomes after severe TBI. Levels correlated significantly with GCS and CT findings, and predicted survival at 6 months
Berger, Hayes, Richichi, Beers, & Wang, 2012	Examined levels of UCH-L1 and SBDP-145 in serum of children with mild, moderate, and severe TBI, and the abilities of these markers to predict outcome. Levels of both markers were significantly elevated in children with moderate and severe TBI over controls, and correlated with Glasgow Outcome Scale measures
Czeiter et al., 2012	Determined that measures of GFAP, UCH-L1, and SBDP could improve outcome prediction for a cohort of patients with severe TBI when combined with the International Mission for Prognosis and Analysis of Clinical Trials in TBI prognostic calculator
Mondello et al., 2012a	Examined levels of UCH-L1 in CSF and serum of individuals with severe TBI. Levels correlated with injury severity and survival outcome
Mondello et al., 2012b	Evaluated the correlation of ratios of UCH-L1 and GFAP with differing intracranial pathologies after brain trauma; the ratio of these two markers of neuronal and glial damage provided information that may help to identify differential pathophysiological mechanisms after trauma, with therapeutic implications

Reference	Description
Papa et al., 2012a and Papa et al., 2012b	Related studies examined serum levels of GFAP and UCH-L1 in patients with mild and moderate TBI compared to controls, and assessed the association of these markers with positive CT and need for neurosurgical intervention. GFAP and UCH-L1 levels could be used to differentiate between mild and moderate TBI and were significantly higher in TBI patients who received neurosurgical interventions than those who did not

Role of CCCRP-Sponsored Projects

The CCCRP's Neurotrauma portfolio has included funding a full range of activities for the identification and development of biomarkers for TBI through several projects (Table 63). These projects have been critical to characterizing the pathophysiology of TBI in models relevant to blast injury, identifying biomarkers with diagnostic power, and rigorously evaluating lead biomarkers in clinical studies. USAMRMC's support has enabled the large pivotal ALERT-TBI trial of the lead candidates UCH-L1 and GFAP to be conducted, the data from which is expected to provide key support for regulatory review of these biomarkers for TBI diagnostic applications.

Table 63. CCCRP-Sponsored Projects for BANDITS TBI Biomarkers

Project Title (Award Number)	Organization/Principal Investigator	Funding
Biochemical Markers of Brain Injury: An Integrated Proteomics-Based Approach (DAMD17-03-1-0066, W81XWH-07-2-0075, W81XWH-10-C-0251, PR064667,W81XWH-06-1-0517)	Ronald Hayes, Ph.D. (Banyan)	$3,687,522 (2003–2011)
BANDITS with Modification-Assessment of Biomarkers of Concussion and Acute TBI (W81XWH-06-1-0517, W81XWH-07-2-0075, W81XWH-10-C-0251)	Ronald Hayes, Ph.D. (Banyan)	$30,220,934 (2006–2011)
Pathological Fingerprints, Systems Biology, and Biomarkers of Blast Brain Injury (W81XWH-08-1-0376)	Stanislav Svetlov, M.D., Ph.D. (Banyan)	$386,306 (2008–2011)
Molecular Signatures and Diagnostic Biomarkers of Cumulative, Blast-Graded Mild TBI (W81XWH-10-1-0876)	Stanislav Svetlov, M.D., Ph.D. (Banyan)	$938,567 (2010–2014)
Analysis of Biomarkers of TBI in Warfighters Returning from Combat Duty (W23RYXI0484001, W81XWH-11-2-0162)	Ronald Hayes, Ph.D. (Banyan)	$250,000 (2011–2014)

From these activities, both preclinical and clinical, a range of peer-reviewed research publications has directly resulted. These include the ten clinical publications introduced above (Table 62), as well as many additional publications from preclinical studies, including those described in Table 64. Together, this sponsored body of work has advanced the study of biomarkers for TBI, enabling the continued clinical testing and validation of the two strong candidates that have emerged.

Table 64. CCCRP-Sponsored Publications for BANDITS TBI Biomarkers

Reference	Description
Research in Rat Models of TBI	
Ringger et al., 2004	Examined the relationship of cranial and CSF levels of SBDP with injury magnitude and outcome measures in a rat model of TBI, identifying SBDP as a novel marker for TBI

Reference	Description
Larner, McKinsey, Hayes, & Wang, 2005	Characterized up-regulation of caspase 7 in the brain following TBI in a rat model, indicating caspase 7 may contribute to neuronal cell death
Liu et al., 2006a	Evaluated enzyme-mediated degradation patterns of multiple proteolytic substrates in the brain following TBI in a rat model
Liu et al., 2006b	Examined axonal injury in a rat model of TBI, and characterized resulting degradation products of myelin basic protein (MBP)
Ottens et al., 2008	Characterized the proteolytic processing of MBP in a rat model of TBI, and verified the presence of cleaved MBP in CSF
Liu et al., 2010	Determined UCH-LI levels in serum and CSF were significantly elevated after TBI in a rat model
Svetlov et al., 2010	Examined GFAP and UCH-L1 in brain, CSF, and blood in a rat model of peak overpressure blast exposure, identifying varying temporal patterns of these markers of glial and neural injury
Glushakova et al., 2012	Investigated the relationship of CSF concentrations of UCH-L1, GFAP, SBDP150, SBDP145, and SBDP120, to neuropathology in a rat model of excitotoxicity. Levels of these markers significantly increased in the CSF after excitotoxic treatment correlating with neurodegeneration in the brain
Svetlov et al., 2012	Characterized the pathology of primary peak overpressure blast injury and blast accompanied by strong head acceleration (composite blast) in rat models, including changes in serum markers
Zoltewicz et al., 2013	Examined SBDP150, GFAP and UCH-L1 levels in plasma, CSF, and cortex in a rat model of penetrating brain injury. The markers had different temporal patterns after injury across the varying sample matrices, but were determined to be effective indicators of brain damage
Advanced Protein Methods for Biomarker Identification and Assay Development	
Haskins et al., 2005	Reported the rapid discovery of putative protein biomarkers of TBI by proteomic methods
Ottens et al., 2005	Developed a multidimensional proteomic platform for resolving and differentially analyzing complex biological samples
Kobeissy et al., 2006	Used proteomic methods to discover protein changes induced in the brain by TBI in a rat model. Results included 59 differentially expressed proteins, of which 21 decreased and 38 increased after TBI
Yao et al., 2008	Used high-throughput immunoblotting techniques to compare changes in brain and blood protein levels between animal models of acute brain injury; protein profiles after injury were distinct for penetrating injury compared to transient middle cerebral artery occlusion
Zoltewicz et al., 2012	Characterized antibody reagents for GFAP detection from CSF and blood. The antibodies non-preferentially detected both intact GFAP and GFAP breakdown products

References

Banyan Biomarkers, Inc. (2014, August 28). Banyan Biomarkers, Inc. Licenses Protein Markers to Help Evaluate Traumatic Brain Injury. Retrieved from http://www.enhancedonlinenews.com/news/eon/20140828005661/en

Banyan Biomarkers, Inc. (2014, June 24). Company Fact Sheet. Retrieved from http://www.banyanbio.com/wp-content/uploads/banyanonepager_20142406.pdf

Banyan Biomarkers, Inc. (2015). Evaluation of Biomarkers of Traumatic Brain Injury (ALERT-TBI). Retrieved from https://clinicaltrials.gov/show/NCT01426919 (Identification No. NCT01426919)

Berger, R. P., Hayes, R. L., Richichi, R., Beers, S., & Wang, K. K. W. (2012). Serum concentrations of ubiquitin C-terminal hydrolase-L1 and αII-spectrin breakdown product 145kDa correlate with outcome after pediatric TBI. *Journal of Neurotrauma*, 29(1), 162-167.

Brophy, G. M., Mondello, S., Papa, L., Robicsek, S. A., Gabrielli, A., Tepas III, J., … Wang, K. K. (2011). Biokinetic analysis of ubiquitin C-terminal hydrolase-L1 (UCH-L1) in severe traumatic brain injury patient biofluids. *Journal of Neurotrauma*, 28(6), 861-870.

Czeiter, E., Mondello, S., Kovacs, N., Sandor, J., Gabrielli, A., Schmid, K., … Buki, A. (2012). Brain injury biomarkers may improve the predictive power of the IMPACT outcome calculator. *Journal of Neurotrauma*, 29(6), 1770-1778.

Faul, M., Xu, L., Wald, M. M., & Coronado, V. G. (2010). Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002-2006. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Retrieved from http://www.cdc.gov/traumaticbraininjury/pdf/blue_book.pdf

Glushakova, O., Jeromin, A., Martinez, J., Johnson, D., Denslow, N. D., Streeter, J., … Mondello, S. (2012). CSF protein biomarker panel for assessment of neurotoxicity induced by kainic acid in rats. *Toxicological Sciences, 130*(1), 158-167.

Haskins, W. E., Kobeissy, F. H., Wolper, R. A., Ottens, A. K., Kitlen, J. W., McClung, S. H., … Wang, K. K. (2005). Rapid discovery of putative protein biomarkers of traumatic brain injury by SDS-PAGE-capillary liquid chromatography-tandem mass spectrometry. *Journal of Neurotrauma, 22*(6), 629-644.

Hayes, R., Wang, K., & Mondello, S. (2011, February). Development of Novel Biomarkers of TBI: from Bench to Bedside to FDA Approval. Presentation at the Santa Clara Valley Brain Injury Conference. Retrieved from http://www.tbi-sci.org/conference/pdf/DevelopmentofNovelBiomarkersofTraumaticBrainInjuryFromBenchtoBedsidetoFDAApproval.pdf

Initial Capabilities Document for Theater Combat Casualty Care. (2006, December 14).

Jagoda, A. S., Bazarian, J. J., Bruns, J. J., Cantrill, S. V., Gean, A. D., Howard, P. K., … Centers for Disease Control and Prevention. (2008). Clinical policy: neuroimaging and decision

making in adult mild traumatic brain injury in the acute setting. *Annals Emergency Medicine, 52*(6), 714-748.

Joint Trauma System (JTS). (2014, December). JTS & CCAT Clinical Practice Guidelines. Retrieved from http://www.usaisr.amedd.army.mil/clinical_practice_guidelines.html

Kobeissy, F. H., Ottens, A. K., Zhang, Z., Liu, M. C., Denslow, N. D., Dave, J. R., … Wang, K. K. (2006). Novel differential neuroproteomics analysis of traumatic brain injury in rats. *Molecular & Cellular Proteomics, 5*(10), 1887-1898.

Larner, S. F., McKinsey, D. M., Hayes, R. L., & Wang, K. K. W. (2005). Caspase 7: Increased expression and activation after traumatic brain injury in rats. *Journal of Neurochemistry, 94*(1), 97-108.

Liu, M., Akle, V., Zheng, W., Dave, J., Tortella, F., Hayes, R., & Wang, K. (2006a). Comparing calpain-and caspase-3-mediated degradation patterns in traumatic brain injury by differential proteome analysis. *The Biochemical Journal, 394*, 715-725.

Liu, M. C., Akle, V., Zheng, W., Kitlen, J., O'Steen, B., Larner, S. F., … Wang, K. K. (2006b). Extensive degradation of myelin basic protein isoforms by calpain following traumatic brain injury. *Journal of Neurochemistry, 98*(3), 700-712.

Liu, M. C., Akinyi, L., Scharf, D., Mo, J., Larner, S. F., Muller, U., … Wang, K. K. (2010). Ubiquitin C-terminal hydrolase-L1 as a biomarker for ischemic and traumatic brain injury in rats. *European Journal of Neuroscience, 31*(4), 722-732.

Mondello, S., Akinyi, L., Buki, A., Robicsek, S., Gabrielli, A., Tepas, J., … Wang, K. K. (2012a). Clinical utility of serum levels of ubiquitin C-terminal hydrolase as a biomarker for severe traumatic brain injury. *Neurosurgery, 70*(3), 666-675.

Mondello, S., Jeromin, A., Buki, A., Bullock, R., Czeiter, E., Kovacs, N., … Hayes, R. L. (2012b). Glial neuronal ratio: a novel index for differentiating injury type in patients with severe traumatic brain injury. *Journal of Neurotrauma, 29*(6), 1096-1104.

Mondello, S., Muller, U., Jeromin, A., Streeter, J., Hayes, R. L., & Wang, K. K. W. (2011b). Blood-based Diagnostics of Traumatic Brain Injuries. *Expert Review of Molecular Diagnostics, 11*(1), 65-78.

Mondello, S., Papa, L., Buki, A., Bullock, M. R., Czeiter, E., Tortella, F. C., … Hayes, R. L. (2011a). Neuronal and glial markers are differently associated with computed tomography findings and outcome in patients with severe traumatic brain injury: A case control study. *Critical Care, 15*(3), R156.

Mondello, S., Robiscek, S. A., Gabrielli, A., Brophy, G. M., Papa, L., Tepas, L., … Hayes, R. L. (2010). aII-Spectrin breakdown products (SBDPs): Diagnosis and outcome in severe traumatic brain injury patients. *Journal of Neurotrauma, 27*(7), 1203–1213.

Ottens, A. K., Kobeissy, F. H., Wolper, R. A., Haskins, W. E., Hayes, R. L., Denslow, N. D., & Wang, K. K. (2005). A multidimensional differential proteomic platform using dual-

phase ion-exchange chromatography-polyacrylamide gel electrophoresis/reversed-phase liquid chromatography tandem mass spectrometry. *Analytical Chemistry*, 77(15), 4836-4845.

Ottens, A. K., Golden, E. C., Bustamante, L., Hayes, R. L., Denslow, N. D., & Wang, K. K. (2008). Proteolysis of multiple myelin basic protein isoforms after neurotrauma: characterization by mass spectrometry. *Journal of Neurochemistry, 104*(5), 1404-1414.

Papa, L., Akinyi, L., Liu, M. C., Pineda, J. A., Tepas, J. J., Oli, M. W., … Wang, K. K. (2010). Ubiquitin C-terminal hydrolase is a novel biomarker in humans for severe traumatic brain injury. *Critical Care Medicine, 38*(1), 138-144.

Papa, L., Lewis, L. M., Falk, J. L., Zhang, Z., Silvestri, S., Giordano, P., … Wang, K. K. (2012a). Elevated levels of serum glial fibrillary acidic protein breakdown products in mild and moderate traumatic brain injury are associated with intracranial lesions and neurosurgical intervention. *Annals of Emergency Medicine, 59*(6), 471-483.

Papa, L., Lewis, L. M., Silvestri, S., Falk, J. L., Giordano, P., Brophy, G. M., … Wang, K. K. (2012b). Serum levels of ubiquitin C-terminal hydrolase distinguish mild traumatic brain injury from trauma controls and are elevated in mild and moderate traumatic brain injury patients with intracranial lesions and neurosurgical intervention. *Journal of Trauma and Acute Care Surgery, 72*(5), 1335-1344.

Pineda, J. A., Lewis, S. B., Valadka, A. B., Papa, L., Hannay, H. J., Heaton, S. C., … Hayes, R. L. (2007). Clinical significance of α ii-spectrin breakdown products in cerebrospinal fluid after severe traumatic brain injury. *Journal of Neurotrauma, 24*(2), 354-366.

Ringger, N. C., O'Steen, B. E., Brabham, J. G., Silver, X., Pineda, J., Wang, K., … Papa, L. (2004). A novel marker for traumatic brain injury: CSF αII-spectrin breakdown product levels. *Journal of Neurotrauma, 21*(10), 1443-1456.

Saatman, K. E., Duhaime, A. C., Bullock, R., Maas, A., Valadka, A., Manley, G. T., & Workshop Scientific Team and Advisory Panel Members. (2008). Classification of traumatic brain injury for targeted therapies. *Journal of Neurotrauma, 25*(7), 719-738.

Svetlov, S. I., Prima, V., Glushakova, O., Svetlov, A., Kirk, D. R., Gutierrez, H., … Hayes, R. L. (2012). Neuro-glial and systemic mechanisms of pathological responses in rat models of primary blast overpressure compared to "composite" blast. *Frontiers in Neurology, 3*(15), DOI: 10.3389/fneur.2012.00015.

Svetlov, S. I., Prima, V., Kirk, D. R., Gutierrez, H., Curley, K. C., Hayes, R. L., & Wang, K. K. (2010). Morphologic and biochemical characterization of brain injury in a model of controlled blast overpressure impact. *Journal of Trauma, 69*(4), 795-804.

Tanielian, T. & Jaycox, L.H., eds. (2008). Invisible wounds of war: psychological and cognitive injuries, their consequences, and services to assist recovery, Santa Monica, Calif.: RAND Corporation, MG-720-CCF. Retrieved from http://www.rand.org/pubs/monographs/MG720.html

The CDC, NIH, DoD, and VA Leadership Panel. (2013). Report to congress on traumatic brain injury in the United States: Understanding the public health problem among current and former military personnel. Retrieved from http://www.nashia.org/pdf/report-to-congress-on-traumatic-brain-injury-2013-a.pdf

The Management of Concussion/mTBI Working Group. (2009, April). Management of Concussion/mild traumatic Brain Injury: VA/DoD Evidence Based Practice. Retrieved from http://www.dcoe.mil/Content/navigation/documents/VA%20Dod%20Management%20of%20Concussion%20mild%20Traumatic%20Brain%20Injury%20Summary.pdf

U.S. Army Medical Research and Materiel Command (USAMRMC). (2007). USAMRMC products portfolio. Fort Detrick, MD. Retrieved from http://mrmc.amedd.army.mil/assets/docs/about/Products_Portfolio_11.pdf

U.S. Centers for Disease Control and Prevention (CDC). (2014, February 24). Rates of TBI-related Emergency Department Visits, Hospitalizations, and Deaths — United States, 2001–2010. Retrieved from http://www.cdc.gov/traumaticbraininjury/data/rates.html

Yao, C., Williams, A. J., Ottens, A., Lu, X.-C., Chen, R., Wang, K. K., … Dave, J. R. (2008). Detection of protein biomarkers using high-throughput immunoblotting following focal ischemic or penetrating ballistic-like brain injuries in rats. *Brain Injury*, *22*(10), 723-732.

Zoltewicz, J. S., Mondello, S., Yang, B., Newsom, K. J., Kobeissy, F., Yao, C., … Tortella, F. C. (2013). Biomarkers track damage after graded injury severity in a rat model of penetrating brain injury. *Journal of Neurotrauma*, *30*, 1161-1169.

Zolltewicz, J. S., Scharf, D., Yang, B., Chawla, A., Newsom, K. J., & Fang, L. (2012). Characterization of antibodies that detect human GFAP after traumatic brain injury. *Biomarker Insights*, *7*, 71-79.

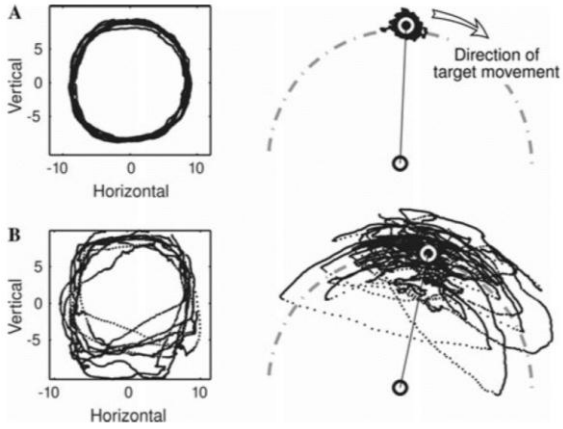
Eye-Tracking Rapid Attention Computation for Neurological Assessment

The Brain Trauma Foundation has developed an eye-tracking approach that may be used to screen for mTBI within minutes in the field.

- R&D Partner Organization:
  - Brain Trauma Foundation
- Principal Investigator:
  - Jamshid Ghajar, M.D., Ph.D.
- The Eye-TRAC program has been funded through multiple awards from 2008 to the present

Key Outcomes and Impact:

- Irregularities in eye movement during tasks of attention distinguish individuals with mTBI from healthy controls
- Eye-Tracking Rapid Attention Computation (Eye-TRAC) combines eye-tracking goggle hardware with analytical software to enable screening
- Performance correlates with neuroimaging and neurocognitive test findings
- Currently undergoing validation in a large trial of athletes, military personnel, and civilians with and without mTBI (Eye-TRAC Advance)
- May provide a simple, fast screening method to aid in determination of an individual's fitness for military duty



Visual Tracking by (A) A Control Subject and (B) A Subject with Chronic Postconcussive Symptoms (Maruta et al., 2010a)

Overview

In an effort to ensure that injured warfighters who have sustained an mTBI are provided expeditious and appropriate care, the DoD has investigated several categories of noninvasive devices that have the potential to rapidly screen for mTBI based on neurological assessment, including eye-tracking devices. People who sustain a concussion often have behavioral and cognitive disabilities that are difficult to detect. Characteristics such as accurate predictive timing in eye tracking, one measure of how well someone pays attention, can provide insight into such disabilities. The Brain Trauma Foundation has sought to better understand eye-tracking brain function in military and athlete populations to help assess those who are affected by concussion. They have developed eye-tracking goggles and identified sensitive tests to understand the relationship between eye tracking and cognitive domains such as processing speed, reaction time, attention, and predictive timing (Brain Trauma Foundation, 2014). This system of the eye-tracking goggle hardware along with analytical processing software and research-backed algorithms for diagnosis is known as Eye-Tracking Rapid Attention Computation (Eye-TRAC) and was designed to be used by service members in theater to instantly determine if they have sustained cognitive or attention deficits indicative of mTBI.

Eye-TRAC has been developed by the Brain Trauma Foundation in partnership with SyncThink Inc., using SyncThink's EYE-SYNC goggle technology (Figure 32; SyncThink Inc., 2014). Many characteristics and features of Eye-TRAC hardware have been optimized for military field use, including its portability, durability, capability to store information, and ability to operate by battery up to several weeks before requiring electrical recharging.

Figure 32. Goggles in use during Testing (Brain Trauma Foundation, 2014)

The Eye-TRAC is currently in a large DoD-funded study that is referred to as the Eye-TRAC Advance (ETA) study. The diagnostic capabilities of the system are being evaluated for selectivity, reliability, sensitivity, and validity in individuals of varying ages (with and without mTBI) and in military personnel who have undergone 26 hours of sleep deprivation to determine differentiation of indicators of mTBI from exhaustion (Brain Trauma Foundation, 2014). If the validity of Eye-TRAC screening continues to bear out in this study, it is hoped that in the future the portable eye-tracking goggles will be implemented far forward in military operations, and find their way to the sideline of sporting fields across the U.S.

Capability Gap Alignment

Validation and adoption of Eye-TRAC for noninvasive mTBI screening could address aspects of several capability gaps (Table 65). The technology provides a new approach for objective screening for mTBI, the need for which is highlighted specifically in several DHP ICD capability gaps.

Table 65. Capability Gaps Addressed by Noninvasive Neurological Assessment of TBI through Eye Tracking

Requirement Sources	Capability Gaps Addressed
GDF	• **JCM-1-1** – Inadequate ability to diagnose, resuscitate, and stabilize casualties with survivable wounds
TC3 ICD	• **Theater Hospitalization, Area Medical Support** – Diagnose, resuscitate, and stabilize casualties with survivable wounds • **First Response Medical Care** – Stabilize injuries, monitor response to treatment
DHP ICD	• **EPA1** – Insufficient understanding of the effects of a blast event on neurologic tissue to develop immediate therapeutics and mitigation strategies for long-term negative effects • **TI1** – Insufficient current first-responder (medical and non-medical) capacity and capability to initially assess, treat, and maintain severe trauma cases in the prehospital environment: - Insufficient tools that enable both non-medical and medical first responders - The technologies do not exist to fulfill some of the needs (e.g., stabilizing the airway or truncal hemorrhage) • **TI14** – Lack the ability to use modern imaging or emerging biomarkers in the diagnosis of TBI • **MHS5** – Inability to objectively and definitively identify or treat TBI (or make RTD determination) in the prehospital environment where there are no visible external indications (across the spectrum from mild, moderate, to severe) • **MHS9** – Lack of capability to objectively and definitively identify and treat TBI/concussion immediately following traumatic event • **RTD1** – Lack of objective assessment tools to determine fitness for duty in the case of sub-acute injury in the prehospital environment

Requirement Sources	Capability Gaps Addressed
	• **MBF1** – Lack of understanding of TBI (combat and non-combat related): - Reliance upon self-reporting (over self-reporting and under self-reporting are both common) • **MBF2** – Inability to diagnose on the battlefield • **RHBC1** – Lack the understanding of the short-term and long-term effects of TBI (combat and non-combat related) on individuals: - Effectiveness of current mTBI screening criteria - Objective screening capability to detect and measure suspected mTBI

Impact on the Battlefield/Warfighter

The Eye-TRAC has not yet reached the battlefield, but it is being evaluated in large-scale trials, and shows promise for enabling mTBI screening in combat environments. The Eye-TRAC may facilitate rapid identification of service members with injury-related complications that could have not only persistent health consequences, but also an immediate negative impact on unit performance. The Eye-TRAC can measure millisecond eye-target synchronization in predictable smooth pursuit eye movements during trials of less than 30 seconds; assessment protocols of less than 5 minutes have been used in clinical studies (Maruta, Lee, Jacobs, & Ghajar, 2010a). This rapid assessment could be key for quick decision making with respect to triage or return to duty in times when demands are high and resources are limited. Unlike more severe TBI, not all mTBI patients display acute signs and symptoms that are easily recognizable, even by trained medical staff. Rapid simple-to-use tools for the assessment of mTBI will help to ensure warfighters receive the care they need. Quantitative measures of predictive timing, such as the visual tracking measured by Eye-TRAC, may be a useful adjunct to guide the assessment of dysfunctions of attention and to determine if the service member needs medical attention (Maruta et al., 2010a).

The Eye-TRAC can measure millisecond eye-target synchronization in predictable smooth pursuit eye movements during trials of less than 30 seconds; assessment protocols of less than 5 minutes have been used in clinical studies.

Clinical Practice

Impact on Clinical Practice Guidelines

As with other injuries, early identification and treatment of mTBI, including understanding injury severity, is critical for positive patient outcomes. Subjective patient self-report is the leading method of diagnosing mTBI (Maruta et al., 2010a). Most neurocognitive tests of mTBI assessment rely on measures that lack specificity, making it difficult to disentangle the different effects of brain injury on various cognitive functions. In particular, there currently exist few methods for the accurate measurement of deficits in sustained attention (Contreras et al., 2008).

New capabilities using more objective and sensitive physical measures such as predictive visual tracking will affect how mTBI is initially evaluated. The data that will result from the large-scale ETA study will have the potential to alter current CRs or CPGs pertaining to the assessment, triage, and diagnosis of mTBI in deployed settings if the Eye-TRAC device can be implemented (Table B-1).

Supporting Publications

Several published clinical studies may contribute support for future adoption of the technology and integration clinical practice guidance (Table 66). Across these studies, predictive visual tracking has shown promise as an attention metric to identify mTBI. Deficits in visual tracking performance can be distinguished in individuals who have experienced mTBI relative to controls, and these deficits have been shown to correlate with neuroimaging findings (Maruta et al., 2010a).

Table 66. Supporting Publications for Eye-TRAC Clinical Evaluation

Reference	Description
Maruta, Suh, Niogi, Mukherjee, & Ghajar, 2010b	Examined eye movement in subjects with chronic postconcussive syndrome and evaluated the correlation of errors in gaze with neuroimaging and neurocognitive testing measures; gaze error was significantly correlated with mean fractional anisotropy parameters in white matter tracts frequently damaged in mTBI and with attention and working memory measures in neurocognitive testing
Maruta et al., 2012	Examined visual tracking in individuals within 2 weeks of mTBI, and compared synchronization between gaze and target during tracking with that of control subjects. Subjects with mTBI had worse visual tracking performance than 95 percent of normal subjects
Maruta, Heaton, Kryskow, Maule, & Ghajar, 2013	Studied circular visual tracking in healthy, young adults, and established test-retest reliability of visual-tracking measures. Instances of extremely poor performance were identifiable outside the margin of error determined by test-retest measures, suggesting the approach may provide useful discriminatory power for assessment
Maruta et al., 2014	Tested whether reduced cognitive function associated with mTBI and sleep deprivation can be detected and distinguished using indices of predictive visual tracking. Subjects with mTBI subjects performed significantly worse in visual tracking tasks than sleep-deprived subjects

Beyond these publications, results of the large-scale ETA trial currently underway that has targeted enrollment of over 5,000 athletes, 5,000 military participants, and several hundred civilian participants, will be key to bringing Eye-TRAC to the battlefield to achieve its potential (Brain Trauma Foundation, 2014).

Role of CCCRP-Sponsored Projects

Key projects for the development and clinical evaluation of Eye-TRAC for head injury screening applications have been sponsored by the Neurotrauma portfolio (Table 67). Among these, support of the ETA trial is now critical to the ongoing rigorous validation of the device.

These efforts together have supported all of the peer-reviewed publications of clinical research introduced above in Table 66, which have yielded important results toward to the clinical validation of Eye-TRAC. These publications have demonstrated the impact of mTBI on visual attention during eye-tracking tasks and the potential of this approach to discriminate mTBI from the confounding condition of sleep deprivation.

Table 67. CCCRP-Sponsored Projects for Eye-TRAC

Project Title (Award Number)	Organization/ Principal Investigator	Funding
Differentiating the Severity of Mild and moderate TBI using High Temporal Resolution Attention Metrics and MRI-Diffusion Tensor Imaging (W81XWH-08-2-0177)	Jamshid Ghajar, M.D., Ph.D. (Brain Trauma Foundation)	$199,651 (2008–2009)
Eye-Tracking Rapid Attention Computation (PT075553)	Jamshid Ghajar, M.D., Ph.D. (Brain Trauma Foundation)	$5,146,688 (2008–2014)
Eye-TRAC Advanced (formerly referred to as Eye-TRAC Application) (ERMS 11034006)	Jamshid Ghajar, M.D., Ph.D. (Brain Trauma Foundation)	$10,461,697

References

Brain Trauma Foundation. (2014). EYE-TRAC advance. Retrieved from https://www.braintrauma.org/eta

Coldren, R.L., Kelly, M.P., Parish, R.V., Dretsch, M., & Russell, M.L. (2010). Evaluation of the Military Acute Concussion Evaluation (MACE) for use in combat operation more than 12 hours after injury. *Military Medicine 175*, 477-481.

Contreras, R., Kolster, R., Voss, H. U., Gahar, J., Suh, M., & Bahara, S. (2008). Eye–target synchronization in mild traumatic brain-injured patients. *Journal of Biological Physics, 34*(3-4), 381-392.

Joint Trauma System (JTS). (2014, December). JTS & CCAT clinical practice guidelines. Retrieved from http://www.usaisr.amedd.army.mil/clinical_practice_guidelines.html

Maruta, J., Lee, S. W., Jacobs, E. F., & Ghajar, J. (2010a). A unified science of concussion. *Annals of the New York Academy of Sciences, 1208*(1), 58-66.

Maruta, J., Suh, M., Niogi, S. N., Mukherjee, P., & Ghajar, J. (2010b). Visual tracking synchronization as a metric for concussion screening. *The Journal of Head Trauma Rehabilitation, 25*(4), 293-305.

Maruta, J., Tong, J., Lee, S. W., Iqbal, Z., Schonberger, A., & Ghajar, J. (2012). EYE-TRAC: Monitoring attention and utility for mTBI. In Proceedings of SPIE: Military Medicine I, 8371, 83710L-1.

Maruta, J., Heaton, K. J., Kryskow, E. M., Maule, A. L., & Ghajar, J. (2013). Dynamic visuomotor synchronization: Quantification of predictive timing. *Behavior Research Methods, 45*(1), 289-300.

Maruta, J., Heaton, K., J., Maule, A. L., & Ghajar, J. (2014). Predictive visual tracking: Specificity in mild traumatic brain injury and sleep deprivation. *Military Medicine, 179*(6), 619-625.

Scherer, M. R., Claro, P. J., & Heaton, K. J. (2013). Sleep deprivation has no effect on dynamic visual acuity in military service members who are healthy. *Physical Therapy, 93*(9), 1185-1196.

SyncThink Inc. (2014). Our Device. Retrieved from http://www.syncthink.com/our-device

Miniature Field Deployable System for Rapid TBI Assessment

BrainScope's Ahead device is a portable screening tool that uses EEG to rapidly assess injury severity in patients who have suffered a TBI.

- R&D Partner Organization:
  - BrainScope Company, Inc.
- Principal Investigators:
  - Doug Oberly
  - William Koppes

Key Outcomes and Impact:

- Quantitative EEG algorithm has been developed to assist in determining whether a patient is likely to have a CT-positive brain injury, aiding the decision for further clinical action
- The first generation Ahead M-100 device employing this algorithm received FDA clearance in November 2014 (DEN140025)
- Further miniaturization and ruggedization is underway to achieve a robust device that can be deployed for portable prehospital EEG assessment in theater
- Future clinical trials in hospital emergency departments and with university sports programs are planned to continue to evaluate the use of the technology and refine the algorithm for assessment of TBI

Ahead M-100 Handheld Device (Hack, 2011)

Overview

Rapid assessment of a patient following a head injury is critical in clinical outcomes; however, a lack of capabilities for fast, objective evaluation of the brain outside of the hospital environment to detect potential structural injuries and aid in clinical decision making can slow or prevent clinical intervention. BrainScope's miniature field-deployable system for rapid mTBI assessment, known as the Ahead, is a small handheld device for TBI triage in the far forward environment. The first generation Ahead M-100 device has been fully developed and is aimed at providing an easy-to-use, noninvasive, POC tool that can augment an initial assessment of brain function (BrainScope, 2015).

The Ahead M-100 device obtains high-quality EEG to provide an interpretation of the structural condition of a patient's brain following a TBI within 24 hour of injury. The device is not intended for use as a standalone assessment for TBI, but rather as an adjunct to aid in the evaluation of patients being considered for CT scan. In November 2014, the Ahead M-100 device received FDA clearance for adjunctive assessment of TBI through the *de novo* process (*de novo* Number DEN140025; BrainScope Ahead 100, 2014). This clearance was achieved with a marketing application supported by data from the DoD-funded B-AHEAD II clinical trial, which assessed head injury in emergency departments using the Ahead M-100 device (NCT01556711). BrainScope is continuing R&D of the system to adapt with evolving technology, creating a second generation of

Figure 33. Adaptation of BrainScope's EEG Technology for use with a Small Handheld Device (Metcalf, 2014)

the device called the Ahead M-200. This work has been supported through a DoD award, and has included miniaturizing and adapting the hardware for use with existing smartphone-like platforms, and continuing to integrate advances in algorithms for classification as increased EEG data is accumulated from clinical trials (Figure 33). A clinical trial of the Ahead M-200 is currently recruiting patients presenting with closed head injury in emergency departments. This trial, B-AHEAD III, will seek to validate the database of brain electrical activity recordings that has been developed and the clinical utility of the second generation device (NCT02367300).

Capability Gap Alignment

With clearance of the Ahead M-100 device now achieved, continued evaluation and validation of the Ahead technology in studies underway in hospital emergency departments may enable its delivery to the battlefield, which could address a number of capability gaps (Table 68).

Table 68. Capability Gaps Addressed by Portable EEG Assessment of Brain Function

Requirement Sources	Capability Gaps Addressed
GDF	• **JCM-1-1** – Inadequate ability to diagnose, resuscitate, and stabilize casualties with survivable wounds
TC3 ICD	• **Theater Hospitalization, Area Medical Support** – Diagnose, resuscitate, and stabilize casualties with survivable wounds • **First Response Medical Care** – Stabilize injuries, monitor response to treatment
DHP ICD	• **TI1** – Insufficient current first-responder (medical and non-medical) capacity and capability to initially assess, treat, and maintain severe trauma cases in the prehospital environment: - Insufficient tools that enable both non-medical and medical first responders - The technologies do not exist to fulfill some of the needs (e.g., stabilizing the airway or truncal hemorrhage) • **TI14** – Lack the ability to use modern imaging or emerging biomarkers in the diagnosis of TBI • **MHS5** – Inability to objectively and definitively identify or treat TBI (or make RTD determination) in the prehospital environment where there are no visible external indications (across the spectrum from mild, moderate, to severe) • **MHS9** – Lack of capability to objectively and definitively identify and treat TBI/concussion immediately following traumatic event • **RTD1** – Lack of objective assessment tools to determine fitness for duty in the case of sub-acute injury in the prehospital environment • **MBF1** – Lack of understanding of TBI (combat and non-combat related): - Reliance upon self-reporting (over self-reporting and under self-reporting are both common) • **MBF2** – Inability to diagnose on the battlefield • **RHBC1** – Lack the understanding of the short-term and long-term effects of TBI (combat and non-combat related) on individuals: - Effectiveness of current mTBI screening criteria - Objective screening capability to detect and measure suspected mTBI

Impact on the Battlefield/Warfighter

For active duty military personnel in theater, blasts are the leading cause of TBI, with the majority (87 to 90 percent) of these cases being classified as mTBI (DVBIC, 2015). In the military, many symptoms of mTBI are difficult to distinguish from the effects of stress and sleep deprivation, increasing the potential of their going unexamined or undiagnosed (Cernich, Reeves, Sun, & Bleiberg, 2007). However, even in the case of a closed head injury due to blast that presents as mild, structural brain lesions may occur that can be disabling or deadly if not

managed. The Ahead technology offers the capability to assess the presence or absence of structural abnormality such as hematoma in mTBI, either aiding in identifying potential pathological features that merit further evaluation by CT scan, or ruling out the concern. An objective technology to rapidly support this categorization for even very mild brain injuries may save lives, reduce radiation exposure, and decrease costs through a reduction in the use of neuroimaging (BrainScope, 2015). Although the Ahead technology is not yet fielded by the U.S. military, continued development and clinical trials are being conducted that are critical to validating the feasibility and clinical utility of the use of this adjunctive tool in combat casualty care. If the technology is validated and deployed, the rapid assessment it enables can be used to improve clinical outcomes.

Clinical Practice

Impact on Clinical Practice Guidelines

Early assessment and classification of TBI is critical to improve clinical outcome. For brain injury that occurs in the field, the patient does not receive assessment by neuroimaging until they arrive at a Role 3 facility where CT or MRI can be performed. The current standard of care does not include portable assessment devices that can provide objective measures of structural brain abnormality rapidly after injury in a prehospital environment. Implementation of the Ahead technology could affect this gap for assessment of TBI in the field, however, providing additional information more immediately after injury to aid triage and clinical decision making. Examples of CPGs that inform the diagnosis and management of TBI in the deployed setting which may be adjusted to integrate a new adjunctive screening tool for TBI are provided in Table B-1.

Supporting Publications

Several clinical studies of the first generation Ahead M-100 device in emergency settings provided support for its clearance for adjunctive use to identify brain abnormalities in TBI patients. These studies, along with future publications resulting from further study of the next generation Ahead M-200, may contribute to the body of evidence for future changes in CRs, CPGs, and other clinical tools (Table 69).

Table 69. Supporting Publications for the Use of Ahead Portable EEG for TBI Assessment

Reference	Description
Naunheim, Treaster, English, Casner & Chabot, 2010	Validated the quantitative EEG algorithm's ability to discriminate TBI in an emergency department setting. The algorithm provided a sensitive indicator of brain function, and may be used to suggest whether or not a patient requires a CT scan
Naunheim & Casner, 2010	Case report of the use of the automated Ahead M-100 EEG device to identify a brain abnormality in a patient with a normal neurological exam
Naunheim, Treaster, English, & Casner, 2011	Used the Ahead M-100 to assess patients presenting with headache or altered mental status in the emergency department setting. When assessing 153 patients, the device achieved 96 percent sensitivity and 87 percent specificity for detecting brain abnormality
O'Neil, Prichep, Naunheim, & Chabot, 2012	Assessed the use of brain activity quantified by EEG for initial screening of mTBI patients in the emergency department. Performance of the device was superior to use of the New Orleans Criteria for identifying patients with a positive CT
Hanley et al., 2013	Used brain electrical activity to identify intracranial hematomas in emergency department patients

Reference	Description
Prichep et al., 2014	Described technology and analytical approaches implemented in the derivation of the algorithms forming the foundation of the Ahead M-100 technology
Prichep, Naunheim, Bazarian, Mould, & Hanley, 2015	Used brain electrical activity to identify intracranial hematomas in TBI patients presenting in the emergency department. Evaluation of 394 closed head injury patients provided validation and extension of previous findings, supporting the use of the quantitative EEG algorithm to sensitively detect intracranial hematomas (95.7 percent sensitivity, 43.9 percent specificity)

Role of CCCRP-Sponsored Projects

Key projects for the validation of the Ahead M-100 device for use in TBI patients and for the continued development of the next generation of miniaturized, optimized Ahead technology have been sponsored under the Neurotrauma portfolio.

Table 70. CCCRP-Sponsored Projects for Ahead Portable EEG

Project Title (Award Number)	Organization/ Principal Investigator	Funding
Assessment of Head Injury in the Emergency Department: A Prospective Clinical Validation of the BrainScope: Ahead™ M-100 (B-AHEAD II Trial) - FDA Pivotal Trial Proposal (ERMS 11056001)	Doug Oberly, M.S. (BrainScope)	$7,483,030 (2012–2014)
Miniature Field Deployable System For Rapid TBI Assessment (W81XWH-12-C-0163)	William Koppes, M. S. (BrainScope)	$2,679,874 (2012–2014)
Army Rapid Innovation Fund (RIF) Research Contract to BrainScope Inc. (W81XWH-14-C-1405)	BrainScope	$3,000,000 (2014–2016)

Support of the B-AHEAD II trial enabled BrainScope to obtain the data for its successful application to FDA. Additional funding has enabled continued adaptation of the device concept to a more miniaturized, rugged version capable of operating through a small commercial handheld device with custom software. Moving forward, funding recently awarded in September 2014 to BrainScope through USAMRMC under the Defense Medical Research and Development Program, in conjunction with funds from the U.S. Navy, will support further clinical studies in hospital emergency departments and with university sports programs (Gormley, 2014). It is expected that results from these clinical studies will yield publications that will contribute to the clinical implementation of the Ahead device by the military.

Support of the B-AHEAD II trial enabled BrainScope to obtain the data for its successful application to FDA.

References

BrainScope (2015, January). Retrieved from http://www.brainscope.com/index1.shtml

BrainScope Company, Inc. (2013). Assessment of Head Injury in the Emergency Department Using BrainScope Ahead Technology (B-AHEAD II). Retrieved from https://clinicaltrials.gov/ct2/show/NCT01556711 (Identification No. NCT01556711)

BrainScope Company, Inc. (2015). Validation of TBI detection system for head injured patients (B-AHEAD III). Retrieved from https://clinicaltrials.gov/ct2/show/NCT02367300 (Identification No. NCT02367300)

BrainScope Ahead 100 de novo No. DEN140025. (2014, Nov 17). Retrieved from http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?ID=DEN140025

Cernich, A., Reeves, D., Sun, W., & Bleiberg, J. (2007). Automated neuropsychological assessment metrics sports medicine battery. *Archives of Clinical Neuropsychology*, *22*, 101-114.

Defense and Veterans Brain Injury Center (DVBIC). (2015, January). Retrieved from http://dvbic.dcoe.mil

Gormley, B. (2014, September 30). BrainScope collects $15.9M from military for traumatic brain injury detection. Retrieved from http://www.brainscope.com/news-and-media/20140930b/index.shtml

Hack, D. M. (2011). Research Advances in Medical Care for Polytrauma Injuries and Blast Injuries. Presentation at the 2011 Military Health System Conference, Washington, D. C. Retrieved from http://dvbic.dcoe.mil/dod-worldwide-numbers-tbi

Hanley, D. F., Chabot, R., Mould, W. A., Morgan, T., Naunheim, R., Sheth, K. N., … Prichep, L. S. (2013). Use of brain electrical activity for the identification of hematomas in mild traumatic brain injury. *Journal of Neurotrauma*, *30*(24), 2051-2056.

Joint Trauma System (JTS). (2014, December). JTS & CCAT Clinical Practice Guidelines. Retrieved from http://www.usaisr.amedd.army.mil/clinical_practice_guidelines.html

Metcalf, A. (2014, Nov 21). Bethesda company receives FDA clearance for brain injury monitoring tool. Retrieved from http://www.bethesdamagazine.com/Bethesda-Beat/2014/Bethesda-Company-Receives-FDA-Clearance-for-Brain-Injury-Monitoring-Tool/

Naunheim, R. S., & Casner, T. (2010). Novel method for detecting brain abnormality in a patient with epidural hematoma: a case report. *The American Journal of Emergency Medicine*, *28*(3), 386-e1.

Naunheim, R. S., Treaster, M., English, J., Casner, T., & Chabot, R. (2010). Use of brain electrical activity to quantify traumatic brain injury in the emergency department. *Brain Injury*, *24*(11), 1324-1329.

Naunheim, R. S., Treaster, M., English, J., & Casner, T. (2011). Automated electroencephalogram identifies abnormalities in the ED. *The American Journal of Emergency Medicine*, *29*(8), 845-848.

O'Neil, B., Prichep, L. S., Naunheim, R., & Chabot, R. (2012). Quantitative brain electrical activity in the initial screening of mild traumatic brain injuries. *Western Journal of Emergency Medicine*, *13*(5), 394.

Prichep, L. S., Dastidar, S. G., Jacquin, A., Koppes, W., Miller, J., Radman, T., … Huff, J. S. (2014). Classification algorithms for the identification of structural injury in TBI using brain electrical activity. *Computers in Biology and Medicine*, *53*, 125-133.

Prichep, L. S., Naunheim R., Bazarian J., Mould, W. A., & Hanley D. (2015). Identification of hematomas in mild traumatic brain injury using an index of quantitative brain electrical activity. *Journal of Neurotrauma*, *32*(1), 17-22.

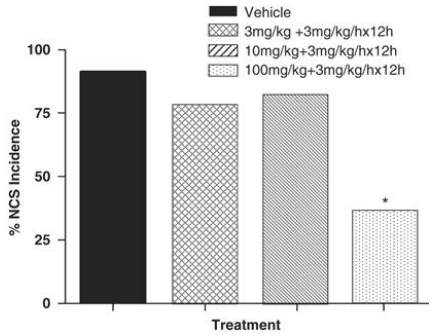
Treatment of TBI with the Neuroprotective Compound NNZ-2566

Neuren Pharmaceuticals is testing the neuroprotective compound NNZ-2566 for treatment of TBI, and is progressing toward an end goal of achieving regulatory approval through the validation of the safety and efficacy of the compound.

- R&D Partner Organizations:
  - Neuren Pharmaceuticals
  - Walter Reed Army Institute of Research (WRAIR)
- Principal Investigator:
  - Larry Glass
  - Frank Tortella, Ph.D.

Key Outcomes and Impact:

- Through collaborative R&D, Neuren and WRAIR have defined the pharmacology and mechanism of action of NNZ-2566
- WRAIR studies demonstrated neuroprotective and anti-inflammatory effects of NNZ-2566 in a penetrating ballistic-like brain injury (PBBI) model, supporting clinical advancement (Shear & Tortella, 2013)
- Phase 2 clinical trials are now ongoing for intravenous NNZ-2566 in moderate to severe TBI patients, and oral NNZ-2566 in mTBI patients (NCT02100150; NCT01366820)



NNZ-2566 Reduces Incidence of Non-Convulsive Seizures in Brain-Injured Rats (Lu et al., 2009)

Overview

To date, there is no pharmacotherapy directly targeting the mechanisms of TBI, and clinical trials in TBI have failed to move forward the use of any new or existing drugs to significantly improve patient outcomes (The CDC, NIH, DoD, and VA Leadership Panel, 2013). The development of TBI drugs has proved tremendously challenging, but the need remains critical. In response to this persistent need, a promising compound developed by Neuren Pharmaceuticals called NNZ-2566 is being evaluated for treatment of TBI. NNZ-2566 is a synthetic analogue of a naturally occurring neuropeptide fragment of the protein insulin-like growth factor 1 (IGF-1) that has demonstrated neuroprotective effects (Figure 34). NNZ-2566 inhibits inflammatory cytokines, pathological microglial activation, apoptosis, and necrosis; these mechanisms are key features of the pathobiology of TBI (Neuren Pharmaceuticals, 2015).

A collaborative relatinship between WRAIR and Neuren has enabled the exploration of NNZ-2566 for treatment of TBI. WRAIR conducted much of the critical work to define the pharmacology and mechanisms of action of NNZ-2566 and to evaluate NNZ-2566 in animal models of TBI, paving the way for continued clinical

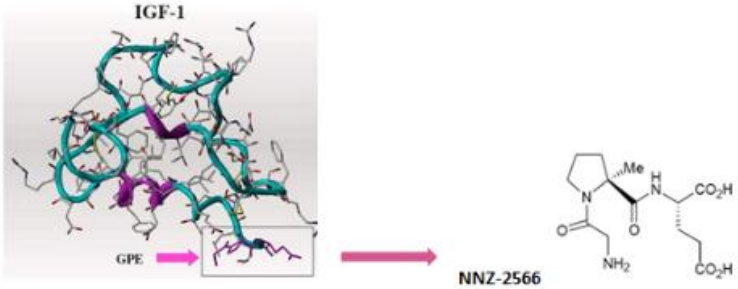


Figure 34. NNZ-2566 is a Synthetic Analogue of a Neuroprotective IGF-1 Derived Neuropeptide (Neuren, 2015)

development. The effort has also included close collaboration with USAMRMC for the regulatory support and technical advice needed to move forward the clinical development of NNZ-2566 for TBI.

As the compound's development has advanced, clinical trials to evaluate the safety and efficacy of NNZ-2566 have been designed. In collaboration with USAMRMC, Neuren is conducting a Phase 2 clinical trial using an intravenous dosage form of NNZ-2566 in moderate to severe TBI patients in trauma centers across the U.S. (NCT00805818; NCT01366820). A second Phase 2 clinical trial now underway is also examining use of an oral dosage form of NNZ-2566 in patients with concussion (NCT02100150). Results from these trials are expected in late 2015, and will guide continued development of NNZ-2566 for the treatment of TBI.

Capability Gap Alignment

Validation of the safety and efficacy of NNZ-2566 is expected to address a number of capability gaps that have been identified to guide military medical R&D with respect to treatment of TBI (Table 71). All three of the requirements sources considered specifically highlight the need for therapies for head injury. Additionally, the insights gained into the molecular mechanism of TBI neuropathology through the study of NNZ-2566 are continuing to contribute to related knowledge gaps.

Table 71. Capability Gaps Addressed by Therapeutics for TBI

Requirement Sources	Capability Gaps Addressed
GDF	• **JCM-1-8** – Inadequate therapy for shock and head injury • **JCM-1-8.1** – Inadequate definitive, restorative, and rehabilitative therapy for head injury and shock • **JHPE-EPC-PN1** – Provide neuroprotection to decrease brain injury. Inability to provide, in advance or on site, countermeasures to prevent morbidity/mortality directly related to TBI
TC3 ICD	• Adjunctive Medications for Trauma Management – Therapy for shock and head injury
DHP ICD	• **EPA1** – Insufficient understanding of the effects of a blast event on neurologic tissue to develop immediate therapeutics and mitigation strategies for long-term negative effects • **MHS5** – Inability to objectively and definitively identify or treat TBI (or make RTD determination) in the prehospital environment where there are no visible external indications (across the spectrum from mild, moderate, to severe) • **MHS9** – Lack of capability to objectively and definitively identify and treat TBI/concussion immediately following traumatic event • **MBF1** – Lack of understanding of TBI (combat and non-combat related): - Insufficient full-spectrum treatment options for TBI (e.g., pharmaceuticals, neuro-protectives, etc.) • **Restorative Care** – Insufficient understanding of the healing process associated with physical injuries to the brain, versus healing process associated with brain's response to other body-wide injuries • **Restorative Care** – Insufficient understanding of the short-term and long-term effects of mTBI on cognitive and behavioral abilities • **Restorative Care** – Lack understanding of long-term data pertaining to functional patient outcomes of initial and long-term mTBI therapies • **RHBC1** – Lack the understanding of the short-term and long-term effects of TBI (combat and non-combat related) on individuals: - Effectiveness of current and emerging mTBI therapies

Impact on the Battlefield/Warfighter

While improvements in personal protective equipment and trauma care have significantly reduced mortality on the battlefield, an increasing number of individuals surviving combat injuries are facing long-term cognitive and physical disabilities (Eastridge et al., 2012; Shear & Tortella, 2013). TBI is associated with increased long-term mortality; reduced life expectancy; and increased incidences of seizures, sleep disorders, neuoroendocrine dysregulation, and psychiatric diseases (Masel & Dewitt, 2010; Shear & Tortella, 2013). In the U.S., approximately 1.7 million TBIs occur each year and, of these, 80,000 to 90,000 individuals suffer from permanent problems resulting from their TBI. These permanent problems may manifest in symptoms that include the following (Intrepid-2566, 2015):

- Concentration, focus, memory, attention, and learning challenges
- Loss of balance, coordination, and fine motor skills
- Alterations in personality and mood
- Irritability, aggression, depression, and lack of motivation
- Changes in sleep patterns, energy levels, and appetite
- Chronic pain, migraines, and headaches

Presently, the standard of care does not include drugs that can directly treat TBI to effectively mitigate these symptoms or improve outcomes. The availability of a successful therapeutic that could inhibit the damaging inflammation and cell death occurring in the brain in response to TBI, preserving brain health and reducing the incidence or severity of these long-term health challenges, would be a tremendous success in both civilian and military populations. For the military, this would not only critically improve quality of life for warfighters sustaining TBI, but also reduce the overall burden of TBI on U.S. forces through improved RTD rates and decreased health care costs. The median annual cost per patient in the U.S. Department of Veterans Affairs (VA) system is nearly four times higher for TBI-diagnosed veterans than those without TBI (Taylor et al., 2012). Administration of NNZ-2566 within 24 hours after injury in animal models of TBI has been demonstrated to reduce negative outcomes associated with TBI, maintaining cognitive function and inhibiting post-injury seizures (Neuren Pharmaceuticals, 2015). It is hoped that NNZ-2566 can progress through clinical trials as a successful TBI treatment with measurably improved outcomes. Results of ongoing clinical trials will soon provide an indication of whether similar effects may be achieved clinically in humans.

Clinical Practice

Impact on Clinical Practice Guidelines

A range of DoD clinical tools for care of TBI with the potential to be altered by a new drug that can be rapidly administered following injury are included in Table B-1.

The current standard of care for TBI relies on early identification of the traumatic event, including injury severity, to improve the clinical outcome. Immediate medical attention is necessary to both maximize survival from severe brain trauma, and minimize permanent problems associated with TBI. The Guideline for Management of Severe TBI lists multiple emergency room approaches for managing severe TBI to achieve stabilization of vitals and enable further assessment and treatment (Brain Trauma Foundation et al., 2007). These include

hyperventilation, intracranial pressure monitoring, anti-seizure medication, and sedation, but there is no currently approved drug therapy as standard of care (Brain Trauma Foundation, American Association of Neurological Surgeons, & Congress of Neurological Surgeons, 2007; DCoE, 2009; Shear & Tortella, 2013). The approval of a drug such as NNZ-2566 for moderate to severe TBI will add a new approach to the arsenal that would be reflected in updated CPGs.

Supporting Publications

There are not yet published clinical data supporting the efficacy of NNZ-2566 in TBI, though there are currently two Phase 2 clinical studies underway to evaluate the drug's safety and efficacy (Table 72).

Table 72. Clinical Trials Examining the use of NNZ-2566 for TBI

Reference	Description
A Safety and Efficacy Study of NNZ-2566 in Patients With mTBI (Cole, 2014; NCT02100150)	Investigating whether the oral formulation of NNZ-2566 is safe, well tolerated, and effective for treatment of adolescents and adults with mTBI
Study of NNZ-2566 in Patients With TBI [including protocol conducted under exception from informed consent] (INTREPID2566) (Bullock, 2015; NCT01366820).	Investigating whether the intravenous formulation of NNZ-2566 is safe and effective in the treatment of moderate to severe TBI

These trials are both assessing many measures of cognitive function and physical and emotional symptoms in treated patients, together with safety and tolerability measures. They seek to provide an initial evaluation of the efficacy of NNZ-2566 for reducing cognitive impairment, psychological sequelae, and global impairment after TBI. In addition, the study in patients with moderate to severe TBI is examining efficacy of the treatment for modifying the acute disease and injury process. Upon completion of these Phase 2 trials, it is expected that published results will serve as an important foundation for the continued study and eventual changes to clinical guidance if the drug proceeds to pivotal Phase 2b/3 studies and achieves approval. Neuren expects completion of enrollment in both Phase 2 trials in 2015, and has reported that early blinded data indicate the drug has been safe and well tolerated in the trials to date (Neuren Pharmaceuticals, 2014).

Role of CCCRP-Sponsored Projects

This work has been driven by a USAMRMC-sponsored CRADA bringing together researchers at WRAIR and Neuren. The CRADA enabled access to NNZ-2566 for WRAIR researchers, whose pharmacological and mechanistic studies in animal models of TBI have supported Neuren's continued clinical development of the drug. This collaboration has also enabled exchange of regulatory support and technical advice for development of the drug in multiple formulations. Under the Neurotrauma portfolio, support has continued to be provided for the two Phase 2 clinical trials that are now testing safety and efficacy of NNZ-

> "During the past decade and under the directive of the CCCRP, our research team established a rodent model of penetrating ballistic-like brain injury (PBBI)… Our pre-clinical NNZ-2566 data from the PBBI model has directly contributed to the recent clinical advancement of this compound into a multi-center Phase II trial for moderate-severe TBI."
>
> Shear & Tortella, 2013

2566 for treatment of both mTBI and moderate to severe TBI (Table 73).

Table 73. CCCRP-Sponsored Projects for the use of for NNZ-2566 for TBI

Project Title (Award Number)	Organization/ Principal Investigator	Funding
Army/Neuren Penetrating Brain Injury CRADA (W81XWH-05-0074)	WRAIR, Neuren Pharmaceuticals	
Phase II Clinical Trial of NNZ-2566 in Traumatic Brain (W81XWH-09-1-0496, W23RYX0055N602)	Larry Glass (Neuren Pharmaceuticals)	$19,627,000 (2009–2015)
Treatment of Traumatic Brain Injury Using NNZ-2566: Clinical Trials (PT074614)	Frank Tortella, Ph.D. (WRAIR)	$4,597,854 (2008–2015)

A number of publications have resulted from research conducted by WRAIR in partnership with Neuren through the CRADA (Table 74). These studies have clarified the mechanisms of action of NNZ-2566 in animal models of brain injury, provided evidence for its neuroprotective effects, and contributed to the understanding of the effects of varying treatment timing and dosage. These efforts were all critical to supporting the clinical advancement of NNZ-2566 into Phase 2 trials for TBI by Neuren.

Table 74. CCCRP-Sponsored Publications for NNZ-2566

Reference	Description
Lu et al., 2009a	Tested NNZ-2566 in the PBBI rat model and identified dose-dependent improvements in behavioral measures after both acute and delayed treatments. Improvements in functional recovery were accompanied by reductions in apoptotic and inflammatory responses
Lu et al., 2009b	Examined NNZ-2566 in a middle cerebral artery occlusion model of brain injury; treatment significantly decreased non-convulsive seizure incidence, frequency, and duration
Wei et al., 2009	Examined the effects of NNZ-2566 in a rat model of PBBI. Treatment significantly reduced the injury-mediated up-regulation of inflammatory cytokines in the brain during acute injury
Cartagena et al., 2013	Determined that NNZ-2566 increases levels of activating transcription factor-3 in the PBBI rat model, providing a potential cellular mechanism for modulation of neuroinflammation

References

Brain Trauma Foundation, American Association of Neurological Surgeons, & Congress of Neurological Surgeons. (2007). Guidelines for the management of severe traumatic brain injury. *Journal of Neurotrauma*, *24* (Suppl 1), S1-S106.

Bullock, R. R. Neuren Pharmaceuticals Limited. (2015a). Study of NNZ-2566 in patients with traumatic brain injury (INTREPID2566). Retrieved from https://clinicaltrials.gov/ct2/show/NCT00805818 (Identification No. NCT00805818).

Bullock, R. R. Neuren Pharmaceuticals Limited. (2015b) Study of NNZ-2566 in patients with traumatic brain injury under EFIC (INTREPID2566). Retrieved from https://clinicaltrials.gov/ct2/show/NCT01366820 (Identification No. NCT01366820)

Cartagena, C. M., Phillips, K. L., Williams, G. L., Konopko, M., Tortella, F. C., Dave, J. R., & Schmid, K. E. (2013). Mechanism of action for NNZ-2566 anti-inflammatory effects following PBBI involves upregulation of immunomodulator ATF3. *Neuromolecular Medicine*, *15*, 504-514.

Cole, W. R. Neuren Pharmaceuticals Limited. (2014). A safety and efficacy study of NNZ-2566 in patients with mild traumatic brain injury (mTBI). Retrieved from https://clinicaltrials.gov/ct2/show/NCT02100150 (Identification No. NCT02100150).

Eastridge, B. J., Mabry, R. L., Seguin, P., Cantrell, J., Tops, T., Uribe, P., … Blackbourne, L. H. (2012). Death on the battlefield (2001-2011): implications for the future of combat casualty care. *Journal Trauma Acute Care Surgery*, *73*, S431-7.

Intrepid-2566: Traumatic Brain Injury Study (Intrepid-2566). (2015, January). Retrieved from https://www.intrepid-2566.com/

Joint Trauma System (JTS). (2014, December). JTS & CCAT Clinical Practice Guidelines. Retrieved from http://www.usaisr.amedd.army.mil/clinical_practice_guidelines.html

Lu, X. C. M., Chen, R. W., Yao, C., Wei, H., Yang, X., Liao, Z., … Tortella, F. C. (2009a). NNZ-2566, a glypromate analog, improves functional recovery and attenuates apoptosis and inflammation in a rat model of penetrating ballistic-type brain injury. *Journal of Neurotrauma*, *26*, 141-154.

Lu, X. C. M., Si, Y., Williams, A. J., Hartings, J. A., Gryder, D., & Tortella, F. C. (2009b). NNZ-2566, a glypromate analog, attenuates brain ischemia-induced non-convulsive seizures in rats. *Journal of Cerebral Blood Flow & Metabolism*, *29*(12), 1924-1932.

Masel, B.E., & Dewitt, D.S. (2010). Traumatic brain injury: A disease process,not an event. *Journal of Neurotrauma*, 27, 1529–1540.

Neuren Pharmaceuticals. (2014, July 17). Neuren announces increase of US$3 million to US Army grant and updates INTREPID clinical trial enrolment outlook. Retrieved from http://www.neurenpharma.com/IRM/Company/ShowPage.aspx/PDFs/1415-10000000/US3mincreasetoUSArmygrantandINTREPIDoutlookupdate

Neuren Pharmaceuticals. (2015, January). NNZ-2566 in traumatic brain injury. Retrieved from http://www.neurenpharma.com/irm/content/nnz-2566-in-traumatic-brain-injury.aspx?RID=332

Shear, D. A., & Tortella, F. C. (2013). A military-centered approach to neuroprotection for traumatic brain injury. *Frontiers in Neurology*, *4*, 73.

Tactical Combat Casualty Care (TCCC) Guidelines. (2014, October). Retrieved from http://usaisr.amedd.army.mil/assets/pdfs/TCCC%20Guidelines%20141028.pdf

Taylor, B. C., Hagel, E. M., Carlson, K. F., Cifu, D. X., Cutting, A., Bidelspach, D. E., & Sayer, N. A. (2012). Prevalence and costs of co-occurring traumatic brain injury with and without psychiatric disturbance and pain among Afghanistan and Iraq War Veteran V.A. users. *Medical Care*, *50*(4), 342-346.

The CDC, NIH, DoD, and VA Leadership Panel. (2013). Report to congress on traumatic brain injury in the United States: Understanding the public health problem among current and former military personnel. Retrieved from http://www.nashia.org/pdf/report-to-congress-on-traumatic-brain-injury-2013-a.pdf

Wei, H. H., Lu, X. C., Shear, D. A., Waghray, A., Yao, C., Tortella, F. C., & Dave, J. R. (2009). NNZ-2566 treatment inhibits neuroinflammation and pro-inflammatory cytokine expression induced by experimental penetrating ballistic-like brain injury in rats. *Journal of Neuroinflammation*, *6*, 19.

Portable Neuromodulation Stimulator for TBI Treatment

Brain stimulation delivered by a handheld portable neuromodulation stimulator (PoNS) device has the potential to enhance the benefits of physical therapy in the treatment of vestibular dysfunction in TBI patients.

- R&D Partner Organizations:
  - Helius Medical Technologies (Helius)
  - NeuroHabilitation Corporation (NHC)
  - University of Wisconsin Tactile Communications and NeuroHabilitation Laboratory (TCNL)

Key Outcomes and Impact:

- The PoNS device is an electrode-covered oral device that delivers nerve impulses to the brain through the tongue
- USAMRMC entered into a CRADA to advance the development of the PoNS device and facilitate its 501(k) clearance by FDA
- Regulatory clearance is being sought for the PoNS device as an adjunct to physical therapy in the treatment of balance disorders in TBI patients. FDA clearance expected in 2016
- Adjunctive use of PoNS can improve and accelerate neuromotor recovery after TBI

The PoNS Device is being Evaluated in TBI Patients for Its Ability to Enhance the Vestibular Benefits of Physical Therapy (Moore, 2014)

Overview

TBI is often accompanied with vestibular dysfunction, which, for some people, persists as a long-term concern. Of the more than 300,000 service members that suffered a TBI since 2000, it is estimated that 30 percent have gait and balance issues due to vestibular dysfunction (Basford, et al., 2003; Ernst et al., 2005; Hoffer, Gottshall, Moore, Balough, & Wester, 2004). Although this dysfunction spontaneously improves within a year for the majority of people with TBI, some plateau, particularly those with severe TBI, and are prevented from returning to high-level physical activities. Pharmacological treatment with vestibular suppressants is not recommended and may be counterproductive (Hain & Yacovino, 2005; Pyykko, Magnusson, Schalen, & Enbom, 1988; The Management of Concussion/mTBI Working Group, 2009). Physical rehabilitation with vestibular and balance exercises is in some cases efficacious, but is not always adequate on its own to enable a return to full function (Herdman, Clendaniel, Mattox, Holliday, & Niparko, 1995; Shepard & Telian, 1995; Yardley, Beech, Zander, Evans, & Weinman, 1998)

For TBI patients with persistent vestibular dysfunction, an innovative form of neuromodulation therapy is being evaluated by USAMRMC, Helius, and NHC. The therapy is delivered noninvasively to the patient using the PoNS, a handheld device that provides small, safe doses of electric current to the brain via cranial nerves in the tongue (Figure 35). The idea is that exercises in conjunction with PoNS therapy can help the brain form

> "The PoNS device is based on almost 40 years of research in the field of neuromodulation – the use of external stimulation to intentionally change and regulate the electrochemical environment of the brain."
>
> Helius Medical Technologies, 2015

new neural pathways for recovering functions such as balance and movement. The goal of the program is to guide the PoNS device through clinical trials, obtain FDA clearance, and take the necessary steps to commercialize in late 2016.

The PoNS augments physical rehabilitation by enhancing the reorganization and functional restoration of neurons. In an early prototype, patients receive neuromodulation therapy by resting a thin oral tab located at the front of the T-shaped device on the front part of their tongue. The oral tab, which is covered with electrodes, delivers low voltage square-pulse bursts to the tongue. The stimulation reaches the brain via cranial nerves V and VIII, which have sensory afferents in the tongue and are enervated within brainstem centers in close proximity to the vestibular nuclei (Figure 35).

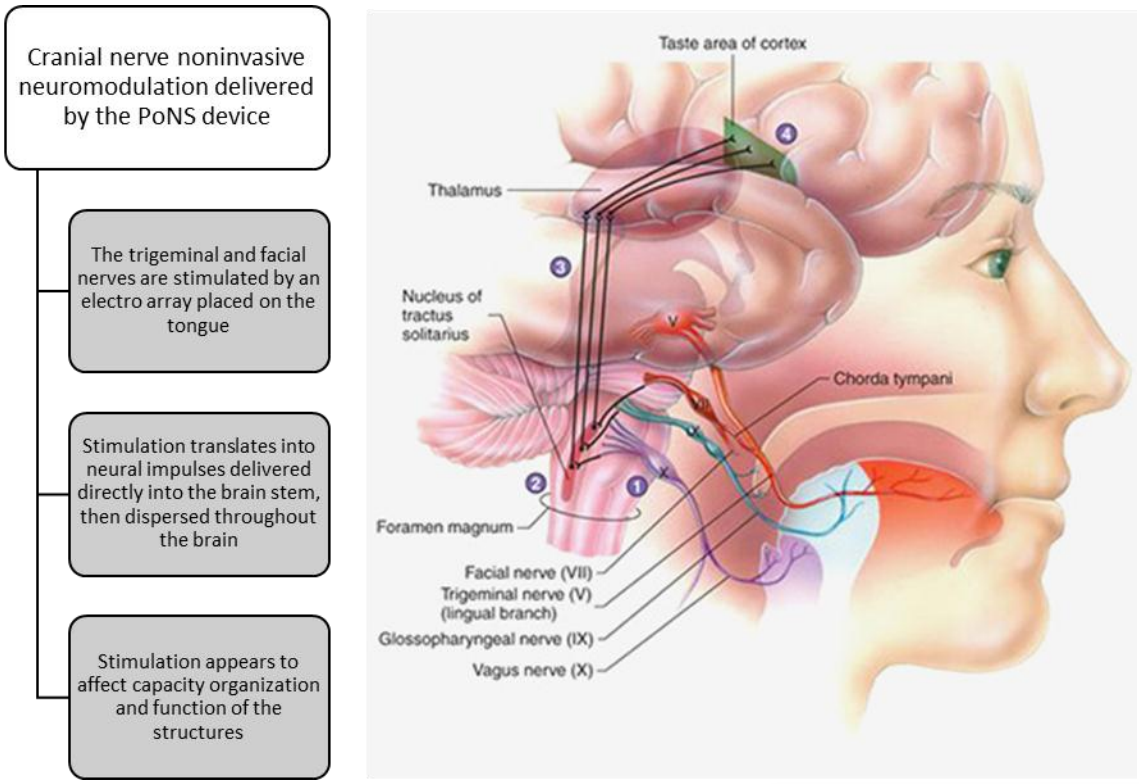


Figure 35. The PoNS Device Delivers Neurostimulation through Nerves i

"This is a great example of innovation and a public/private collaboration with our USAMRMC partners and we are very pleased to take over some of the responsibility to get this technology studied, cleared, and distributed to help patients."

CEO of Helius, Philippe Deschamps

The development of the PoNS device has benefited from strategic partnerships and builds upon decades of neurostimulation research. Many of the early pilot projects and studies were conducted at the TCNL at the University of Wisconsin in Madison. Because of the potential for application of this approach in the treatment of TBI, the USAMRMC entered into a CRADA with the company created to commercialize the technology, NHC, in 2013 to support additional development and trials (Figure 36).

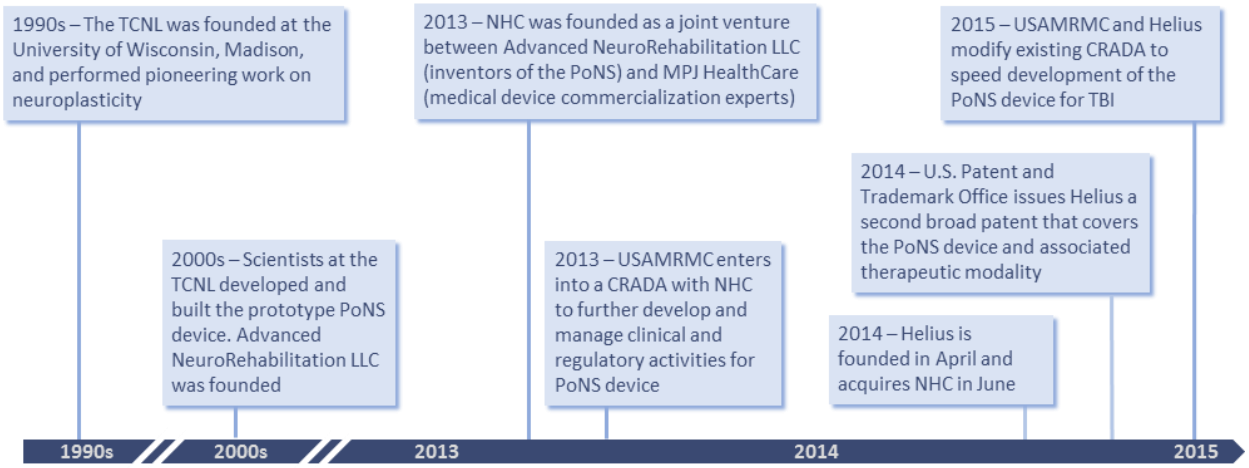


Figure 36. Developmental Milestones of the PoNS Device

Capability Gap Alignment

The need for effective treatment of the neurological symptoms of TBI remains a critical gap in military medicine that has been emphasized by requirements sources. The recent DHP ICD capability gaps place increasing emphasis on long-term strategies, and even go so far as to specifically mention the absence of strategies to treat vestibular dysfunction. It is expected that validation and FDA approval of the PoNS device will contribute to the closure of many of these gaps (Table 75).

Table 75. Capability Gaps Addressed by Neuromodulation for TBI Treatment

Requirement Sources	Capability Gaps Addressed
GDF	• **JCM-1-8.1 –** Inadequate definitive, restorative, and rehabilitative therapy for head injury and shock
DHP ICD	• **MSS2 –** Insufficient hearing and vestibular rehabilitation research for: - Regenerative medicine-based approaches - Technologies supporting restoration to Service member-level capabilities - Hearing loss and tinnitus • **MSS3 –** Lack of assessment or rehabilitation ability for balance issues • **MBF1 –** Lack of understanding of TBI (combat and non-combat related): - Neuroplasticity (brain recovery) following traumatic combat-related TBI - Insufficient full-spectrum treatment options for TBI (e.g., pharmaceuticals, neuro-protectives, etc.) • **Regenerative Care –** Lack of ability to regenerate or restore certain tissues and/or functions (e.g., large bone, vision, GU, over 40 percent burn patients, upper extremity function, spinal cord, peripheral nerves, brain function) • **Restorative Care –** Insufficient understanding of the healing process associated with physical injuries to the brain, versus healing process associated with brain's response to other body-wide injuries • **Restorative Care –** Insufficient understanding of the short-term and long-term effects of mTBI on cognitive and behavioral abilities • **Restorative Care –** Lack understanding of long-term data pertaining to functional patient outcomes of initial and long-term mTBI therapies • **RHBC1 –** Lack the understanding of the short-term and long-term effects of TBI (combat and non-combat related) on individuals:

Requirement Sources	Capability Gaps Addressed
	- Effectiveness of current and emerging mTBI therapies - Lack of evidence-based data to indicate effectiveness of current therapies • **RHBC2 –** Inadequate sustained neuromusculoskeletal rehabilitation clinical research capabilities at local military treatment facilities (only available at major installations)

Impact on the Battlefield/Warfighter

A growing body of pilot projects, case studies, and controlled trials indicate that PoNS therapy can significantly improve neuromotor recovery after TBI, thereby reducing both the time and expense of recovery after TBI. In addition to treating TBI, the PoNS has been successfully used to treat neuromotor dysfunction in multiple sclerosis (MS) patients, and is being investigated as a treatment for Alzheimer's disease and stroke patients (Crown, 2013; Curley, 2013; Danilov, Tyler, Skinner, Hogle, & Bach-y-Rita, 2014). Commercialization and widespread distribution of the PoNS could increase the quality of life for millions who are currently living with neurological disorders. It is estimated that in North America alone over 140 million people over the span of their lifetimes would benefit from the PoNS device for a variety of potential indications (Helius, 2015; Murray, 2014).

Clinical Practice

Impact on Clinical Practice Guidelines

Physical therapy is the most established and prevalent form of rehabilitation for neuromotor dysfunction. A patient with mTBI suffering from dizziness, disequilibrium, and spatial disorientation would be encouraged to adopt a customized vestibular, visual, and proprioceptive exercise routine (The Management of Concussion/mTBI Working Group, 2009). With PoNS treatment, this exercise routine would most likely remain very similar, save for the addition of the PoNS device to stimulate the neural pathway formation for recovery (Figure 37). A daily training regimen with PoNS therapy might consist of two 90-minute one-on-one sessions with a trainer. During this time, the patient would receive PoNS therapy throughout three different training intervals. One 20-minute interval of movement training would focus on training of body segments that normally move in synergistic and adaptive patterns to learn muscle control, joint mobility, relaxation, and strength. During the second 20-minute interval of balance training, the patient would perform progressively challenging balance trials on an adaptive support base to improve balance by recalibrating proprioceptive, tactile, and vestibular inputs. During the final 20-minute interval, cognitive, memory, and attention training would be performed on customized brain-fitness software programs (Curley, 2013). It is expected that fewer sessions would be required to achieve benefit when training with the PoNS. In addition, because the PoNS is noninvasive and portable, it can be easily integrated into in-home rehabilitation therapies and used as needed without constant medical supervision (Chisholm et al., 2014).

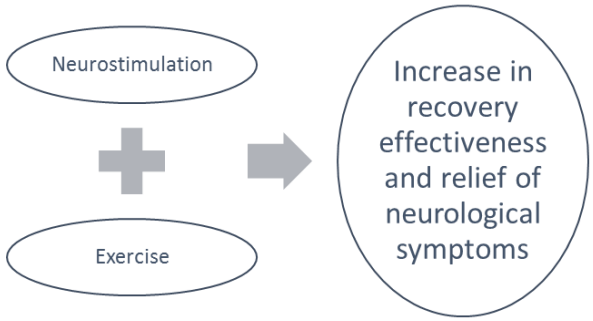


Figure 37. Neurostimulation Plus Exercise Promotes Faster Recovery (Helius, 2015)

Supporting Publications

Cranial nerve noninvasive neuromodulation therapy with the PoNS device is currently being evaluated as an adjunct therapy for multiple indications. Helius is seeking FDA clearance for use of the PoNS device in conjunction with physical therapy in the treatment of balance disorders in patients with mild to moderate TBI (Helius, 2015). They are also seeking clearance from Health Canada for use of the PoNS device as an adjunct to physical therapy in the treatment of gait and balance disorders in MS patients (Helius, 2015). These pivotal trials for clearance are building on support for the approach from a number of key clinical publications that collectively demonstrate the feasibility of PoNS therapy and augmentation of the benefits of exercise by its use. As several ongoing clinical trials continue to explore use of the PoNS device for TBI and other indications, and yield key data for regulatory submission, the complete body of knowledge will inform future changes to clinical practice with the implementation of PoNS therapy (Table 76).

Table 76. Supporting Publications and Clinical Trials for the PoNS device

Reference	Description
Publications	
Tyler, Danilov, & Bach-y-Rita, 2003	Demonstrated that head-body postural coordination in individuals with bilateral vestibular dysfunction could be restored with a head-mounted accelerometer equipped with an electrotactile tongue stimulator
Danilov, Tyler, Skinner, Hogle, & Bach-y-Rita, 2007	Conducted a pilot study to test the effectiveness of training with a balance device that incorporated electrotactile stimulation of the tongue in individuals with a balance dysfunction due to peripheral or central vestibular loss. All individuals demonstrated significant improvements in performance beyond what was expected from standard vestibular rehabilitation therapy
Wildenberg, Tyler, Danilov, Kaczmarek, & Meyerand, 2010	Pilot study evaluated whether stimulation of the tongue can improve behavioral outcomes and lead to a sustained neuromodulatory effect in individuals with balance dysfunction. Results indicated that improvements in sway and susceptibility to optic flow were achieved by cranial nerve noninvasive neuromodulation through alteration of neural activity within structures of the balance-processing network
Tyler et al., 2014	Pilot randomized controlled trial that examined the effect of targeted physical therapy with and without stimulation from the PoNS on walking ability of individuals with MS who have gait disorders. There was greater gait improvement in those receiving stimulation from the PoNS than the control group
Chisholm et al., 2014	Evaluated the feasibility of a lab- and home-based exercise program combining use of the PoNS device with balance and gait training in individuals with spinal cord injuries. Individuals were able to complete the prescribed training regimen and achieve improvement in balance confidence and walking function, indicating that additional studies to evaluate added benefits of PoNS therapy in this population may be merited
Ongoing Clinical Trials	
Enhanced Gait and Balance Training (Thelen, 2013; NCT01896466)	Investigating the effects of gait and balance training with or without cranial nerve noninvasive neuromodulation delivered by the PoNS device in older adults, as a potential approach to a falls prevention program
The Use of the PoNS device in the Treatment of Blunt and Blast Induced Vestibular Disorders (Hoffer, 2013; NCT01771575)	Investigating PoNS therapy to enhance the effectiveness of vestibular rehabilitation for service members who have suffered blunt or blast-related TBI (Sponsored by the U.S. Naval Medical Center, San Diego)
Noninvasive Neuromodulation for Treatment of Symptoms Due to Mild or Moderate TBI (Tyler, 2014a; NCT02158494)	Investigating PoNS therapy to enhance effectiveness of a balance and gait training regimen for patients with TBI

Reference	Description
Exploring the Use of Non-invasive Neuromodulation Combined With Exercise in People With Advanced MS (Tyler, 2014b; NCT02252666)	Evaluating whether cranial nerve noninvasive neuromodulation delivered by the PoNS device can reduce the symptoms of advanced MS and improve postural stability, upper extremity movement, and ability to perform self-transfers
Cranial-nerve Non-invasive Neuromodulation (CN-NINM) for Balance Deficits After Mild Traumatic Brain Injury (Cifu & Walker, 2014; NCT02109198 [pilot]; NCT02125591 [full])	Determining the feasibility of combining PoNS therapy with standard vestibular and balance therapy for treatment of mTBI in a double blind study design. Evaluating improvement in balance after receiving physical therapy augmented by PoNS therapy, based on the primary outcome of changes in the Sensory Organization Test measures (Sponsored by USAMRMC)
Examining the efficacy of Non-invasive Neuromodulation in reducing symptoms of MS (Helius, 2015)	Double-blind, sham-controlled study of the safety and efficacy of the PoNS device in the treatment of MS. Study is underway at McGill University's Montreal Neurological Institute and Hospital and Concordia University's PERFORM Center and has started enrolling patients. Pivotal Phase III trial scheduled to begin Q3 2015 at Montreal Neurological Institute and Hospital. Results expected to be submitted to Health Canada in Q3/Q4 2016
Chronic Balance Deficit Due to Mild-to-Moderate TBI (Helius, 2015)	Pivotal Phase III trial scheduled to begin Q2 2015. Results expected to be submitted to Health Canada and FDA in Q2/Q3 2016

Role of CCCRP-Sponsored Projects

In 2013, USAMRMC signed a CRADA with NHC, the original developers of the PoNS device and now a subsidiary of Helius (Figure 38, Table 77). The agreement enabled USAMRMC to evaluate the PoNS as a therapeutic intervention for service members who have a blast-induced TBI. Testing is now underway at multiple VA and Army hospitals, and, with DoD involvement, approximately 200 individuals have been treated with PoNS therapy in numerous feasibility and pilot studies for a range of indications (Helius, 2015). In addition, USAMRMC is currently sponsoring a pilot and planned subsequent full trial of PoNS therapy combined with standard vestibular and balance therapy for mTBI (Table 76).

Figure 38. USAMRMC enters into a CRADA with NHC to Develop the PoNS Device. Montel Williams (pictured) is a Founder (TCNL, 2013)

In 2015, this CRADA was modified to speed development of the PoNS device for the treatment of TBI. Although the terms of the contract are not yet final, NHC will assume sponsorship of the regulatory pathway for the PoNS device, including the initial registrational clinical trial, with support from USAMRMC. The modified CRADA will also allow USAMRMC to pursue other indications moving forward that may be relevant to injured service members such as tinnitus, PTSD, or sleep disturbances. To facilitate commercialization, USAMRMC has arranged collaborations with its subcommands USAMMA and USAMMDA to provide environmental testing and to ruggedize the PoNS device.

Through the CRADA, USAMRMC has provided approximately $9 million to advance the PoNS device (Table 77). Additional funding is expected from the USAMRMC to help expedite mTBI

clinical trials and prepare a regulatory submission, and for the development of further indications (Helius, 2015).

In addition to cranial nerve noninvasive stimulation as conducted with the PoNS, there are multiple other neurostimulation methods for therapeutically changing the brain. These include indirect stimulation, as with transcranial magnetic stimulation, direct stimulation, as with deep brain stimulation, and other approaches to indirect stimulation via nerves (i.e., vagus nerve stimulation). In addition to supporting development of the PoNS for TBI, the Neurotrauma portfolio has included funding of related studies to investigate the therapeutic benefits of different types of brain stimulation (Table 77). Together, these efforts to study neurostimulation contribute to knowledge of brain injury mechanisms, regenerative processes, and potential new therapeutic approaches for TBI.

Table 77. CCCRP-Sponsored Projects in Support of Neurostimulation Methods for TBI Treatment

Project Title (Award Number)	Organization/ Principal Investigator	Funding
PoNS Device		
Collaboration to advance the PoNS device through FDA approval for assisted physical therapy in the treatment of soldiers and others with balance and gait disorder (USAMRMC, USAMMA, USAMMDA; W81XWH-13-0145 [CRADA])	NHC	$9,000,000 (2013–2015)
Additional Neurostimulation Approaches		
Vagus Nerve Stimulation (VNS) and Rehabilitation in the Treatment of TBI (W81XWH-08-1-0206)	Arlene A. Tan, Ph.D. (Southern Illinois University)	$216,750 (2008–2010)
Electronical Stimulation of the Midbrain to Promote Recovery from Traumatic Forebrain Injury (W81XWH-08-1-0288)	Ian D. Hentall, Ph.D. (University of Miami School of Medicine)	$227,445 (2008–2010)

References

Basford, J. R., Chou, L. S., Kaufman, K. R., Brey, R. H., Walker, A., Malec, J. F., … Brown, A. W. (2003). An assessment of gait and balance deficits after traumatic brain injury. *Archives of physical medicine and rehabilitation*, *84*(3), 343-349.

Chisholm, A. E., Malik, R. N., Blouin, J. S., Borisoff, J., Forwell, S., & Lam, T. (2014). Feasibility of sensory tongue stimulation combined with task-specific therapy in people with spinal cord injury: a case study. *Journal of NeuroEngineering and Rehabilitation*, *11*(1), 96.

Cifu, D. X., & Walker, W. C. (2014). Cranial-nerve non-invasive neuromodulation (CN-NINM) for balance deficits after mild traumatic brain injury (pilot & full trial). Retrieved from https://clinicaltrials.gov/ct2/show/NCT02109198 (Identification No. NCT02109198) and https://clinicaltrials.gov/ct2/show/NCT02125591 (Identification No. NCT02125591)

Crown, J. (2013). Mouth device in clinical trials as possible treatment for TBI. Retrieved from http://www.army.mil/article/96521/

Curley, K. (2013). TBI research overview: Rehabilitation in TBI. Retrieved from http://rwtf.defense.gov/Portals/22/Documents/Meetings/m12/081mrmc.pdf

Danilov, Y. P., Tyler, M. E., Skinner, K. L., Hogle, R. A., & Bach-y-Rita, P. (2007). Efficacy of electrotactile vestibular substitution in patients with peripheral and central vestibular loss. *Journal of Vestibular Research*, *17*(2), 119-130.

Ernst, A., Basta, D., Seidl, R. O., Todt, I., Scherer, H., & Clarke, A. (2005). Management of posttraumatic vertigo. *Otolaryngology-Head and Neck Surgery, 132*(4), 554-558.

Hain, T. C. & Yacovino, D. (2005). Pharmacologic treatment of persons with dizziness. *Neurologic Clinics*, *23*(8), 831-853.

Helius Medical Technologies. (2015). The PoNS device. Retrieved from http://www.heliusmedical.com/

Herdman, S. J., Clendaniel, R. A., Mattox, D. E., Holliday, M. J, & Niparko, J. K. (1995). Vestibular adaptation exercises and recovery: acute stage after acoustic neuroma resection. *Otolaryngology-Head and Neck Surgery*, *113*, 77-87.

Hoffer, M. E. (2013). The use of the PoNS device in the treatment of blunt and blast induced vestibular disorders. Retrieved from https://clinicaltrials.gov/ct2/show/NCT01771575 (Identification No. NCT01771575)

Hoffer, M. E., Gottshall, K. R., Moore, R., Balough, B. J., & Wester, D. (2004). Characterizing and treating dizziness after mild head trauma. *Otology & Neurotology*, *25*(2), 135-138.

Moore, C. (2014, June 19). Increased R&D focus on PoNS neuromodulation therapy device for people with MS; Other neurological conditions. Retrieved from http://multiplesclerosisnewstoday.com/2014/06/19/increased-r-neurological-conditions/

Murray, P. (2014). Helius Medical Technologies feels solution to neurological puzzle within reach. Retrieved from http://www.proactiveinvestors.com/companies/news/56634/helius-medical-technologies-feels-solution-to-neurological-puzzle-within-reach-56634.html

Pyykko, I., Magnusson, M., Schalen, L., & Enbom, H. (1998). Pharmacological treatment of vertigo. *Acta oto-laryngologica. Supplementum. 455*, 77-81.

Shepard, N. T., & Telian, S. A. (1995). Programmatic vestibular rehabilitation. *Otolaryngology-Head and Neck Surgery, 112*(1), 173-182.

The Management of Concussion/mTBI Working Group. (2009, April). Management of Concussion/mild traumatic Brain Injury: VA/DoD Evidence Based Practice. Retrieved from http://www.dcoe.mil/Content/navigation/documents/VA%20Dod%20Management%20of%20Concussion%20mild%20Traumatic%20Brain%20Injury%20Summary.pdf

Thelen, D. G. (2013). Enhanced gait and balance training. Retrieved from https://clinicaltrials.gov/ct2/show/NCT01896466 (Identification No. NCT01896466)

Tyler, M., Danilov, Y., & Bach-y-Rita, P. (2003). Closing an open-loop control system: vestibular substitution through the tongue. *Journal of integrative neuroscience*, *2*(02), 159-164.

Tyler, M. E. (2014a). Noninvasive neuromodulation for treatment of symptoms due to mild or moderate TBI. Retrieved from https://clinicaltrials.gov/ct2/show/NCT02158494 (Identification No. NCT02158494)

Tyler, M. E. (2014b). Exploring the use of non-invasive neuromodulation combined with exercise in people with advanced multiple sclerosis (MS). Retrieved from https://clinicaltrials.gov/ct2/show/NCT02252666 (Identification No. NCT02252666)

Tyler, M. E., Kaczmarek, K. A., Rust, K. L., Subbotin, A. M., Skinner, K. L., & Danilov, Y. P. (2014). Non-invasive neuromodulation to improve gait in chronic multiple sclerosis: a randomized double blind controlled pilot trial. *Journal of Neuroengineering and Rehabilitation*, *11*, 79.

University of Wisconsin Tactile Communications and NeuroHabilitation Laboratory (TCNL). (2013). TCNL joins forces with U.S. Army for research. Retrieved from https://tcnl.bme.wisc.edu/laboratory/news/tcnl-joins-forces-us-army-research

Wildenberg, J. C., Tyler, M. E., Danilov, Y. P., Kaczmarek, K. A., & Meyerand, M. E. (2010). Sustained cortical and subcortical neuromodulation induced by electrical tongue stimulation. *Brain imaging and behavior*, *4*(3-4), 199-211.

Yardley, L., Beech, S., Zander, L., Evans, T., & Weinman, J. (1998). A randomized controlled trial of exercise therapy for dizziness and vertigo in primary care. *The British Journal of General Practice*, *48*(429), 1136-1140.

Appendices

Appendix A – Requirements Sources

Appendix B – Traumatic Brain Injury Clinical Tools

Appendix A – Requirements Sources

Table A-1. Guidance for Development of the Force Capability Gaps within the Combat Casualty Care Research Program's Purview

Area	Gap
Priority 1 Capability Gaps	
Joint Casualty Management (JCM)	• **JCM-1-1** – Inadequate ability to diagnose, resuscitate, and stabilize casualties with survivable wounds • **JCM-1-2** – Inadequate initial emergent resuscitative surgery coupled with life and limb saving actions • **JCM-1-2.1** – Inadequate definitive, restorative, and rehabilitative care and surgery for life and limb and eyesight-saving actions • **JCM-1-3** – Inadequate ability to locate and evaluate casualties • **JCM-1-4** – Inability to stop internal bleeding (non-extremity) • **JCM-1-5** – Poor ability to stop life-threatening extremity bleeding • **JCM-1-6** – Poor ability to ensure casualty airway • **JCM-1-7** – Inability to monitor, evaluate, and triage casualties by combat medical personnel for early identification of life saving interventions • **JCM-1-8** – Inadequate therapy for shock and head injury • **JCM-1-8.1** – Inadequate definitive, restorative, and rehabilitative therapy for head injury and shock • **JCM-1-9** – Inadequate battlefield analgesia with minimal side effects • **JCM-1-10** – Inadequate integrated medical information systems across the taxonomy of casualty care • **JCM-1-11** – Inadequate ability to immediately recognize and correct coagulopathy
Joint Patient Movement (JPM)	• **JPM-TER-ER2** – Interoperability between command, control, communications, and computers (C4) systems in support of reception/staging is lacking. A single joint medical C4 system does not exist. Joint medical C4 systems do not provide operational and clinical situational awareness to nonmedical C4 systems. PM and personnel tracking systems do not interact and are labor intensive • **JPM-TRA-AE2** – En-route care lacks standardization. Standardized joint medical equipment for transport of critical patients is lacking. Joint critical care transport capability and training platforms do not exist. There is no joint directive/ authority to ensure standardized Patient Movement Instructions program compliance • **JPM-TRA-AE3** – Interoperability between C4 systems supporting en route care is lacking. A single joint medical C4 system does not exist. Joint medical C4 systems do not provide operational and clinical situational awareness to nonmedical C4 systems. PM and personnel tracking systems do not interact and are labor intensive
Priority 2 Capability Gaps	
JCM	• **JCM-2-1** – Inadequate stabilization of injuries and ability to monitor response to treatment • **JCM-2-2** – Poor ability to provide tissue oxygenation and compatible shelf-stable blood products • **JCM-2-3** – Poor ability to restore blood volume • **JCM-2-4** – Inability to prevent traumatic disconnect/removal of intravenous lines (IVs) • **JCM-2-5** – Inability to prevent bleeding problems associated with hypothermia • **JCM-2-6** – Inability to prevent vomiting due to pain or medications • **JCM-2-8** – Inadequate casualty evacuation (CASEVAC) by non-standard platforms, attended by combat lifesaver en route • **JCM-2-9** – Inadequate ability to operate in a chemical, biological, radiological, and nuclear (CBRN) environment • **JCM-2-10** – Inadequate ability to diagnose, treat, and prevent dental injury and disease

Area	Gap
Joint Human Performance Enhancement (JHPE)	• **JHPE-EPC-PN1** – Provide neuroprotection to decrease brain injury. Inability to provide, in advance or on site, countermeasures to prevent morbidity/mortality directly related to traumatic brain injury (TBI)
Priority 3 Capability Gaps	
JCM	• **JCM-3-1** – Lack of therapeutics to combat infection • **JCM-3-2** – Inadequate medical intelligence
JPM	• **JPM-TER-EC3** – JPM training platforms and skill-identification tracking systems are lacking. Models to replicate medical processes in joint exercise are lacking. Programs to establish JPM leadership development and education are inadequate

Table A-2. Army Theater Combat Casualty Care (TC3) Initial Capabilities Document (ICD) Capability Gaps

Priority Indicator	Description	Parameters
1	**Theater Hospitalization, Area Medical Support**	Diagnose, resuscitate, and stabilize casualties with survivable wounds
1	**Damage Control Surgery**	Initial emergent resuscitative surgery coupled with life- and limb-saving actions
1	**En Route Care**	Locate and evaluate casualties
2	**First Response Medical Care**	Stabilize injuries, monitor response to treatment
1	**Hemostatic Agents and Equipment**	Internal bleeding, external bleeding
1	**Capability to Control Extremity Bleeding (e.g., Tourniquets and Other Technologies)**	Stop life-threatening extremity bleeding
1	**Airway Management Technology**	Ensure casualty airway
2	**Blood Substitutes**	Provide tissue oxygenation, compatible blood types, shelf stable
2	**Rapid Administration of Fluids**	Restore blood volume
2	**IV Line Stabilization Devices**	Prevent traumatic disinsertion of IVs
2	**Advanced Casualty Locating and Remote Physiologic Monitoring**	Monitor, evaluate, triage casualties by combat medical personnel for early identification of life-saving interventions
2	**Adjunctive Medications for Trauma Management**	Therapy for shock and head injury
3	**Pain Management Medications**	Battlefield analgesia with minimal side effects
3	**Hypothermia Prevention Equipment**	Prevent bleeding problems associated with hypothermia
3	**Anti-Vomiting Medications**	Prevent vomiting due to pain or medications
3	**Sepsis Countermeasures**	Therapeutics to combat infection
2	**Casualty Movement (1)**	Medical evacuation (MEDEVAC) by organic or supporting attended medical evacuation platforms with en route care
2	**Casualty Movement (2)**	CASEVAC by non-standard platforms, attended by combat lifesaver en-route
3	**Collective Protection for Medical Functions**	Ability to operate in a CBRN environment
2	**Medical Situational Awareness**	Integrated medical information system
2	**Public Health, Preventive Medicine**	Medical intelligence
2	**Dental Treatment**	Diagnose, treat, and prevent dental injury and disease
2	**Radiofrequency (RF) Dependent Systems**	RF dependent systems fielded as part of the Tactical Combat Casualty Care (TCCC) capability shall comply with applicable Department of Defense (DoD), Service, Joint, National, and International spectrum management policies and regulations
1	**Coagulopathy Prevention and Treatment Agents**	Immediate recognition and correction of coagulopathy

Table A-3. Defense Health Program Combat Casualty Care ICD Medical Research Capability Gaps

Task	Gap Area
Develop Knowledge (DK)	• **DK1** – Inconsistent approach to producing knowledge products and tools - Inadequate process to introduce public health surveillance into research, development, test, and evaluation (RDT&E) - Inadequate surveillance, data capture, and exposure documentation tracking - Inconsistent use and application of Service's lessons learned information and how it affects the health community's RDT&E • **DK2** – Lead-times for new technology are very long and hindered by the current processes (requirements, funding, development, etc.) • **DK3** – Lack a decision support mechanism that enables timely, accurate decisions and diagnosis at all levels of care • **DK4** – Lack of evidence-based clinical data to support decision-making regarding the protocol (all levels) and timing (particularly for strategic movement) of post-surgical patients • **DK5 –** Lack of a system that formally links Joint Trauma System data into the development of Personnel Protective Equipment (PPE)
Enhance Psychological Abilities (EPA)	• **EPA1** – Insufficient understanding of the effects of a blast event on neurologic tissue to develop immediate therapeutics and mitigation strategies for long-term negative effects • **EPA2** – Insufficient understanding of the predisposition causes and "triggers" of suicidal ideation or suicidal attempts in order to develop mitigation strategies
Enhance Physiological and Physical Abilities (EPPA)	• **EPPA1** – Lack of understanding of how to maintain physical and mental performance under severe stress • **EPPA2** – Lack understanding of physiological and physical factors that cause different reactions to the same trauma • **EPPA3** – Insufficient evidence-based trauma-related literature for the combat environment (Insufficient opportunity to perform randomized controlled trials on the battlefield) • **EPPA4** – Lack understanding of physical and physiological factors that drive individual tolerance to environmental (heat, cold, and altitude) conditions in training and operational settings • **EPPA5** – Lack understanding of physical and physiological factors that drive individual tolerance to sleep deprivation • **EPPA6** – Insufficient understanding of the role of physical fitness as a factor in individual resistance to disease and injury with the desired objective of implementing programs based on empirical data in order to minimize individual disease/injury susceptibility • **EPPA7** – Insufficient understanding of the short and long term effects of the use of or withdrawal from dietary supplements/performance enhancing drugs • **EPPA8** – Lack of an integrated approach to solving gaps related to prevention of psychological issues (i.e., creating psychological resilience) • **EPPA9** – Insufficient approaches to prevent injuries caused by occupational, environmental, or tactical exposure to noise, blast, and directed-energy weapons to eyesight, hearing, and vestibular system, while preserving situational awareness • **EPPA10** – Insufficient approaches to prevent injuries caused by occupational, environmental, or tactical exposure to noise, blast, and directed-energy weapons to epidermis and sensory organs • **EPPA11** – Lack formal system for providing medical evidence-based feedback to PPE developers • **EPPA12** – MILSPEC requirements are not optimized for medical considerations in real-world operational environments • **EPPA13** – MILSPEC requirements are not always properly validated for the personal protection level it is supposed to provide in the operational environment

Task	Gap Area
Triage Injuries (TI)	• **TI1** – Insufficient current first-responder (medical and non-medical) capacity and capability to initially assess, treat, and maintain severe trauma cases in the pre-hospital environment - Insufficient initial and ongoing training for first responders in the pre-hospital environment overall - Insufficient tools that enable both non-medical and medical first responders - The technologies do not exist to fulfill some of the needs (e.g., stabilizing the airway or truncal hemorrhage) - Incorrect alignment of trained skill sets and operational needs - Inconsistent integration of recurrent medical training into overall unit training • **TI2** – Prehospital Trauma Life Support, Advanced Trauma Life Support (ATLS), and TCCC curricula are sometimes in conflict and are not standardized; combat casualty care training/principles at all levels are unequally and inconsistently applied (parts of ATLS not validated) • **TI3** – No common TCCC tactics, techniques, and procedures for first responders and medical practitioners across Services and across the continuum of care • **TI4** – Lack an understanding of the effectiveness of the current pre-hospital triage system to determine if it is valid and correctly performed • **TI5** – Inability to allocate optimal resources for patient movement - Lack sufficient situational awareness (patient, transport, medical resources) - Lack command and control to direct operational elements • **TI6** – First responders lack interoperable ways and means to understand and provide rapid, reliable, and actionable information about a casualty's physiological/psychological status in the pre-hospital environment (for information technology [IT] devices there are no defined key performance parameter requirements; no clearly defined MILSPECS for non-IT) • **TI7** – Current ways and means of documenting at point of injury (POI) hinder ability to capture rapid, reliable and actionable information about a casualty's physiological status in the pre-hospital environment and subsequently transmit it for follow on analysis • **TI8** – Limited ability to properly diagnose and treat seen and unseen non-compressible hemorrhage in the pre-hospital environment • **TI9** – Current ways and means of training medical and non-medical providers for treating trauma are inadequate to maintain proficiency • **TI10** – Reviewing and optimizing planning tools to identify medical capabilities early to accommodate pre-deployment training (Global Force Management issue) - Specifically chosen skill-sets, planning timelines, and force management processes don't facilitate required pre-deployment training - Insufficient identification of critical skills at every level needed for care in the operational environment - Develop pathway for sustainment of these critical skills • **TI11** – Lack of computational algorithms and predictive tools for physiological status that use available information and can predict necessary statuses in an expedient manner • **TI12** – In pre-hospital environment, lack ways and means to enable clinical decision support and have inadequate ways and means to enable clinical decision support at Level III and higher • **TI13** – Insufficient current ability to replicate individual physical requirements of a deployed environment. (Current training scenarios do not effectively simulate the physical requirements of handling equipment and supplies utilized throughout deployment, resulting in complications to both medical treatment and increased incidence of injury (e.g., musculoskeletal due to heavy weights) • **TI14** – Lack the ability to use modern imaging or emerging biomarkers in the diagnosis of TBI

Task	Gap Area
Manage Circulation (MC)	• **MC1** – Current training venues do not adequately replicate the stress of battlefield conditions on the providers • **MC2** – Medical and non-medical first responders frequently misuse medical equipment (i.e., tourniquets) that is provided to control hemorrhage in the TCCC setting • **MC3** – Current system for approving medical equipment, therapies, and products is not responsive to the needs of military medicine (dependent upon U.S. Food and Drug Administration [FDA]-approval for very specific uses) • **MC4** – Limited ability to limit access to unregulated or counterfeit medical equipment and supplies • **MC5** – Untimely and inefficient system to ensure dissemination of recall notices on medical equipment and supplies • **MC6** – Lack of optimal blood expander with oxygenation capability and fluid resuscitative strategy at POI
Manage Breathing (MB)	• **MB1** – Inability to provide analgesia without depressing respiration and circulation in the pre-hospital environment • **MB2** – Lack of treatment strategies in the pre-hospital environment for severe/acute respiratory injuries (e.g., inhalation injuries) including but not limited to extra corporeal life support • **MB3** – In pre-hospital environment there is a lack of understanding of modulation process for acute inflammatory response to injury • **MB4** – In the pre-hospital environment there is a lack of understanding of the optimal oxygen requirements for casualties • **MB5** – First responders do not have a means to provide supplemental oxygen • **MB6** – Limited capability to identify and treat lung function problems and respiratory failure in the pre-hospital environment
Manage the Airway (MA)	• **MA1** – Lack of peer review for deviations from standard clinical practice guidelines necessary to validate, institutionalize, and update the treatment guidelines at POI • **MA2** – Uneven application of standards of care at POI due to physician purview for delegation of credentialing authority • **MA3** – Lack of adequate tools for first responders to establish and maintain the airway in a pre-hospital environment • **MA4** – Lack of authorities and/or skillsets to establish and maintain the airway in a pre-hospital environment • **MA5** – Insufficient capability to diagnose and manage tension pneumothorax in a POI and pre-hospital environment • **MA6** – Lack of ability to identify arterial oxygen and CO_2 levels • **MA7** – Lack of ability to maintain optimal arterial oxygen and CO_2 levels in the pre-hospital environment
Identify and Manage Fractures/Wounds (IMFW)	• **IMFW1** – Lack of a basic understanding of relationships between wounds, bacteria, therapies, nano-particles, toxic industrial chemicals, and systemic responses (both at the POI and at the hospital), to include common definitions of wound infection • **IMFW2** – Limited ability to stabilize long-bone fractures for extended transport in the pre-hospital environment that promotes future healing and reduces incidence of complications (such as heterotopic ossification and fracture non-union) • **IMFW3** – Lack of ability to rapidly detect and treat internal non-compressible bleeding caused by complex pelvic fracture in the pre-hospital environment • **IMFW4** – Lack of ability to identify and monitor internal injuries in extended time in the pre-hospital environment • **IMFW5** – Lack of preventing wound infections (physical capabilities section)

Task	Gap Area
Treat for Shock (TS)	• **TS1** – Lack of optimal resuscitation strategies for casualties who have TBI and are in, or at risk for, hemorrhagic shock • **TS2** – Lack of optimal therapies to manage hypo and hyperthermia in the pre-hospital environment • **TS3** – Lack of suitable resuscitative fluids (e.g., blood products or substitutes) appropriate for administration in the pre-hospital environment in order to prevent shock • **TS4** – Lack of ways and means to effectively screen for and diagnose shock throughout continuum of care • **TS5** – Insufficient understanding of the patient's predisposition to outcomes of hemorrhagic shock (Related to genomics/OMICS, immune-modulation or inflammatory response mentioned above) • **TS6** – Insufficient ways and means to diagnose and manage vascular disruption (with or without hemorrhagic shock)
Manage Blood Circulation (MBC) (Hemorrhage)	• **MBC1** – Lack of non-surgical means to treat non-compressible truncal/torso hemorrhage in the pre-hospital environment • **MBC2** – Lack of ways and means to manage circulations and control junctional and truncal hemorrhaging in the pre-hospital environment
Manage Head and Spine (MHS)	• **MHS1** – Insufficient understanding of the pathobiology of military TBIs, particularly blast-induced neurotrauma • **MHS2** – Insufficient understanding of the cumulative and long term effects of single/multiple over-pressure exposures, to include non-combat exposure (e.g., training) • **MHS3** – Lack of a strategy to prevent progression of traumatic central nervous system injury following complex combat injuries • **MHS4** – Insufficient non-invasive techniques to continuously monitor intra-cranial pressure • **MHS5** – Inability to objectively and definitively identify or treat TBI (or make return to duty [RTD] determination) in the pre-hospital environment where there are no visible external indications (across the spectrum from mild, moderate, to severe) • **MHS6** – Lack of suitable ways and means to detect and manage the spinal cord in casualties with suspected spinal cord injuries in the pre-hospital environment • **MHS7** – Lack of knowledge regarding the effects of different types of PPE on non-impact, blast induced brain injury/damage • **MHS8** – Lack of understanding of the effects of helmet attachments (axial load) with and without traumatic head/neck injury • **MHS9** – Lack of capability to objectively and definitively identify and treat TBI/concussion immediately following traumatic event
Maintain Tissue Viability (MTV)	• **MTV1** – Insufficient understanding of the acute inflammatory response to combat injury and its consequences • **MTV2** – Lack of a comprehensive burn management strategy in the pre-hospital environment • **MTV3** – Lack of knowledge, skills, and tools to provide extra corporeal support in the setting of single and multi-system organ failure across the continuum of care • **MTV4** – Lack of knowledge, skills, and tools to stabilize global tissue metabolism following combat injury • **MTV5** – Lack knowledge, skills, and tools to prevent negative impacts of shock from burns during lengthy transports in the pre-hospital environment • **MTV6** – Limited deployed abilities and therapies to stabilize large area, deep, and partial thickness burns • **MTV7** – At POI, lack adequate ways and means to address the following: - Pain control related to complex soft tissue wounds - Adequate debridement of complex soft tissue wounds - Number the tasks and correspond number with solution - Control of bio burden related to complex soft tissue wounds
Evaluate Casualty for Return to Duty (RTD)	• **RTD1** – Lack of objective assessment tools to determine fitness for duty in the case of sub-acute injury in the pre-hospital environment

Task	Gap Area
Patient Documentation and Communication (PDC1)	• **PDC1** – Lack the suitable, interoperable ways and means to capture, transmit, and store TC3 data in the pre-hospital environment • **PDC2** – Ineffective and inconsistent patient regulating paradigms across Roles and components • **PDC3** – Lack of electronic medical record spanning the spectrum of combat casualty care architecture integrated into the Joint Trauma System DoD Trauma Registry
Identify and Manage Infectious/ Contaminated Patients (IMICP)	• **IMICP1** – Insufficient understanding of indigenous bacterial and fungal flora or implantation of fungal elements and bacteria from debris into complex soft tissue wounds • **IMICP2** – Insufficient understanding of the variety of internal and external bacteria/flora in foreign environments makes it difficult to treat and evacuate patients safely • **IMICP3** – Inability to rapidly identify, diagnose, and mitigate the negative impact of invasive fungal infections associated with complex soft tissue wounds (dismounted complex blast injury- complex battle injury) • **IMICP4** – Lack of understanding of patient-specific (genetic) susceptibility to bacterial and fungal infections • **IMICP5** – Inadequate antimicrobial intervention strategies applicable to multi-drug resistant organisms, bacterial and fungal • **IMICP6** – Insufficient knowledge, skills, and tools to effectively debride, irrigate, and control (dress) complex soft tissue wounds in a prolonged/extended pre-hospital scenario (austere environment) • **IMICP7** – Inadequate tools, techniques, and therapies to manage and/or treat CBRNE/infections to include nosocomial in pre-hospital environment • **IMICP8** – Lack of standard guidelines for declaring patients free of infection • **IMICP9** – Lack of ways and means to address infections in a timely manner
Pain Management (PM)	• **PM** – Current regulatory processes, such as FDA approval, inhibit timely translation of medical research for pain management into fielded capabilities (e.g., fielding morphine replacement)
Recognize Signs of Psychological Trauma (RSPT)	• **RSPT** – Lack of objective tool to evaluate psychological trauma
Maintain Psychological Functioning/Cognitive Functioning (MPFCF)	• **MPFCF1** – Lack of a system to assess and monitor an individual's psychological baseline (to include screening for alcohol/substance abuse issues, and predisposition to behavioral characteristics) • **MPFCF2** – Lack of long-term, effective therapies for psychological trauma • **MPFCF3** – Insufficient post-traumatic event screening to diagnose trauma to prevent degradation of psychological function • **MPFCF4** – Insufficient understanding of the core mechanisms (both physiological responses and therapies) of psychological responses • **MPFCF5** – Lack of understanding of the relationship between degrees of aptitude and psychological resilience across the force • **MPFCF6** – Lack understanding of why emotional and psychological responses to traumatic events manifest differently in different individuals • **MPFCF7** – Insufficient understanding of predisposition to behavioral characteristics (high risk behaviors) that degrade resiliency prior to service • **MPFCF8** – Inconsistent application of individualized cognitive assessments for use at appropriate times to support analysis down the continuum of care

Task	Gap Area
Preserve Life (PL)	• **PL1** – Lack of evidence-based data and metrics to assess the effectiveness of training methodologies, specifically TC3, to include both technical skills such as establishing surgical airways, and cognitive skills, such as decision-making in a complex tactical casualty scenario • **PL2** – Insufficient surgical capability to manage torso hemorrhage, junctional hemorrhage, airway compromise, and tension pneumothorax in a pre-hospital environment due to insufficient tools, techniques, therapies, and trainings • **PL3** – Lack of evidence-based clinical data to support decision-making regarding the protocol (all levels) and timing (particularly for strategic movement) of post-surgical patients • **PL4** – Limited prevention and treatment therapy options for large area, deep, and partial thickness burns • **PL5** – Lack of evidence based data to improve overall combat-related injury infection care • Insufficient understanding of the acute inflammatory response to combat injury and its consequences • **PL6** – Limited therapies for damage control resuscitation in traumatic injury, to include neuronal damage • **PL7** – Insufficient knowledge of the use and effects of regional anesthesia/analgesia modalities for complex war time injuries • **PL8** – Inability to test for the presence of blood pathogens at pre-U.S. hospital (malaria, human immunodeficiency virus, hepatitis, etc. for local blood and direct transfusions) in order to reduce morbidity and mortality in the field
Prevent Loss of Use of Limb(s) (PLUL)	• **PLUL1** – Inadequate psychosocial interventions for individuals with severe bodily distortion (e.g., limb loss, burns, facial trauma, and genital/urinary loss from complex dismounted blast injury) • **PLUL2** – Insufficient understanding of the differences in long term psychological and functional outcomes of primary amputation vice dysfunctional extremity retention • **PLUL3** – There is a lack of understanding of the long term quality of life impact of initial (within the first year) treatment among individuals with limb amputations • **PLUL4** – There is insufficient understanding of the impact of vascular disruption, repair, extremity ischemia and reperfusion and its relationship to long term limb recovery and function - Insufficient modalities to mitigate injurious effects of ischemia reperfusion on skeletal muscle, bone, and peripheral nerve - Insufficient technology for vascular conduits to perform vascular reconstruction - Lack of a standardized, clinically relevant decision support model for severely mangled extremities (i.e., decisions regarding primary amputation vs. pursuit of limb salvage, optimal amputation level to support future treatment (i.e., transplant, prosthetic, etc.) • **PLUL5** – Insufficient knowledge (e.g., immune suppression etc.) and technologies (e.g., modulation, etc.) to facilitate auto- and allotransplantation of tissues and (potentially) functional limbs to support advanced reconstruction modalities • **PLUL6** – Insufficient understanding of the injury complex and approaches to reconstruction and long term rehabilitation and recovery (e.g., dismounted complex blast injuries to include perianal, lower colorectal/anal injuries, genital/urinary to include loss of reproductive function) • **PLUL7** – Current weight/cube requirements of Class VIII materiel adversely affects quality of care and soldier loads and subsequently limits quality care options at POI • **PLUL8** – Lack of good upper extremity prosthetics and amputation solutions (arm, hand, etc.) • **PLUL9** – Insufficient ability to preserve genital-urinary tissue for re-construction capability across the board

Task	Gap Area
Maintain Sensory Systems (MSS)	• **MSS1** – Insufficient therapeutics for ocular injuries (e.g., corneal and retinal wound repair), including regenerative medicine technologies • **MSS2** – Insufficient hearing and vestibular rehabilitation research for: - Improved diagnostics - Regenerative medicine-based approaches - Technologies supporting restoration to Service member-level capabilities - Hearing loss and tinnitus • **MSS3** – Lack of assessment or rehabilitation ability for balance issues
Maintain Brain Function (MBF)	• **MBF1** – Lack of understanding of TBI (combat and non-combat related): - Relationship of the wartime injury (including TBI) and psychiatric morbidity - Neuroplasticity (brain recovery) following traumatic combat-related TBI - Pathobiology and body responses of long-term and acute TBIs (see earlier TBI discussion) - Relationship between TBIs and psychological reactions to combat stress - Insufficient data that ties blast exposure to injury in order to establish correlation - Insufficient full-spectrum treatment options for TBI (e.g., pharmaceuticals, neuro-protectives, etc.) - Reliance upon self-reporting (over self-reporting and under self-reporting are both common) - Lack of coherent strategy for development of improved neuro-cognitive assessment tool • **MBF2** – Inability to diagnose on the battlefield
Conduct Mental Rehabilitation (CMR)	• **CMR** – Insufficient understanding of triggers, and individual responses to them, that result in suicidal, acute mental decompensation, breakdown/acute posttraumatic stress disorder (PTSD), and homicidal ideation
Repair Physical Injuries (RPI) Throughout the Body	• **RPI 1** – Lack ability to conduct non-invasive physiological monitoring (intra-cranial, compartment syndrome, intra-abdominal pressure, etc.) • **RPI 2** – Insufficient understanding of how to mitigate the negative impact of long flights on a critically injured patient (altitude, temperature, duration) • **RPI 3** – Insufficient approaches to repair injuries caused by occupational, environmental, or tactical exposure to noise, blast, and directed-energy weapons to eyesight, hearing and epidermis
Identify Infectious Disease (IID)	• **IID** – Limited infectious disease detection and diagnostic ability in an austere and/or pre-hospital environment
Regenerative Care	• **Regenerative Care** – Lack of ability to regenerate or restore certain tissues and/or functions (e.g., large bone, vision, genitourinary (GU), over 40 percent burn patients, upper extremity function, spinal cord, peripheral nerves, brain function) • **Regenerative Care** – Lack of evidence-based understanding and knowledge of benchmarks for regenerative medicine (e.g., relevant animal models, regulatory guidelines, and technology)
Restorative Care	• **Restorative Care** – Insufficient understanding of the healing process associated with physical injuries to the brain, versus healing process associated with brain's response to other body-wide injuries • **Restorative Care** – Insufficient understanding of the short term and long term effects of mild TBI (mTBI) on cognitive and behavioral abilities • **Restorative Care** – Insufficient understanding of human immunosuppression response to skin graft rejection/acceptance, specifically for patients with massive skin injuries • **Restorative Care** – Inability to replace large bone, vision, hearing, GU, specifically for patients with over 40 percent burns, wounds to the upper extremity function, spinal cord, peripheral nerves, brain function • **Restorative Care** – Lack understanding of long term data pertaining to functional patient outcomes of initial and long-term mTBI therapies

Task	Gap Area
Rehabilitative Care (RHBC)	• **RHBC1** – Lack the understanding of the short-term and long-term effects of TBI (combat and non-combat related) on individuals: - Relationship between mTBI and PTSD - Effectiveness of current and emerging mTBI therapies - Effectiveness of current mTBI screening criteria - Objective screening capability to detect and measure suspected mTBI - Co-morbidities associated with TBI - Lack of evidence-based data to indicate effectiveness of current therapies • **RHBC2** – Inadequate sustained neuromusculoskeletal rehabilitation clinical research capabilities at local military treatment facilities (only available at major installations)
Re-Integrate	• **Re-Integrate** – Inadequate understanding of the impact of societal factors (alcohol and drug use, high risk behavior) on resilience and recovery

Appendix B – Traumatic Brain Injury Clinical Tools

The following table contains a selection of Department of Defense (DoD) clinical tools used in the management of traumatic brain injury (TBI). These include clinical practice guidelines (CPGs), clinical recommendations, algorithms, and other tools that may be impacted by the introduction of new diagnostic and treatment capabilities developed through the Neurotrauma portfolio.

While the table is not an exhaustive list of the continually evolving tools supporting the assessment and care of individuals with TBI, it reflects important relevant examples.

Table B-1. DoD Clinical Tools for TBI

Source	Clinical Tool
Resources Monitored and Updated by the Joint Trauma System	• DoD Instruction (DODI) 6490.11 – DoD Policy Guidance for Management of Mild Traumatic Brain Injury (mTBI)/Concussion in the Deployed Setting • Joint Theater Trauma System (JTTS) Clinical Practice Guideline (CPG) – Use of Magnetic Resonance Imaging (MRI) in Management of Mild Traumatic Brain Injury (mTBI)/Concussion in the Deployed Setting • JTTS CPG – Management of Patients with Severe Head Trauma • Tactical Combat Casualty Care Guidelines
Resources Supplied through the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (DCoE)	• Assessment and Management of Dizziness Associated with Mild TBI – Clinical Recommendation • Concussion Management Algorithm Pocket Cards • Military Acute Concussion Evaluation • U.S. Department of Veterans Affairs/Department of Defense CPG for Management of Concussion/Mild Traumatic Brain Injury