Statement for the Record

House Committee on Veterans' Affairs Subcommittee on Health and Subcommittee on Oversight and Investigations

"Oversight Hearing on the Department of Veterans Affairs medical and prosthetic research program"

Submitted by the Coalition to Heal Invisible Wounds

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Chairman Wenstrup, Chairman Bergman, Ranking Member Brownley, Ranking Member Kuster, and Members of the Subcommittees:

On behalf of the Coalition to Heal Invisible Wounds, thank you for this opportunity to provide written testimony regarding the VA's research partnerships, priorities and the extent to which the VA effectively translates research findings to the clinical setting to the benefit of Veteran patients. We commend the Subcommittees' leadership in addressing these critical issues.

The Coalition to Heal Invisible Wounds was founded in February 2017 to advance policy reforms that widen and expedite the pipeline for new therapies and diagnostics for post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI). Coalition members innovate at all stages of the therapy development life-cycle and also serve Veterans who most urgently require mental health interventions.[1]

According to the VA PTSD Psychopharmacology Working Group: "The urgent need to find effective pharmacologic treatments for PTSD should be considered a national mental health priority."[2] Despite the "high prevalence and costly impact" of PTSD in military personnel and Veterans, "most patients are treated with medications or combinations for which there is little empirical guidance regarding benefits and risks," and there is "no visible horizon for advancements in medications that treat symptoms or enhance outcomes in persons with a diagnosis of PTSD." The scenario is similar for TBI and these two conditions often coexist but may also occur independently in the VA population.

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[1] The Coalition's members are Cohen Veterans Bioscience (co-chair), the Military Veterans Project, NAMI Montana, Otsuka America Pharmaceutical Inc. (co-chair), and Tonix Pharmaceuticals.

[2] John H. Krystal et al., *It Is Time to Address the Crisis in the Pharmacotherapy of Posttraumatic Stress Disorder: A Consensus Statement of the PTSD Psychopharmacology Working Group*, J. Biological Psychiatry (2017) http://www.biologicalpsychiatryjournal.com/article/S0006-3223(17)31362-8/abstract

The Coalition believes that better diagnostics and therapies will spur more Veterans to seek care. According to a 2017 survey of over 4,000 Iraq and Afghanistan Veterans of America (IAVA) members, 46 percent report having PTSD, while 19 percent report having TBI.[3] Only 16 percent of IAVA members believe troops and Veterans are getting the care they need for mental health injuries and stigma remains the top reason Service members and Veterans are not seeking care. A major reason why IAVA members stop seeking care is that they do not think that the treatment will work.

An implicit promise of world-class health care is a strong research function. Veterans have earned the right to world-class health care. Better research will lead to better care of our Veterans who suffer from PTSD, TBI, and other mental health conditions that are prevalent among the veteran population. We strongly believe that the VA can become a leading partner in delivering new therapies and diagnostics; it has many outstanding assets and institutional strengths, as well as the desire to overcome the institutional hurdles to establishing advanced research partnerships.

The Coalition seeks to advance discrete reforms at the VA to support cutting-edge research partnerships. We focus on enhancing big-data research partnerships, standardizing approval and oversight of multi-site clinical trials to accelerate the development of new therapies, and spurring the development of new brain health diagnostics for clinical use. Ultimately, the VA can align its management of clinical trials much closer to best practices, which will lead to increased clinical trial success rates and the accelerated development of new diagnostics and therapies for conditions that disproportionately impact Veterans. We believe that in 2018, with appropriate oversight from Congress, the VA can pursue several targeted reforms that would serve as significant first steps in this process:

1. Permit sponsors to use commercial IRBs accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP);

2. Clarify that the Central Office has the authority to determine all information security requirements for a multi-site trial, direct the VA to develop a central list of compliant vendors and direct the VA to staff the office appropriately;

3. Direct the VA to study the obstacles sponsors face in recruitment and develop a plan to support Veteran participation in clinical trials;

4. Develop a master plan to support clinical research; and,

5. Direct the VA to work with pertinent Federal and non-governmental partners to deploy at least two additional brain health diagnostic measurements for clinical use at VA facilities before 2023.

We are grateful for the opportunity in this testimony to describe in more detail both these initial steps and the overall trajectory for reform.

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[3] 2017 Member Survey; Iraq and Afghanistan Veterans of America." Accessed May 9, 2018. https://cultureondemand.github.io/iava-report/

A. Conduct and Support for VA's Research Partnerships

We support the work of the Subcommittees and the VA to bridge the gap between basic research and clinical research. This work complements ongoing examinations within the Office of Research and Development, at NAVREF and their member Nonprofit Research and Education Corporations (NPC), and within the private-sector research community as to how the VA can help get more research into the clinic. Major stakeholders share an understanding that the current diagnostic and therapeutic options available to Veterans are not sufficient, and that creating a more predictable and streamlined research approval and oversight process at the VA will attract more investment to address conditions that are specific to or prevalent among the Veteran population. Enhancing research pathways also will help the VA deliver better care to Veterans.

An important place to begin bridging the gap is to standardize clinical trial reviews. While some VA clinics have been able to participate in multi-site clinical trials, sponsors report a widespread lack of standardization in the approval and oversight of sponsored clinical research at the VA. This delays VA trial site start dates, increases research costs, and discourages research sponsors from partnering with the VA. We encourage the Subcommittees to comprehensively review how the VA can streamline the approval process, identify and propagate best practices, and develop true continuity in the approval and administration of clinical trials. For 2018, three reforms, described below, are close at hand and would immediately draw more clinical research to the VA.

1. Institutional Review Boards (IRBs)

IRB reviews ensure that clinical trials abide by clear ethical guidelines and protect the well-being of research participants, but sponsors need the reviews to be prompt and consistent. Despite earnest efforts by many within the VA to standardize and improve the IRB process (namely, by standing up a central IRB), the IRB process continues to be a source of major delays for sponsors. In fact, despite a decade or more of work on the central IRB, some multi-site clinical research sponsors, due to frustrations with the central IRB, have reverted to using local IRBs. In light of the high-quality, private-sector options available, we do not advise further efforts to enhance the current IRB process as it relates to sponsored research. Instead, we recommend that the Subcommittees move to permit sponsors to use commercial IRBs accredited by the AAHRPP. Stakeholders within the NPC, industry and non-profit communities broadly support this proposal.

Allowing the use of accredited commercial IRBs would allow for predictable and frequent IRB review processes and timelines. In pursuing this reform, it is important to consider and account for, where relevant, how this step would impact the role of other review committees, VA requirements for education and training, VA-specific regulatory requirements related to human subjects research, and the workload for the local and NPC IRBs. We believe that each of these considerations can be adequately addressed.

2. Information Security Officer (ISO) Reviews

ISO reviews seek to ensure the safety of patient data. The reviews are often lengthy and unpredictable, leading to security requirements for the same study that can differ by VA clinic. Local ISOs are extremely busy and have variable knowledge of clinical research data storage and transfer requirements. Guidelines for ISOs can be unclear and outdated, while many ISOs feel organizational pressure to pursue the most conservative approach, and constrain the VA from participating in cutting-edge research. Further, there is no central list of compliant research vendors, so vendors are vetted and re-vetted by local ISOs.

A centralized information security review for multi-site clinical research would allow for a more thorough, standardized, and appropriate review process, while reducing delays that often occur at the local level. The VA has begun to move in this direction. The Central Office recently set up an office to assist local ISOs with reviews of multi-site research. However, the Central Office does not have clear authority to manage all information security requirements for a multi-site trial. Congress should clarify that the Central Office has the authority to determine all information security requirements for a multi-site trial, that it should develop a central list of compliant vendors and direct the VA to staff the office appropriately. These steps would standardize the scope and timing of the ISO review process, as well as send positive signals to potential research sponsors.

3. Clinical Trial Recruitment

Veterans should have the right to be fully informed of all of their treatment options, including the potential benefits and risks of clinical trial participation. This allows Veterans the opportunity to benefit personally from cutting-edge research opportunities and assist the wider community as a whole through trial participation. In fact, in oncology and increasingly other areas of medicine, clinical trials are now the standard of care. Research sponsors report widely varying experiences recruiting research participants. Some VA sites, for example, maintain a database of VA patients that have indicated their desire to be contacted about new opportunities to participate in a study and allow sponsors to effectively recruit. Other VA sites do not offer this or other institutional supports for recruitment, leading to extended recruitment timelines and increased cost of the research. Some sponsors have been unable to fill the patient population needed for the trial, compromising the ability to understand the efficacy of the treatment being tested.

Recruitment problems are not unique to the VA. According to researchers at Vanderbilt and Duke Universities, nearly 1 in 5 clinical trials are either terminated for failed participant accrual, or are completed with less than 85 percent of the expected enrollment. Recruitment challenges increase the cost and reduce the speed with which advances in medicine reach Veterans and the general population.

VA research stakeholders have expressed an array of difficulties related to recruitment, but it is not yet clear what specific reforms the VA could undertake to best facilitate enrollment. We would advise that Congress direct the VA to study the obstacles sponsors face in recruitment and to develop a plan to support Veteran participation in clinical trials.

B. Translating Research Findings to the Clinical Setting to the Benefit of Veteran Patients.

1. Master Plan to Support Clinical Research

While improving clinical trial management will spur more private sector activity, the VA should also play a direct role in bridging the gap between basic research and clinical research. Today, grant money is divided across too many different projects, leaving each with too little money to appropriately design and run a clinical trial, and unable to lead to the next step of investigation. The VA should assess how federal agencies and the private sector are supporting clinical research into new diagnostics and therapies for conditions that disproportionately impact Veterans. The VA should then develop a master plan that provides for strategic support of clinical research, including for private sector activity, to speed developments that address those conditions. The plan should include innovation grants for external research, such as the Industry Innovation Competition, in which the VA spurs activity in the private sector to help solve VA's most pressing challenges. The plan should complement the comprehensive plan for biomarker discovery and validation described blow.

2. Diagnostics Research Mandate

As our members engage every day with Veterans suffering from PTSD and TBI, they see an urgent need for mechanism-based diagnostic tools to precisely diagnose those conditions. Using symptom-based diagnostic tools alone diminishes the ability of physicians to effectively diagnose these multi-faceted disorders as well as overcome the known challenges of diagnosis such as stigma and delays in qualified clinical assessment. In 2013, while still serving as Director of the National Institute of Mental Health, Dr. Tom Insel stated that "the diagnostic system has to be based on the emerging research data, not on the current symptom-based categories," and that "we must set our sights higher" than a 19th century approach.[4] "Indeed, symptom-based diagnosis, once common in other areas of medicine, has been largely replaced in the past half century as we have understood that symptoms alone rarely indicate the best choice of treatment." Clinicians need new tools to more precisely diagnose those suffering from PTSD and TBI, which requires the VA to effectively translate research findings to the clinical setting for the benefit of Veteran patients.

Diagnostics are objective, measurable predictive factors that help doctors improve care. For example, the FDA recently approved a blood test to improve the diagnosis of concussions, which could eliminate the use of unneeded CT scans in at least a third of those with suspected brain injuries. Writing in the VA's PTSD Research Quarterly, VA researchers determined that "we appear to have reached a watershed in the development of biologically-based interventions for the prevention and treatment of PTSD."[5] Further, understanding the multiple and interacting mechanisms of malfunction in each stress system will be critical to advance the diagnosis and treatment of trauma-related mental health disorders into the precision medicine era.

According to a recent literature search of PTSD biomarker discovery studies, researchers identified over 800 PTSD biomarker candidates, but none have been validated or approved by

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[4] "Post by Former NIMH Director Thomas Insel: Transforming Diagnosis." NIMB Director's blog. Posted April 29, 2013. Accessed May 9, 2018. https://www.nimh.nih.gov/about/directors/thomas-insel/blog/2013/transforming-diagnosis.shtml

[5] "Biomarkers for Treatment and Diagnosis." PTSD Research Quarterly. Accessed May 9, 2018. https://www.ptsd.va.gov/professional/newsletters/research-quarterly/V26N1.pdf

the FDA for clinical use. There are many reasons for the failure to validate PTSD candidate biomarkers to date, but most can be overcome by bringing together large data sets and standardization of research techniques. For example, targeted research based on big data analysis is more likely to direct researchers toward plausible candidates that can be replicated and validated. Given the state of the science, we believe this is not only possible but also probable by 2023.

To bridge the gap between basic research and the needs of Veterans and their doctors, Congress should require the VA to work with pertinent Federal and non-governmental partners to build a comprehensive plan for biomarker discovery and validation including the deployment of at least two additional brain health diagnostic measurements before 2023 for clinical use at VA facilities, and funding a broader long-term biomarker study through the Department of Defense (DOD). The statutory objective would help VA leadership marshal sufficient resources and implement administrative reforms to boost public-private partnerships and power the discovery of biomarkers.

C. Conclusion

The Coalition to Heal Invisible Wounds thanks the Subcommittees for its work to strengthen VA medical and prosthetic research program. We strongly believe that the VA has the potential to be a world-class research partner to the private sector, enabling better health care for Service members and Veterans, and the initiatives proposed above would provide significant initial progress toward that goal.

. We encourage the Subcommittees to continue to engage with stakeholders to develop a multi-year plan that provides for continual improvements to data-sharing, clinical trials and therapy and diagnostics research. Comprehensive reforms would address the many other pacing limiters of clinical research, such as limitations on protected time for physician-researchers participating in sponsored research, and budget and Cooperative Research and Development Agreement (CRADA) negotiations. Comprehensive reform would also advance the best practices that have helped clinical trials succeed at the VA, such as the lead site model pioneered by several innovative NPCs.