LARA Quarterly Progress Report: 1/1/22 – 3/31/22

Wayne State Warriors Marijuana Clinical Research Program: Investigating the Impact of Cannabinoids on Veterans' Behavioral Health

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Project Aims:

In this randomized, controlled clinical trial we will recruit veterans with PTSD who report using cannabis. **We are conducting two studies that are complementary and linked via their aims and methodology**. In **Study 1**, 200 veterans will be randomized into one of four different THC:CBD dose conditions (High THC:High CBD; High THC: Low CBD; Low THC:High CBD, and Low THC:Low CBD) for a 12-week treatment phase. In **Study 2**, 150 veterans will be assigned into *either* a naturalistic group (n=75) that will be followed as they continue to use cannabis as they normally do (observation only), or into a "THC reduction group" (n=75) in which veterans are asked to switch from their typical cannabis product to using a lower THC/higher CBD product; adherence to this switch will be incentivized using contingency management. **Both studies** involve assessments bi-weekly throughout a 12-week treatment phase, and at 3- (post-treatment), 6-, 9, and 12-months post-baseline. Study 1 will also include additional weekly assessments. **Primary outcomes** include clinical assessments of PTSD symptom severity, mood and anxiety symptoms, and suicidality. **Secondary measures** include (1) neurocognitive function; (2) overall health, sleep quality, pain, healthcare utilization, and quality of life; (3) individual differences in fear learning and extinction associated with PTSD symptom severity; (4) saliva for DNA analysis to examine genetic and epigenetic markers associated with the endocannabinoid system; and, (5) urine, blood, and saliva samples to quantify levels of endocannabinoids and their metabolites (e.g., anandamide [AEA] and 2-AG), as well as THC and CBD and their metabolites, to examine whether these levels vary as a function of THC:CBD dose mixtures and differentially affect outcomes. Data will be analyzed to determine which THC and CBD levels might be associated with the outcome measures. These data will be used to (1) develop a predictive algorithm that will help determine personalized profiles of patients who may be at increased risk for suicide; and, (2) develop a profile of who might most benefit from cannabinoid therapeutics.

• Project Milestones – Percent (%) completion of the project objectives

N/A. We are currently in the start-up process and recruitment for Study 2 is scheduled to begin in May, 2022.

• Project Progress – Brief outline of the work accomplished during the reporting period and the work to be completed during the subsequent reporting period(s).

During the second quarter we continued to build infrastructure needed to support the logistical operation of study related elements including participant recruitment and study visit mechanics. A significant amount of effort has been dedicated to anticipating potential obstacles and identifying solutions to these obstacles. For example, cannabis products are not approved for use within the Department of Veterans Affairs (VA) at present which requires the study team to recruit Veteran participants from Detroit-area community-based organizations. We

have established contact with 15 Veterans groups including the Veterans of America, Michigan Veterans Affairs Agency, and Veterans of Foreign Wars (VFWs) to create a recruitment network capable of reaching Veterans either for whom cannabis is an existing treatment strategy or might be an attractive intervention for them to alleviate their symptoms of PTSD, depression, and suicidality. Recruitment documents including study flyers and informational brochures have been created, approved by our IRB and printed for advertising and distribution to these and other organizations. Social media and other advertising platforms to supplement recruitment have also been identified. We are creating a website dedicated to the research program where veterans and their families can get information about the studies, complete initial screening for eligibility, access other resources, and contact us. The website is near completion and should be up and running by May 15, 2022, when we plan to start recruiting for Study 2.

We sought and obtained Departmental Review Board and University Institutional Review Board approval for both studies. The clinical staff has completed training on how to administer all of the study-related measures and conduct the diagnostic interviews. We have created online versions of all questionnaires and measures so veterans can complete them online, and we have set up a clinical trial tracking system for both studies. Our safety plan is finalized and our Data Safety Monitoring Board (DSMB) has been established. We have identified a cannabis administration device that will address concerns about potential diversion or use of more than the daily allotted amount (Study 1). As it will not be possible to obtain all four THC:CBD concentrations in the quantities needed from a single grower we are currently in contact with three federally-registered DEA Schedule I growers to determine the best way to procure cannabis plant material. We likely will have to work with more than one company, which will require the submission of additional IND applications. However, we do not anticipate any difficulties obtaining these additional INDs and expect to have them issued during the next quarter.

Protocol details relating to secondary outcomes have been finalized and include a system for endocannabinoid collection, processing, storage, and analysis, and coordination of the genotyping analyses at the WSU Genome Sciences Core (for genotype-phenotype associations).

We expect to begin recruiting for Study 2 in early May, with recruitment for Study 1 to follow by the end of June. In addition to the progress noted above, there are also some changes that we will be making or would like to make to the study procedures:

- There will be a change in study leadership effective June 1, 2022. Dr. Norrholm has accepted a visiting professorship position out of state. Dr. David Ledgerwood (who is already lead investigator on Study 2) will assume Co-PI duties. There will be no change in salary/percent effort for Dr. Ledgerwood. Dr. Norrholm's salary will not be covered by this grant while he is at another university, and we plan to allocate those funds to (1) pay for two consultants; (2) provide honoraria for our DSMB members; and, (3) provide salary for a recruiter (see below).

- We have asked Dr. Ryan Vandrey (Johns Hopkins University), and Dr. Marcel Bonn-Miller (University of Pennsylvania) to be consultants on the trials. Dr. Vandrey brings over 20 years of experience studying the behavioral pharmacology of cannabis and

conducting controlled laboratory studies with adult research volunteers, clinical trials, web-based survey research, and natural history studies with patient populations using cannabis/cannabinoids for therapeutic purposes. His work helped characterized the cannabis withdrawal syndrome, furthered our understanding on the comparative pharmacokinetics and corresponding pharmacodynamics of cannabinoids across routes of administration, examined the effects of cannabis on sleep, and evaluated risks and benefits of medicinal use of cannabis/cannabinoids for various health conditions. He will provide consultation on regulatory issues and study procedures. We would like to pay Dr. Vandrey for 15 hrs of consulting in 2022-2023, 10 hrs in 2024, and 5 hrs each in years 2025 and 2026 (total of 35 hrs at $200/hr = $7,000). Dr. Bonn-Miller has conducted seminal work on the links between substance use and anxiety disorders, and more specifically on associations between cannabis use and PTSD. He will provide guidance on study procedures. We would like to pay Dr. Bonn-Miller for 10 hrs of consultation in 2022-2023, and then 5 hrs in 2024, 2025, and 2026 (total of 25 hrs at $200/hr = $5,000).

- We would like to offer honoraria to our DSMB members in recognition of their time and effort on this project. Board members are: John Hopper, MD (internal medicine/addiction medicine), Anthony King, PhD (trauma specialist), and Arash Javanbakht, MD (psychiatrist who specializes in anxiety/trauma). We would like to offer honoraria in the amount of $2000/year for each member (total $24,000 over 4 years). These amounts are consistent with other studies we and our colleagues have conducted, and reflect the considerable time and effort that are required to review patient safety and efficacy data from complex clinical trials.

- We would like to hire a full-time recruiter to oversee recruitment efforts, conduct telephone screenings, manage the website screening data, and schedule in-person screening. We would like to allocate the remainder of Dr. Norrholm's salary coverage for this person.

• Noteworthy Accomplishments – Identify and describe any milestones reached or noteworthy accomplishments completed during the period.

N/A – Still in study start-up

• Delays – Brief description of problems or delays, real or anticipated, which should be brought to the attention of the Grant Administrator.

We are currently experiencing an unexpected difficulty in obtaining cannabis as none of the DEA Schedule I cannabis growers is able to supply the THC:CBD concentrations in the quantities of plant material needed for Study 1. The company that is able to supply what we need is not a federally-registered grower for researchers. Thus, although for convenience we had wanted to obtain all four THC:CBD concentrations from one grower, and wanted to work with a Michigan company, we are now planning to obtain cannabis plant material from more

than one federally-registered grower, which requires submitting additional IND applications. We expect these new INDs will be granted by mid-June. Please note that Study 2 is not affected by this situation and recruitment will start next month.

• Attachments and Other Materials – Provide project materials developed and implemented during the reporting period (e.g. newspaper articles, newspaper advertisements, forms, brochures, announcements, studies, reports, analyses, audits, etc.).”

Attached are the IRB-approved Study 1 and Study 2 flyers and brochures that are being used to recruit participants and are being distributed to local providers to publicize this LARA-funded study within their patient populations.

Respectfully submitted,

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April 15, 2022