Written Statement

House Committee on Veterans' Affairs Subcommittee on Health Hearing

"Beyond the Million Veterans Program: Barriers to Precision Medicine."

Testimony on behalf of the Coalition to Heal Invisible Wounds

Dr. Magali Haas, President and CEO, Cohen Veterans Bioscience

June 26, 2018

Introduction

Dr. Magali Haas, PhD. CEO and President of Cohen Veterans Bioscience and co-founder of the Coalition to Heal Invisible Wounds.

Good afternoon, Chairwoman Brownley, Ranking Member Dunn, and distinguished Members of the Subcommittee. Thank you for the honor to testify before the Subcommittee and for the opportunity to discuss the barriers to precision medicine. It is also a pleasure to testify alongside Dr. Carolyn Clancy, Deputy Under Secretary for Health for Discovery, Education and Affiliated Networks with the Veterans Health Administration Department of Veterans Affairs (VA), and with fellow Coalition member, Matt Kuntz.

Cohen Veterans Bioscience

Cohen Veterans Bioscience (CVB) was founded in 2014 under its original name of Orion Bionetworks to address brain disease research and in 2015 expanded its focus in response to the clear need to provide optimized care for our nation's Veterans suffering from post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI). We are a national, nonpartisan research 501(c)(3) public charity organization dedicated to fast-tracking the development of diagnostic tests and personalized therapeutics for the millions of Veterans and civilians who suffer the devastating effects of trauma-related and other brain disorders. CVB is leading the way in responding to this critical challenge by organizing a multi-stakeholder complementary network of international subject-matter experts and employing the most innovative scientific tools to support a common roadmap for identifying diagnostic biomarkers, building predictive disease models and developing treatments for PTSD and TBI. We are rethinking how we study brain disease, how we define it, how we identify new targets and how we advance precision medicine approaches, and our portfolio of projects exemplifies our commitment to accelerating the field of brain health.

Our portfolio includes several large-scale programs, specifically in the area of PTSD and TBI, which allow us to rapidly and empirically develop and test new diagnostics and treatments that will speed personalized medicine approaches to clinicians and will directly benefit the Veteran and civilian communities. Examples of our research programs are listed below:

- ***Adaptive Platform Trial in Post-traumatic Stress Disorder:*** The only approved medications for the treatment of PTSD are the selective serotonin reuptake inhibitors (SSRIs) sertraline (Zoloft®) and paroxetine (Paxil®), which were approved over 17 years ago[1]. However, their efficacy for treating PTSD is limited, with response rates rarely exceeding 60% and only 20-30% of patients achieving complete remission[2]. The VA 2017 Consensus Statement of the PTSD Psychopharmacology Working Group concluded that there is a deficient pipeline of new PTSD medications and an assessment of recent trial failures has generated concerns about how to best identify new targets for medication development and optimally design clinical studies[3]. The high failure rate of previous clinical trials can be attributed not only to the lack of validated biomarkers for PTSD, which prevents clinicians from predicting whether a patient will respond to a given therapeutic in a clinical trial, but also, and most critically, to the field's historical use of traditional clinical trial designs, which lack the ability to implement prospectively planned modifications to one or more aspects of the trial based on the heterogeneity of the patient population.

  In September 2018, Cohen Veterans Bioscience was granted a research award by Advanced Technology International (MTEC Consortium Manager) on behalf of the U.S. Army Medical Research and Materiel Command (MRMC)[4]. The award is for a three and a half year study to comparatively test the efficacy and safety of pharmacotherapeutics for PTSD via a well-powered adaptive platform trial (APT). Cohen Veterans Bioscience will lead this program and serve as a Clinical Coordinating Center, establishing a clinical trial infrastructure for the trial's governance structure that includes a Joint Steering Committee with representatives from the VA, the National Institute of Mental Health, the FDA, and the Defense Health Agency's Psychological Health Center of Excellence. This clinical trial is scheduled to start in the spring of 2020 and will incorporate biological measurements to support a precision medicine approach to PTSD treatment. During the period of performance, at least two active drugs (pending selection) will be tested simultaneously incorporating biological measurements to support a precision medicine approach to PTSD treatment. The APT will also incorporate extensive biomarker testing to identify and enable the validation of more precise diagnostics, biomarkers that can predict the response to specific treatments, or biomarkers that could be used for stratifying patients in clinical trials. The results of this trial aim to identify a drug to move forward for Phase 3 testing starting in 2023 and ultimately lead to an alternative FDA-approved drug or changes to clinical practice guidelines for the treatment of military-related PTSD.

---

[1] Jeffereys M. Clinician's guide to medications for PTSD. Sep 12, 2011. Available at: http://www.ptsd.va.gov/professional/pages/clinicians-guide-to-medications-for-ptsd.asp. Accessed October 20, 2011.

[2] Berger W et al. Pharmacologic alternatives to antidepressants in posttraumatic stress disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2009; 33:169–180.

[3] Krystal J. 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

[4] Cohen Veterans Bioscience Adaptive Clinical Trial press release. October, 2018. Available at: https://www.cohenveteransbioscience.org/2018/10/04/cvb-receives-resarch-award-dod-ptsd-clinical-trial/. Accessed on June 24, 2019.

- ***Research Alliance for PTSD/TBI Innovation and Discovery Diagnostics (RAPID-Dx):***

  RAPID-Dx is CVB's flagship biomarker discovery collaborative, with the aim to fast-track the development of objective diagnostics for PTSD, TBI and other trauma-related brain disorders. Developing biomarker-based diagnostics is essential to shifting diagnosis & treatment of PTSD and TBI from a syndromic, symptom-based approach to a biological, mechanistically-based one that targets the effects of trauma at their molecular roots. To date, no biomarkers have been sufficiently validated and independently replicated to allow for use in stratifying these highly heterogenous patient populations, predicting disease course, or supporting diagnostic development. To advance discovery and validation, CVB is coordinating a multi-disciplinary, multi-institution, public private partnership program that will bring together large, well-characterized cohort studies of PTSD and TBI, encourage collaboration amongst investigators to share large biomarker and imaging legacy datasets in a centralized, cloud-based platform, and support large-scale analyses of stored biosamples on high performance bioassay platforms. This will ultimately inform precision medicine approaches for more effectively treating veterans and others suffering from trauma-related brain disorders.

- ***Digital Health:*** In July 2018, we announced the formation of Early Signal, LLC, a wholly owned, non-profit subsidiary of Cohen Veterans Bioscience.[5] The new subsidiary allows CVB to continue its innovative approach to translational research by advancing needed diagnostics and precision medicine for brain disorders including PTSD, TBI and MDD, and expands our capabilities in digital health and data-driven research. Early Signal has developed a leading digital health platform for recording and analyzing a range of information, reported from wearables and other sensors, directly related to the well-being of patients living with brain disorders. By tracking variables such as sleep, physical activity, stress and cognition, we aim to better understand what changes in patients with brain disorders over time and to use this multifactorial data to improve the ability of clinicians to diagnosis a wide range of brain disorders and to treat them using precision medicine approaches.

The Coalition to Heal Invisible Wounds

CVB is a founding co-chair of the Coalition to Heal Invisible Wounds, which launched in February 2017.[6] The Coalition advocates for policy reforms to widen and expedite the pipeline for new therapies and diagnostics for PTSD and TBI. By deepening public-private cooperation and adopting targeted reforms, the VA and Department of Defense (DOD) can become leading partners in delivering new therapies and diagnostics to doctors.

---

[5] Cohen Veterans Bioscience press release. September, 2018. Available at: https://www.cohenveteransbioscience.org/2018/09/06/cohen-veterans-bioscience-expands-digital-health-platform-with-early-signal-expertise/. Accessed June 24, 2019.

[6] 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. More on the Coalition to Heal Invisible Wounds is available at invisiblewounds.org.

Doctors need better tools to diagnose and treat Servicemembers and Veterans suffering from PTSD and TBI. Only 16 percent of IAVA members, as surveyed in 2017, 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.[7] The Coalition's mission is guided by four overlapping concerns:

1. A staggering 6,000 Veterans have committed suicide each year from 2008 to 2016. In 2016, the suicide rate was 1.5 times greater for Veterans than for non-Veteran adults.[8]

2. Treating the underlying condition can help reduce the risk of suicide, but a 2015 Journal of the American Medical Association (JAMA) study found that about two-thirds of Veterans receiving prolonged exposure therapy, considered by Stanford researchers to be "the gold standard of behavioral therapy for PTSD,"[9] "retained their PTSD diagnosis after treatment."[10]

3. Treatment-resistant PTSD is a common clinical problem in Veterans, since currently "available medications are often ineffective in usual clinical practice."[3]

4. The VA found in 2016 that "most [PTSD] 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…PTSD."

The lack of clinical research in PTSD and TBI has led to treatment regimens that resemble trial and error. In 2013, while still serving as Director of the National Institute of Mental Health, Dr. Tom Insel stated that "the diagnostic system [for mental disorders] has to be based on the emerging research data, not on the current symptom-based categories."[11] In Veterans mental health, precision medicine has a simple meaning: we want diagnostics and therapies that work.

The lack of precision medicine in PTSD care contributes to the high rate of treatment-resistant PTSD in Veterans. Clinicians need new tools to diagnose precisely those suffering from PTSD and TBI, which can only be achieved by systematic reviews of existing evidence, and a greater investment in both basic and translational research and in large-scale and well controlled clinical trials. It also requires improved clinical trial processes and clinical trials that include Veterans. We owe Veterans our commitment to prioritize clinical research.

---

[7] "IAVA 2017 Annual Member Survey: A Look into the Lives of Post-9/11 Veterans" Published October 2017. Available at: https://iava.org/wp-content/uploads/2016/05/IAVA_Survey_2017_v11update.pdf

[8] "VA National Suicide Data Report 2005–2016." Published September 2018. Available at: https://www.mentalhealth.va.gov/docs/data-sheets/OMHSP_National_Suicide_Data_Report_2005-2016_508.pdf.

[9] Stanford Medicine News Center. "Biology may make certain PTSD patients unresponsive to behavioral therapy." April 3, 2019. Available at: http://med.stanford.edu/news/all-news/2019/04/biology-may-affect-ptsd-patients-response-to-therapy.html.

[10] Steenkamp, MM, et. al. "Psychotherapy for Military-Related PTSD: A Review of Randomized Clinical Trials." Journal of the American Medical Association. 2015 Aug 4. pp. 489-500.

[11] "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

The 100 Days Faster Initiative

We ask today that the Subcommittee help the VA overhaul its clinical trial startup practices. According to data from two major contract research organizations, in the last four years VA sites have taken an average of 265 days to activate a site (from receipt of registration and contract to active).[12] Non-VA sites have averaged 141 days. Because of these lengthy delays, many clinical research sponsors do not attempt to bring clinical research to the VA, and have not done so for decades.

The lack of clinical trials at VA sites means that Veterans lack access to the frontier of medicine for many disease conditions. For Veterans suffering from PTSD, TBI, hearing loss, alcohol and other substance use disorders (SUDs), cancer, and other conditions, a clinical trial may be the next or only available treatment option. This is most acute in oncology, where only a small fraction of the hundreds of clinical trials annually in the United States use VA sites. Of 34,000 oncology clinical trials in the United States listed on clinicaltrials.gov, fewer than 800 have taken place at a VA facility.[13] What happens when a cancer study does not open in a VA facility? A Veterans suffering from that form of cancer is more likely to die sooner. Countless birthday, anniversaries, graduations, births, and other milestones missed in part because of inadequate clinical trial procedures at VA sites.

We believe that timely and high impact reform is within reach. The VA Office of Research and Development (ORD) and the National Association of Veterans Research and Education Foundations (NAVREF), have led a multi-stakeholder review of the causes of clinical trial startup delays. Both CVB and the Coalition have engaged in this review, called Access to Clinical Trials (ACT) for Veterans, which has identified numerous areas ripe for immediate reform.

We believe that with targeted reforms, the VA can become 100 days faster, on average, at clinical trial startup by 2021. We call this the 100 Days Faster Initiative, and last month organized a multi-stakeholder letter to the House and Senate Committee leadership calling for congressional support of the goal. Achieving this goal would build the institution of the VA, bringing it to near-parity with leading clinical research institutions in the United States.

As the causes of clinical trial startup delays extend throughout numerous functions within the VA, it is imperative Congress provide the VA statutory guidance to achieve the 100 days faster objective.

Informed by the ACT for Veterans process and other engagement with leading stakeholders in the clinical research community, we recommend that the subcommittee develop legislation that provides for the following reforms:

1. **Allow the use of commercial Institutional Review Boards (IRBs) in sponsored clinical research.**

[12] Personal communications with contract research organizations in July 2018 and January 2019.

[13] Source: Clinicaltrials.gov search of clinical trials conducted in oncology at VA sites. Accessed June 24, 2019.

Slow and inconsistent reviews by IRBs constitute a major factor in start-up delays. IRB reviews ensure that clinical trials abide by clear ethical guidelines and protect the well-being of research participants. VHA Handbook 1200.05, revised January 2019, states: "A VA facility may not use a commercial IRB as an IRB of Record." Yet, commercial IRBs accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP) are widely employed outside of the VA and are highly regarded in the research community for thorough and timely procedures. Over the past two years, the VA ORD has been exploring policy changes to allow the use of commercial IRBs as another option to local IRBs or the VA Central IRB. The VA should immediately remove all barriers to allowing the use of commercial IRBs in sponsored clinical research.

2. **Authorize and provide performance benchmarks for Office of Research Reviews within the Office of Information Technology (IT)**

   A centralized information security analysis would allow for a more thorough and appropriate review, while reducing delays that often occur at the local level. Local information security officers (ISOs) have variable levels of knowledge related to clinical research data storage and transfer requirements, and limited time to understand the research requirements which leads to security requirements for the same study that differ by VA clinic.

   Since 2018, the VA Central Office, Office of IT, has hired ten ISOs to assist local ISOs with clinical research approvals, covering the entire national research program for activities across all of the more than 100 VA sites. Codifying this function within the Office of IT and requiring that it fulfill specific objectives, such as developing an approved vendor list, would allow for a more thorough and appropriate review, while reducing delays that often occur at the local level.

3. **Authorize and provide performance benchmarks for Office of Research Reviews within the Office of Privacy (IT)**

   Similar to information security reviews, a centralized privacy review would allow for a more thorough and appropriate review, and standardize outcomes. Medical Center privacy officers have variable levels of knowledge related to clinical research privacy requirements, and thus privacy protocols can vary significantly between clinical trial sites. Similar to the Central Office IT Team, the VA should hire dedicated privacy officers dedicated to multi-site clinical research. Codifying this function within the Office of Privacy and requiring that it fulfill specific objectives would allow for a more thorough and appropriate review, while reducing inconsistencies that often occur at the local level.

4. **Refocus the Role of the Research and Development Committee**

   Stakeholders both within and outside of the VA have identified the R&D Committee as worthy of refocusing toward other aspects of the research and development process, including identifying emerging research needs at local VA facilities, and removing the R&D Committee's role as the final approval for a clinical trial site. Unique to VA facilities, after a trial sponsor has secured all of the required substantive approvals for a trial site, the local Research and Development (R&D) Committee provides the final approval before a site can begin its trial (VHA Directive 1200.01). This is a unique

requirement, not found at academic and other institutions that host clinical trials, and can delay start-up by several weeks.

Taken together, these four reforms would help the VA make substantial progress toward improving its average clinical trial start-up period by 100 days. We look forward to working with the Subcommittee to identify other steps Congress can support toward this goal.

Conclusion

The Coalition to Heal Invisible Wounds thanks the Subcommittees for its work to strengthen the VA's capacity to support the development of precision medicine. Veterans have earned the right to world-class health care, and an implicit promise of world-class health care is a strong research function. We strongly believe that the VA has the potential to be a world-class research partner, enabling better healthcare for Servicemembers and Veterans. Achieving the 100 Days Faster Initiative would provide significant initial progress toward that goal. On behalf of CVB and the Coalition to Heal Invisible Wounds, I thank you for your attention to these matters.