Interagency Strategic Plan

Research and Development of Blood Products and Related Technologies for Trauma Care and Emergency Preparedness

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Table of Contents

Introduction 1
BARDA 2
DoD 2
FDA OCET 2
NHLBI 3
Threats and Capability Gaps 4
Capability Gaps 5
Vision, Mission, and Core Values 6
Vision 6
Mission 6
Core Values 6
Strategic Goals 7
Goal 1: Enhanced Coordination 7
Enhanced Coordination Objectives 7
Goal 2: New and Improved Blood Products 7
New and Improved Blood Product Objectives.. 7
Goal 3: Maximize Survivability 8
Maximize Survivability Objectives 8
Goal 4: System Enhancement 8
System Enhancement Objectives 8
Goal 5: Personnel Readiness and Science Preparedness 9
Personnel Readiness and Science Preparedness Objectives 9
Approach to Interagency Collaboration and Coordination 10
Competencies and Resources 11
Implementation and Optimization 13
1. Interagency communication, program assessment, and planning 13
2. Transagency leadership support 14
3. Commitments and Agreements 14
Current and Future Collaborations 15
Current Collaborations 15
Future Collaborations 16

References 19
Appendix A – Points of Contact 20
Appendix B – Stakeholder Organizations 21

List of Tables

Table 1. Distinctive Competencies Within and Across Agencies 11

Acronyms and Abbreviations

ARS	Acute Radiation Syndrome
ASBP	Armed Services Blood Program
ASCO	American Society of Clinical Oncology
ASPR	Office of the Assistant Secretary for Preparedness and Response
BARDA	Biomedical Advanced Research and Development Authority
CBRN	Chemical, Biological, Radiological, Nuclear
CCCRP	Combat Casualty Care Research Program
CDC	Centers for Disease Control
CONOPS	Concept of Operations
DBDR	Division of Blood Diseases and Resources
DHHS	Department of Health and Human Services
DoD	Department of Defense
FDA	U.S. Food and Drug Administration
FDA OCET	U.S. Food and Drug Administration Office of Counterterrorism and Emerging Threats
HHS/ASH	Office of the Assistant Secretary for Health
HIV	Human Immunodeficiency Virus
HTLV	Human T-Cell Lymphotrophic Virus
IDSA	Infectious Diseases Society of America
IED	Improvised Explosive Device
JPC-6	Joint Program Committee 6
MCM	Medical Countermeasures
NATO	North Atlantic Treaty Organization
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NORAD	North American Aerospace Defense Command
PDHA	Platelet-Derived Hemostatic Agent
PHEMCE	Public Health Emergency Medical Countermeasures Enterprise
PROPPR	Pragmatic Randomized Optimal Platelet and Plasma Ration Study
R&D	Research and Development
RECESS	Red Cell Storage duration Study
ROC	Resuscitation Outcomes Consortium
SBIR	Small Business Innovation Research
SNS	Strategic National Stockpile
TACTIC	Trans-Agency Consortium for Trauma Induced Coagulopathy
TATRC	Telemedicine and Advanced Technology Research Center
U.S.	United States
USAMMDA	U.S. Army Medical Materiel Development Activity
USNORTHCOM	United Stated Northern Command
VA	U.S. Department of Veteran Affairs

Introduction

Therapies, including blood components and related products, are essential in treating patients with congenital and acquired diseases of the hematopoietic, hemostatic, and immune system; as well as patients with cancer, viral hemorrhagic diseases; or after surgery, trauma, and acute radiation sickness.

Intensive blood use is expected to occur at levels which will overwhelm blood supplies as they exist with current capabilities and technologies, both in civilian mass casualty events and in military battlefield trauma. The development of effective medical countermeasures (MCM) will require a focused and sustained interagency research and development (R&D) effort.

New technologies are needed to provide safer, more effective, and more logistically supportable blood and related products to treat patients with, or at risk of developing, acquired bleeding disorders as a result of trauma, acute radiation exposure, or other causes.

As three of the primary agencies with major programs in R&D related to blood products, the Biomedical Advanced Research and Development Authority (BARDA), the Department of Defense (DoD), and the National Heart, Lung, and Blood Institute (NHLBI) are uniquely positioned to partner in addressing these issues, which have significant implications for each respective agency, as well as for the United States (U.S.) population. Providing leadership, coordination, and oversight for the Food and Drug Administration's (FDA) national and global health security, counterterrorism, and emerging threats portfolios, the U.S. Food and Drug Administration Office of Counterterrorism and Emerging Threats (FDA OCET) serves in a critical advisory and facilitative role with regard to development and availability of blood products.

BARDA, the DoD, and the NHLBI have built robust interagency collaborative relations in recent years, which provide proof of concept and a strong foundation on which to build a plan for expanded interagency cooperation in the future, and the FDA OCET has been proactively engaged via an advisory capacity. In response to a recommendation issued by the National Security Staff during the 28 May 2013 "Catastrophic Events, Blood Availability" meeting, the 2015 Interagency Strategic Plan for Research and Development of Blood Products and Related Technologies for Trauma Care and Emergency Preparedness expands upon this foundation of collaboration. It is also responsive to the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) broad framework for interagency cooperation in emergency preparedness and the recommendations of the GAO report to expand trans-federal cooperation (GAO, 2009; GAO, 2013). This strategic plan provides a specific framework for cooperation in R&D, focused on blood products and related technologies for emergency preparedness.

This plan is informed by the 2012 PHEMCE Strategy (U.S. Department of Health and Human Services [DHHS], 2012), the 2007 "Shaping the Future of Research" Strategic Plan for the National Heart, Lung, and Blood Institute (U.S. DHHS, 2007), the 2011 BARDA Strategic Plan (U.S. DHHS, 2011), the DoD Combat Casualty Care Research Program: Policy Review (DoD, 2015), the 2015 DoD Hemorrhage and Resuscitation Research and Development Strategic Plan

(DoD, 2015; Pusateri and Dubick, 2015), and the more than 30 participants from multiple agencies who composed the Interagency Collaboration working group. The current plan focuses on blood products, but accounts for other areas of injury research and could serve as the basis for a national research action plan (NRAP).

BARDA

BARDA's mission is to develop and procure medical countermeasures that address the public health and medical consequences of chemical, biological, radiological, and nuclear (CBRN) accidents, incidents and attacks, pandemic influenza, and emerging infectious diseases.

Specifically, BARDA supports the advanced development and procurement of drugs, vaccines and other products that are considered priorities for national health security. BARDA funding bridges the "valley of death" characterizing the late stages of product development. BARDA's support ensures continuity of funding at a critical point for MCMs developed by industry or emerging from the basic research and preclinical development activities sponsored by the National Institutes of Health (NIH). In procuring MCMs for the Strategic National Stockpile (SNS), BARDA enhances the capabilities of the Centers for Disease Control and Prevention (CDC) to organize an effective response to a national security emergency or disaster.

BARDA is a core component of the Office of the Assistant Secretary for Preparedness and Response (ASPR) and as such contributes to the broader ASPR mission to "Lead the country in preparing for, responding to, and recovering from the adverse health effects of emergencies and disasters by supporting our communities' ability to withstand adversity, strengthening our health and response systems, and enhancing national health security."

DoD

The U.S. DoD Combat Casualty Care Research Program (CCCRP) conducts research programs to develop means to reduce mortality and morbidity in wounded service men and women. The program spans all significant categories of trauma, including traumatic brain injury, traumatic hemorrhage, and others. Hemorrhage is the leading cause of potentially preventable death from combat trauma. Therefore, the DoD's Hemorrhage and Resuscitation R&D Program develops new methods and technologies to control bleeding, replace lost blood volume, and mitigate the pathophysiologic response to traumatic hemorrhage. A significant component of the program is related to the development of improved blood products for use in austere and conflict environments around the world, including near the point of injury, at forward surgical units and deployed hospitals, on ships, and in the air.

FDA OCET

FDA OCET provides leadership, coordination, and oversight for FDA's national and global health security, counterterrorism, and emerging threats portfolios. It performs critical advisory and facilitation functions that contribute significantly to the other agency programs regarding the

development and availability of blood products for emergency preparedness. FDA OCET also supports intramural and extramural regulatory science projects to develop tools, standards, and approaches to assess medical countermeasures.

NHLBI

The NHLBI provides global leadership for research, training, and education programs to promote the prevention and treatment of heart, lung, and blood diseases and enhance the health of all individuals so that they can live longer and more fulfilling lives. The breadth of the Institute's programs reflects the breadth of its mandate, which includes three of the four leading causes of death in the United States.

While necessarily focusing considerable effort and resources on diseases that affect large numbers of people, the Institute also recognizes its obligation to address those conditions that do not themselves constitute a major public health burden but do impose serious health burdens on affected individuals. To achieve its vision, the NHLBI stimulates basic discoveries about the causes of disease, speeds the translation of basic discoveries into clinical practice, fosters training and mentoring of emerging scientists and physicians, and communicates research advances to the public. The NHLBI creates and supports a robust, collaborative research infrastructure in partnership with private and public organizations, including academic institutions, industry, and government agencies. The NHLBI collaborates with stakeholders and the media to maximize the use of research results and leverage resources to address the public health needs of the Nation.

Within the NHLBI, the Division of Blood Diseases and Resources (DBDR) supports research on the causes, prevention, and treatment of nonmalignant blood diseases, including anemias, sickle cell disease, and thalassemia; premalignant processes such as myelodysplastic and myeloproliferative disorders; hemophilia and other abnormalities of hemostasis and thrombosis; and immune dysfunction. Funding encompasses a broad spectrum of research ranging from basic biology to medical management of blood diseases. In addition the NHLBI/DBDR works collaboratively to identify research questions in areas of vascular injury including trauma and sepsis that have direct relevance to enhancing the knowledge base about appropriate biologic interventions in an injury setting.

In addition, DBDR has a major responsibility for research to assure the adequacy and safety of the Nation's blood supply. The Division also has a leading role in applying scientific advances in transfusion medicine and stem cell biology to the development of new cell-based therapies to repair and regenerate human tissues and organs.

Threats and Capability Gaps

The United States faces myriad threats to its national health security in both civilian and military environments including release of CBRN agents, pandemic influenza, infectious disease, transfusion-transmitted disease, and the need to operate in austere environments (U.S. DHHS, 2012). In response to these threats, the Interagency Collaboration provides a robust and flexible R&D capability, responsible for expanding the window for definitive care and increasing the supply of readily accessible, quality blood products with broad clinical application.

- **CBRN Agents.** The accidental, deliberate, or naturally-occurring release of CBRN agents, which may be novel or reemerging, places individuals and/or populations at risk for illness, death, fear, societal disruption, and economic damage. For instance, chemical and biological agents, including threats such as nerve agents, cyanides (e.g., hydrogen cyanide, cyanogen chloride), bacterial toxins, and hemorrhagic fevers, are capable of placing populations at risk and producing societal and economic disruption. Radionuclide agents induce a range of blast radius-dependent traumas, both at time of initial blast and during rescue operations, which require acute treatments and interventions. In addition, exposure to CBRN agents may reduce or eliminate the available donor pool, subsequently increasing overall morbidity. Importantly, radionuclide threats, such as improvised nuclear devices, may result in mass casualties with acute radiation syndrome (ARS). Specific radionuclide threats include, but are not limited to, Co-60, Cs-137, Sr-90, I-131, Ir-192, Po-210, U-235, Pu-239, and Am-241.

- **Pandemic Influenza.** Inadequate detection and response capabilities, including MCM production and distribution, limit the United States' and the global community's ability to effectively respond to pandemic influenza. The need exists for a global MCM capacity. Additionally, pandemic influenza may reduce the available donor pool, as only asymptomatic individuals without close contact with someone with influenza for a period longer than one week are permitted to donate.

- **Infectious Disease.** Infectious diseases caused by various agents such as Babesia, dengue, Ebola, and Nipah viruses; and methicillin-resistant *Staphylococcus aureus*, also present a risk to the available donor pool.

- **Transfusion-Transmitted Disease.** Bacteria such as *Yersinia*, *Proteus*, *Escherichia*, *Staphylococcus*, *Enteroccocus*, *Pseudomonas*, and *Serratia*, as well as viruses such as human immunodeficiency virus (HIV), hepatitis viruses, human T-cell lymphotrophic viruses (HTLVs), Parvovirus B19 are threats currently known to the blood supply. Prions, such as those that cause Creutzfeldt-Jakob disease, cannot be destroyed by any conventional sterilization or pathogen-inactivating methods. As new threats to blood safety are identified, the need for stringent blood donor selection, screening, pathogen inactivation methods, and development of new decontamination techniques remains critical for reducing transfusion-transmitted disease and improving blood safety.

- **Explosive Injuries and Penetrating Trauma.** Improvised explosive devices (IED), along with gunshot wounds, are among the most common causes of battlefield injury and

death in military environments. IEDs and gunshot wounds are also common in civilian environments, as evidenced by events such as the 2013 Boston Marathon bombing and multiple active shooter events since that time. Research is required to reduce fatality following explosive or penetrative injuries.

- **Austere Environments.** In both military and civilian environments, injury frequently occurs in austere and/or geographically remote locations, which may limit or delay access to medical personnel or facilities to deliver treatment. In civilian mass casualty scenarios, infrastructure breakdown may cause significant logistical constraints. Research to enhance the delivery of care in austere and/or remote environments is critical for improving survival following traumatic injury.

- **Military Threats.** In military populations, battlefield injuries present unique logistical and other challenges associated with austere environments, extended distances to treatment facilities, and prolonged evacuation times. Eastridge et al. (2012) identified that approximately 25% of deaths on the battlefield are potentially survivable, with 90.9% of those potentially survivable casualties resulting from severe blood loss, hemorrhage, and/or hemorrhagic shock. Safe and effective blood products are vitally important for treatment of battlefield injuries, as indicated by the magnitude of blood products provided to military, civilian, and enemy combatants in theater (over 300,000 units transfused from 2001-2014).

The interagency effort also faces obstacles unique to the strategic collaboration, including: limited funding; rapid changes in prioritization; a decision making process that may sometimes be driven by short-term fiscal necessity rather than long-term goals; and the inadequacy of current blood products for meeting clinical needs during emergency response.

Capability Gaps

Research within the strategic plan is informed by eight capability gaps prioritized by the Joint Program Committee for Combat Casualty Care (JPC-6) in 2010, and those gaps identified by the interagency working group. The Initial Capabilities Document for Department of Defense (DoD) Combat Casualty Care Medical Research and Development (2015) is also informative. These gaps highlight the capability areas where the agencies should dedicate resources to improve care and enhance survivability:

- Inadequate ability to diagnose, resuscitate, and stabilize casualties with survivable wounds
- Inability to stop internal and external bleeding
- Inadequate therapy for shock and head injury
- Poor ability to stop life-threatening extremity bleeding
- Inadequate ability to immediately recognize and correct coagulopathy
- Poor ability to provide tissue oxygenation and compatible shelf-stable blood products
- Poor ability to restore blood volume
- Inability to prevent bleeding problems associated with hypothermia
- Inadequate ability to replenish or prevent destruction of the hematopoietic system

Vision, Mission, and Core Values

Vision

The Interagency Strategic Plan for Research and Development of Blood Products and Related Technologies for Trauma Care and Emergency Preparedness is committed to maximizing patient outcomes following combat trauma or mass casualty events by accelerating research to expand the window for definitive care and increasing the supply of readily accessible, quality blood products and related technologies with broad clinical application.

Mission

The Interagency Strategic Plan for Research and Development of Blood Products and Related Technologies for Trauma Care and Emergency Preparedness is an effort among the DoD and DHHS (specifically NIH/NHLBI, ASPR/BARDA, and FDA OCET), in collaboration and coordination with other key U.S. Government stakeholders, to **improve patient outcomes** following combat trauma or mass casualty events, and to foster the restoration of health through **leveraging of capabilities across agencies** and **enhanced research** targeted towards filling critical gaps in the delivery of blood products, blood related resources, and related technologies.

Core Values

Members of this interagency strategic collaboration will focus on the following:

- **Commitment.** Maintain sustained commitment and excellence across leadership and generations, demonstrating a willingness to take risks for the common good;
- **Coordination and Collaboration.** Practice fairness, transparency, and respect between agencies to foster coordination and collaboration and enable co-development of programs;
- **Patient-Focus.** Maintain dedication to filling capability gaps surrounding unmet medical needs and focus on patient outcomes in the United States, sharing knowledge and/or technologies with other countries;
- **Showcase Success.** Showcase the successes of individual agency and interagency successes in order to build momentum;
- **Stewardship.** Practice stewardship of brain trust, scientific trust, and public funding used towards military and civilian health in catastrophic events; and
- **Trust.** Foster interagency trust by demonstrating honesty and integrity throughout coordination efforts.

Strategic Goals

Goal 1: Enhanced Coordination

Enhance interagency coordination and collaboration to foster a complete understanding of all portfolios engaged in the blood product and emergency preparedness effort, and to ensure adequate response.

Enhanced Coordination Objectives

- Objective 1.1: Promote frequent and transparent interagency communication and cooperation.
- Objective 1.2: Promote coordination efforts, including expectation for transparency and defined roles with private sector partners.
- Objective 1.3: Establish commitment to interagency priorities, leveraging coordination efforts to minimize the impact of shifting agency priorities.
- Objective 1.4: Leverage resources across agencies to maximize fiduciary impact.
- Objective 1.5: Establish a robust, engaged, and committed leadership team dedicated to advancing blood product and emergency preparedness efforts.
- Objective 1.6: Sustain leadership commitment across and within agencies, including commitment during leadership turnover and shifting priorities.
- Objective 1.7: Establish and maintain a leadership team with clearly defined roles, responsibilities, and accountability measures.

Goal 2: New and Improved Blood Products

Develop new blood products and improve existing, commercially available blood products for use in combat theater, civilian populations, and emergency preparedness.

New and Improved Blood Product Objectives

- Objective 2.1: Enable the development of readily available, sustainable products with broad applicability in routine care and emergency/pandemic situations.
- Objective 2.2: Advocate for reliable, consistent, and sustainable long-term funding (10–15 year commitment) of the blood product and emergency preparedness priorities (i.e., portfolios).

- Objective 2.3: Develop products or technologies targeted at sustaining and maintaining survivability for up to 72 hours prior to hospitalization.
- Objective 2.4: Seek improved therapeutic indices for all interventional blood products (e.g., advocate for use of pathogen-attenuated blood products that have or will receive regulatory approval for use in response to mass casualty events).

Goal 3: Maximize Survivability

Maximize patient survivability in combat theater, civilian populations, and emergency environments.

Maximize Survivability Objectives

- Objective 3.1: Identify and/or develop products to reduce hemorrhage.
- Objective 3.2: Develop products with general applicability in non-emergency environments to ensure availability during catastrophic events.
- Objective 3.3: Promote and maintain visibility into training to enhance personnel competency and readiness, as it relates to products for use during catastrophic events.
- Objective 3.4: Develop devices, therapies, and techniques to stop internal, junctional, and extremity bleeding as close as possible to the point of injury.
- Objective 3.5: Focus on next generation resuscitation approaches for stabilization of hemostatic, inflammatory, and metabolic systems of casualties in the pre-hospital environment (to include metabolic and tissue stabilization, diagnostic and therapeutic development for coagulopathy, and inflammatory modulation)
- Objective 3.6: Develop technologies for stabilization and prolonged field care of patients with injuries such as burn, complex orthopedic, combined radiation and trauma, and others

Goal 4: System Enhancement

Foster system enhancement to incorporate requirements for product development, availability, and sustainment.

System Enhancement Objectives

- Objective 4.1: Maintain visibility into product distribution and implementation.
- Objective 4.2: Enhance logistics training and education programs within the product development lifecycle.

- Objective 4.3: Institute requirements targeted at enabling fielding, maximizing product shelf-life, and easing constitution in the field.
- Objective 4.4: Optimize product and/or training/education distribution through incorporation of requirements in program announcements.
- Objective 4.5: Maintain visibility into, and monitor results of, fielding initiatives to inform R&D efforts and processes through implementation of feedback.
- Objective 4.6: Work within the existing national infrastructure to enhance the logistical response capability for treating individuals with injuries resulting in severe loss of hematopoietic capacity (e.g., evacuation of casualties in a radiation/nuclear event to sites where appropriate bone marrow reconstitution can be performed).
- Objective 4.7: Foster development of interagency solutions through consideration of other agency requirements, such as civilian mass casualty, special population, and military requirements, throughout the product development lifecycle.

Goal 5: Personnel Readiness and Science Preparedness

Establish and maintain personnel readiness and science preparedness.

Personnel Readiness and Science Preparedness Objectives

- Objective 5.1: Promote research and surveillance to increase product safety, reduce adverse effects, and capture the interventional, data collection, and long-term monitoring of victims of mass casualty events.
- Objective 5.2: Promote and maintain visibility on training and education to enhance personnel readiness, specifically include training on trauma use of blood products.
- Objective 5.3: Foster and support ongoing dialogue and strategic partnering with all relevant entities that constitute the U.S. emergency response network (including civilian and military primary, secondary and tertiary responders) to establish and maintain readiness and preparedness for mass casualty events.

Approach to Interagency Collaboration and Coordination

The interagency effort aims to enhance the ability of BARDA, the DoD, and the NHLBI to advance research and development, and to provide more power for funding allocation through collaboration and coordination, with FDA OCET assistance in a consultative and facilitation role. To achieve this, the approach set forth in the strategic plan shall be applied, in general terms, to cooperative efforts among the agencies; goals and executable action plans for specific projects are not prescribed. However, the strategic plan provides the foundation to identify and implement strategic initiatives, as necessary.

This plan provides justification for exploring new collaborations, initiating work, and expanding cooperation. However, for specific projects that are complex or require significant resources, specific agreements between the agencies will be formalized.

The following assumptions represent the external conditions that the interagency collaboration cannot control, but which will affect the success of the efforts. The following dependencies were identified by the interagency working group as essential for optimal development of relevant MCM programs and for successful interagency cooperation. These dependencies provide a framework of common understanding, and should be considered and promoted whenever possible in the execution of this strategic plan.

Assumptions

- Blood products will be used in civilian populations and will require FDA approval.
- Extended evacuation times will increase the proportion of deaths following injury.
- Inter/intra-agency efforts and coordination will continue to be prioritized.
- “Just-in-time” is not an applicable model for product development and storage. Product warehousing will be required.
- There will be a continued need for blood products.

Conditions

- Academia and industry will maintain interest in developing commercially viable products.
- Management (to include government oversight, agency leadership, and directorate leadership) will be supportive of blood product and emergency preparedness product research and development.
- Mechanisms for portfolio management will be functional.
- The U.S. Government will provide substantial funding to support research and development of blood products and related technologies for trauma care and emergency

preparedness (particularly at the discovery phase and for capability maintenance). Minimal, but adequate, funds will exist to develop critical products.

- The scientists, research, and experience exists to address blood product and emergency preparedness needs.

Competencies and Resources

Important and distinctive competencies and resources exist within and across agencies that can be leveraged to benefit interagency programs, outlined in Table 1. The core partners will proactively optimize these competencies, while sharing and allowing access to these resources, where possible, for the benefit of MCM programs of mutual interest. Additionally, the core partners agree to leverage funding through cooperative programs for the benefit of these programs.

Table 1. Distinctive Competencies Within and Across Agencies

Competency	BARDA	DOD	NHLBI	FDA OCET
Access to knowledge base for training	•	•	•	•
Clinical product development	•	•	•	
Regulation of clinical therapeutics				•
Research and development	•	•	•	•
Coordination and relationship maintenance	•	•	•	•
Coordination of FDA's MCM initiative to facilitate the development of safe and effective MCMs against chemical, biological, radiological, and nuclear agents and emerging threats, such as pandemic influenza				•
Core-service networks and relationships including: nonclinical networks, contracts/manufacturing, and clinical trials networks	•	•	•	
Development and coordinated implementation of FDA policies and procedures to foster the development and availability of medical products that will be needed to counter a public health emergency, including efforts to safeguard MCMs from adulteration or disruption of supplies during public health emergencies.				•
Engagement in activities throughout the entire product development lifecycle		•	•	•
Expertise in military and civilian trauma		•	•	

Facilitate communication within FDA and with external partners on counterterrorism policy, public health emergency preparedness, and global health security			•	•
FDA focal point for the HHS PHEMCE and DoD MCM programs to support the warfighter				•
Field testing and evaluation	•	•		
Implementation of comprehensive FDA plans and strategies in collaboration with FDA centers and offices, and with external U.S. Government and international partners				•
Interaction with small businesses	•	•	•	•
Leadership, coordination, and oversight for FDA's national and global health security, counterterrorism, and emerging threats portfolios				•
Medical logistical support for civilian disaster (rapid response network)	• (ASPR)			
Organizations focused on clinical development	•	•		•
Planned emergency research (capacity and network building)	• (ASPR)		•	•
Point of entry on policy and planning matters concerning global health security, counterterrorism, and emergency threats	• (ASPR)			•
Scientific readiness	•	•	•	•
Service labs for combat casualty care		•		
Subject matter expertise including: manufacturing, translation, blood banking, basic science, applied science, clinical trials, etc.	•	•	•	•

Resources. The core partners will share and allow access to resources among the agency participants where possible, in the following areas:

- Access to findings of review panels, workshops, and other significant meetings
- Analysis of Alternatives with Cost Benefit Analysis developed by each agency
- BARDA and DoD Industry Days
- Core Services and Institutional Facilities
- Drug, Device, and Biologic Development Resources and Expertise
- Inclusion in meetings, workshops, etc., applicable to MCM programs of mutual interest

- Inclusion in progress reviews for selected MCM programs of mutual interest, where appropriate
- Internal threat assessment, planning, and programmatic assessment documentation
- Market Research and Outreach
- Private Sector relationships
- Shared Meetings
- Small Business Innovation Research (SBIR)/Tech Watch activities
- Subject Matter Expertise

Implementation and Optimization

1. Interagency Communication, Program Assessment, and Planning

Through regular, frequent, and structured communications, program assessments, and planning sessions, this interagency collaboration will continuously assess MCM capability gaps along with current and planned programs to assess challenges and opportunities and to plan programs that optimize the ability to leverage the key collaboration and cooperation factors. The following guidelines will be adhered to in order to ensure continued communication, program assessment, and planning activities:

- Quarterly conference calls including primary representatives from each agency to assess challenges and opportunities.
- Twice yearly in-person meetings to review progress and planning in cooperative programs and to discuss challenges and opportunities for further collaboration (to replace quarterly calls as appropriate).
- Inclusion of interagency partners on product teams and other committees that are focused on specific projects, with full access to relevant documentation provided. Inclusion of interagency partners on regularly occurring calls and meetings for each specific project, as determined by the project leadership team.
- Invitation to internal program reviews in areas of mutual interest.
- Cooperative sponsorship of workshops, conferences, and meetings in areas of mutual interest.
- Yearly review of progress for senior leadership

2. Transagency Leadership Support

The support of each Agency's leadership for cooperative programs will be essential for continued success of this interagency collaboration.

3. Commitments and Agreements

For specific projects that are complex or require significant resources, specific agreements between the agencies will be signed. However, for the general activities described in this plan, the plan provides the justification for exploring new collaborations, initiating work, and expanding cooperation.

Current and Future Collaborations

Current Collaborations

BARDA, the DoD, and the NHLBI are currently engaged in a number of collaborations in the field of blood products. Cooperation includes information sharing and partnering to leverage funding, competencies, and other resources across the agencies. These three entities have contributed investments totaling $266.6 million for FY10–15, which has resulted in significant collaborative successes.
For over 10 years, the NHLBI has run the Resuscitation Outcomes Consortium (ROC), which is a program that brings together a number of government and nongovernment funding partners, including the DoD, to co-fund and run a multi-center clinical trial consortium specializing in multi-center clinical trials in pre-hospital emergency care. This pioneering program has conducted a number of important clinical studies in trauma and cardiac arrest.

The NHLBI and DoD are utilizing the ROC to sponsor a study of the pre-hospital use of tranexamic acid in traumatic brain injury. In this collaboration, the DoD is providing primary sponsorship and oversight for the study, while the NHLBI-led ROC team conducts the study and provides supplemental funding. This partnership facilitates a significantly more comprehensive study than either agency could have conducted independently.

The NHLBI and DoD are also working closely to determine the best approaches for transfusion in trauma and critically ill patients. In 2010, the NHLBI sponsored a multicenter clinical trial examining the potential negative effects of longer-stored red blood cells in critical patients. The NHLBI's Red Cell Storage Duration Study (RECESS) was designed to determine the effects of transfusion of red cells stored for 10 days versus red cells stored for 21 days. The DoD sponsored an ancillary study in which additional samples were collected from the enrolled patients and extensive biochemical and cellular analyses were conducted to provide insight into the underlying molecular mechanisms. This approach provides another way in which the two agencies were able to accomplish significantly more working together than either could have independently, while also optimizing the scientific impact of each volunteer subject in the study.

In 2011, the DoD and NHLBI partnered for the Pragmatic Randomized Optimal Platelet and Plasma Ratio Study (PROPPR). The DoD provided full funding but referred to the NHLBI for management and oversight, leveraging the NHLBI's existing infrastructure and experience in managing large multi-center clinical trials under the ROC.

The Trans-agency Research Consortium for Trauma Induced Coagulopathy (TACTIC) has been the most comprehensive interagency effort between the NHLBI and DoD to date. Both agencies are mutually interested in identifying the mechanisms of coagulopathy of trauma and ultimately developing specific diagnostics and therapeutics to prevent or treat this bleeding disorder. From 2009 to 2012, the agencies stayed in communication through a number of formal and informal meetings to discuss opportunities to cooperate. In 2012, the DoD announced a program to fund three clinical studies on the pre-hospital use of plasma for traumatic hemorrhage. With extensive interagency cooperation and input, the NHLBI established a comprehensive science program to

fund a multi-institutional consortium of basic scientists to study the underlying mechanisms of the coagulopathy of trauma. This team will partner with selected DoD researchers who have been funded to conduct pre-hospital trauma studies (the three plasma studies and one other). Further, this will allow the prospective collection of specialized samples for study by the basic science teams. This program is the most comprehensive study ever conducted on the coagulopathy of trauma and represents a unique opportunity to execute an interagency program that neither agency could have conducted on its own.

BARDA, the NHLBI, and the DoD are also engaged in productive interagency partnerships. These agencies have been communicating and coordinating in the area of blood products since at least 2012. Recognizing the critical importance of plasma for the treatment of combat casualties, the DoD is sponsoring two programs to develop a FDA approved dried plasma. Dried plasma will greatly reduce the logistical constraints related to keeping fresh, frozen plasma frozen during shipment and storage in austere environments. BARDA recognizes similar logistical constraints relevant to mass casualty scenarios in the civilian sector. Therefore, BARDA is sponsoring the development of a third, technologically distinct approach to give the U.S. Government a three product strategy. All agencies are fully sharing information about the programs and have cross-membership on steering committees (Pusateri et al., 2015).

Platelets are extremely important in the treatment of both ARS and traumatic hemorrhage. For several years, the DoD has been sponsoring the development of a platelet-derived hemostatic agent (PDHA) for the treatment of acute bleeding in combat casualties. BARDA, the DoD, and the NHLBI partnered in the development of this product in 2013, when BARDA took the lead in advanced development of a PDHA for both ARS and trauma-related indications and the NHLBI provided significant expertise. The lead product was developed by DoD up to technology readiness level 5 (i.e., ready for first-in-human study) and then transitioned to BARDA. BARDA has committed to full funding for this program. The DoD continues to develop the back-up product, to give the U.S. Government a two product strategy until an interagency down-select is made. The agencies also share cross-membership on steering committees and full information sharing for these programs.

Future Collaborations

The current plan focuses on blood products, but accounts for other areas of injury research and could serve as the basis for a national research action plan (NRAP). Continued interagency collaboration in the field of blood products and related technologies for trauma care and emergency preparedness is critical for sustaining success of several ongoing efforts and also for efficiently advancing new technologies providing safer, more effective, and more logistically supportable blood and related products to treat patients. The entities will prioritize innovative and collaborative funding mechanisms and integrated opportunities. Areas for further collaboration that have been identified include, but are not limited to, the following:

Leveraging Existing Programs and Infrastructure

BARDA will continue to accept proposals through their Broad Agency Announcement for Advanced Research and Development of Medical Countermeasures. Through this solicitation, NHLBI and the DoD will have the opportunity to fund interagency agreements.

The DoD currently has a large program focusing on the development of pathogen reduction technologies. In seeking to establish a program of their own, BARDA will leverage best practices from the DoD and may also seek opportunities to maximize fiscal and scientific impact by partnering with the DoD to create an interagency program.

BARDA, the NHLBI, and the DoD will commit to greater leveraging of cross-service contracts in order to reach maximal impact. For instance, BARDA and the DoD could leverage the NHLBI's extensive clinical network, while NHLBI could in turn utilize core services that BARDA and the DoD possess.

New Initiatives

The NIH (NHLBI, National Institute of Neurological Disorders and Stroke, and National Institute of General Medical Sciences) are evaluating a new mechanism for emergency research to replace the aforementioned ROC. This will enable any U.S. scientist with an interest in injury states (from discovery to clinical/implementation) to apply for funding. This mechanism would allow for a much more open process, save independent review, and should broaden the field of emergency research, thereby expanding the developmental pipeline for treatment of injury states. Through this solicitation, BARDA and the DoD would have the opportunity to fund interagency agreements.

The NHLBI intends to leverage BARDA's expertise and guidance in the development of a concept of operations (CONOPS) for a radiation injury and treatment network. BARDA's historical breadth of knowledge in radionuclide agents would allow the NHLBI to evaluate how it could develop a comprehensive, technically relevant CONOPS in an expedited fashion. In addition, the community involved in the network will be greatly enhanced by this partnership. Likewise, BARDA will continue to leverage both NHLBI and DoD expertise in blood products and emergency medicine.

The DoD will pursue future programs examining next generation resuscitation, which is not blood product-based (e.g., oxygen carriers, immune modulation). The future next generation resuscitation programs will also focus on sustaining casualties that have to be managed in the field for up to 72 hours. BARDA is currently developing models targeted at increasing therapeutic impact on casualties, in which advances in non-blood based resuscitation are necessary. Both BARDA and the NHLBI will likely collaborate with the DoD in developing next generation resuscitation programs.

The TACTIC and PROPPR studies listed in the current collaborations section will be funneled into the DoD's systems biology program and represent a real possibility of generating new therapeutics. In the future, BARDA, the DoD, and the NHLBI should consider supporting the development of diagnostics and therapeutics for coagulopathy of trauma, which are based on both systems biology and traditional scientific methodologies.

BARDA, the DoD, and the NHLBI will explore supporting applications on the use of stem cell technologies as resuscitative agents, alternative blood products, and for use in inflammatory modulation.

Development of improved, more logistically supportable platelets for transfusion is an area of great mutual interest for Agencies. Current DoD efforts developing improved products, such as

cryopreserved and extended shelf-life liquid stored platelets are promising. As a minimum, information sharing will be expanded in these areas. The potential for greater collaboration will also be evaluated.

The potential impact of radiation, alone or combined with traumatic injury is another area of mutual interest for BARDA, DoD, and the NHLBI, especially with respect to coagulopathy, transfusion, and resuscitation. The potential for collaborative work in this area will be explored.

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Appendix A – Points of Contact

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Appendix B – Stakeholder Organizations

Stakeholder Organizations
American College of Emergency Physicians
American Red Cross
American Society of Clinical Oncology (ASCO)
Armed Services Blood Program (ASBP)
Centers for Disease Control (CDC)
Congress
Critical Care Research Coordinators
DoD (i.e., North American Aerospace Defense Command [NORAD], U.S. Air Force, U.S. Army, U.S. Navy, and U.S. Northern Command [USNORTHCOM])
Families
Government (i.e., Local, State, and Federal Government)
Health Care Providers
Infectious Diseases Society of America (IDSA)
Media
Medical Care System (Emergency Response
National Guard
National Aeronautics and Space Administration
National Institute of Allergy and Infectious Diseases
National Institute of General Medical Sciences
National Marrow Donor Program
North Atlantic Treaty Organization (NATO) Allied Forces
Non-Government Organizations
Office of the Assistant Secretary for Health (HHS/ASH)
Patient/Recipient
Private Sector (Corporations)
Researchers
State Department
Telemedicine and Advanced Technology Research Center (TATRC)
Transportation Agencies
U.S. Army Medical Materiel Development Activity (USAMMDA)
U.S. Department of Veteran Affairs (VA)
U.S. Food and Drug Administration (FDA)
U.S. Government
Volunteer Blood Donors