PROCEEDINGS OF THE SECOND ANNUAL BRAIN TRAUMA BLUEPRINT STATE OF THE SCIENCE SUMMIT:

Pathways to Effective Treatments for Traumatic Brain Injuries

June 5 - 6, 2019

HEROIC   MISSION
HONORABLE   PATRIOTIC
DEDICATED   RESPECT
DUTY   ALWAYS
SERVICE   COUNTRY
BRAVE   SEMPER
READY   DEFEND
COMMITMENT
COURAGEOUS
SELFLESS
INTEGRITY
VALIANT

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Abstract

Overview: The Brain Trauma Blueprint (BTB) is a roadmap to advance precision therapeutics for survivors of brain trauma by outlining research endeavors and fostering collaboration across the broader stakeholder community. One pivotal component of the Blueprint Process is to convene key stakeholders at a State of the Science Summit (SoSS) to survey the current scientific knowledge, identify knowledge gaps, and consider new scientific and clinical models to fill these gaps. The theme of the second SoSS, held in June 2019, was *Pathways to Effective Treatments for Traumatic Brain Injuries (TBIs)*. This summit focused on the chronic sequelae of TBI and aimed to identify current knowledge gaps in the etiology and mechanisms of persistent symptoms. The resulting prioritized list of specific recommendations that address the identified knowledge gaps were then used to create actionable research priorities that will inform funding efforts and accelerate the development of a new generation of precision diagnostics and targeted therapeutics.

Outcomes: The BTB implementation team was comprised of a Scientific Planning Committee of ten key thought leaders with deep expertise in TBI and an additional 14 domain experts in TBI epidemiology, preclinical and translational science, patient phenotypes and biotypes, biomarker development, clinical trial design, and implementation science to engage with Cohen Veteran Bioscience's BTB executive team to envision, plan, and execute the summit. The SoSS was designed as a two-day retreat that convened over 100 stakeholders representing a variety of prominent academic institutions, government agencies including the Veterans Administration, Department of Defense, and the National Institutes of Health, patient advocacy groups and not-for-profit funding organizations. Attendees discussed the current state of the field, including the heterogenous mechanisms of injury, methods of diagnosis, and failures in clinical trials. They also addressed how subtyping patients to better select potential treatments for specific disease patterns could assist clinicians in successfully advancing potential treatments through clinical trials. Through breakout and group discussions, attendees worked to build consensus around knowledge gaps, discuss strategies to leverage the combined intellectual resources of the scientific and clinical communities in order overcome those gaps, and generated research priorities to hasten the development of precision-therapeutic options for individuals living with TBIs.

Conclusion: The SoSS strengthened the cohesion of the TBI scientific, clinical and patient communities and enhanced opportunities for future collaboration by providing a cohesive strategy to generate research priorities that will address long-term TBI sequelae. The summit resulted in a synthesis of the current state of the science in six specific domains of TBI and a strategic list of next steps in these specific areas that the community can leverage to conduct or fund future research. These documents will be updated and released to the broader community as peer-reviewed scientific publications. As the community funds and conducts research efforts that address the identified knowledge gaps, the BTB implementation team will continue working with key stakeholders to ensure that these documents are updated and move towards precision diagnostics and treatments for patients recovering from TBIs.

Background

Traumatic brain injuries (TBIs) affect at least 2.87 million Americans each year, including 288,000 hospitalizations and more than 56,000 deaths (*1*). Of the survivors, approximately 80,000 will suffer from long-term disabilities (*1*). Tragically, these numbers are likely underestimates as they are based only on cases identified in the emergency room and exclude individuals who do not seek or have access to care, a common occurrence among patients with mild TBI.

Traditionally, TBI has been classified at the time of injury as mild, moderate, or severe, based on the Glasgow Coma Scale (GSC) score (*2*), the primary diagnostic criteria for assessing the severity of TBI. However, this broad classification schema does not take into account the large heterogeneity of the pathophysiology that underlies these injuries incurred through multiple causes. Additionally, clinicians and researchers alike recognize that diagnosis of the condition at the time of injury may not accurately predict patient outcomes; other factors, including subjective measures, fluctuating presentations, the presence of additional disorders, and the patient's environment all influence long-term outcomes. Hence, the ability of these classifications to accurately predict patient outcomes is generally poor.

The management of patients immediately following TBI of all severities has improved in recent years. However, despite initial hospitalization and inpatient rehabilitation services, a substantial proportion of people with moderate or severe TBI experience lasting cognitive and psychological effects, unemployment, lower attainment of education, challenges in their social environment, and further decline in their daily lives (*3*). Even mild TBI (often referred to as concussion) can lead to persistent symptoms and functional impairments, with 10-30% of cases treated in an emergency department continuing to have symptoms three months following the initial trauma (*4*). Patients presenting to the clinic months after their TBI are often prescribed treatment plans based on their self-reported symptom burden and family reports. Complicating treatment further, guidelines are based on sparse evidence and, therefore, driving their adoption has been limited. With no Food and Drug Administration (FDA)-approved treatments for TBI, the development of targeted therapeutics for the chronic stages of TBIs will require a clearer understanding of their biological underpinnings.

Identifying gaps in our understanding of the long-term effects of TBI across the injury spectrum is an important step in developing better treatments and implementing them effectively in the clinic. To accomplish this task, Cohen Veterans Bioscience (CVB) is leading the development, advocacy and implementation of a Brain Trauma Blueprint (BTB) that will accelerate the progression toward a new generation of precision diagnostics and targeted therapeutics for trauma-related brain disorders. The BTB was initiated to advance precision therapeutics by mapping and tracking the impact of research endeavors and is facilitated through a series of State of the Science Summits (SoSS's) to foster collaboration across a multidisciplinary stakeholder community (researchers, clinicians, policymakers, patients and funders) to advance translational research. The BTB is operationalized through the establishment of a Scientific Planning Committee to guide the development of State of the Science summaries. These summaries include an in-depth exploration of major gaps in the understanding of TBIs as identified by key stakeholders and are augmented by an SoSS. Each summit brings in broader expertise to further develop a path forward by assessing the current scientific knowledge, identifying knowledge gaps, and considering new scientific and clinical models to fill these gaps. The goal of the summaries is to build a prioritized roadmap focused on accelerating TBI therapies from preclinical research and development stages to patients having access to new

therapies as well as to highlight for the research community, government leaders, legislators and private foundations the specific needs of this population.

Building on a successful, inaugural BTB SoSS, *Diagnosis of Trauma-Related Disorders with a Focus on Post-Traumatic Stress Disorder (PTSD)*, held in 2018, CVB leveraged the same methods to plan for and carry out the 2019 SoSS with a focus on TBI.

Methods

Establishment of a Scientific Planning Committee

The second annual SoSS was launched in January 2019 with the establishment of a chartered Scientific Planning Committee (SPC) consisting of interdisciplinary thought leaders from diverse perspectives and deep expertise in TBI. Employing various research tools to envision, plan and execute the steps needed to synthesize the state of the science in TBI clinical development, the SPC focused on the following key domains of research that reflect important factors in advancing precision solutions in TBI: epidemiology, preclinical and translational science, patient phenotypes and biotypes, biomarker development, clinical trial design, and implementation science. The role of the SPC was to guide the development of the SoSS as an engaging and dynamic working meeting with defined deliverables that would help move the field forward. The SPC helped to develop the agenda, identify speakers and invite a broad array of expert stakeholders to join in the meeting preparation and activities. The SPC aimed to leverage and engage the broader ecosystem to gain consensus on the work in progress and the areas that are not yet fully addressed, if at all.

2019 TBI Scientific Planning Committee Members

Stephen Ahlers, PhD
Director, Operational and Undersea Medicine Directorate at Naval Medical Research Center

David X Cifu, MD
Associate Dean for Innovation and System Integration Virginia Commonwealth University, Senior TBI Specialist U.S. Department of Veterans Affairs

Fiona Crawford, PhD
President and CEO, Roskamp Institute

Jam Ghajar, MD, PhD, FACS
President, Brain Trauma Foundation, Clinical Professor of Neurosurgery at Stanford University School of Medicine

Jessica Gill, PhD, RN, FAAN
Deputy Scientific Director of the Division of Intramural Research at the National Institute of Nursing Research

Grant Iverson, PhD
Director, Sports Concussion Program, MassGeneral Hospital for Children; Director, Neuropsychology Outcome Assessment Laboratory, Department of Physical Medicine and Rehabilitation, Harvard Medical School, and Spaulding Rehabilitation Network; Associate Director, Traumatic Brain Injury Program, Home Base, A Red Sox Foundation and Massachusetts General Hospital Program

Michael McCrea, PhD, ABPP
Professor, Neurosurgery and Neurology; Director, Brain Injury Research Program, Medical College of Wisconsin

James Stone, MD, PhD
Vice Chairman of Clinical Research, Associate Professor of Radiology and Medical Imaging, University of Virginia

Elisabeth A Wilde, PhD
Associate Professor, Department of Neurology, University of Utah and George E Wahlen VA Salt Lake City Healthcare system, Department of Physical Medicine and Rehabilitation Baylor College of Medicine

Kristine Yaffe, MD
Professor of Psychiatry, Neurology and Epidemiology, Roy and Marie Scola Endowed Chair, Vice Chair of Research in Psychiatry, UCSF

Scientific Planning Committee Charter

Each summit is led by an SPC comprised of senior content experts in specific research domains. SPC members are selected based on the following characteristics: (1) a unique vantage point to contribute to the curation of the event (e.g., diversity in background, domain, or techniques); (2) considered thought leaders in their fields; and (3) proven flexibility and freedom to think outside of the box, bringing original, creative ideas and processes to understand what is fundamentally needed to identify research gaps and assess new research opportunities to fill these gaps.

A common goal of each SoSS is to complete a survey of the current scientific knowledge (i.e., a landscape summary), posit knowledge gaps, and consider new models to fill these gaps. The SPC collaboratively develops subdomain summary documents that relate to the topic as identified by discussions among the SPC and the BTB executive team. Additionally, the SPC curated various stakeholder groups: (1) an extended science committee of scientists to help develop the aforementioned summaries; (2) summit speakers and moderators who engaged the meeting participants on the major themes; and (3) summit attendees who contributed to both the interactive meeting and the state of the science summaries, which were augmented by the discussions held throughout the summit.

Working groups developed during the summit critically investigated research gap areas in a data-driven manner and mapped the opportunities needed to fill them. Importantly, the SPC was also charged with developing a meeting format to promote cross-functional and cross-organizational discussion of the major themes and questions posed. The goal was collaboration on defining shared research priorities. Finally, the SPC guides a process to ensure that all findings are broadly disseminated across the relevant ecosystem in real time with the support of the meeting attendees, the BTB team, and our strategic partners.

Specific deliverables of each SPC includes:
1. Designing an innovative and effective agenda through regular participation in group and/or individual calls
2. Identifying prominent speakers and key stakeholders that would drive the selected agenda toward its objectives
3. Identifying and critiquing information for the landscaping effort
4. Co-leading domain specific workgroups to engage leaders and drive discussion and consensus
5. Providing timely feedback on the landscaping documents prepared by the BTB team

Questions to be addressed in the summaries:
1) What is our current understanding of the pathogenic mechanisms or etiology of TBI?
2) How do preclinical and clinical work inform the translational research gaps?
3) What efforts are underway to advance our knowledge of TBI mechanisms and their relationship to the varied long-term consequences of TBI?
4) What are the lessons learned from failed TBI clinical trials?
5) What is the evidence behind the current diagnosis and treatment selection criteria?
6) What are real-world approaches to the diagnosis and effective treatment of the chronic neuropsychiatric sequelae of TBI?
7) What is the strength of the evidence for current interventions and clinical practice?

To further advance our understanding, sessions and subdomain breakouts also considered:

1) Frameworks for a new mechanism-based taxonomy, specifically bridging symptoms and biotypes or constructs and addressing causality
2) Tools to advance major research efforts such as data science tools, imaging, biomics, wearables, and other advance technologies
3) Infrastructure and systems to support research and development across the translational science pipeline
4) Evidence to optimize and design better clinical trials

The Summit

The SoSS, *Paths to Effective Treatments for Traumatic Brain Injuries*, was held in June 2019 at the Kellogg Center in Washington, DC and focused on the chronic sequelae of TBIs. The summit's goals were to (1) establish an understanding of the root cause issues and obstacles in advancing TBI diagnosis and treatment solutions, (2) landscape existing research efforts that address these challenges, (3) identify knowledge gaps and brainstorm new opportunities, (4) generate a prioritized list of specific recommendations that address identified issues & gaps across the field, and (5) share this blueprint broadly with researchers, legislators, public and private funding organizations, and the public to inform translational research, now and in the future.

More than 100 stakeholders, representing a variety of prominent academic institutions and government agencies, including the FDA, Veterans Administration (VA), Department of Defense (DoD), and the National Institutes of Health (NIH), Veteran Service Organizations, patient advocacy groups, and not-for-profit funding organizations, gathered to advance the BTB summaries during assembly sessions and breakout working sessions by contributing their unique expertise using a collaborative approach to create an effective translational research activity blueprint. The summaries, which were provided to attendees beforehand to optimize productivity, served as the launching point for the sessions.

The SPC designed the meeting such that it was not redundant with other efforts in the field and that all attendees had a clear understanding of the current state of the field before the start of the meeting. To that end, the SPC identified key areas of research that reflect important factors in advancing precision medicine in TBI: epidemiology, preclinical and translational science, patient phenotypes and biotypes, biomarker development, clinical trial design, and implementation science. Alongside CVB team members, the SPC and the expanded science committee synthesized the state of the science related to pathways for effective treatment of TBI for each of these topics. These summaries served as the launching point for the working sessions during the meeting and optimized productivity.

Assembly Sessions

Two assembly sessions, which included all summit participants and consisted of lectures and debates, were held to add depth and breadth to the conversations and generate consensus from the audience on select topics that spanned the six domains.

Day 1: Summit leadership reiterated the mission of the initiative, the call to action for the group, and clinicians and a patient offered perspectives on the challenges of developing treatments to mitigate the long-term sequelae of TBI. Before dividing into breakout sessions, leaders in TBI research across several governmental institutions presented a landscape of current research priorities. The SPC highlighted the summaries' key concepts, providing domain overviews that would serve as the focus areas of the breakout group discussions.

Day 2: Participants received additional context of the policy and regulatory realms within which they would need to conceptualize opportunities and challenges. Presentations and panels provided multiple approaches in discussing a path forward to provide a framework for how participants collectively might approach the development of future precision medicine in TBI. Finally, each group leveraged the combined intellectual resources of the full community to deliver a prioritized recommendation list.

The following recaps provide session summaries and key takeaways:

1) **Session Theme: Perspectives on the Chronic Sequelae of TBI**
   Speakers: Nicole Harmon, PhD, Executive Director, External Affairs, Cohen Veterans Bioscience; Lt. Johnny Cebak, MD, PhD

   Session Goal: To introduce the SoSS and the goals of the meeting and to provide a patient perspective on the chronic sequelae of TBI

Nicole Harmon, PhD, CVB, introduced the summit by discussing the overall goals of the meeting. By bringing together a diverse group of participants, including scientists from academia, life sciences, government, health providers, technology, patients, and caregivers, the goal of the SoSS was to convene the best minds to build a brain trauma blueprint for the future.

Lt. Johnny Cebak, PhD, provided a patient perspective on the chronic effects of TBI. He was a medic in the Marines in Iraq, saw improvised explosive device blasts on a daily basis, and witnessed around 400 casualties. In one instance during his time in the military as part of an armored infantry unit, Lt. Cebak was thrown from a vehicle and submerged in a ravine that led to serious injury. However, because the unit did not have adequate manpower, Lt. Cebak was required to return to his job one day after the injury. He immediately recalled having nightmares, was unable to focus, and, as he described, was "a different person". Two weeks after returning home, Lt. Cebak described his symptoms as "living in a fog", which included problems with attention, balance, and sequelae of PTSD. After returning home from duty, he started to fail in school, struggle in his relationships and turn to self-medication with drugs and alcohol. With family support, Lt. Cebak became aggressive with his treatment with the VA, targeting various symptoms with stimulants, beta-blockers, therapy, and anti-depressants. He was able to persevere enough to complete two bachelor's degrees and a PhD focused on TBI and subsequently entered medical school. However, this is not the case for many individuals who suffer from the long-term effects of TBI. Lt. Cebak emphasized that many of his friends have succumbed to or are still fighting the sequelae of combat exposure.

Key Take-Aways: Treatments for the chronic symptoms of TBI are needed. Creative thinking, bringing together key minds, and working together will help move the field forward.

2) **Session Theme: Welcome by Cohen Veterans Bioscience**
   Speakers: Magali Haas, MD, PhD; CEO and President, Cohen Veterans Bioscience

   Session Goal: To preview the goals and processes of the meeting, consider the overall mission, and deliver the call to action.

The second session included a welcoming address by CVB's Chief Executive Officer and President, Dr. Magali Haas. Dr. Haas thanked veteran and Dr. Cebak for sharing his serious and inspirational story and sought to raise awareness that even diagnosis of mild TBI is a real concern and that there are many cases in which individuals are not diagnosed and might continue to have long-lasting effects. She shared that some important progress has been made in recent years, on the diagnostic side of TBI, with approvals by the FDA of three new aides-in-diagnostics for TBI. However, she noted that future progress requires that the field undertakes to revise the framework of diagnostic criteria are based on – which informs the gold-standard reference for developing diagnostic tests. Current diagnostic criteria are based on clinical symptoms and presentation at time of trauma, not the specific biological process that results from the trauma or its subsequent trajectory and severity. She suggested that a more holistic approach be adopted that measures disease processes through multi-modal platforms such as genetics, imaging, wearables and track disease processes over time to understand the systemic changes and disease process for a new mechanistic-based diagnostic approach.

The goal for the treatment of TBI and related comorbidities is personalized and precision therapeutics, but effective treatment requires a paradigm shift in how researchers approach the problem initially. Dr. Haas shared how CVB is building platforms with strategic partners to incentivize a team-science approach toward finding solutions for trauma-related diseases efficiently. Instead of defining conditions syndromically based on observation, we must look at the molecular, circuit-based reasons these conditions are developing. This starts by combining multi-modal data types using advanced computational approaches for these disorders. For example, the RAPID-Dx framework is an infrastructure to bring together data through the BRAIN Commons – a resource for the research community to share, store, and analyze data – and increase the power for meaningful research outcomes. This approach has already enabled success in the field of PTSD genetics by integrating 56 studies worldwide and generating the first genome-wide significant findings for PTSD. The study identified six single-nucleotide polymorphisms, showing that this knowledge-sharing approach can work and could be applied to the field of TBI. CVB has leveraged this methodology for other work in neuroimaging biomarkers for PTSD. In the space of neuroimaging, CVB helped launch the development of a normative neuroimaging library of over 3,000 subjects to inform currently available FDA-approved tools for interrogating advanced imaging. These are just two examples where collaborative approaches, married to a roadmapped effort for PTSD, is yielding progress. Dr. Haas called on those assembled, to help build a blueprint to further efforts to objectively diagnosis and treat TBI as a product of this Summit.

Key Take-Aways: This meeting and the resulting recommendations document aim to add value to the efforts that are already underway for TBI. This meeting intended to understand the state of the science, determine necessary next steps and understand how each stakeholder can contribute towards that effort.

3) **Keynote: One Bite at a Time: Clinical Trials – Specific Aspects of TBI**
   Speaker: David Brody, MD, PhD; Director at the Center for Neuroscience and Regenerative Medicine, the USU/NIH Traumatic Brain Injury Research Group

Session goal: To highlight some of the reasons promising TBI therapeutics fail to translate and introduce potential pathways toward bringing effective treatments to the clinic.

David Brody, MD, PhD, gave a call to action for TBI. Over 30 late-phase clinical trials have failed to translate to a therapeutic; this could be due to a number of reasons, including insufficient sample size, heterogeneity, or design, patient or outcome issues. As Dr. Brody noted, we have been making the same mistake with increasing confidence. A potential path forward is to perform clinical trials that are focused on one subdomain at a time, or as General Creighton Adams said, "when eating and elephant, take one bite at a time." This strategy would include identifying specific subdomains, symptoms, and candidate treatments, and then designing rigorous, multicenter, randomized, blinded, controlled clinical trials. To this end, the field needs a clinical trial infrastructure, smart clinical designs, selective patient subsets that are likely to benefit from specific treatments, and domain-specific primary and secondary outcome measures. This platform approach could reduce the time, cost, and logistical barriers associated with individual trials (*5*).

Dr. Brody described an initiative of the Center for Neuroscience and Regenerative Medicine to perform 30 clinical trials for candidate treatments in ten years at the cost of ten trials. His work considers several TBI subdomains such as mood disorders, sleep disorders, post-traumatic headaches, and cognitive disorders, as well as several treatment approaches, including pharmacology, cognitive behavioral therapy (CBT), lifestyle interventions, and neuromodulation therapies such as repetitive transcranial magnetic simulation (rTMS). Therapies like CBT might help with mood disorders; behavioral therapy could help relieve fatigue; and computer-based brain fitness training may improve working memory. For pharmacology, one direction includes developing an evidence base for FDA-approved drugs that are being used "off-label" in the clinic for TBI patients, such as anti-epileptic treatments for mood lability or stimulants for cognitive endurance. For lifestyle interventions, mood disorders could be treated with intense daily cardiovascular exercise, sleep and fatigue may be ameliorated with gentle cardiovascular exercise, headaches might be relieved by removing specific food triggers, and cognitive disorders could potentially be addressed by prescribing a diet that is low in refined sugar. For neuromodulation therapies, rTMS has potential to ameliorate mood disorders. In addition, hybrid and combination therapies could be a successful way to treat subdomains. There is also an urgent need to establish a network of partner clinical trial sites that can operate under the approval of a single institutional review board (IRB).

Dr. Brody then discussed an exemplar: individual connectome mapping-based TMS for depressive symptoms and TBI patients (*6*). TMS is an FDA-approved therapeutic that induces electrical currents, which cause action potentials to fire and stimulate the cortex directly under a magnetic stimulator. The goal of this study was to make a reliable map of the dorsolateral prefrontal cortex with the resting-state functional connectivity of individual

subjects. The researchers mapped the dorsal attention and default-mode network, which are strongly anti-correlated; the hypothesis is that stimulating the dorsal attention network will downregulate the default-mode network including the subgenual anterior cingulate, which can be overactive in depression. Deep brain targets often have a correlate or anti-correlate in more accessible cortical regions, so if one wants to inhibit a deep brain region, one could target a cortical correlate. The trial included 15 enrolled patients and performed 20 sessions of bilateral rTMS on this targeted area. While the sham placebo group showed a reduction in depressive symptoms, there was also a substantial effect of rTMS, with dramatic reductions in depression readouts, specifically lassitude, as patients showed increased energy. Neuroimaging further revealed changes in the functional connectivity of the brain (i.e., remapping of the network architecture), but it was not obvious which portions of the resting-state network architecture are most correlated with changes in symptoms. Notably, the patients were more likely to seek other therapies and make lifestyle changes after the therapy. A large multicenter trial is underway to test this approach compared to the standard, FDA-approved TMS protocol using a Bayesian adaptive design. The trial will also investigate unilateral versus bilateral methods.

Key Take-Aways: Numerous late-stage trials have not been successful and the "one bite at a time" approach addresses some shortcoming of trials while maintaining rigorous scientific designs. The costs and time investment of individual trials can be reduced using a network of partner clinical trial sites.

4) **Panel Discussion: Implementation Science: The Clinical Perspective**
   Moderator: Noel Gunther, Executive Director, BrainLine
   Speakers: David Cifu, MD, Senior TBI Specialist, US Department of Veterans Affairs; Uzma Samadani, MD, PhD, Associate Professor, Department of Bioinformatics and Computational Biology, University of Minnesota, Neurosurgeon, Minneapolis VA Medical Center; Christopher T Whitlow, MD, PhD, MHA, Chair of American College of Radiology Head Injury Institute, Diagnostic Radiologist Researcher at Wake Forest Baptist Health Hospital; Thomas DeGraba, MD, Chief Innovations Officer, National Intrepid Center of Excellence

Session goal: To discuss current practice models for acute care, radiologic diagnosis, rehabilitation medicine, and management guidelines.

This panel discussed a clinician perspective to implement evidence-based guidelines in an effort to understand the brain injury population, including changes in personality, behavioral health and comorbidities. Dr. David Cifu discussed the need for implementation to successfully bring therapies to the clinic. Despite many clinical practice guidelines, the field has not yet reached a consensus on what recommendations are evidence based and should be followed. This lack of consensus or plan to educate clinicians and get "buy in" from patients often results in poor prognostics and long-lasting sequelae. Many strategies for implementation and dissemination have been used in other fields; TBI guidelines could borrow these techniques and develop a better decision tree and infrastructure to improve care.

Dr. Uzma Samadani noted a common misconception among Veterans is that non-life-threatening brain injury is not treatable and hence there is no need for TBI patients to go to the emergency room. This misconception is

reinforced by the current medical system, which does not focus on the classification of the pathophysiology of the problem and results in a large population of patients who never seek care and spiral into downstream problems like self-medicating and falling behind in jobs, schools, and relationships. There is a need not only for solutions in the acute setting but also for solutions that are translatable to the community and the direct-consumer setting.

Dr. Christopher T. Whitlow discussed the standard triage approach for TBI care using existing guidelines. Dr. Whitlow noted that patients are currently imaged indiscriminately, but this might not be the most cost-effective or appropriate approach. Alternative ways such as genetic testing, physical exams, and biomarkers can reduce the cost and direct the patients towards more effective treatments. For patients with mild TBI, there is a lack of infrastructure to manage their symptoms or even consider therapeutics. Stratification could help identify patients who will not achieve optimal recovery with time. Prevention and mitigation of exposure are also important aspects of care that should not be ignored.

From the military service perspective, Dr. Thomas DeGraba discussed the need to better understand the mild TBI population. A more comprehensive, holistic approach to these patients is required to address their many overlapping symptoms. For severe trauma, there are processes in place to monitor compliance to guidelines; however, the field currently lacks the ability to monitor the use of guidelines for mild trauma and for community clinicians. By harnessing multiple disciplines, a treatment paradigm should combat multiple symptoms, considering how each one might impact another. Moreover, family members should be part of the process for a patient's treatment and management. A big challenge for Veterans is that they have two personas—one in battle and one at home. In Dr. DeGraba's experience, irritability is the number one symptom that Veterans say they want to address.

Key Take-Aways: The concept of implementation needs to be included in every discussion on TBI treatment. The panel discussed developing a composite understanding of all of the symptoms at the same time to create a treatment paradigm that puts into play a treatment that will affect the symptoms as a whole, but this involves integrative medicine and a common set of standards and guidelines that must be implemented across the medical spectrum.

5) **Session Theme: National Priorities: Government Investment**
   Speakers: Stuart Hoffman, PhD, Scientific Program Manager for Brain Health and Injury at the US Department of Veterans Affairs; Patrick Bellgowan, PhD, Program Director, Repair and Plasticity, National Institute for Neurological Diseases and Stroke; Carlos Peña, Director, Office of Neurological and Physical medicine Devices, Office of Product Evaluation and Quality, Center for Devices and Radiological Health, FDA; Saafan Malik, MD, Director of Research and Acting Deputy Division Chief, Defense and Veterans Brain Injury Center J9-Research, Development Directorate, Defense Health Agency

Session goal: To explore portfolio investments to date and priorities by institutions.

Dr. Stuart Hoffman discussed government efforts that have focused on brain injury months to years after the last recorded insult. In response to an Executive Order in 2011 that set out to prevent, diagnose, and treat TBI, PTSD, and mental health conditions, the DoD, VA, Department of Health and Human Services, and Department of

Education worked together to develop a National Research Action Plan (NRAP), which formed an official cross-departmental relationship and announced larger projects in TBI, including longitudinal studies. Efforts by the Chronic Effects of Neurotrauma Consortium, headed by Dr. Cifu and formed in response to the NRAP, have included (1) a longitudinal study focused on 1,800 Veterans and Service members with combat-related mTBI, (2) a retrospective database of two million Veterans using electronic medical records from the DoD and VA, (3) six additional prospective clinical studies reviewed and approved by the consortium, (4) a long-term basic science study of human tau-producing mice exposed to repetitive concussions, and (5) the development of a diffusion-tensor imaging phantom to standardize imaging platforms for TBI. The work has revealed that TBI, at any level, increases the risk of dementia, which is dose-dependent based on the intensity of injury. Dr. Hoffman also described correlations between chronic pain and TBI severity, among other examples. Finally, Dr. Hoffman described other funding initiatives including: (1) a VA preclinical open-field blast exposure site that focuses on the chronic effects of blast injury; (2) a Biomedical Laboratory Research and Development collaborative merit review award for TBI to bring together new ideas and propose joint funding to develop innovative research; (3) VA/Office of Research and Development/Rehabilitation Research and Development special-emphasis areas, including exoskeleton research for TBI and the effect of prolonged exposure to opioids on long-term outcomes following TBI; and (4) clinical studies on growth-hormone replacement in Veterans with a history of mild TBI.

Dr. Patrick Bellgowan gave a broad overview on how the NIH funds TBI research and provided examples of three initiatives they are moving forward. The National Institute of Neurological Disorder and Stroke (NINDS) funds basic, translational, and clinical research and the NIH as a whole has more than doubled its expenditures on TBI in the last 10 years, with increased funding for mild TBI and the chronic effects of head trauma. As an investigator-driven institute, the science is driven by researchers. While there is still a majority of preclinical research, development of the Common Data Elements (CDEs), which align and standardize outcomes by allowing researchers to use the same data measures and compare data across clinical studies, has led to an increase in clinical research opportunities; preclinical CDEs are also underway, aiming to improve communication, transparency, and rigor. One goal is to develop novel preclinical outcome measures for TBI that are pathophysiologically specific and clinically relevant, through the Translational Outcomes Project in Neurotrauma Consortium. Biomarker studies are also a big focus of NINDS, including those in the discovery, validation and clinical utility phase.

Dr. Carlos Peña gave a regulatory primer on medical devices. The FDA aims to find high-quality, safe and effective medical devices for patients. There have been advances in diagnostic medical devices for head injury that have gone through the FDA process. Importantly, the FDA offers guidance to help sponsors through the process. Pre-submission guidelines give an opportunity, at no cost, to obtain FDA feedback prior to Investigational Device Exemption or marketing submissions. Mapping out expectations with the FDA early can help investigators make more informed and optimal decisions along the way.

Dr. Saafan Malik gave an overview about programs and priorities for TBI at the Defense Health Agency and DoD. Rather than being investigator driven, the DoD uses a requirement-driven approach for funding. The Military Health System is a complex organization that aims for a comprehensive approach to finding solutions for TBI. The DoD aims to bridge research and clinical gaps by investing in foundational and clinical research studies as well as in product and policy recommendations. The research investment strategy addresses the highest-priority needs,

and the aim is to see projects all the way through to the clinic, including training clinicians to adopt new approaches.

One issue discussed in this session was the lack of consensus on definitions for TBI. Current efforts in the field are working towards standardizing definitions, allowing them to be more precise. Terminology from the FDA comes from communication with researchers and finding consensus in the field; for indications for use, the FDA bases definitions on how they were studied in clinical studies.

Collaborations between government groups has been successful, but industry investment is lagging for TBI. Initiatives where groups are coming together to advance research are making progress, such as the NIH Helping to End Addiction Long-Term initiatives in the pain field.

Key Take-Away: Mild TBIs and their chronic outcomes have received increased attention from government funding agencies. One goal is to increase partnerships with other federal colleagues and modernize the managing of the infrastructure. Because of the complexity, there must be synergy between the different organizations; better coordination will allow for improvements in research output and forums such as the SoSS.

6) Breakout Working Session

All attendees participated in one of four working group breakout sessions, each led by SPC members and a facilitator. Each breakout session centered around one of four domains of TBI. Prior to the meeting, strawman summaries of the state of the science were drafted for each of the four areas as a tool to facilitate the working group discussions. The goal of the working sessions was to review, revise and augment these summaries and identify any open questions. The SPC defined the agenda and questions to address throughout the working sessions. These small breakout groups were tasked with synthesizing the key concepts within the domain, the main gaps in our knowledge, and the tools that might be needed to achieve this knowledge. The discussions are summarized below and were incorporated into the more extensive SoSS summaries.

Preclinical and Translational Science group: Led by SPC members Fiona Crawford, PhD, (Roskamp Institute) and Stephen Ahlers, PhD, (Naval Medical Research Center) and extended SPC members Patrick Kochanek, MD, MCCM, (University of Pittsburgh), Susanna Rosi, PhD, (University of California, San Francisco), and Douglas Smith, MD, (University of Pennsylvania), and facilitated by Chantelle Ferland-Beckham, PhD, (CVB), the Preclinical and Translational Science group discussed how to use data from preclinical models to better inform applied clinical research in TBI, how to assess these models and how to standardize preclinical models to study mild injury. The group emphasized that bi-directional communication between preclinical researchers and the clinic is important, as models need to recapitulate human patient phenotypes. They also discussed harmonizing outcome measures between animals and humans to better understand what might be clinically relevant and understand how models can be better used to inform clinical research and vice versa. The group also highlighted that the chronic effects of mild TBI are understudied, especially in the preclinical field. Comorbidities and preexisting conditions are not yet modeled in animals. These studies take time and are a big investment. Overall, participants felt that the major priorities in the field include:

1. Developing and augmenting preclinical models based on clinical relevance
2. Focusing on chronic studies of mild TBI
3. Focusing on making negative data available either as publications or searchable in a database
4. Performing cross-species validation of phenotypes/models.
5. Considering understudied variables like loss of consciousness, age, sex, and comorbidities

Biomarkers group: Led by SPC members Jessica Gill, PhD, RN, FAAN, (National Institute of Nursing Research), James Stone, MD, PhD, (University of Virginia), and Elisabeth Wilde, PhD, (University of Utah/George E. Wahlen VA Salt lake City Healthcare System), and extended SPC members Kimbra Kenney, MD, (Walter Reed National Military Medical Center) and Ina Wanner, PhD, (University of California, Los Angeles), and facilitated by Rajeev Ramchand, PhD, (Cohen Veterans Network), the Biomarkers group examined how fluid biomarkers might advance treatment development and what steps are needed to facilitate development of more robust biomarkers. Ideal biomarkers should be sensitive, specific and selective for or linked to brain injury. Biomarkers should also be safe, characterized in biofluid dynamics, reproducible and relatively operational. Combining modalities will help optimize and improve the care provided to patients with TBI. This group's goal was to parse out biomarkers, understand their dynamics and determine the best ways to use them for clinical development and care. Participants felt that the major priorities in the field include:

1. Considering the timing of data acquisition and timing over the course of the post injury trajectory for biomarkers
2. Harmonizing and standardizing data across different platforms to ensure reproducibility and quality control
3. Integrating modalities within the same patients and at the same time points
4. Identifying and integrating constellations of related data from different modalities to target specific patient populations

Patient Phenotypes and Biotypes group: Led by SPC member Jamshid Ghajar, MD, PhD, FACS, (Brain Trauma Foundation; Stanford University School of Medicine) and extended SPC members Anthony Kontos, PhD, (University of Pittsburgh Medical Center) and Adam Ferguson, PhD, (UCSF) and facilitated by Lee Lancashire, PhD, (CVB), the Patient Phenotypes and Biotypes group evaluated the extent to which methods to enrich patient subtypes (i.e., cognitive, ocular-motor, headache/migraine, vestibular, and anxiety/mood) could inform treatment development and how to best characterize these subtypes. The discussion focused on post-concussion, clinically prevalent impairments and symptoms, called clinical phenotypes. Setting, mechanism, age, gender and pre-concussion conditions can all affect outcomes of TBI. The goal of the group was to propose a framework for a new classification, bridging clinical phenotypes and biotypes and ultimately having more objective measures to develop biotypes to replace phenotypes. Participants felt that the major priorities in the field include:

1. Gathering clinically rich patient data to characterize patients, from acute to chronic
2. Understanding the nature of current treatment delivery (education and implementation)
3. Gaining evidence for clinical measures that relate to assessment for specific phenotypes for clinical trials

Clinical Trial Design group: Led by SPC members Grant Iverson, PhD, (Harvard Medical School; Spaulding Rehabilitation Network) and Dr. Cifu and extended SPC members Lisa Brenner, PhD, ABPP, (VA Rocky Mountain Mental Illness Research Education and Clinical Center), David Wright, MD, (Emory University School of Medicine),

Mike Bell, MD, (Children's National Health System), Ramon Diaz-Arrastia, MD, PhD, (University of Pennsylvania), Dr. Brody, and Don Stein, PhD, (Emory University School of Medicine), and facilitated by Terry Frangiosa, (CVB), the Clinical Trial Design group considered the current best practices of clinical trial design and recommendations for strategies for future implementations. Rather than viewing TBI as a unidimensional disorder, the field should focus on treatments that have evidence to support efficacy for a particular symptom intended for a specific group of patients. The field should focus on treatment approaches beyond pharmaceuticals, such as devices and lifestyle changes. Network theory could inform clinical trials by clarifying the architecture of the symptoms and problems. Clinical trials should utilize better outcome measures for TBI that focus on specific symptoms. Participants felt that the major priorities in the field include:

1. Establishing an infrastructure for a clinical trial network
2. Improving knowledge gained from Phase 2 research
3. Rather than treating TBI as a homogenous disease, developing specific outcome measures for specific domains in precision-medicine trials
4. Improving post-hoc analysis of clinical trials
5. Using patient-centered outcomes that solve the need of the patients

Day 2

7) Session Title: Review of Day One Discussions
Moderator: Retsina Meyer, PhD, Scientific Program Manager, CVB
Speakers: Lisa Brenner, PhD, ABPP, Director, VA Rocky Mountain Mental Illness Research Education and Clinical Center; **Douglas Smith, MD,** Robert A. Groff Professor Of Teaching And Research In Neurosurgery Perelman School of Medicine, University of Pennsylvania**; Elizabeth Wilde, PhD,** Associate Professor, University of Utah and George E. Wahlen VA Salt Lake City Healthcare System**; and Mary Jo Pugh, PhD, RN, Professor Epidemiology, University of Utah** and George E. Wahlen VA Salt Lake City Healthcare System

Session goal: To discuss the overall conclusions from the working groups on Day 1.

On Day 2 of the SoSS, a conversational panel discussion summarized the themes from the working groups. The panel included one member from each working group: Drs. Smith (Preclinical and Translational Science), Pugh (Patient Phenotypes and Biotypes), Wilde (Biomarkers), and Brenner (Clinical Trial Design). In addition to listing the overall conclusions described from discussions in the working groups, the panelists delved deeper into gaps in the field and possible solutions to fill them.

Responding to a question from the audience, Dr. Smith discussed possible criteria for establishing translational validity. He highlighted that imaging and blood biomarkers could provide information in a non-invasive way. In addition, he described developing the same type of outcome measures in animals and humans, such as electroencephalography (EEG) or imaging. This would allow for improved harmonization with researchers being able to more reliably compare animals to humans. In response to a question about individuals who looks mild initially and may have a disabling condition in three months, Dr. Smith discussed why having a more focused target term, such as axonal injury, inflammation, focal contusion, and vascular injury, is more useful in prognostics rather than using scales such as mild, moderate or severe. He argued that we should target the underlying pathology and

not the symptom condition or opinion. Dr. Smith also noted that no single animal model can recapitulate the level of complexity as observed in humans with TBI. Rather, models must emphasize different aspects of the pathophysiology of TBI, which will steer researchers and clinicians away from broad terminology like "concussion" and "TBI". Finally, Dr. Smith focused on ways to assess animal models more deeply, such as (1) developing the same outcome measures in humans and animals and (2) improving the granularity when defining phenotypes.

Much of the discussion around biomarkers, led by Dr. Wilde, focused on the timing of the markers evaluated and the differences in the pattern and magnitude over the course of recovery. In addition, Dr. Wilde discussed data harmonization and standardization. There is a need to integrate modalities in patient populations and timepoints. Dr. Wilde discussed how data from one modality is usually difficult to integrate with other data since they may not come from the same point in time. In the clinic, determining precise timing can be difficult due to imperfect patient recall of the injury, especially in cases with loss of consciousness or in military settings whether there is a "fog of war". These circumstances can alter an individual's perception of the passage of time. However, it may not always be possible to have data collected at the same timepoint. Using mathematical algorithms, it is possible to integrate the time and control for it to perform the same correlations. This could lead to better predictions of the outcomes.

In response to questions about barriers to patient consent in getting participants soon after an injury occurs, Dr. Wilde noted that collecting data from people very soon after an injury can be challenging and expensive, although it is possible. Recruiting patients in the emergency room, for example, is difficult because patients might be uncomfortable and/or waiting for procedures, or recruitment may be difficult due to the specific location in which the patient was sent. Nonetheless, researchers have recruited patients within 24 hours of an injury for biomarker and imaging studies. Dr. Wilde also emphasized that the risk history of an individual (e.g., socioeconomic status, current/past residences, participation in sports) is important for biomarker development—some biomarkers might be sensitive to injuries only at a certain timepoint while other biomarkers may detect past trauma load.

After listing the key points from the Patient Phenotypes and Biotypes group, Dr. Pugh discussed the lack of consensus around using two different approaches to phenotyping: (1) using a data-driven approach or (2) starting from human symptoms such as oculomotor or cognitive. Dr. Pugh also noted that there is a large gap in how to best phenotype; it isn't merely the injury that is phenotyped, but also the background of the patient, including exposures and history, among other factors. This argument suggested that more data are necessary to phenotype patients. Dr. Pugh and the working group emphasized that there is a need for clinically rich data to characterize patients from acute to chronic. This could be accomplished by using data from electronic health records to provide a minimal dataset. Big data could also be leveraged to develop patient clusters; longitudinal analyses could evaluate how these clusters change over time. Dr. Pugh noted that with the clinical trials that did not deliver positive effects, it was unknown whether this was due to treatment effects or whether the effects were due to enormous homogeneous population on which a small portion of these trials are effective, but the signal was too weak to emerge. She indicated that knowing what type of care is happening broadly, we can phenotype and better understand whether specific kinds of care lead to better outcomes for specific individuals.

Dr. Brenner emphasized the need for a clinical trial infrastructure, similar to the NIH Strokenet (7), to prevent researchers from having to "reinvent the wheel" every time they initiate a trial. This would involve supporting

anything from design to recruitment to data collection and harmonization across sites. A second area of discussion was how to improve the knowledge gap gained during Phase 2 research, so it is more applicable to Phase 3 trials and how to have these trials run more than one at a time. A third discussion area was developing outcome measures for specific domains, a precision medicine focus. An aspect of this infrastructure could also include phenotyping of the patient base, which would provide a rich reservoir of data that is accessible to clinical trials. Discussion centered on getting the field and funders to value replication as much as innovation and provide important clues from failed clinical trials. To increase efficiency, trials could run in tandem to test multiple interventions at a time. A final recommendation was to improve the post-hoc analysis of clinical trials. Perhaps most importantly, the field should use patient-centered outcomes to solve the pressing needs of the patients.

Synthesis of Working Groups

Group leaders convened after the breakout sessions to synthesize the identified gaps and priorities at a high level. The goal was to determine if there were any similar themes across the groups or areas that stood out as priorities for review with all attendees. Five major themes emerged:

1. Timing
   a. Age of injury
   b. Age of sampling
   c. Repeat injury
   d. Lifetime/cumulative injury
   e. Variable injury type
   f. Continual or frequent data collection
2. Rigor
   a. Improving knowledge gain in Phase 2 (e.g., Bayesian methods)
   b. Outcomes: Objective quantifiable measures
3. Data Standardization, aggregation, harmonization/comparability
   a. Definition/metrics
   b. Objective/variable measures
   c. Resurrect prior trial data
   d. Negative data publication/searchability
4. Patient/Subject
   a. Disorder of interest
   b. Phase 2 knowledge gain
   c. Outcomes – objective
   d. Endophenotypes/domain of function
   e. Phenotypic enrichment in clinical trials
   f. Patient-focused drug development
   g. Precision medicine: preclinical, clinical trial design, biomarkers
5. Infrastructure
   a. A clinical trial network that includes:
      i. Subtypes of patients
      ii. Multiple outcomes
      iii. Accessible patient pool

      iv.   Clear pipelines/points of engagement

Key Take-Away: The four working groups identified several important gaps in the TBI field that are hampering clinical development. The afternoon working session's goal was to build on these gaps and begin to develop prioritized solutions.

8) **Session Title: TBI Policy Update**
   Speakers: Roger Murry, Executive Director, Coalition to Heal Invisible Wounds

Session Goal: To discuss how policy can address the national mental health priority of finding effective treatments for PTSD and TBI.

Founded in 2017, the Coalition to Heal Invisible Wounds (CHIW) aims to bridge Congress with the Veterans' research and the clinical community. The Coalition's Executive Director, Roger Murry, highlighted some of the roles of the organization, including consulting and lobbying with Congress. CHIW's mission is to secure federal policy reforms that help to develop new therapies and diagnostics for Veterans diagnosed with PTSD and TBI. The organization's current focus is to boost the VA's capacity by leveraging industry partners and making the process for clinical trial startup at the VA 100 days faster. This involves allowing the use of commercial IRBs, speeding up the information security review process and reforming the Research and Development Committee. Although Congress has provided access to care and boosted basic research on TBI and PTSD, there is an urgent need to pivot to the development of new treatments. Congress hopes to prevent Veteran suicides and solve the brain-health crisis. As few in Congress have clinical research experience, organizations like CHIW can bring forward compelling ideas; once Congress receives a funding or statutory request, the Coalition sees this process through to completion.

Mr. Murry provided an update on Congress's outlook for TBI. In 2018, Congress took three actions related to TBI: (1) passing the VA MISSION Act, which requires the VA to set standards for provision of TBI care by non-VA providers; (2) authorizing a one-year VA pilot program through the No Hero Left Untreated Act, which provides access to magnetic EEG/electrocardiogram-guided resonance therapy to treat Veterans with PTSD or TBI; and (3) passing the TBI Program Reauthorization Act of 2018, a five-year, $23M reauthorization of Centers for Disease Control and Prevention programs focused on data collection and access to care. For 2019, two provisions of the Commander John Scott Hannon Veterans Mental Health Care Improvement Act are being considered, including developing clinical practice guidelines. Some of the issues on the Coalition's watch list include developing TBI research networks, pushing for a congressional mandate for TBI research, updating the National Research Action Plan, and enhancing data sharing for TBI.

Key Take-Away: Working with Congress to secure federal policy reforms is an important aspect of spurring the development of new therapies and diagnostics for Veterans diagnosed with PTSD and TBI.

9) **Session Theme: Advancing Brain Health for TBI: Quantitative Neuroimaging for Precision Medicine and Clinical Translation in the Learning Healthcare System**

Speaker: Dr. Christopher T Whitlow, MD, PhD, MHA, Chair of American College of Radiology Head Injury Institute, Diagnostic Radiologist Researcher at Wake Forest Baptist Health Hospital

Session goal: To discuss the current status and future directions of the neuroimaging field with respect to TBI.

Dr. Christopher T. Whitlow discussed the role of imaging in TBI. His talk centered around three main topics: (1) the current state of the science in imaging; (2) moving imaging forward by using it as a quantitative tool; and (3) new and emerging tools for imaging the brain and analyzing and comparing these data with other biomarkers. Imaging is a large part of clinical practice, with non-contrast computed tomography (CT) being a first line of imaging that can predict mortality and unfavorable outcomes in these patients. Magnetic resonance imaging (MRI) may be indicated in cases with normal CT but unexplained neurologic findings. Unfortunately, these conventional neuroimaging techniques often fail to detect issues for patients with symptoms, especially when patients present with mild injuries; this leads to the necessity for more advanced methods that might identify abnormalities not been seen on CT. For instance, MRI diffusion tensor imaging, BOLD functional MRI, MR spectroscopy, perfusion imaging, positron emissions tomography (PET)/SPECT, and magnetoencephalography (MEG) can identify changes in the brain compared to a control group. The next step for the field is to determine what information can be extracted from these data that might help in clinical practice. Clinicians could take advantage of these datasets to use quantitative rather than qualitative approaches to practice, which allow clinicians to extract and understand the signals. For example, a qualitative assessment of a T1-weighted image may observe a mild degree of diffuse cerebral loss. A quantitative review, by contrast, would involve brain segmentation to quantify the amount of gray and white matter loss.

Dr. Whitlow's group is exploring quantitative approaches to MRI, such as cerebral blood flow imaging and brain functional connectivity and is developing a normative patient dataset. For longitudinal data, this approach would only work using the same scanner each time. Down the road, phantom scanner set-ups could help decrease the error between scanners. Other quantitative approaches target endophenotypes; for example, for cerebrovascular reactivity, researchers can use MEG to measure electrical activity to pull out default mode activity, assess delta waves which increase after TBI, or changes in sub-concussive exposure in athletes who experience repetitive hits to the head that do not reach the threshold of concussion. To assess molecular imaging, Dr Whitlow's group can use PET/CT and extract quantitative metrics from brain using specific ligands in an attempt to get at the mechanism. Another way to improve the use of neuroimaging in the field of TBI – where patients are heterogeneous, have comorbidities, and often show similar symptoms as individuals without TBI – is to apply methods like machine learning and artificial neural networks. Researchers can leverage advanced statistical techniques to separate groups that are similar. This could facilitate a big-data approach to identifying and stratifying subtypes for clinical trials. Finally, Dr. Whitlow discussed tools that should be validated against biomechanical exposure, the impact itself. While difficult to measure exposure, there are devices that can be used to assist clinicians in these trials. This will allow researchers to regress the biomechanical data out to show that as exposure increases, the brain changes. By looking at an individual participant, researchers could use these tools to identify the region of the brain that has the most shear and stress. This could help stratify patients based on the location and magnitude of exposure.

Key Take-Away: The neuroimaging field is seeing major advances that could provide deeper insights into TBI patients.

10) **Panel Discussion: R&D and Regulatory Challenges Panel**
   Moderator: Dr. Magali Haas
   Speakers: Ronald L Hayes, PhD, Founder and Chief Science Officer, Banyan Biomarkers, Inc; Stephen Xenakis, MD, Brigadier General (Ret.), US Army, Fisher Wallace Laboratories; William S Korinek, PhD, CEO, Astrocyte Pharmaceuticals, Inc.; Rosina Samadani, PhD CEO, Oculogica; Michael E Singer, PhD, CEO, BrainScope Company, Inc.; Michael Hoffman, Deputy Director, Division of Neurological and Psychical Medicine Devices, FDA

Session goal: To provide real-world experience from regulatory agencies and entrepreneurs on the regulatory approval process.

To begin the session, Michael Hoffman (FDA) offered important points for designing clinical tests of medical products that are seeking FDA approval. The FDA primarily considers benefits and risks, looking for clinically meaningful results, duration of treatment, and preclusion of additional therapies. It is important to work with the FDA at an early stage to ensure that the study design is well thought out, including inclusion and exclusion criteria, interventions and comparators, endpoints, and a pre-specified statistical analysis plan. Studies should have a clear definition of the study population and co-morbid conditions. Mr. Hoffman noted that clinically meaningful outcomes require a diagnostic gold standard, which is lacking, but there also needs to be gold standards for outcome measures. Mr. Hoffman also discussed that some medical devices have been marketed directly to consumers for concussion diagnosis, treatment, or management without FDA evaluation. To provide the public with the best and safest advice, the FDA has put together a list of cleared devices on their website.

Several industry professionals discussed their experiences with the regulatory approval process for medical devices for TBI. Ronald L. Hayes, PhD, is the founder of Banyan Biomarkers, Inc., which received the first FDA clearance for a blood-based biomarker that can distinguish between mild and moderate TBI at the acute phase. Dr. Hayes noted that Banyan started its process in 2002; thus, this process was slow and expensive. Banyan relied on support from the DoD. Stephen Xenakis, MD, Brigadier General (Ret.), U.S. Army, (Fisher Wallace Laboratories) emphasized that 2.8 million individuals have been sent to war. Many have returned suffering from injuries that we fail to treat. While he knows the scientists are working hard, he emphasized that we are failing our Veterans. Even with new biomarkers, there are no new diagnostic platforms or treatments on the horizons. He further emphasized that we continue to debate the same issues about the clinical challenges. Dr. Xenakis argued that the most important thing is to think about the patients and find ways to make their lives better in addition to working to understanding the etiology and treatment options.

Dr. William S. Korinek emphasized that the field must show progress and success in clinical trials to reduce skepticism and make the field appealing again to industry and venture investors. Dr. Rosina Samadani noted that developing a sound business model is key to convincing funders to support a product. Dr. Michael E. Singer also emphasized that the biggest hurdle for companies to achieve FDA clearance is funding. The company has seven

FDA clearances for their EEG product, which was a long process that required rigorous clinical studies and funding. Furthermore, getting FDA clearance was only the beginning of the road. Many steps are required to reach success following FDA approval. Dr. Hayes pointed out some short-term opportunities to change the medical practice, such as cross-validating existing FDA-cleared technologies as a quick path to securing the confidence needed to get treatments into practice to help TBI patients live their lives.

The panelists noted that TBI is that funding is a major issue for TBI. They noted that TBI has a reputation of being a death march and that it is very difficult to raise venture capital. These difficulties make it challenging to raise public funds. However, paths to move therapeutic innovation into the clinical space exist, but there needs to be progress and approvals. Collectively, the group highlighted the benefit of developing a game plan to address the problem given the current information and evaluate how we can use that information to develop a reasonable set of treatments and interventions. The panelists hoped that their companies' successes in progressing through the FDA regulatory approval process would pave the way for shorter and simpler processes for others.

Key Take-Aways: Major challenges continue to impede regulatory success, including the lack of gold standards for diagnostics, outcomes and funding. Science discovery is just one aspect of ensuring that a patient receives a new treatment; the spectrum of getting a product through regulatory approval, building a sustainable business model, marketing and educating clinicians, as well as the practicality of that process, are all barriers to success.

11) WORKING LUNCH BREAKOUTS

Attendees broke out into four groups to reevaluate the state of the science and prioritize solutions for gaps identified in Day 1. Several priorities emerged for the field of trauma-related research, including data standardization, aggregation, harmonization/comparability, and rigor. Attendees also addressed the need for an infrastructure for a clinical trial network, the importance of making preclinical research clinically relevant and improving the phenotyping/biotyping of patients.

Conclusions of the breakouts:
- Data standardization, aggregation, harmonization/comparability, and rigor
    - A section of NIH grant reporting could include a short version of negative data
    - The NIH could mandate publishing or making available negative data, such as through NIH E-journals for negative findings, BioArchive, or F1000
    - Standard operating procedures should be in place for preclinical research to ensure reproducibility in protocols; these could be published in places such as BioProtocol
    - For neuroimaging, efforts should focus on decreasing measurement error and variability across devices to standardize data collection
    - Funding should be increased for data analysis/data mining of existing/soon-to-be-acquired data, as this could be an efficient way to make progress. For example, CT images from patients are accessible (as well as many legacy blood samples) and could be used to identify subcohorts of patients
    - There should be more focus on generating data that is comparable across groups, as it is difficult to pool data when it has been measured in different ways or at different times

- o Genetic approaches (e.g., genome-wide association studies) could help establish symptom clusters and provide information about mechanisms
- An infrastructure for a clinical trial network
  - o The network should apply principles from other successful efforts, such as StrokeNet and the National Cancer Institute
  - o The network should include imaging, biostatistics and biomarker cores
  - o A primary focus should be quality assurance on how the data is handled and controlled, with oversight by a government steering committee
  - o The network should include a patient and family core and require a plan for stakeholders
  - o Implementation and dissemination should be part of the clinical trial network. For instance, the network should update clinical practice guidelines on a yearly basis, or as needed
  - o The network should be accessible to junior investigators and include a diverse portfolio of high- and low-risk trials
  - o The network could incorporate patient recruitment, where patients receive a battery for all studies as well as study-specific testing, helping to gather data
- Make preclinical research clinically relevant
  - o A consensus statement should be developed on clinical correlates via an NINDS-sponsored symposium on clinical relevance with key opinion leaders; this effort would lead to a white paper that outlines the need for a culture change and a set of recommendations for determining the clinical relevance of a given TBI model
  - o Funding agencies' grant applications could add a requirement for investigators to clearly outline the clinical relevance of a model and demonstrate rigor/reproducibility
  - o Clinicians could consult on preclinical experimental design, and innovations in diagnostics in humans could be brought back to the preclinical space
- Improve phenotyping/biotyping of patients
  - o Researchers should perform algorithmic assessment and clustering of patients based on this clinical assessment
  - o Big data should be leveraged to describe these clusters biologically; these clusters could form the basis of patient stratification for selection in clinical trials
  - o Researchers should consider lifetime TBI and pharmaceutical history (15% of people in VA system are on five or more medications)
  - o A retrospective data-analysis working group and a clinical assessment working group would be beneficial

12) Session Theme: Closing Session Call to Action
Speaker: Rachel Ramoni, DMD, ScD, Chief Research and Development Officer, US Department of Veterans Affairs

Session goal: To discuss the strategic priorities of the VA to help Veterans

Dr. Rachel Ramoni discussed how the TBI field could work together to fill knowledge gaps. She highlighted the importance of using the money in TBI research wisely. This can be accomplished by improving transparency in the

design and execution of the research, avoiding siloed work, in which underpowered studies and redundancy are the norm and ensuring that negative and positive results of all well-conducted studies are made available and readily discoverable. Researchers need to set objectives and relentlessly coordinate and collaborate to accomplish these objectives, sharing information and creating the necessary structures to do this. Finally, individuals and organizations should focus on the areas in which they can be most useful. The VA aims to increase Veterans' access to high-quality trials, increase the real-world impact of VA research, and put VA data to work for Veterans. One effort has been to develop an open-blast core via the Truman VA to study the chronic effects of blast injury, which includes a world-class preclinical bioimaging center and a preclinical neurobehavioral center. Three strategic priorities might include: (1) increasing Veterans' access to high-quality trials; (2) putting VA data to work for Veterans; and (3) increasing the real-world impact of the research.

Key Take-Aways: A coordinated effort among multiple TBI-focused public and private organizations will be necessary to address the prioritized gaps discussed during the summit. The VA is willing to support preclinical knowledge gaps for TBI research and will spearhead the coordination across organizations.

OVERALL CONCLUSIONS

The second annual SoSS leveraged the brain power of leaders across the brain health spectrum and strengthened the cohesion of the scientific, clinical, and patient communities within TBI by bringing awareness of global research efforts and removing siloed approaches to research through provocative discussions driving toward innovation. The summit resulted in a document that reviewed the state of the science within specific domains of TBI and produced a strategic list of next steps for these areas. Working groups will meet to refine and further these summaries into a special issue of a peer-reviewed journal. From this effort, the brain health community will have a roadmap to guide and accelerate future translational research. These priorities will be shared broadly with stakeholders to encourage adoption to inform TBI research, treatment, and funding initiatives and will be reassessed on a regular basis. The effort will be reviewed at a regulator cadence as new innovation and treatments arise as well as broadening the effort across brain health.

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