State of Michigan
Department of Licensing and Regulatory Affairs

Marijuana Regulatory Agency

VETERAN MARIJUANA RESEARCH (VMR) GRANT PROGRAM

2021

REQUEST FOR PROPOSALS

VETERAN MARIJUANA RESEARCH (VMR) GRANT

RESPONSE DOCUMENT

ESTIMATED TIMELINE	
Issue Date	June 1, 2021
Inquiries Due	June 11, 2021
Inquiries Response Posted	June 18, 2021
Proposals Due	July 16, 2021
Anticipated Start Date	July 30, 2021

PART V: INFORMATION REQUIRED FROM APPLICANT(S)

Applicant(s) must submit one proposal. Electronically submitted proposals must have a scanned signature or e-signature and cannot exceed 15 MB.

Applicant(s) must provide responses to each section below. Be as descriptive as possible and answer each question in its entirety; some questions have multiple components. In your responses, provide a straight-forward, concise description of the applicant(s)'s ability to meet the requirements of the RFP. Questions that do not apply should be answered "N/A."

V-A Identification of Organization

State the full name and address of the organization, the organization's federal identification number, the organization's telephone and fax numbers, and what percentage of the organization is located in Michigan.

BEGIN APPLICANT RESPONSE

Wayne State University

Sponsored Program Administration

5057 Woodward Avenue

13th floor, Suite# 13202

Detroit, MI 48202-4050

Federal ID # 38-6028429

Tele: (313) 577-2653

Fax: (313) 577-5055

100% located in Michigan

END APPLICANT RESPONSE

V-B Authorized Negotiator

State the name of one (1) contact person and his/her telephone number, fax number, and electronic mail address. The contact person must be authorized to be the negotiator for the proposed Grant Agreement with the State.

BEGIN APPLICANT RESPONSE

Patty Yuhas Kieleszewski

Associate Director, Contract Administration

Sponsored Program Administration

5057 Woodward Avenue

13th floor, Suite 13203

Detroit, MI 48202-4050

Tele: (313) 577-9227

Fax: (313) 577-5055

Email: aa6841@wayne.edu

END APPLICANT RESPONSE

V-C Method for Addressing the Problem

State in succinct terms the applicant(s)'s proposed method for addressing the problem presented in Section III-B, Problem Statement. Describe any significant obstacles the applicant(s) has had coordinating and managing clinical trial research.

BEGIN APPLICANT RESPONSE

I. EXECUTIVE SUMMARY

It is abundantly clear that US veterans face myriad Post Traumatic Stress Disorder (PTSD) and other trauma-related challenges. Despite robust efforts to mitigate symptoms, more than 6,400 military veterans committed suicide in 2018. Clinical research documents that a significant portion of veterans seeking assistance for PTSD report utilizing cannabis to control symptoms, though research into the interaction between mental illness and this drug is lacking. In addition, research is extremely limited regarding if and how cannabis could be a new frontier of treatment for veterans who now suffer due to their service.

Wayne State University's Translational Neuroscience Initiative (TNI) focuses the most highly funded Department of Psychiatry in Michigan on coalescing bench, clinical, and translational research. TNI ensures that campus-wide neuroscience work is integrated, seamless, and focused on great potential. Two of the faculty with expertise in veteran health and PTSD (Drs. Norrholm and Jovanovic), have been recruited to Wayne State through the TNI, and will be part of the consortium leadership along with experts in cannabis research (Drs. Lundahl and Ledgerwood). Within this consortium, cannabis research will be emphasized and we will explore the biochemical mechanisms through which it could be employed to treat PTSD, anxiety, sleep disorders, depression, and suicidality.

II. VISION STATEMENT

With our highly experienced clinical research team at Wayne State, we propose to expand the exploration of potential therapeutic effects of cannabis/cannabinoids to improve patient quality of life and to reduce PTSD and depressive symptoms that can precede suicidality. These efforts, in turn, could ultimately inform education and public health policy. The proposed investigations have the potential to broaden the scope and reach of cannabinoid research and treatment and, as such, (1) advance the field of cannabinoid therapeutics, so that clinicians will have empirical data to guide discussions of therapeutic cannabinoid use and associated risks with their patients, (2) provide trauma-exposed users with greater access to dedicated educational resources, such as community workshops and conferences, so they can make informed decisions about cannabinoid use, and (3) seek to improve their health outcomes and lower healthcare utilization rates and costs.

Faculty members have the necessary expertise in neurosciences and clinical trial research to boldly move cannabis research forward. This initiative would involve innovation and insights across the University's campus including the School of Medicine, College of Nursing, Eugene Applebaum College of Pharmacy and Health Sciences, School of Social Work, and others. An ability to successfully manage large-scale initiatives is evidenced by faculty leadership in the Perinatology Research Branch of the NIH, NC-Designated Comprehensive Cancer Center, Center for Urban Responses to Environmental Stressors (CURES), and more.

Wayne State University is poised and ready to lead the way in cannabis research for veterans.

It is vital to understand that Wayne State University and the TNI are remarkably situated to orchestrate world-class cannabis bench, clinical, and translational research. Located in the heart of Detroit and already strongly aligned with the John D. Dingell Veterans Affairs Medical Center, the relationships necessary for success are already established and functioning. Because faculty are already working closely with Veterans, within area VA Medical Centers and community veterans programs, expanding cannabis research with veterans would be a natural expansion of the current scope of work.

In addition, the infrastructure for fiduciary responsibility already exists within Wayne State University and the TNI currently utilizes these systems and processes. All finances and related account audits are expertly managed by Sponsored Programs Administration as this division manages the University's entire research portfolio. All human and animal model research, including safety regulations, is overseen by the university's Institutional Review Board, which would also apply its oversight to this research.

As part of a cannabis-focused research initiative, a consortium of researchers and clinicians would convene to establish and manage this endeavor. They would document research goals, review and approve projects, and exercise financial review. This consortium would meet regularly to guide the initiative and ensure that goals are achieved. A true coalition, this effort would move cannabis research forward to meet the vital needs of our veterans.

III. OBSTACLES

We have identified four primary obstacles to this line of research which can be effectively addressed through the Veteran Marijuana Research program. These obstacles include:

(1) Federal regulations are currently largely prohibitive to conducting human cannabis research. There is a significant body of literature from pre-clinical animal studies to suggest that cannabis, related cannabinoid compounds, and the mammalian endocannabinoid system should be a principle area of focus of empirical study in better understanding the role of these systems in trauma-, stressor-, anxiety-, mood-, and substance related disorders as well as developing novel treatments for the latter. ***Drs. Lundahl and Greenwald have the necessary FDA, DEA, and NIH licenses and certificates to conduct human cannabis research and have been doing such studies for over 20 years.***

(2) Sources of extra- and intramural funds to support large scale, community-based studies of cannabis and its potential therapeutic benefits is lacking despite the infrastructure and expertise being readily available within the Wayne State University system. ***Funding through the Veteran Marijuana Research Program will support the first, large-scale, randomized, controlled clinical trial examining the efficacy of cannabinoids to treat PTSD and suicidality in US armed forces veterans.***

(3) Recruitment, enrollment, and retention of Veterans in clinical research studies can have its unique set of barriers, both institutional (ie., VA regulations and policy) and logistical (ie., Veterans' access to healthcare and research opportunities). ***As part of the proposed project, we will create a mobile system of assessment, drug delivery, and study maintenance aimed at overcoming the previously mentioned barriers.***

(4) Veteran reports of cannabinoid use to treat their symptoms are widespread, however, at present the Department of Veterans Affairs is not supportive of cannabinoid therapeutic trials. ***Establishing the proposed large-scale, community-based study of cannabinoid use and its potential to reduce fear, decrease anxiety, increase mood, and lessen Veteran suicidality would provide an attractive alternative research and clinical arena for treatment seeking Veterans.***

END APPLICANT RESPONSE

V-D Management Summary

(1) Describe management procedures that will be used by the organization to complete the proposed project.

(2) Describe the organization's quality control measures, including measures for ensuring compliance as well as eligibility determination. In your description, include information regarding separation of duties.

(3) Selected applicant(s) must provide fiscal control and financial accounting procedures that will assure that grant funds will be accounted for and properly dispersed in a way that will allow the Issuing Office to clearly review and verify all grant related expenditures. Describe the organization's internal control policy:

- Identify the type of accounting system/software the organization will use to account for grant funds,
- Identify how duties will be separated,
- Describe how the organization will account for grant funds, i.e., will grant funds be placed in a separate bank account, will the grant funds be assigned a unique code(s) within the organization's overall accounting system. Ensure funds are maintained in a non-interest-bearing account.
- Indicate whether internal and external audits of the organization's operations are performed on an annual basis. Selected applicant(s) must provide a copy of the organization's most recent audited financial statement as well as a copy of the organization's most recent single audit as required by OMB Circular 200.36

(4) Describe your agency's data security plan.

BEGIN APPLICANT RESPONSE

(1-3) Management Procedures, Quality Control Measures, and Financial Accounting Procedures

Wayne State University (WSU) has a Sponsored Program Administrative (SPA) department that all grant awards must go through. Once the grant is awarded, we are notified by our SPA office and an index or account number is set up for that specific grant or fund award. The SPA office prepares the financial reports for the agency at each reporting period. They also send notifications and reminders if progress reports are due. The SPA office will load the budget based on what was submitted to the agency in our BANNER Accounting system.

At the department level, once a grant index number is established, our administrative team meets to review the contract. Cordell Crutchfield is our grant & contract administrator within the department of Psychiatry. Sonya Blair is our HR program specialist, Michelle Caton and Valerie Felder are purchasing agents, and Jennifer Ballard-Traynor is the administrative director. The administrative team meets to review the contract with the PI. The purpose of the initial meeting is to understand the project, review the budget, and read through the contract so we are all on the same page with the requirements.

Sonya will add effort to the grant based on the budget and the PI's sign off on who is actually working on the grant. This is done through an Electronic Personnel Action Form (EPAF), which is an online system for making personnel changes. Once she processes, it is reviewed by Jennifer, then by individuals in HR and the School of Medicine's Business Affairs office. All approvers will review the budget loaded in our Banner Accounting system, to ensure there are funds in the "personnel" expense account before approving.

The research team, including PIs, Co-PIs, or research coordinator will submit orders via email to either Michelle or Valerie. The orders are then placed in our WayneBuy Procurement System. At WSU, all purchasing orders must be pre-approved before making the purchase. Upon receiving the

order form from the research team, Michelle and/or Valerie will enter that order in WayneBuy. Once submitted, there are several approvers that must review the order before a Purchase Order is submitted to the vendor. Jennifer reviews all orders that are placed within the department. She reviews the grant budget to determine if the good/service was initially budgeted for. If it was, she approves it, if it was not, she will reach out to the PI for justification of the purchase. All charges on the grant must be 100% for that specific study. Once approved, it then goes to Business Affairs to review against the budget posted in Banner. Then it goes to the SPA office to review to ensure compliance with that specific grant. Lastly, a representative from the Purchasing office will review to ensure the requisition is compliant with the University. There are several approvers in this process to create a separation of duties and to ensure compliance for both the granting agency and the University.

Once the PO is approved, it is sent to the vendor to fulfill the order. The vendor will then submit an invoice to WSU for payment. Invoices under $1,000 do not require departmental review. Any invoice over $1,000 needs to be reviewed by the department to ensure the good or service was received. Then a receipt is entered in the WayneBuy system which prompts Disbursements to make the payment. All payments are made by the Disbursement office and do not go through the Department. Departments at WSU do not have the ability to issue payments to vendors.

All travel has to be preapproved in our Concur TravelWayne system. In this system, the user needs to estimate the expenses, enter the conference or research related travel information, indicate the index number to charge, and upload the conference brochure or research purpose. The request needs to be approved by Jennifer for grant compliance and budget review and to the Chair, Dr. David Rosenberg. Once approved, the traveler can submit receipts to an expense report in the system. These are reviewed first by Jennifer and then by the Business Affairs office. Once fully approved, the expense is posted to the grant index in Banner.

WSU uses the Clincard System to pay out research subject incentives. These are debit cards that are loaded with funds once a research participant completes a milestone. Jennifer sets up the studies in the Clincard system based on the approved IRB protocol for the study. She will enter the study name, grant index number, and the payment milestones. The physical cards are ordered through the Procurement office. The cards do not have funds on them until they are loaded through the Clincard system. We do not keep cash or preloaded debit/gift cards for the purpose of paying subjects. Users are given access to the Clincard system to load the cards once a participant is seen. A separate user will be added as a card approver once funds are loaded. The approver does not have access to the clincards as to separate duties. The system also requires social security numbers for each subject being paid, and the university runs reports on a regular basis to ensure no SSN matches a WSU employee's SSN. The university front loads funds to the Clincard system and each month charges are posted to Banner based on the index number for each study.

WSU uses the Banner ERP system to manage student and employee information and financial data for all funding received. Access to Banner relies on strict security measures and is only given to eligible employees. To separate duties, administrative employees in the Department of Psychiatry only have read-only access to Banner. The grant budget is loaded by SPA, the personnel expenses are added by the above EPAF system, expenses are added as WayneBuy and TravelWayne expenses are approved and paid, and research subject payments are posted monthly as they are paid out.

Our SPA office will invoice the granting agency on a monthly basis (unless otherwise stated in the contract) for all expenses that have posted to the grant in Banner. Invoices are normally to be paid 30 days upon receipt of the invoice. Once the invoice is paid, it is recorded under the grant so that we are able to track the revenue in that same index number.

An audit or review is performed each year in compliance with regulatory requirements or Board of Governor mandates. In certain instances, to achieve efficiencies, these audits may be performed biannually. Below is a link to our internal auditor web page with information on what systems are audited, the timeliness of audits, best practices, safeguarding assets, etc. https://internalaudit.wayne.edu/

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(3) All clinical research and participant encounters performed as part of this project will be subject to at least four levels of oversight from the Departmental to the Federal level. First, the Department of Psychiatry and Behavioral Neurosciences in the Wayne State School of Medicine has a Departmental Review Board (DRB) that reviews and approves research conducted by faculty in the Department. This is a prerequisite step to submission to Wayne State University's Institutional Review Board (IRB), the principal research oversight committee located at the University. Additionally, Dr. Lundahl, one of the project's Principal Investigators, is required to submit progress reports regularly as part of her approved and funded program of studies using cannabinoids to both the US Food and Drug Administration (FDA) and the US Drug Enforcement Administration (DEA).

(4) Data Security

Access to the Database

All data collected for this project will be stripped of all identifiable information and each participant will be assigned an individual code. These codes will be kept in a master file, separated from the identifiable information, by using a different passcode and kept in a different folder in a password protected server. All of the data for this project will be collected specifically for research purposes. Hard copy files will be kept in locked file cabinets within locked offices. Electronic data (e.g., digital audio-files of diagnostic interviews used for consensus diagnostic purposes) will be kept in a secure folder on a secured, password protected server, with access restricted to staff for this specific research study. Participant numbers without personal identifiers assigned to each participant will be the only means by which collected information is labeled. The master code is the only list that will link the names of the participants with their participant numbers will be kept in a secure, password- protected computer account on a separate drive from research coded data and will be accessible only to IRB- approved members of the research team.

Back-up of Database

The site research coordinator will back up the data from REDCap on a weekly basis onto the secure research server at Wayne State University. WSU will permit study monitors and oversight boards with access to data files and scanned case report forms stored on a WSU Box account. The study monitor will download a copy of the data files and scanned case report for data collection and quality assurance purposes. Our statistician will create static analytic files for interim and final analyses and will report the date the data is finalized, and number of subjects included in that database.

END APPLICANT RESPONSE

V-E Work Plan

Provide clear and concise work plans for meeting the following components, with detailed explanation:

1) Provide for the coordination and overseeing of clinical trial(s) to determine the efficacy of marijuana in treating the medical conditions of U.S. armed services veterans and preventing veteran suicide.
2) Recruit and evaluate researchers to accomplish the goals of this grant.
3) Demonstrate the ability to work with researchers who can garner the United States Food and Drug Administration approval for the clinical trials.
4) Ensure the maximum amount of grant dollars are used to coordinate and oversee clinical trials with a minimal amount of grant dollars used for administrative costs.
5) Work with organizations closely tied to veterans and veterans' programs.
6) Provide the Grant Administrator with a grant budget to which monitoring and reporting will be tied. Please see attachment A for the budget template to be used.

7) Establish research goals, approve projects, exercise financial and management oversight, and document and review results. See Workplan below

8) Publish the results of the clinical trials.

BEGIN APPLICANT RESPONSE

Items 1-3 are addressed in detail in the **Work Plan** below and many elements are met by the experience and qualifications of the assembled clinical research team (see below).

4) The research team has decades of experience in conducting human subjects research including the neuropsychopharmacological and psychophysiological aspects of the proposed project in addition to randomized clinical trials (RCTs) with Veterans, traumatized populations, and substance users. The team is well versed in the management of multi-million dollar federally- and privately-funded projects. Logistics, institutional support infrastructure, and fiduciary responsibility exists within Wayne State University and the Translational Neuroscience Initiative (TNI). All finances and related account audits are expertly managed by Sponsored Programs Administration as this University division manages Wayne State's entire research portfolio.

5) Our research team has ongoing collaborations with several Veterans Affairs Healthcare Systems, including but not limited to, Detroit (MI), Ann Arbor (MI), Toledo (OH), Long Beach (CA), Tuscaloosa (AL), West Haven (CT), and Portland (OR). Dr. Norrholm, for example, has had ongoing federal research support focused on Veterans' mental health, PTSD, suicidality, and substance use since 2007. Dr. Norrholm's laboratory group and the Psychiatry Department at Wayne State have established relationships with: (1) five VFW (Veterans of Foreign War) posts (Posts 345, 4162, 1407, 4553, 2233) and (2) multiple veterans' organizations including Disable American Veterans, Vietnam Veterans of America, Volunteers of America (MI), Michigan Veterans Affairs Agency, Grand Rapids Home for Veterans, Emmanuel House, and Piquette Square. In addition, our clinical research team has direct contact with multiple military bases including Battle Creek Air National Guard Base, Selfridge Air National Guard Base, US Coast Guard Sector Detroit, Fort Custer Training Center, and Camp Grayling Joint Maneuver Training Center as well as with the Michigan Army National Guard State Surgeon, the Assistant Adjutant General, and the Adjutant General and Director of Military and Veterans affairs. Addressing Veterans' mental health continues to be a primary focus of the clinical research team assembled for the proposed project.

(6) The grant budget will be provided to our departmental pre & post award administrators, Jennifer and Cordell. Jennifer will monitor all grant expenses on a quarterly and as-needed basis and send accounting reports to the PI(s) on this project. Expenses are monitored for compliance and to stay within the original budgeted categories. Jennifer will work with the SPA office on the financial reporting requirements of this grant.

(7-8) See **Work Plan** details below

Work Plan

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

Specific Aims

Use of marijuana (*Cannabis* plant material) and cannabinoids (specific drugs in the plant) is prevalent in the military veteran community and many traumatized individuals report that cannabis self-medication can alleviate stress, anxiety, depressed mood, and disturbed sleep. However, at present, there are no scientifically-derived guidelines on safe or therapeutic use of cannabinoids. Few US researchers can administer cannabis to human patients and research study participants, mostly due to the daunting number of approvals/monitoring required from a range of federal (e.g., FDA, NIDA, DEA), state, or local agencies, institutions, or organizations. Limited drug supply (there is only one federal supplier of cannabis for research in the US), lack of established laboratory practices for conducting such research, and few funding sources are also constraints.

With our highly experienced clinical research team here at Wayne State, we propose to address the lack of

empirical data to support the use of cannabis for treating PTSD and suicidality in US armed forces veterans. This work will foster increased investigation of potential therapeutic effects of cannabis/cannabinoids to improve patient quality of life and reduce PTSD and depressive symptoms that can precede suicidality. These efforts, in turn, could inform educational efforts and public health policy by (1) providing clinicians with empirical data to guide discussions with their patients of therapeutic cannabinoid use and associated risks, (2) providing trauma-exposed users with greater access to dedicated educational resources so they can make informed decisions about cannabinoid use, and (3) improving their health outcomes and lowering healthcare utilization rates and costs.

In the proposed randomized, controlled clinical trials we will recruit veterans with PTSD who report using cannabis. In **Study 1**, 200 veterans will be randomized into one of four different THC (Δ^9-tetrahydrocannabinol) : CBD (cannabidiol) dose conditions (High THC:High CBD; HighTHC:Low CBD; Low THC:High CBD, and Low THC:Low CBD) for a 12-week treatment phase. In **Study 2**, 150 veterans will be randomized into *either* a naturalistic group that will be followed as they continue to use cannabis as they normally do (observation only), or into a "THC reduction group" 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 at baseline, weekly and bi-weekly throughout a 12-week treatment phase, and at 12-week (post-treatment), 6-, 9-, and 12-months post-baseline. 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, which have been associated with PTSD symptom severity; (4) psychophysiological reactivity to trauma reminders presented within virtual reality environments and state-of-the-art technology; (5) saliva for DNA analysis to examine genetic and epigenetic markers associated with the endocannabinoid system; and (6) 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 see 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.

The overall strategy is to recruit veterans with PTSD who use cannabis to manage mental health symptoms (anxiety, depression, PTSD and/or suicidality). Those who report moderate use will be prioritized for Study 1, and those who report light or heavy cannabis use will be prioritized to Study 2. This all-inclusive recruitment strategy allows us to enroll a representative population of veterans and draw broad-ranging inferences from our data. It also maximizes efficiency as both trials can be run concurrently.

The specific aims of these clinical trials are to:

AIM 1 (Study 1): Determine whether 12 weeks of daily use of four randomly-assigned THC:CBD certified cannabis mixtures differentially reduces: (a) PTSD symptom severity and suicidal ideation in the natural setting, and (b) excess physiological and subjective fear responding to virtual reality (VR) trauma cue presentation in the experimental laboratory setting.

AIM 2 (Study 1): Determine whether physiological and subjective responses to acute administration of four different THC:CBD certified mixtures in the experimental laboratory predicts clinical improvement in naturalistic PTSD symptoms, suicidal ideation, and reductions in physiological and subjective fear responses.

AIM 3: (Study 2-A) Characterize psychiatric symptoms, health, pain, sleep, psychophysiological response to VR-based trauma-related cues, and quality of life in relationship to naturalistic cannabis use quarterly over a one-year period.

AIM 4: (Study 2-B) Determine whether participants who switch to lower THC/higher CBD cannabis products report clinical reductions in PTSD symptom severity and suicidality. These participants will be compared to those in AIM 3, who will be instructed to use their products as they usually do and will be followed naturalistically.

***Exploratory Aims (Study 1 and Study 2)*:**

***AIM 5a*:** Determine whether plasma and saliva THC and CBD levels during and following 12-weeks of daily administration of four vaporized cannabis conditions correlate with changes in PTSD, mood, and suicidal symptoms.

AIM 5b: Determine whether circulating plasma and saliva endocannabinoids (eCBs) during and following 12-weeks of daily administration of four vaporized cannabis conditions correlate with changes in PTSD, mood, and suicidal symptoms.

In short, this project will provide the unique ability to administer and assess the effects of cannabinoids on Veterans' mental health from a psychobiological perspective in an unprecedented manner.

Background and Significance

The rate of suicide among United States military veterans is alarming, and there is evidence that the numbers are growing. More than 6,400 US veterans died by suicide in 2018 [1], which is more than 17 suicides per day. Despite making up only 8% of the US population, veterans accounted for 14% of all suicide deaths in US adults. The age- and sex-adjusted suicide rate for veterans increased from 18.5 suicides per 100,000 in 2005 to 27.5 deaths in 2018, a staggering increase over just a decade. High suicide rates in veterans are likely due to untreated, or undertreated, depression and post-traumatic stress disorder (PTSD) as well as psychological problems associated with these disorders [2].

An estimated 13-31% of US Veterans experience PTSD, compared to 6-10% of the general population. Many veterans seeking treatment for PTSD and trauma-related problems report using marijuana for self-treating PTSD and depression-related disturbances in daily life including stress, anxiety, hyperarousal, negative mood, executive function (cognitive) deficits, pain and poor sleep quality [3]. Marijuana, or cannabis, contains many chemicals, known as cannabinoids, that have unique behavioral effects. Common cannabinoids include: delta-9-tetrahydrocannabinol (THC), the primary psychoactive compound in the marijuana plant; cannabinol (CBN), which is not psychoactive; and cannabidiol (CBD), which is commonly used over-the-counter for a number of conditions, although empirical evidence for the efficacy of CBD is still being examined. Cannabis and CBD can be consumed in multiple forms (e.g., flower, hash, oil, wax, food products, tinctures), using several different routes of administration such as inhalation (smoking or vaporizing), ingestion, and topical application. Despite anecdotal reports from veterans that marijuana and CBD provide pain relief, improve sleep, and reduce PTSD symptoms, there are few placebo-controlled clinical trials investigating the efficacy of cannabinoids for these conditions and co-occurring suicidality.

Consistent with patient reports, results from a national survey of military veterans [4] indicated 75% would consider using cannabis as a treatment option for pain or mental health issues, 83% support legalizing medical cannabis, and 68% believe that the US Department of Veterans Affairs should allow research exploring the use of cannabis as a therapeutic option. Importantly, while 20% of veterans acknowledged having used cannabis for medical purposes, marijuana remains a Schedule I controlled substance and federal regulations prevent clinicians in the VA system from recommending or prescribing cannabis as medicine, even though it is legal in the State of Michigan.

The role of cannabis use in suicidal behavior is unclear. Lifetime prevalence of cannabis use disorder has been linked to suicide attempts in veterans, even after controlling for PTSD, depression, and alcohol and other drug use disorders [5]. However, currently it is not known whether cannabis use increases suicidal behavior among veterans with mental health problems [6] or whether veterans with mental health problems and elevated suicidality are more likely to use cannabis to manage symptoms. Indeed, epidemiological data from the 2012 Canadian Community Health Survey revealed that cannabis use may reduce the association between PTSD, and severe depression and suicidality [7]. Thus, research is needed on ways that cannabis use might be linked to a decreased risk of veteran suicide. Furthermore, emerging data link both PTSD and depression [8,9] to disruption in the endogenous cannabinoid (or endocannabinoid, eCB) system, which plays a key role in regulating stress, emotion regulation, and fear extinction [10]. However, few studies have examined the impact of cannabis or cannabinoid administration on circulating eCB levels, and whether changes in circulating eCBs correspond with changes in PTSD, mood, and suicidal symptoms.

Innovation

Public opinion and broader acceptance of the use of medical cannabis has outpaced the science on potential therapeutic benefits of cannabinoids. Although results of animal studies and some anecdotal reports in humans suggest therapeutic promise for cannabinoids, the few studies evaluating the effects of cannabis on PTSD symptoms in humans are limited by the lack of scientific rigor, small sample sizes, and failure to distinguish among conditions (e.g., acute traumatic experience, chronic traumatic encounters, multiple trauma exposures) that led to development of the disorder [11]. Large, well-controlled, randomized clinical trials are needed to examine therapeutic benefits of cannabis for treatment of PTSD and comorbid disorders. ***Our proposed trial (Study 1) would be the first randomized, controlled clinical trial to examine the therapeutic potential of cannabinoids for treating veterans with PTSD and suicidal ideation.*** The trial is methodologically rigorous with a focus on research that will be innovative (cutting edge) and have real-life implications for treatment of veterans experiencing chronic suicidality (high public health significance). Strong methodological elements including random assignment to treatments, well-validated assessments, extensive clinician training, thorough measurement of treatment fidelity, long-term follow-up of research participants, and intent-to-treat analysis (i.e., assessment of all participants regardless of whether they complete the intervention). ***Study 2 will complement and extend Study 1 by examining whether switching to a different cannabis product with lower THC and higher CBD content may improve clinical outcomes in a real-world setting***. Taken together, this comprehensive approach will ensure our work has a high impact in the scientific literature, thus increasing the possibility that treatment providers and organizations will have access to, and ultimately, implement our findings. Our team has extensive experience conducting randomized controlled trials (the gold standard) for numerous mental health conditions. Of note, we are the only research group in the Midwest that has the federal and state licenses that permit us to administer cannabis and cannabinoids to human volunteers, which uniquely positions us to conduct this significantly impactful clinical trial. Our team has extensive experience (1) administering THC and CBD, alone and in combination, and assessing their effects in a randomized, double-blind, placebo-controlled trial; (2) recruiting and retaining military veterans in studies on PTSD; (3) designing and conducting long-term clinical treatment trials; (4) conducting laboratory measures of fear conditioning and trauma-related physiological reactivity in veterans with PTSD; (5) assessing and treating psychiatric disorders, including depression, anxiety, PTSD, and suicidality; and, (6) successfully completing large scale, complex studies with multiple investigators across multiple sites. Our team also has expertise in (7) the role of eCBs in stress regulation and psychiatric risk and during the trial, we will examine changes in circulating eCB concentrations and associations with symptom improvements.

Methods Common to Study 1 and Study 2

Research Settings

Tolan Park Medical Building (WSU medical campus). All screening, baseline, post-treatment, and follow-up in-person assessments (except for fear conditioning and trauma cue psychophysiological reactivity) will occur in the Human Pharmacology Laboratory (HPL) in the Tolan Park Medical Building, centrally located near Detroit Medical Center and the John D. Dingell VA Medical Center. Cannabis administration during the baseline session will occur in the HPL in specially equipped and ventilated rooms that enable drug administration, behavioral testing, intensive physiological monitoring and data collection. Test rooms are linked to a central monitoring suite on the same hallway (occupied by the research assistants) for audio-visual surveillance. Fear conditioning and trauma cue psychophysiological reactivity assessments will occur in the laboratory space comprising the Detroit Trauma Project (PI: Jovanovic), which is located down the hall from the HPL.

Pharmacology Lab Van (PLV). Two Ford Transit Cargo Vans will be purchased and outfitted with a phlebotomy station, -20C° small freezer for storing blood and saliva samples, portable vitals monitor, small DEA-compliant locking safe in which to store cannabis, and a psychophysiology testing area for assessing participant reactivity to virtual reality-based, trauma-related cues that will be presented through an Oculus head mounted display in an isolated section of the vehicle. These vans will be staffed with two research assistants and a security guard who will safely and securely deliver weekly cannabis doses to participants at their homes. (*Note: Only cannabis to be delivered on a given day will be stored in the van's safe*.) Each week the van will arrive at a participant's house. Participants will enter the van to receive their weekly cannabis doses, return unused doses from the previous week, and have their vitals checked. On weeks 2, 4, 6, 8, 10, and 12 they will also undergo the psychophysiological trauma reactivity procedures and provide saliva samples. Blood samples will be obtained in the van at weeks 6 and 12.

Participant Recruitment and Selection

The Wayne State University IRB will approve all procedures. *Inclusion criteria*. To be enrolled in the trial, each participant must: (1) be a healthy veteran who has served in a branch of the US armed forces; (2) report using marijuana at least 4x/month up to 3x/day, and not more than 1 gram (approx. 3 joints or 1 blunt) per day, (3) provide baseline urinary THC metabolites >50 ng/ml; (4) currently meet DSM-5 criteria for moderate-to-severe PTSD with symptoms of at least 6 months duration (the anchor, or index, trauma does not have to be related to military service); (5) be between 19-69 years old; (6) agree to abstain from using non-study cannabis or CBD products during the trial; (7) not be seeking treatment for Cannabis Use Disorder; (8) be stable on psychotropic medications and/or psychotherapy before the study begins; and, (9) agree to adhere to study procedures. Participants will be recruited via veterans groups and associations, local newspaper ads, social media (e.g., Craigslist, Facebook), word-of-mouth referrals, and flyers posted throughout the Wayne State medical campus. Candidates will undergo a brief telephone screen to assess initial inclusion/exclusion (e.g. age, drug use, medical and psychiatric contraindications). If screening reveals the individual may be eligible, s/he will be scheduled for an in-person interview. Candidates must be in good health to participate; those with contraindications will be excluded. All candidates will undergo psychiatric evaluation and will be asked to report their substance use history by interview and structured questionnaire methods. They will undergo medical evaluations using medical history, physical exam, standard lab tests (complete blood chemistry, urinalysis, urine pregnancy test for females) and 12-lead ECG. Candidates will be told of positive findings from these evaluations and referred for care. Although the in-person screening is designed to be completed in two visits, occasionally it is necessary to have candidates return for a third day to complete all the screening assessments.

Exclusion criteria. Candidates will be excluded if they: (1) are pregnant (urine HCG), lactating (self-report), or heterosexually active and not using medically approved birth control (oral or depot contraception, IUD, condom/foam, sterilization, tubal ligation); (2) have a current or past bipolar or psychotic disorder as determined using the SCID-5; (3) are determined to be at immediate high risk for suicide based on the C-SSRS; (4) meet DSM-5 criteria for Substance Use Disorder other than Nicotine Use Disorder and Cannabis Use Disorder; (5) have allergies or other contraindications for smoking cannabis, (6) have a current diagnosis or evidence of significant or uncontrolled hematological, endocrine, cerebrovascular, cardiovascular (e.g. systolic BP >140 or <95 mmHg, diastolic BP >90 mmHg, abnormal ECG), systemic (e.g., liver, renal, inflammatory), pulmonary (e.g., asthma, COPD), immunocompromising (e.g., AIDS, COVID-19), or neurological disease (e.g., seizures, dementia, TBI); (7) exhibit cognitive impairment (<80 IQ); and, (8) are unable to provide informed consent.

Study volunteers will undergo a telephone screening to determine initial eligibility before being invited for in-person interview. Those who appear to meet eligibility criteria will attend two screening visits (screening measures are described below). During the first screening session the PI or her designee will describe study procedures and requirements. Candidates will be asked to read the consent form. Particular attention will be given to reviewing required procedures (e.g., abstaining from use of non-study cannabis during the trial) and possible side effects of the drugs (THC and CBD) with candidates. Measures used to ensure confidentiality will be reviewed with candidates. After answering candidates' questions, if their understanding is satisfactory to study staff, the consent form will be signed in the presence of the PI and a witness. Female participants must sign a form agreeing to immediately notify the experimenter if they become pregnant.

Screening Measures

The ***Shipley Institute of Living Scale*** [12] yields an estimated IQ score. Candidates must score >80 to give informed consent. The ***Medical History Questionnaire*** is a comprehensive self-reported assessment of participant medical history routinely used in our lab. The ***Semi-structured Clinical Interview for DSM-5*** (SCID) [13] will be used to assess psychiatric and substance use symptoms (for exclusion) and to ascertain PTSD and Substance Use Disorder diagnoses. The ***Drug History and Use Questionnaire*** (DHUQ) is an extensive alcohol and drug use questionnaire we developed and have published on; it will be used to establish potential participants who have prior experience smoking nicotine and/or marijuana cigarettes and with opioids. Menstrual cycle phase is a possible confound. We will record females' self-reported menstrual cycle phase at screening and during the study and will examine the data to determine whether THC- or CBD-induced effects vary between males and females at differing cycle phases. To maintain progress on the proposed study, it is not feasible to control time of drug exposure, but we will have these data to include as statistical covariates.

***Proposed Clinical Trial 1 - Randomized Study*: Experimental Methods**

Overview of Study Design. This randomized, double-blind, placebo-controlled trial will examine effects of THC and CBD on self-reported PTSD symptom severity and suicidal ideation in 200 US armed forces veterans in an outpatient setting. A total of 200 veterans will be randomized into one of four treatment groups (50 in each: High THC:Low CBD, High THC:High CBD, Low THC:High CBD, and Low THC:Low CBD, which will serve as a functional placebo). Following a baseline assessment session, participants will be provided with 1 gram of cannabis (according to their assigned THC:CBD dose condition) each day throughout a 12-week treatment phase. Participants will be instructed to smoke or vaporize *ad libitum* from each day's supply, leaving any unused cannabis for that day in the original packaging, and will be instructed not to smoke, vaporize or consume any other cannabis or CBD products during the trial. At the end of 12 weeks (post-treatment), the assessment battery will be administered, and again at 6-, 9-, and 12-month post-baseline. Study duration for each participant will be approximately 1 year from the time he/she is enrolled in the study.

Clinical Trial Methods

Drug Dose Selection, Preparation and Administration

Cannabis (THC and CBD). Cannabis flower will be purchased in bulk from a dispensary in the Detroit-metro area***** and prepped using a digital scale with weight adjustments to achieve the exact dose conditions shown in Table 1. The four cannabis dose conditions have been carefully selected based on what is used in the literature and on our own experience administering smoked THC and CBD to experienced cannabis smokers in our laboratory. Our data and those from others demonstrate these concentrations have excellent safety profiles.

Table 1. Cannabis Dosing Conditions

	THC% (mg per 300mg plant material)	CBD% (mg per 300mg plant material)
High THC: High CBD	15% (25 mg)	15% (25 mg)
High THC: Low CBD	15% (25 mg)	8% (8 mg)
Low THC: High CBD	8% (8 mg)	15% (25 mg)
Low THC: Low CBD	8% (8 mg)	8% (8 mg)

**NOTE: If we are not able to purchase cannabis bulk material from a dispensary, cannabis will be obtained from the National Institute on Drug Abuse (NIDA) Drug Supply Program, which has provided cannabis for Dr. Lundahl's previous studies. Dr. Lundahl and Dr. Greenwald already hold all the necessary DEA licenses and FDA certifications to obtain cannabis from NIDA. A third option would be to purchase bulk cannabis flower from one of the two companies that recently were granted DEA Cannabis Producer licenses.*

In the **baseline** session (Aim 2), participants will vaporize 300 mg of cannabis (equivalent to about 1 marijuana cigarette, or joint) using Medic® vaporizers (Storz & Bickel, Germany). Per Table 1, this fixed amount of plant material will contain differing proportions of THC and CBD. Standardized puff topography will be: 5-sec prepare, 5-sec inhalation, 10-sec breath-hold, 5-sec exhalation, and 40-sec inter-inhalation interval. Thus, subjects will prepare/inhale/hold/exhale over 20-sec, wait 40-sec, then initiate the next inhale/hold/ exhale sequence (cued by research assistant). The 10-inhalation smoking episode will take ≈10-min. Participants will receive the dose for the cannabis condition to which they were randomized after they enrolled in the study. Both participants and research staff will be blind to the cannabis condition.

During the **12-week treatment phase**, participants will receive 7 sealed packets, each labeled with the participant's unique barcode ID and date, and each containing 1 gram of cannabis in the THC:CBD dose for their assigned cannabis condition. Each week's supply will be delivered on the same day each week by research staff using our Pharmacology Lab Van (PLV). Participants will be instructed to use as little or as much as they want of each daily packet, to leave any unused cannabis in that day's packet, and to open only one packet per day. Each packet with unused cannabis will be taken back to the lab and weighed for drug accountability. Thus,

participants will have weekly deliveries of 7 days' worth of doses at a time, for the duration of the 12-week treatment phase. Participants will also be instructed to smoke or vaporize each day's cannabis dose using their preferred method (e.g., joint, bong, pipe, vaporizer). The PLV will have a locked safe that holds only the cannabis that is being delivered on any given day. The main supply of cannabis will be kept in a locked freezer in a locked room (per DEA guidelines) in the Human Pharmacology Laboratory at Tolan Park; only Drs. Lundahl and Greenwald have access to this room.

Study Measures
See Table 2 (below) for a schedule of assessments. All instruments will be administered by trained, master's level psychology graduate students and trained research assistants under the supervision of Drs. Lundahl and Ledgerwood, who are both licensed clinical psychologists.

Primary Outcome Measures.
The primary outcomes of the proposed study include change from baseline (pre-treatment) to the end of the 12-week treatment phase (post-treatment) in PTSD symptom severity and suicidal ideation. PTSD will be assessed with the ***Clinician-Administered PTSD Scale for DSM-5 Total Severity Score*** (CAPS-5) [14] and ***Post-Traumatic Stress Disorder Symptom Checklist for DSM-5*** (PCL-5) [15]. The CAPS-5 is a well-validated, semi-structured clinician interview that determines the presence and severity of PTSD symptoms and diagnosis consistent with the DSM-5 and allows for assessing changes in symptom severity over time [16]. PTSD diagnosis is based on meeting the DSM-5 symptom cluster criteria (minimum threshold of symptoms with a score ≥ 2) with a qualifying criterion A index trauma. The CAPS-5 Total Severity Score is calculated by summing the total score for each of the four symptom categories to assess past-month PTSD symptoms on a specific traumatic event: intrusion (Category B), Avoidance (Category C), Mood and Cognition (Category D), and Hyperarousal (Category E). CAPS-5 Total Severity scores range from 0–80, where higher scores indicate worse PTSD severity. Suicidality will be assessed using the ***Columbia Suicide Severity Rating Scale*** (C-SSRS) [17], and ***Suicide Behavior Questionnaire- Revised*** (SBQ-R) [18]. The C-SSRS is a clinician-administered measure of suicidal thoughts and behaviors over time. A baseline form is used to assess lifetime suicidal ideation, intensity, and behavior, and can be compared to current suicidal ideation and intensity assessed over the clinical trial. The SBQ-R is a brief (4-item), self-administered questionnaire that taps into four dimensions of suicidality (lifetime ideation/attempt, frequency of recent ideation, risk of suicide attempt and self-reported likelihood of future suicidal behavior), and will be measured at all time-points.

Secondary Measures.
Demographics including Age, sex, gender identity, marital status, race/ethnicity, education, employment status and annual income will be assessed.

The ***Beck Depression Inventory-II*** (BDI-II) [19] assesses neurovegetative depressive symptoms. One item asks specifically about suicidal thoughts and will be checked immediately after administration; a score on this item greater than 0 (range is 0-3 with 0 indicating "none") will trigger clinical follow up.

The ***State Trait Anxiety Inventory Form Y*** (STAI) [20] is a 40-item questionnaire with 2 scales assessing state and trait anxiety (somatic and cognitive symptoms).

Executive Function Assessment: Working Memory be assessed using the **Wechsler Memory Scale- Fourth Edition, Visual Working Memory scale** [21]. The **Wisconsin Card Sort Task** (WCST) assesses abstraction and the ability to shift or maintain cognitive set [22, 23]. Inability to shift cognitive set in the face of new information is indicative of perseveration. **Iowa Gambling Task** (IGT) The IGT is .a computer-based measure of decision-making in which participants are given a hypothetical amount of money to play, and must choose between four decks of cards (labelled A, B, C and D) that are presented on the computer screen [24]. Decks A and B are associated with higher (hypothetical) monetary rewards, but also associated with higher punishment (money lost) than decks C and D. Overall, decks A and B result in losses, while decks C and D result in gains.

The gains and losses associated with each card turn are not predictable. Risky decision-making is associated with more selection from decks A and B than decks C and D.

Health/Quality of Life: The **Short Form 36** (SF-36) is a brief measure of overall self-reported health that is associated with other objective health measures [25]. The **Quality of Life Inventory** (QOL) [26] assesses satisfaction in 17 life areas (work, health, recreation, goals, etc.) and will be used to assess quality of life changes over time. **Brief Pain Inventory** (BPI) [27] will be included to assess pain, and will be completed at baseline and each follow-up assessment. Daytime sleepiness, which is indicative of sleep problems, will be assessed using the **Epworth Sleepiness Scale** (ESS) [28]. We will also assess the number of times participants utilize emergency room, urgent care, specialist, and general practitioner services on a monthly basis (**healthcare utilization**).

Daily diaries will be completed by participants to record time of cannabis use and route of administration. Participants will also record any alcohol and other drug use (biologically verified using saliva testing).

Endocannabinoids (eCBs) are lipophilic (fatty acid) molecules that circulate in bodily fluids and can be readily measured. Parallel collection of blood and saliva samples for eCB measurement is highly innovative and important, because eCB levels may differ in plasma and saliva. We realize that levels of anandamide (arachidonoyl ethanolamide, AEA) in saliva were undetectable in one report [29]. However, a more recent study found levels of eCBs including AEA in the range of 0.2-90 nM in human saliva [30], well above detectable and quantifiable limits of our liquid chromatography mass spectrometry (LC-MS) methods (3 fmol or 1 ml sample of 0.003 nM AEA on the column). All samples will be stored in the HPL on-site freezer (–20º C) and transferred to the WSU Lipidomics Core, a state-of-the-art facility, for analyses of plasma and saliva levels of eCBs.

Physiological Measures

Vital signs (heart rate, oxygen saturation, skin temperature, and blood pressure) will be assessed at screening, baseline, and at each weekly visit in the PLV. Saliva samples will be collected at baseline, pre- and post-acute cannabis administration, every 2 weeks during the 12-week treatment phase, and at all follow-up sessions. Blood samples will be collected at baseline, pre- and post-acute administration, and at the end of the 12-week treatment phase. Saliva and plasma will be analyzed to determine endocannabinoid, THC, and CBD metabolite levels.

Fear conditioning testing:

We will administer an established fear-potentiated startle paradigm that we have shown to be sensitive to PTSD symptoms as well as drug effects (e.g., dexamethasone; 3,4-methylenedioxymethamphetamine or MDMA). Participants will be presented with two visual geometric shapes, one at a time, on a computer screen. The fear conditioning testing will occur across three phases designed to assess fear learning (Acquisition), fear reduction (Fear Extinction), and the possible return of fear (Extinction Recall). During fear acquisition, one stimulus (termed a reinforced conditioned stimulus; CS+) will be repeatedly paired with an aversive airblast to the throat (termed the unconditioned stimulus; US) while a second shape (termed the non-reinforced conditioned stimulus; CS-) will not paired with an airblast. We have employed this procedure for over 15 years and can reliably produce a conditioned fear response, which is indexed by changes in the eyeblink startle response to each stimulus. After fear is learned (i.e., participants know which shape signals danger and which shape signals safety), we then proceed with extinction training, in which the previously reinforced stimulus is repeatedly presented without the airblast. As the individual learns that the stimulus no longer predicts the airblast, the fear response is diminished. The extinction recall phase procedure is identical to the extinction learning phase and involves repeated presentations of the previously reinforced stimulus without the airblast. Extinction learning is the fundamental basis for most exposure therapies for specific phobia, anxiety, and PTSD. Extinction recall is the laboratory analog of maintaining treatment gains or the lack of symptom relapse. Our clinical research team has found extinction learning to be altered or impaired in people with PTSD. This assessment will occur at baseline and again at post-treatment (week 13) in the Detroit Trauma Project lab.

Psychophysiological reactivity to trauma cues

We will then present a task designed to measure trauma-related physiological activation, including increased acoustic startle response, changes in heart rate and heart rate variability (HRV), and skin conductance response

in the presence of virtual reality (VR)-based cues associated with one's previous trauma (e.g., Middle East combat scenarios, forward operating base (FOB)-related traumas, or military sexual trauma). We are able to tailor virtual cues to the specific trauma type experienced by the individual. This methodology can detect individual differences in hyperreactivity of the sympathetic nervous system. Our group has shown that trauma-potentiated startle is reduced in parallel with PTSD symptoms over the course of exposure-based treatment [31]. In the proposed project, we will work with our VR hardware and software developers to create virtual traumatic scenarios that are consistent with patient/participant trauma to augment our existing library of virtual environments and stimuli. Our work coupled with recent VR-based prolonged exposure therapy studies suggests that this type of immersive presentation of trauma-related stimuli can reduce PTSD symptoms and suicidality [32]. This assessment will occur at baseline in the Detroit Trauma Project lab and biweekly throughout the 12-week study timeline with a remote VR-psychophysiological system in the PLV and then again post-treatment (week 13) back in the DTP lab.

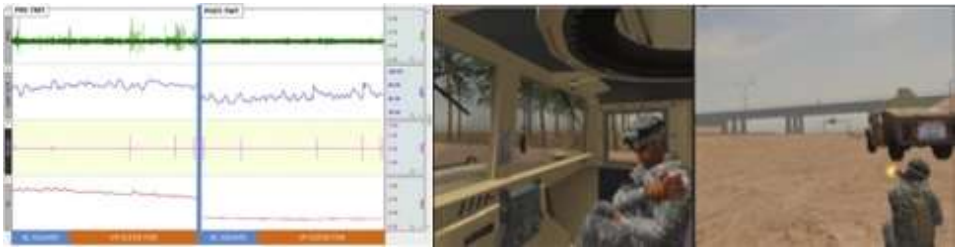

Figure 1. Left panel: Reduction in psychophysiological reactivity to VR scenes pre- and post-treatment. Acoustic startle (green trace marked EMG) and skin conductance (SCR) are markedly reduced after treatment. Right: examples of VR combat scenes used with psychophysiological measurements.

THC and CBD Pharmacokinetics. Blood samples (8 ml each) will be collected into 10-ml Vacutainer tubes containing EDTA. Samples will be taken at Baseline (in Study 1, pre- and post-cannabis administration) and at the end of the 12-week treatment phase (post-treatment). After collection, each tube will be inverted several times then centrifuged for 15 min. Plasma will be transferred to cryogenic tubes and frozen at -20ºC in the lab or the PLV (depending on where the sample was collected), prior to being packaged with dry ice and taken to the WSU Lipidomics Core for analysis. Saliva samples will be collected into saliva kit tubes at Baseline (in Study 1 pre- and post-cannabis administration), every two weeks during the 12-week treatment phase, and at 3-, 6-, 9-, and 12-month follow-ups. Mass spectrometry (lower limit of quantitation of 0.1 ng/ml) will be used to analyze THC, CBD and metabolite (e.g., 11-OH-THC) concentrations in these samples under blinded conditions. We will derive peak concentration (C_{max}), time to peak (T_{max}) and 4-hr area under the curve (AUC) measures.

Subjective Cannabis Effects Rating Form [33]. After the acute cannabis smoking episode during the baseline session, participants will complete VAS ratings of "good drug effect," "bad drug effect," "strength of drug effect," liking," "sedated," and "desire to take again," and whether the drug was active or placebo.

Subjective Effects Scale VAS (SES). These 33 items are adapted from Haney et al. [34] and include the phrase "I feel…" followed by adjectives describing a mood (e.g., "anxious, "friendly," "down," etc), a drug effect (e.g., "high," "stimulated, "a good drug effect") or a physical symptom (e.g., "hungry," "tired," "restless"). These visual analog scale (VAS) items are presented as a series of horizontal 100-mm lines, anchored on the left by 0 ("not at all" or "dislike a lot" depending on the item) and 100 ("a lot" "extremely" or "very much" depending on the item) on the right. Each line is labeled with a phrase and participants are instructed to place a mark on each line (i.e., from 0-100) indicating how they feel at the moment.

Table 2. Assessment timeframe for Study 1.

Assessment	Baseline	Weekly During Treatment	Every Two Weeks During Treatment	3-(post-treatment), 6-, 9-12-month post-baseline
Demographics, Substance use history, Shipley, SCID-5, DHUC	**X**			
CAPS-5	**X**			**X***
BDI-II, STAI, PCL-5, SBQ and SBQ-R, Epworth	**X**	**X**		**X**
C-SSRS, BPI, QOL, SF-36, ESS	**X**			**X**
Working Memory, WCST, IGT	**X**			**X**
Vitals	**X**	**X**		**X**
Physiological reactivity to VR trauma cues, Collect saliva for THC/CBD Pharmacokinetics and endocannabinoid levels	**X**		**X**	**X**
Fear Conditioning/Extinction/Recall	**X**			**X**
Cannabinoid and Endocannabinoid Plasma Levels	**X**			**X****

*** Baseline and 12-month post baseline only.**

**** Baseline and 3-month (post-treatment) only.**

Research Design

Participants in Study 1 (n=200) will be randomized into one of four THC/CBD conditions and complete a 12-week treatment period. All participants (i.e., both groups and both studies) will undergo the same assessments at baseline (pre-treatment), at 12-weeks (post-treatment), and at 6-, 9-, and 12-months post-baseline. Assessment measures are described above and are shown in Table 2.

Baseline Session. Participants will be asked not to use any alcohol or drugs for 24-hr before arriving at the lab, but will be allowed to smoke 1 tobacco cigarette just prior to the session. Upon arrival at the Human Pharmacology Laboratory, participants will provide urine and breath samples to test for recent drug or alcohol use. At approximately 0900, baseline assessments will begin. These include **physiological** (heart rate, oxygen saturation, skin temperature, blood pressure, saliva sample for DNA analysis, blood sample to analyze plasma endocannabinoid, THC, CBD, and metabolite levels); **psychological** (CAPS-5, PCL-5, C-SSRS, SBQ-R, BDI-II, STAI, Brief Pain Inventory, Epworth Sleepiness Scale); **neurocognitive** (WCST, IGT, CVLT); **overall health** (Short-Form 26, Quality of Life); **fear conditioning** testing, and **trauma cue reactivity** (described above). These assessments will occur in randomized and counterbalanced order. At the completion of these assessments, participants in Study 2 will be provided with lunch or snacks, will schedule the first cannabis delivery/PLV visit, and then leave the laboratory.

Acute Cannabis Administration. Following baseline assessments, participants will be escorted down the hall to the Detroit Trauma Project Lab and prepared with wireless Biopac electrodes under the right eye to measure electromyogram (EMG) recordings of the eyeblink muscle contraction (startle reflex), on the hand to record skin conductance response (SCR), and three electrodes on the torso in the Lead II formation to measure HR and HRV using electrocardiogram (ECG). Fear Acquisition, or the repeated pairing of the shape CSs with the airblast USs, will occur as a single session prior to any drug administration. After the fear acquisition procedure concludes, participants will be escorted back to the HPL and seated in an experimental chamber equipped for cannabis administration. They will then undergo acute cannabis administration as described above. Immediately prior to and at 5- and 10-minutes after cannabis administration vital signs will be recorded and subjective drug effects will be examined using visual analog scale items (e.g., "I feel a good drug effect", "I feel high", etc).

Participants will then be escorted back to the Trauma Lab to undergo a fear extinction task in which the previously reinforced CSs are presented without the airblast. Fear Extinction will be timed to occur at peak cannabis acute intoxication. Thus, we will assess subjective and physiological responses to participants' assigned THC:CBD dose mixture, and measure fear conditioning, extinction, and trauma cue reactivity immediately prior to and after acute cannabis administration. We will examine whether individual differences in response to acute cannabis administration help predict treatment outcome.

Twenty-four hours after the fear extinction phase, participants will return to the Detroit Trauma Project Lab to complete a test of Extinction Recall, an assessment that determines whether the fear learned on the previous day has remained diminished or has returned (see Figure 2 below for schematic illustration of these tasks). Following the Extinction Recall test, the VR-based trauma-cure reactivity test will occur.

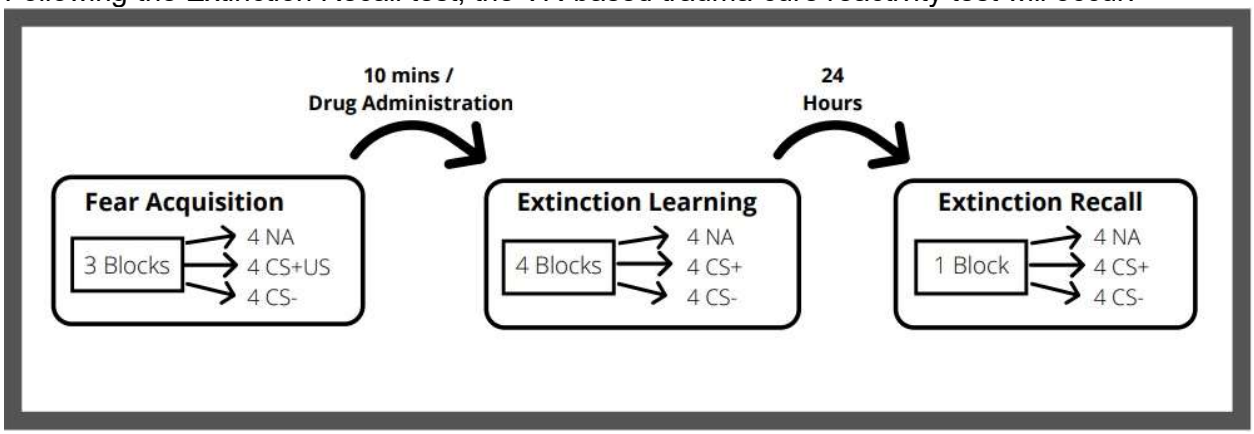

Figure 2. Schematic illustration of the fear learning procedures to be completed at baseline, post-treatment, and 3-month follow-up visits. NA = noise probe alone; CS+ = conditioned stimulus reinforced with airpuff unconditioned stimulus, US; CS- = conditioned stimulus not reinforced with US

12-Week Treatment Phase. Participants will begin the 12-week treatment phase no earlier than 3 days after the baseline session. During this phase, each participant will have an assigned day of the week on which the PLV will come to their house during an agreed-upon time window to deliver the coming week's assigned cannabis dose, which will be pre-packaged in labeled, separate containers for each day of the week. Participants will come to the van to sign for and collect their dose, and will also provide a blood sample for endocannabinoid and THC/CBD plasma analyses. Daily diaries will also be collected on these weekly visits. On weeks 2, 4, 6, 8, 10 and 12, participants will also undergo the physiological trauma reactivity test in the PLV which will contain a specially equipped section for psychophysiological assessment. The posttreatment visit (week 13) will also include an assessment of Fear Acquisition, Extinction Learning, and Extinction Recall using the tasks presented at baseline. This assessment will occur in the Detroit Trauma Project lab as was the case at baseline. The visual shapes will be counterbalanced to minimize practice effects. This will allow us to probe for possible beneficial effects of the 12-week cannabinoid treatment on fear learning and extinction; effects that have the potential to be extended into exposure-based PTSD therapies. Exposure therapy is one of the most successful interventions for PTSD and its comorbidities and can significantly reduce PTSD symptom severity and relapse. This can, in turn, increase mood and decrease suicidality. Participants will also complete the psychological and overall health questionnaires electronically (via smartphone, tablet, or computer) every week.

Post-Treatment Phase Assessments. The major follow-up assessment time-points will be 12-week (post-treatment), 6-, 9-, and 12-months post-baseline. Assessments conducted will include the entire battery described above and in Table 2. Assessments will occur in the Human Pharmacology Laboratory and Detroit Trauma Project Laboratory at Tolan Park.

***Proposed Clinical Trial 2 - Naturalistic Observation and Harm Reduction Study*: Experimental Methods**

Overview of the Study Design

The primary goal of the Naturalistic Pilot and Harm Reduction Study is to follow participants who are screened as reporting that they already use cannabis (in the form of THC and/or CBD) for psychiatric symptom relief. We will also collect pilot data among a self-selected group of participants who agree to limit their cannabis use to products that are lower in THC (than their baseline use) and higher in CBD to examine whether this results in better self-reported symptom management (THC Reduction Group). This will be a two-arm, quasi-experimental study designed to assess differential symptom relief among participants who choose to continue their natural cannabis use for symptom relief, and those who agree to reduce THC levels and maintain higher CBD levels. Assessments will occur at baseline, and 3-, 6-, 9- and 12-months post-baseline for both the naturalistic group and the THC reduction group. The THC reduction group will also provide blood samples every other week for the first 3 months to examine changes in THC and CBD plasma concentrations corresponding to use of reduced THC and higher CBD products.

Participant Recruitment and Selection

US military veterans (n=150) who report they currently use cannabis products to cope with mental health symptoms, including depression, anxiety, PTSD and suicidality, will be recruited and followed longitudinally for one year. **The inclusion and exclusion criteria will be identical to *Proposed Clinical Trial 1***. Participants who are excluded from Study 1 based on higher levels of cannabis use (> 1 gram/day), but who otherwise would be eligible for the study, will be asked to participate in the naturalistic study. This method will allow us to maximize our recruitment efforts.

Participants who are enrolled in the study will be asked if they would be willing to alter their current cannabis use by switching to products that contain 50% less THC than their usual products and contain CBD that is equal to or greater than the THC in this new product. Those who agree will also be enrolled in a contingency management (CM) protocol (described fully below) to encourage them to maintain these levels for a period of 12 weeks. Participants will be recruited until we have 75 participants who agree to participate in this THC reduction group. Once we achieve 75 participants in either the THC reduction group, or the naturalistic group, we will cease recruitment to that group and focus on recruitment for the group that has not achieved a sample size of 75. These methods will allow us to recruit enough participants to compare those who agree to change their CBD/THC levels to those who do not.

Procedures and Measures

Participants will undergo all assessments and payments as described above in the “Assessment Materials” section (see Table below), with the exception that they will not complete weekly assessments during treatment. Participants will be remunerated for completing assessments as described below. Participants in the Naturalistic Observation group will only undergo assessments, and will have no additional contact with our lab. Participants in the THC Reduction group will undergo additional procedures as described below. Both the Naturalistic Observation group and the THC Reduction group will be told they may use as much or as little of their cannabis product as they normally would. Participants will self-select whether they wish to participate in the Naturalistic Observation or THC Reduction arm of the study. The procedures for the THC Reduction group procedures are described more fully below.

Table. Assessment timeframe for Study 2.

Assessment	Baseline	Every Two Weeks during the first 3 months	3-, 6- 9-, 12- month
Demographics, Substance use history, Shipley, SCID-5, DHUC	**X**		
CAPS-5	**X**		**X***
BDI-II, STAI, PCL-5, SBQ and SBQ-R, Epworth	**X**		**X**
C-SSRS, BPI, QOL, SF-36, ESS	**X**		**X**
Working Memory, WCST, IGT	**X**		**X**
Blood draw for THC/CBD and Endocannabinoid Plasma Concentrations	**X**		**X****
Saliva Sample Collection for THC, CBD, and Endocannabinoid Levels	**X**	**X**	**X**

*** Baseline and 12-month only, **Baseline and 3-month (post-treatment) only..**

THC Reduction Group. Participants in this group will be asked to use cannabis products that contain 50% less THC concentration than their current cannabis products, along with a CBD concentration equal to or greater than the new THC concentration. For example, if a participant is currently using cannabis flower that contains 40% THC, they would be asked to switch to a product that contains 20% THC and at least 20% CBD. Those using edibles containing 10 mg of THC would be asked to switch to an edible containing 5 mg of THC and at least 5 mg of CBD. Participants who agree to be in the switch condition will have the chance to earn CM incentives for providing evidence that they are purchasing and using products within this range. Specifically, participants will be asked to take a photo of the packaging of any cannabis product they purchase that clearly shows the THC and CBD levels. Thus, we will ask participants to purchase these products at established dispensaries that use consistent packaging and labeling practices. Each week that a participant provides evidence (in the form of a cell phone picture and a purchase receipt) that they have purchased cannabis products within the ranges above, they may receive prize incentives by spinning a virtual prize wheel. This CM program is based on that developed by Petry et al. [35, 36] and used in Dr. Ledgerwood's lab [37-39]. Participants will start with one prize spin the first week they meet the above target criteria, and the number of spins will escalate weekly by one for every subsequent week the participant meets the criteria (up to a maximum of 10 spins weekly). If the participant does not provide evidence for meeting the above target, his/her number of spins will be reset to five for the next time he/she meets the target.

The virtual prize wheel will be broken into 100 segments. Of these, half will say "good job" and not be associated with a prize, 25 will state ''small prize!'' and will be worth about $1.00, 20 segments will state ''large prize!'' are worth $20.00, and five segments will state ''jumbo prize!'' and will be worth $100.00. A participant who completes the target behaviors every week for a period of 12 full weeks may earn up to $971 in reinforcement.

Manipulation check: The THC Reduction group will also provide blood samples at baseline and 3-months, as well as saliva samples at baseline, every 2 weeks during the 12-week treatment trial (collected in the PLV), and at all follow-up assessment timepoints. THC, CBD, endocannabinoids and metabolite plasma analysis will be performed as described in Study 1. This analysis will serve to verify that participants are reducing their THC levels. If THC and CBD levels indicate that participants have not reduced their use accordingly, these levels will be used as covariates in analyses of symptom change or data from non-adherent participants will be excluded (i.e., sensitivity analysis).

Clinical Plan for Addressing Elevated Suicidality
Because of the nature of the study, it is probable that we will experience situations where participants experience increases in suicidal ideation. Exacerbations in suicide risk may be detected in a variety of ways: 1) a participant may report increased suicidality or suicidal behaviors to a research assistant; 2) participants may note increased suicidality on the C-SSRS, SBQ or BDI-II; or 3) we may become aware of increased suicidality through a clinical or collateral sources such as a therapist or family member.

In the event that a participant reports suicidal ideation, either at the initial study intake or during the study, the RA will immediately contact Drs. Lundahl and/or Ledgerwood who are licensed clinical psychologists in the State of Michigan. Both Drs. Lundahl and Ledgerwood have experience working with individuals who have depression and express suicidal ideation. Dr. Lundahl and/or Ledgerwood will meet with the participant and conduct a risk assessment. Important components of a suicide risk assessment include assessment of the presence of suicidal ideation, past attempts, plan for an attempt, lethality of the suicide plan and past attempts, and accessibility to means for a suicide attempt. Dr. Lundahl and/or Ledgerwood will assess each of these specific domains. In cases where the participant is not at immediate risk (i.e., the participant is experiencing mild thoughts about death, has no intention or plan to commit suicide, reports many things to live for, has a strong social support network and has a forward-looking perspective), Dr. Lundahl or Ledgerwood will continue to monitor the individual, make frequent assessments of his/her suicidality at subsequent visits and assessment time-points, and they will refer the individual to outpatient mental health treatment. Assessments of suicidality are routinely conducted every two weeks in the study, but Dr. Lundahl and/or Ledgerwood will conduct more frequent follow-up in cases where the participants' risk of suicide is significantly elevated from prior assessment time-points. In cases where the suicide risk is high (i.e., wish to die, suicide plan, access to methods, etc.), or unknown, Dr. Lundahl and/or Ledgerwood will conduct further assessment, and may hospitalize the participant if s/he believes that the participant may attempt suicide upon leaving the facility. We have adopted a similar policy in our ongoing studies.

Compensation
All participants will be paid $50 for each in-person screening session (total of 2-3 sessions = up to $150). Participants in Study 1 will be paid $100 for the baseline session, $30 for each weekly telephone/RedCap questionnaire assessment/saliva collection (total of 12 assessments = $360), $25 for each bi-weekly in-van assessment (6 visits = $150), and $100 for each of the 3-, (post-treatment), 6-, 9-, and 12-month follow-up assessments, with a $100 bonus for completing all follow-up assessments (total of $500). Thus, participants have the opportunity to earn up to $1235 (including payment for screening) for completing the 1-year study.

Participants in Study 2-A will be paid $100 for the baseline session and $100 each for 3-, (post-treatment), 6-, 9-, and 12-month follow-up assessments with a $100 bonus for completing all follow-up assessments. Thus, Study 2-A completers can earn up to $750 (including payment for screening).

Participants in Study 2-B will earn the same amount as participants in Study 1 (i.e., up to $1235) plus have the opportunity to earn an additional $971 in incentives across a 12-week period if they provide verification of low THC/high CBD cannabis use. Thus, Study 2-B participants can earn up to $2206 (including payment for screening).

Study Timeline
The proposed study will take about 5 years. In the first three months we will hire additional research staff, train existing staff, set up study questionnaires on Qualtrics, purchase necessary supplies, obtain IRB approval, and start recruiting. We anticipate needing to recruit and screen about 900 candidates to enroll 500 volunteers. Based on our previous studies, we expect 30% attrition, and thus will end with 350 completers (200 in Study 1 and 150 in Study 2 (75 in the "use as usual" group and 75 in the "THC Reduction" group). We will recruit new participants until the end of the 4th year, with all participants completing their follow-ups in the 5th year. Because participants in Study 2 can be either light or heavy cannabis users, whereas those in Study 1 must be moderate users, the studies will not compete for volunteers. Also, we will conduct both trials simultaneously to maximize efficiency.

Data Analyses

Data analyses for both studies will be conducted by Dr. Ghosh and Ms. Baffoe in the WSU Biostatistics Core. Both studies are repeated measures, independent sample designs. All variables will be examined for outliers (z-scores ≥ 3.3) and normality of distribution (skewness, kurtosis). Appropriate transformations will be used (e.g. Box-Cox, Power etc.) when distributional assumptions are not fulfilled before the final analysis. Sphericity will be verified (Mauchly's Test) prior to repeated-measures analysis of variance and Huynh-Feldt correction for repeated measures will be applied. Variables for which baseline differences exist will be used as covariates.

Study 1. **Aim 1** - Least-squares mean score changes from baseline to post-treatment will be analyzed using a mixed model for repeated measures (MMRM), with treatment, week, and treatment-by-week interaction as fixed effects, and baseline value as a covariate. This MMRM analysis will be based on the missing at random (MAR) assumption to estimate the treatment effect that would have been observed had participants continued their assigned treatment, to incorporate the actual treatment received and treatment retention into the treatment effect assessment. Separate analyses will be run for PTSD symptom severity, suicidal ideation, psychiatric symptoms, health, pain, quality of life and other continuous variables. We will be able to examine trends in symptom severity over time at each follow-up time-point. **Aim 2** will be analyzed using 4 (cannabis condition) x 2 (time: pre-post cannabis administration) mixed-factor repeated measures analysis of variance (RM-ANOVA), with time as the repeated factor. Significant interactions will be analysed using simple effects tests. PTSD symptom severity, mood/anxiety and suicidal ideation will all be analyzed separately.

Study 2. Analysis for **Aim 3** (Characterize psychiatric symptoms, health, pain, sleep, psychophysiological response to trauma-related cues, and quality of life in relationship to naturalistic cannabis use quarterly over a one-year period) will be descriptive and will involve exploring the relationship between cannabis use (including amount used, frequency of use, THC/CBD concentrations), and long-term changes (improvements or worsening) in mental health symptoms, including PTSD symptoms, anxiety ,depression, suicidality, health, pain, sleep and others. We will use several statistical methods depending on the specific questions we are exploring including repeated measures ANOVA, multiple regression and logistic regression analyses. We will focus on symptom changes from baseline to each of the four follow-up time periods (3-, 6-, 9-, and 12-months. **Aim 4** (Determine whether participants who switch to lower THC/higher CBD cannabis products report clinical reductions in PTSD symptom severity and suicidality) will be analyzed using a generalized linear mixed-effects model (GLMM). GLMM allows for within- and between-subjects comparisons but is superior to repeated measures analysis of variance by incorporating all data under the assumption that missed data are missing at random. Separate analyses will be run for PTSD symptom severity, suicidal ideation, psychiatric symptoms, health, pain, quality of life and other continuous variables. We will be able to examine trends in symptom severity over time at each of the follow-up time-points.

Lipidomics Core Analyses

Analysis of eCBs in any biological matrix is possible by state-of-the-art LC-MS methods, as demonstrated by published protocols [29, 40-43]. Yet, caution is required during sample collection and processing for LC-MS analysis to prevent hydrolysis of fatty acyl ethanolamides by fatty acid amide hydrolase (FAAH) and non-enzymatic isomerization of 2-acylglycerols. Addition of FAAH inhibitors in the sample during collection and use of aprotic solvents for extracting eCBs helps alleviate these problems [29]. These are part of standard protocols at our Lipidomics Core Facility. Blood samples (1-2 mL each) will be collected into Vacutainer tubes containing EDTA as an anticoagulant and 1 mmol of URB937 (FAAH inhibitor, Cayman Chemical). Each tube will be inverted several times then centrifuged at 900g for 15 min to obtain plasma fraction. Plasma will be transferred to cryogenic tubes. Saliva samples will be collected under non-stimulated conditions via oral swab (Salimetrics®, State College, PA) placed under the subject's tongue for ~2min. After collection, swabs will be returned to a storage tube containing the FAAH inhibitor.

We will measure four primary eCBs: AEA, 2-acyl-glycerol (2-AG), palmitoylethanolamide (PEA), and oleoylethanolamide (OEA). Importantly, the analytic method includes all eCBs simultaneously without increased costs, thus we will also examine other eCBs including all fatty acid variants of ethanolamides, 2-fatty acyl glycerols, epoxy eCBs [44], and prostaglandin ethanolamides. Our analytical method for the eCB system is

similar to a published protocol [41] with the following differences: Samples are spiked with internal standards for AEA-d8, 2-AG-d8, 1-AG-d8, oleoylethanolamide-d4, and 1-PGE_2-d4 glycerol along with URB597 to inhibit FAAH. Methanol is added to the sample to a final concentration of 15% and applied to pre-conditioned StrataX C18 SPE cartridges (Phenomenex, 30 mg sorbent, 1 ml). The loaded columns are washed with water containing 15% methanol, dried under vacuum, and eluted with a 1:1 mixture of acetonitrile and ethyl acetate. The eluates are dried under a stream of nitrogen, the residue is reconstituted in HPLC mobile phase mixture consisting of methanol – water – ammonium formate – formic acid (Mobile Phases A: 5:95:2mM:0.1; B:95:5:1mM:0.1, respectively) at 15%B. The reconstituted samples are subjected to HPLC on Luna C18(2) (3µ, 2x150 mm, Phenomenex) column. The gradient program with respect to the composition of B is as follows: 0-1 min, 50%; 1-8 min, 50-80%; 8-15 min, 80-95%; and 15-22 min, 95%. The flow rate is 0.2 ml/min. The HPLC eluate is directly introduced to ESI source of QTRAP5500 mass analyzer (SCIEX) in the positive ion mode with following conditions: Curtain gas, GS1, and GS2: 35 psi, Temperature: 600 ˚C, Ion Spray Voltage: 5100 V, Collision gas: low. Declustering potential and collision energy used for each eCB are the same as published [41]. The eluate is monitored by Multiple Reaction Monitoring (MRM) method to detect unique molecular ion – daughter ion combinations for each eCB. The MRM is scheduled to monitor each transition for 120 s around the established retention time for each eCB. Mass spectra for each detected eCB are recorded using the Enhanced Product Ion (EPI) feature to verify the identity of the detected peak in addition to MRM transition and retention time matched with the standard. Data are collected using Analyst 1.6.2 software and the MRM transition chromatograms are quantified by MultiQuant software (both from SCIEX). The internal standard signals in each chromatogram are used for normalization for recovery and relative quantitation of each analyte.

Psychophysiological data (EMG, SCR, HR/HRV) will be analyzed using the AcqKnowledge and Mindware data analysis packages in Dr. Norrholm's lab. These will be used to process, filter and summarize the physiological data for the fear conditioning and trauma-cure reactivity tests.

Future Directions

Results from the proposed trials could benefit U.S. veterans immediately in terms of symptom management, and will significantly advance scientific knowledge about this area which, in turn, could inform treatment and public policy. In addition, results from these studies will inform future clinical trials designed to assess the most efficacious use of cannabinoids for reducing PTSD severity and suicidality among veterans. For example, we can use the information from these trials to determine the lowest doses that can be used to confer benefit and lower risks of use. We may explore whether cannabis might be generally useful for symptom reduction, or would better be studied as adjuncts to behavioral treatment approaches, such as exposure therapy. Another focus would be personalized medicine, where we might be able to predict, based on genetics, symptom severity, and response to cannabis, who might or might not do well on specific THC/CBD ratios and doses. Depending on the findings of our proposed studies, we anticipate that any clinical trial work may focus on: the efficacy of cannabis to enhance treatment response during fear extinction paradigms for reducing suicidality (including virtual reality approaches); incorporation of other pharmacotherapeutic approaches, such as selective serotonin reuptake inhibitors (SSRIs) during treatment; examination of differential cannabis routes of administration, such as vaporizers, cigarettes or oral (based on results from pharmacokinetic studies); exploration of different uses of cannabis in the treatment of suicidality, including targeting anxiety, depressive symptoms and sleep; and other directions. Data from the current proposed project would provide compelling support for NIH applications proposing any of these future avenues of research.

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END APPLICANT RESPONSE

V-F Current and Prior Experience and Funding Disclosure

Current and prior experience in administering clinical trials is important to the selection process. Each applicant(s) must provide a copy of the organization's most recent audited financial statement and single audit (if applicable). The audited financial statement and single audit must be sent under separate cover.

Proposals submitted by applicant(s) should include:

(1) A description of the organization's experience in conducting the type of work proposed. Include current activities and activities for the previous ten years. Include project results.

(2) If applicant(s) received a similar grant award from the State of Michigan in prior years for the type of project proposed, provide a summary of project accomplishments. Include a plan for addressing and resolving past problems.

(3) Current funding source(s) and the level of funding for the current year and the previous ten years.

BEGIN APPLICANT RESPONSE

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(1) Wayne State University is a premier, public, urban research university located in the heart of Detroit where students from all backgrounds are offered a rich, high quality education. Our deep-rooted commitment to excellence, collaboration, integrity, diversity and inclusion creates exceptional educational opportunities preparing students for success in a diverse, global society. Founded in 1868, Wayne State University offers a range of academic programs through 13 schools and colleges to nearly 28,000 students. The campus in Midtown Detroit comprises 100 buildings over 200 acres including the School of Medicine, the Eugene Applebaum College of Pharmacy and Health Sciences and the College of Nursing. The university is home to the Perinatology Research Branch of the National Institutes of Health, the Karmanos Cancer Center, a National Cancer Institute-designated comprehensive cancer center, and a National Institute of Environmental Health Sciences Core Center - Center for Urban Responses to Environmental Stressors (CURES).

As part of a broad institutional initiative in Integrative Biosciences, the Translational Neuroscience Initiative (TNI) at Wayne State University (WSU) fosters interdisciplinary, integrative, and collaborative approaches to understand translational neuroscience and its applications to post-traumatic stress disorder (PTSD).

The TNI serves as headquarters to promote integrative and collaborative research in basic and clinical neuroscience and is situated in the new 200,000 sq. ft. Integrative Biosciences Center (IBio) that houses coordinated inter- and trans-disciplinary research teams, and a Clinical Research Center. IBio is a fulcrum for leading-edge technology platforms and specialized resources in support of advanced studies in precision medicine. Through research, clinical care, community engagement, and education, the TNI team of researchers and community partners seek to discover, investigate, and solve complex health problems that affect the human nervous system.

The team assembled as part of this proposal is situated at two primary sites on the campus of Wayne State in the heart of midtown Detroit: Tolan Park Medical Building and the Integrative Biosciences Center (IBio).

Tolan Park houses the Department of Psychiatry's Substance Abuse Research Division which currently conducts investigations of the pharmacological, environmental, and individual difference determinants of drug seeking/use, behavioral economic approaches to substance abuse and policy, novel medication and behavioral therapy trials in substance-using populations (e.g. HIV+, nicotine and opioid dependence, pregnant women, co-occurring psychiatric problems), screening and brief intervention using technological advances, epidemiologic studies in special populations, and health services research. Several experimental chambers are equipped with a specialized ventilation system to allow for smoked marijuana administration. The **Human Pharmacology Laboratory (HPL)** laboratory occupies half of the 2nd floor at Tolan Park, covering about 4,500 sq. ft. The Co-Investigator (Dr. Greenwald, who is Director of the Division and Laboratory) was directly involved in designing this modern space with the architects, ensuring appropriate security (WSU Police and DEA), and working with WSU Information Technology personnel to ensure computer capabilities, Ethernet connectivity, password-protected server access, etc.The HPL has 2 screening rooms, 5 private testing rooms (equipped with specialized HVAC negative-pressure system to allow smoking on-site), and a central monitoring room with computers and audio/visual (with digital-recording) equipment. Research assistants monitor participants throughout sessions. Test rooms are equipped with Macintosh computers coupled to the monitoring room. Other equipment includes physiological monitors, automated external defibrillator and a crash cart. There is a physical examination room with ECG, exam table, weighing scale, phlebotomy, and centrifuge. There is ample office and storage space for research support staff (e.g. receptionist, research/clinical assistants). Students occupy workstations in this space. There is also a confidential file locked storage room, locked supplies storage room, copier/mail room, common day (break) room with vending machine, and toilets. A locked DEA-compliant room located in the laboratory is used for drug storage (locked safe, freezer/refrigerator, -20°C freezer for storing biological samples) and handling/preparation (Dr. Greenwald holds DEA Schedule I and Schedule II-V Researcher licenses and Michigan state licenses for the laboratory and handling controlled substances).

The Integrative Biosciences Center (IBio) is a state-of-the-art, translational facility that currently houses clinicians and investigators engaged in both basic, wet bench science as well as human clinical trials. The building has a fully staffed Clinical Research Service Center that includes patient exam rooms, a research-dedicated pharmacy, a laboratory with the capacity to run multiple metabolic and enzymatic assays as well as a dedicated

psychophysiological suite in which the proposed study work will be performed. The psychophysiological suite is divided into three components: (a) a sound attenuated chamber coupled to the BIOPAC MP160 Recording System that simultaneously measures acoustic startle, electrocardiogram, skin conductance (perspiration), and respiration; (b) a WorldViz virtual reality system capable of presenting limitless environments as needed for assessing symptom severity and delivery of exposure-based treatment of specific phobias, PTSD, and substance and alcohol abuse, and (c) a private clinical interview space within which to conduct assessments.

In addition to the world class facilities afforded by Wayne State University, the proposed study team has a long history of national and international collaborations with academic and medical "hubs" dedicated to PTSD research including the National Center for PTSD, the National Intrepid Center of Excellence located at Walter Reed National Military Medical Center, the Program for Anxiety and Traumatic Stress Studies at Cornell University, the Division of Depression and Anxiety Disorders at McLean Hospital, Harvard Medical School, Emory Healthcare Veterans Program, the Multidisciplinary Association for Psychedelic Studies (MAPS) as well as with government institutions such as the Department of Veterans Affairs and the Department of Defense.

(2) Current and past State of Michigan funding for INVESTIGATORS on the Current Proposal

David Ledgerwood, PhD

Completed State of Michigan Support

Dani Meier (PI), Mid-State Health Network 10/2018 – 9/2019
Title: Michigan Gambling Disorder Prevention Project – FY19 Proposal Mid-State Health Network
Study Goals: To examine the prevalence of gambling disorder among youth and among substance abuse patients in Michigan.
Amount: Direct: $33,704

State of Michigan Department of Health, Bureau of Substance Abuse and Addiction Services David Ledgerwood (PI) 10/2012 – 9/2013
Title: Evaluation of the Clinical Need for Residential Treatment Services for Problem Gambling in Michigan
Study Goals: To evaluate the clinical need for residential treatment services for problem gambling in the State of Michigan
Role in project: PI

PROJECTS WERE UNRELATED TO THE CURRENT PROPOSAL.

Mark Greenwald, PhD

Active State of Michigan Support

Michigan State University (Mark Greenwald, 10% effort over 2 years)
"MI CARES 2" (Michigan Collaborative Addiction Resources and Education System)
Purpose: Expand our online educational training curriculum (https://micares.msu.edu, currently for board-certified physicians only) to medical students interested in pursuing addiction medicine specialization.
Source: MDHHS State Opioid Response Grant, subcontract through Spectrum Health (PI: Cara Poland)
09/01/20 – 8/31/22
Total direct costs = $60,989

Completed State of Michigan Support

Michigan State University (Mark Greenwald, content expert, 10% effort over 2 years)
"*MI CARES 1*" (Michigan Collaborative Addiction Resources and Education System)
Purpose: Collaborate with 4-member expert team to develop an online educational training curriculum for physicians interested in pursuing addiction medicine specialization; available at https://micares.msu.edu
Source: SAMHSA grant 1H79TI081712 to MDHHS (State Opioid Response Grant), subcontract through Michigan State University
3/01/19 – 2/28/21
Total direct costs = $55,000

State of Michigan Opioid Management Project Award to Kids Kicking Cancer Goldberg (PI), Greenwald (local PI)
Title: The Heroes Circle Opioid Project
Purpose: Determine whether an intervention based on martial arts, relaxation and breathing exercises can help methadone-maintained patients (with opioid use disorder) reduce their behavioral and physical dependence on methadone without increasing substance use.
08/01/2018-07/31/2019
Amount: $90,836 (WSU subcontract)

PROJECTS ARE/WERE UNRELATED TO THE CURRENT PROPOSAL.

(3) Current and past funding for INVESTIGATORS on the Current Proposal

Leslie H. Lundahl, PhD

Active Research Support

R21 DA047662
Role: Principal Investigator
Title: *"**Human Laboratory Model to Screen Drugs with Opioid Analgesic-Sparing Effects: Cannabidiol/Morphine Combinations**."* Purpose: The objective of this study is to develop a rigorous human laboratory paradigm to evaluate potential opioid-sparing compounds that could lead to medications that reduce reliance on chronic use of high dose opioid medications for safer and more effective pain relief.
Source: NIH/NIDA
03/01/19– 02/28/22
Total Direct Costs: $275,000

R21 DA040150
Role: Principal Investigator
Title: *"**Effects of Stress- and Drug Cue-Exposure on Craving and Marijuana Seeking Behavior in Regular Cannabis Users**."* Purpose: To understand cue- and stress-induced cannabis abuse to effectively target these risk factors for intervention, we propose to investigate subjective, physiologic, and endocrine responses to a pharmacologic stressor combined with drug-related cues in chronic cannabis users, and examine additive effects on marijuana craving and seeking.
Source: NIH/NIDA
5/01/17 – 05/31/22 (NCE)
Total Direct Costs: $275,000

R01 DA044946-02

Role: Co-Investigator (PI: Mark Greenwald, PhD)
Title: *"**Opioid/Benzodiazepine Polydrug Abuse: Integrating Research on Mechanisms, Treatment and Policies**."* Purpose: (1) Determine from behavioral health treatment records prevalence of patients' presenting BZD/opioid PSU vs. BZD or opioid use alone, and relationships between drug use and psychiatric/physical comorbidities, medications, demographics, and treatment outcomes; (2) Among patients, characterize substance use and deficits in affective, neurocognitive, behavioral, and health function; (3) Determine whether simultaneous vs. concurrent BZD/opioid users differ in affective phenotypes, neurocognitive and behavioral measures.
Source: NIH/NIDA
Proposed funding period: 09/01/18 –08/31/23
Total direct costs = $1,684,808

Completed Research Support

R01 DA015462-09A1
Role: Co-Investigator (PI: Mark Greenwald, PhD)
Title: ***"Biobehavioral Studies of Opioid Seeking: Effects of Buprenorphine/Naloxone Dose on Experimental Stress Reactivity and Opioid Abstinence."*** Purpose: In this 3rd funding cycle, determine in volunteers with opioid use disorder whether: (1) short-term maintenance on buprenorphine/naloxone dose-dependently attenuates biobehavioral responding to an experimental pharmacological stressor (yohimbine/hydrocortisone), and (2) stressor reactivity predicts opioid abstinence during and up to 3 months after outpatient buprenorphine/naloxone dose tapering.
Source: NIH/NIDA
9/30/16 – 7/31/20 (NCE)
Total Direct Costs: $1,500,491

R21 DA040770
Role: Principal Investigator
Title: ***"Marijuana Cue-Reactivity and Seeking Behavior in Regular Cannabis Users: Pilot Test of Glutamatergic Modulation."*** Purpose: Determine whether: (1) marijuana cues increase marijuana puff-seeking behavior, and whether craving moderates this effect, (2) N-acetylcysteine, relative to placebo, attenuates marijuana cue-reactivity or drug seeking.
Source: NIH/NIDA
08/15/16 – 07/31/19 (NCE)
Total Direct Costs: $247,000

R01 DA034537
Role: Co-investigator (PI: David Ledgerwood, PhD)
Title: ***"Behavioral Treatments for Smoking Cessation in HIV."*** Purpose: This clinical trial will test the efficacy of prize-based contingency management for promoting smoking reduction and cessation, using urinary cotinine and expired carbon monoxide as behavioral targets.
Source: NIH/NIDA
9/1/13-8/31/17 (NCE)
Total Direct Costs: $1,268,634

R01 DA032678
Role: Co-investigator (PI: Mark Greenwald, PhD)
Title: ***"Behavioral Economic Analysis of Medical Marijuana Use in HIV+ Patients."*** Purpose: Remediate knowledge and policy gaps related to medical marijuana use by studying subgroups of marijuana-using HIV/AIDS patients (certified medical users, non-certified therapeutic users and recreational users) in Michigan's largest HIV primary care clinic with a prospective mixed-method approach that uses behavioral-economic simulations of marijuana demand, longitudinal health monitoring, and probability survey

procedures.
Source: NIH/NIDA
9/15/11– 6/30/16
Total Direct Costs: $1,019,851

2 R01 DA015462
Role: Co-investigator (PI: Mark Greenwald, PhD)
Title: ***"Biobehavioral Studies of Opioid Drug-Seeking Behavior."*** Purpose: Determine the neurochemical mechanisms of stress-potentiated opioid-seeking and biobehavioral responses.
Source: NIH/NIDA
09/30/11– 11/30/15
Total Direct Costs: $751,403

R01 DA026761Role: Principal Investigator
Title: ***"Smoked Marijuana Discrimination and Marijuana Choice in Humans: A Laboratory Model."*** Purpose: To develop and test a laboratory model of smoked marijuana discrimination and choice to self-administer marijuana for testing medications for treatment of cannabis use disorders.
Source: NIH/NIDA
7/2009 – 6/30/12
Total Direct Costs: $500,000

1P30 NR010676-01
Role: Co-investigator (PI: Shirley Moore, PhD (School of Nursing, Case Western Reserve University)
Title: ***"Center of Excellence to Build the Science of Self-Management: A System Approach"***
Project: "Parenting of Young Children By Women in Substance Abuse Treatment" (Project PI: Linda Lewin, Wayne State University School of Nursing)
Source: NIH/National Institute of Nursing Research
1/01/10– 9/30/12
Total Direct Costs: $450,648 (for 2012)

R01 DA026861
Role: Co-investigator (PI: Mark Greenwald, PhD)
Title: ***"Human Laboratory Model of Cocaine Treatment: Behavioral Economic Analysis."*** Purpose: Determine the extent to which the magnitude and probability of non-drug positive reinforcement attenuates cocaine demand elasticity.
Source: NIH/NIDA
8/01/09 – 10/31/12
Total Direct Costs: $890,000

Seth D. Norrholm, PhD

Active Research Support

1 I01 CX002149-01 Theodoroff (PI) 07/1/2020 -06/30/2024
Title: Evaluating Possible Auditory and Psychological Biomarkers of Sound Intolerance
Supporting Agency: VA CSR&D
This project addresses the critical need to understand the pathophysiology that leads to severe decreased sound tolerance (DST). By examining the relationship between auditory and
psychological biomarkers, this study will provide clinically relevant information on where deficits exist in sensory and/or neurological structures that lead to severe DST.
Role: Co-PI
Amount: $1,189,745

NIMH Rasmusson (PI) 5/01/2020 – 04/30/2025
Title: Facilitation of Extinction Retention and Reconsolidation Blockade in PTSD by Intravenous Allopregnanolone
Supporting Agency: NIMH (R01NIH MH122867, PI: Rasmusson)
This study is testing the use of allopregnanolone to enhance fear extinction learning and to prevent the return of conditioned fear in previously traumatized individuals with PTSD.
Role: Co-investigator
Amount: $603,176

Pharmacotherapies for Alcohol and Substance Use Disorders 02/01/2019-09/30/2022
(PASA) Consortium (Petrakis/Davis/Norrholm)
Title: Kappa Opioid Receptor Antagonist for the Treatment of Alcohol Use Disorder and Comorbid PTSD
This study is testing a novel potential psychopharmaceutical treatment for Veterans and Service Members with AUD and comorbid PTSD. This study will test the safety and preliminary efficacy of BUP/NTRX in the treatment of AUD in military populations with comorbid PTSD.
Role: Co-Principal Investigator
Amount: $1,893,454

NIMH Nugent (PI) 7/1/2016-6/30/2021
Title: Understanding the Interplay of Social Context and Physiology on Psychological Outcomes
in Trauma-Exposed Adolescents
The present investigation, translational in implications for intervention, will model the early interplay of biomarkers and social context influencing symptom development in 250 trauma-exposed adolescents (13-17 years).
Role: Co-Investigator
Amount: $250,000

Completed Research Support

VA Merit Program Norrholm (PI) 10/1/2015 – 3/31/2020
Title: Neurobiological Correlates of Fear in Veterans with Military Sexual Trauma
The goal of this project is to investigate the psychophysiological (fear learning/extinction), neuroendocrine, and genomic underpinnings of increased vulnerability in women for developing PTSD in the aftermath of Military Sexual Trauma (MST)
Role in project: Principal Investigator
Amount: $600,000

JWMRP Rizzo (PI) 10/01/2014-9/30/2019
DoD/Joint Warfighter Medical Research Program (JWMRP)
BRAVEMIND: Advancing the Virtual Iraq/Afghanistan PTSD Exposure Therapy for Military Sexual Trauma (MST)
The goal of this project is to integrate psychophysiological methodologies with virtual reality-based prolonged exposure therapy for Veterans with Military Sexual Trauma (MST)
Role in project: Co-Investigator (PI: Rizzo)
Amount: $250,000

R01 MH100122 Jovanovic (PI) 7/1/2013-3/31/2018
NIMH
Development, Trauma, and Genotype Effects on Biomarkers of Anxiety in Children
The goal of this project is to prospectively examine effects of genotype, age, and puberty on fear-potentiated startle and dark-enhanced startle in children and

adolescents from a high-risk population.
Role in project: Co-Investigator

Department of Defense (DOD) Norrholm (PI) 09/30/2008-07/31/2013
Congressionally Directed Medical Research Programs (CDMRP)
Conditioned fear extinction and generalization in posttraumatic stress disorder (PTSD)
The goal of this project was to investigate the acquisition and extinction of fear in veterans from Operations Iraqi Freedom, Enduring Freedom, and New Dawn with an emphasis on the genetic bases of PTSD.
Role in Project: Principal Investigator
Amount: $650,000

NARSAD Norrholm (PI) 070/1/2008 - 6/30/2010
Conditioned fear extinction and generalization in posttraumatic stress disorder (PTSD) and major depression
The goal of this project was to examine the acquisition, extinction, and generalization of learned fear in a population of OIF/OEF/OND combat veterans with and without PTSD or co-morbid depression.
Role in Project: Principal Investigator
Amount: $60,000

Tanja Jovanovic, PhD

Active Research Support

R01 NIH MH111682 Jovanovic (PI) 09/23/2016-6/30/2021
Title: Impact of Trauma Exposure on Critical Periods in Brain Development and Fear Processing in Children Role in project: Principal Investigator
This longitudinal study will examine the timing and duration of trauma exposure in children ages 9-11.
Role in project: Principal Investigator
Amount: $389,424 (R01 MH111682-01); $110,599 (Supplement: R01 MH111682_03S1)

R01 NIH MH110364-01A1 Jovanovic/Neigh (MPI) 04/22/2016-06/30/2021
Title: Biological Mechanisms of Stress Disorders Co-Morbid with HIV in African American Women
This study will examine trauma-related psychiatric symptoms and fear-potentiated startle response, as well as glucocorticoid receptor response in women with HIV.
Role in project: Principal Investigator
Amount: $250,000

U01 NIH MH110925 McLean (PI); Jovanovic (Site PI) 09/23/2016-8/31/2021
Title: Longitudinal Assessment of Post-traumatic Syndromes
Prospective Examination of Risk for PTSD after Trauma Exposure Assessed in the Emergency
Department
A multi-site study to examine the effects of acute trauma in a longitudinal design
Role in project: Site PI
Amount: $140,137

R01 NIH MH108641 Nugent (PI); Jovanovic (Site PI) 7/1/2016-6/30/2021
Title: Understanding the Interplay of Social Context and Physiology on Psychological Outcomes in Trauma-Exposed Adolescents
The present investigation, translational in implications for intervention, will model the early interplay of biomarkers and social context influencing symptom development in 250 trauma-exposed adolescents.
Role in project: Site PI
Amount: $250,000

R01 NIH HD099178 Javanbakht (PI) 4/7/2020-12/31/2024
Title: Biological and Environmental Factors Affecting Risk and Resilience Among Syrian Refugee Children
This longitudinal study will examine epigenetic changes, along with psychophysiology, and PTSD symptoms in in Syrian refugee families resettled in the USA
Role in project: Co-Investigator
Amount: $ 499,290

R01NIH MH122867 Rasmusson (PI), Jovanovic (Site PI) 5/01/2020-04/30/2025
Title: Facilitation of Extinction Retention and Reconsolidation Blockade in PTSD by Intravenous Allopregnanolone
This project will evaluate whether allopregnanolone vs. placebo facilitates extinction retention and enables fear reconsolidation blockade.
Role in project: Site PI
Amount: $603,176

Completed Research Support

R01 NIH MH100122-01 Jovanovic (PI) 07/1/2013 - 3/30/2019
Title: Development, Trauma, and Genotype Effects on Biomarkers of Anxiety in Children
This R01 application will prospectively examine effects of genotype, age, and puberty on fear-potentiated startle and dark-enhanced startle in children and adolescents from a high-risk population.
Role in project: Principal Investigator

NARSAD Independent Investigator Award Jovanovic (PI) 09/15/2015-09/14/2017
Title: Impact of Trauma Exposure on Fear Neurocircuitry and DNA Methylation in At-Risk
Children
The goal of this project is to examine development of fear inhibition neurocircuitry in children with trauma exposure using functional MRI
Role in project: Principal Investigator

R21 NIH MH106902-01A1 Smith/Jovanovic (MPI) 01/13/2016-12/31/2017
Title: Prospective Determination of the Epigenetic Response to Trauma
This study will characterize how the epigenome responds for the first 3 months after a traumatic
event and characterize the DNA methylation changes that occur acutely within the first weeks
up to 1 mo and 3 mo.
Role in project: Co-PI

David Ledgerwood, PhD

Active Research Support

R61HL155793-01 NIH/NHLBI P Cunningham (MUSC, MPI), Sylvie Naar (FSU, MPI) 4/30/2021
-4/30/2023
Title: Clinical Trial of the Fit Families Multicomponent Obesity Intervention for African American American Adolescents and Their Caregivers: Next Step from the ORBIT Initiative (Co-Investigator)
Study Goals: To develop and test a behavioral intervention designed to increase physical activity,
diet monitoring and weight loss among teens and their primary caregivers.
Role in project: Co-PI
Amount: Direct $535,121 – all sites

R01CA243910 NIH/NCI E.J. Edelman (MPI), S. Bernstein (Yale; MPI) 9/18/2019-8/30/2024

Title: A SMART Approach to Treating Tobacco Use Disorder in Persons Living with HIV
Study Goals: To use a tailored smart design study to examine the efficacy of combined medication (NRT, varenicline) and behavioral treatment (contingency management) for smoking cessation among people living with HIV.
Role in project: Consultant

R01MD011322 NIH/National Institute on Drug Abuse P.I.(Co): D. Ledgerwood (Co-PI) P. Cunningham (Co-PI) 8/2016 – 9/2021
Title: Behavioral Incentives to Increase Caregiver Engagement in Juvenile Drug Court
Study Goals: To assess the efficacy of adolescent and caregiver contingency management
treatments for enhancing adherence to Juvenile Drug Court and substance
Role in project: Co-PI
Amount: Direct: $149,022 – Wayne State University amount

MGRP-LG-15-13 Manitoba Gambling Research D. Ledgerwood (MPI), L. Najavits (Boston U; MPI)
12/2015 – 9/2021
Title: Online Coping Skills Counseling for Problem Gambling and Trauma
Role in project: MPI
Amount: Direct: $449,999 CDN

Completed Research Support

R21 CA222939-01A1 C. Kopetz (PI)
Title: Intermittent and Daily Smoking: A Comparison Between Mechanisms
Study Goals: To investigate the role of social sues compared to smoking cues on smoking-relevant outcomes in intermittent and daily smokers.
Role in project: Co-PI
Amount: Direct: $275,000

R01DA034537-01A1 NIH/National Institute on Drug Abuse David Ledgerwood (PI)
8/2013 –
7/2019
Title: Behavioral Treatments for Smoking Cessation in HIV
Study Goals: To assess the efficacy of contingency management treatments for smoking
cessation in individuals receiving treatment for HIV. We also propose evaluating a stepped care model to provide appropriate levels of care based on initial treatment response.
Role in project: PI
Amount: Direct: $1,109,615

Dani Meier (PI), Mid-State Health Network 10/2018 – 9/2019
Title: Michigan Gambling Disorder Prevention Project – FY19 Proposal Mid-State Health Network
Study Goals: To examine the prevalence of gambling disorder among youth and among substance abuse patients in Michigan.
Amount: Direct: $33,704

Level IV (Approved) Ontario Problem Gambling Research Centre David Ledgerwood (PI)
10/2011 – 9/2016
Title: Effectiveness of Cognitive-Motivational Behaviour Therapy in Community Treatment

Study Goals: To examine the effectiveness of a combined CBT/MI treatment approach for pathological gambling administered by community-based therapists.
Role in project: PI
Amount: Total Direct: $508,109

U01HL097889 NIH/NHLBI Sylvie Naar-King (PI) 9/2009 – 6/2014
Title: Intervention Procedures for Adherence to Weight Loss Recommendations in Black Adolescents
Study Goals: To develop interventions to address obesity in adolescents, and to examine the efficacy of these interventions.
Role in project: Co-PI (20% in Year 1; 5% subsequent years; Project Lead for Pilot study of Contingency Management for weight loss in obese adolescents)

State of Michigan Department of Health, Bureau of Substance Abuse and Addiction Services
David Ledgerwood (PI) 10/2012 – 9/2013
Title: Evaluation of the Clinical Need for Residential Treatment Services for Problem Gambling in Michigan
Study Goals: To evaluate the clinical need for residential treatment services for problem gambling in the State of Michigan
Role in project: PI
Amount: Total Direct: $43,318

R01 DA026861 NIH/NIDA Mark Greenwald (PI) 7/2009 – 6/2012
Title: Human Laboratory Model of Cocaine Treatment: Behavioral Economic Analysis
Study Goals: Determine the extent to which non-drug alternatives (positive reinforcement and punishment), combined with novel medications, attenuate cocaine demand elasticity.
Role in project: Co-PI (10%)

R01 DA026761-01 NIH/NIDA Leslie Lundahl (PI) 7/2009 – 6/2012
Title: Smoked Marijuana Discrimination and Marijuana Choice in Humans: A Laboratory Model
Study Goals: To develop and test a laboratory model of smoked marijuana discrimination and choice to self-administer marijuana for testing medications for treatment of cannabis use disorders.
Role in project: Co- PI (10%)

Mark K. Greenwald, PhD

Active Research Support

Mark Greenwald (PI; 4% effort)
"*Effects of Pharmacological Stress and rTMS Interventions on Executive Function in Opioid Use Disorder*"
Purpose: (1) Evaluate how stress impacts domains of behavior including (1a) executive function and (1b) opioid-seeking behavior; and (2) Determine whether rTMS stimulation attenuates (2a) executive dysfunction, (2b) stress-reactivity, and (2c) opioid-seeking in individuals with OUD.
Source: Peter F. McManus Charitable Trust
01/01/20 – 04/30/22
Total costs = $74,977

Mark Greenwald (Contact PI; 25% effort) and Timothy Roehrs (HFHS), Co-PIs

"*Dual Orexin Antagonism as a Mechanism for Improving Sleep and Drug Abstinence in Opioid Use Disorder*"
Purpose: Determine whether daily treatment with a dual OX-1/2 receptor antagonist, relative to placebo, can improve outpatient opioid abstinence (Aim 1), improve inpatient sleep efficiency (Aim 2), and whether improved sleep efficiency predicts increased opioid abstinence (Aim 3) among patients with opioid use disorder.
Source: NIH/NIHLBI U01 HL150551
09/23/19 – 08/31/23
Total direct costs = $3,533,857

Mark Greenwald (Contact PI, 10% effort in R21 years) and Cynthia Arfken (Co-PI)
"*Opioid/Benzodiazepine Polydrug Abuse: Integrating Research on Mechanisms, Treatment and Policies*". Purpose: (1) Determine from behavioral health treatment records the prevalence of patients' presenting BZD/opioid PSU vs. BZD or opioid use alone, and relationships between drug use and psychiatric (primarily affective) and physical comorbidities, medications, demographics, and treatment outcomes; (2) Among newly admitted patients, characterize substance use pattern and assess deficits across domains (affective, neurocognitive, behavioral, health); (3) Determine in BZD/opioid PSU whether: (a) at baseline, simultaneous vs. concurrent BZD/opioid users exhibit different profiles on affective phenotypes, and on neurocognitive, and behavioral measures including more lifetime drug-use consequences, and greater price-inelasticity for opioid and BZD using behavioral economic simulation methods; (b) experimental drug administration of alprazolam/morphine vs. either drug alone or placebo, will differentially alter affective/hedonic phenotypes in 3 different behavioral choice procedures.
Source: NIH/NIDA R21 DA044946
09/30/18 –08/31/21 (NCE); R33 continuation (3-year project) is pending
Total direct costs = $416,454

Christine Rabinak, PI (WSU Dept. of Pharmacy Practice)
Role: Co-Investigator, 5% effort
"*Effects of THC on Retention of Memory for Fear Extinction Learning in PTSD*". Purpose: (1) Assess effects of THC on extinction memory recall and brain activation, and (2) Determine whether an optimal THC dose will reduce PTSD symptom severity and increase between-session extinction during prolonged exposure therapy.
Source: NIH/NIMH R61/R33 MH111935
02/01/17 – 01/31/22
Total costs: $3,813,623

Mark Greenwald (PI, 30% effort)
"*Biobehavioral Studies of Opioid Seeking: Effects of Buprenorphine/Naloxone Dose on Experimental Stress Reactivity and Opioid Abstinence*".
Purpose: In this 3rd funding cycle, determine in volunteers with opioid use disorder whether short-term maintenance on buprenorphine/naloxone dose-dependently attenuates biobehavioral responding to an experimental pharmacological stressor.
Source: NIH/NIDA 2 R01 DA015462-09A1
09/30/16 – 07/31/21 (NCE)
Total direct costs: $1,500,491

Hilary Marusak, PI (Christine Rabinak, primary mentor, WSU Dept. of Pharmacy Practice)
Role: Co-mentor; in-kind effort
"Endocannabinoids and the Development of Extinction Recall Neurocircuitry in Adolescents"
Purpose: (1) Characterize neurobehavioral mechanisms of recall of extinction within and between adolescence and young adulthood; (2) Assess effects of FAAH genetic variation in endocannabinoid signaling on extinction recall within and between adolescence and young adults; and (3) Examine whether endocannabinoid genetic variability mediates the link between adolescent trauma exposure and extinction recall in adolescents and young adults.
Source: NIH K01 MH119241
Funding period: 07/01/19 – 06/30/24

Total direct costs: $249,000

Completed Research Support

Leslie Lundahl, PI
Role: Co-investigator, 5% effort
"*Human Laboratory Model to Screen Drugs with Opioid Analgesic-Sparing Effects: Cannabidiol/ Morphine Combination*s"
Purpose: Develop a human experimental model to assess drugs that may enhance the analgesic effects of opioids, so that lower doses of opioids may be used for pain relief.
Source: NIH/NIDA R21 DA047662
02/01/19 – 01/31/21 (NCE)
Total direct costs = $275,000

Leslie Lundahl, PI
Role: Co-Investigator, 5% effort
"*Effects of Stress- and Drug Cue-Exposure on Marijuana Seeking Behavior in Regular Cannabis Users*". Purpose: Determine in marijuana users whether yohimbine pretreatment and drug-related cues increase marijuana-seeking behavior.
Source: NIH/NIDA R21 DA040150
03/23/17 – 03/22/19 (NCE)
Total direct costs = $275,000

Mark Greenwald, PI, 3.5% effort
"*Heroes Circle Opioid Project*"
Purpose: Determine whether an intervention based on martial arts, relaxation and breathing exercises can help methadone-maintained patients (with opioid use disorder) reduce their behavioral and physical dependence on methadone without increasing substance use.
Source: State of Michigan award to Kids Kicking Cancer; subcontract
07/01/18 – 09/30/19
Total costs = $90,836

Christine Rabinak, PI (WSU Dept. of Pharmacy Practice)
Role: Mentor; in-kind effort
"Effects of FAAH Genotype on Fear-Related Brain Activation During Fear Extinction". Purpose: Determine whether fatty acid amide hydrolase (FAAH) genetic variability is evident at behavioral and neural levels during recall of extinction learning, and might contribute to the cause of PTSD in humans via effects on brain endocannabinoid levels.
Source: NARSAD Young Investigator Award
01/15/17 – 01/14/19
Total direct costs: $70,000

Leslie Lundahl, PI
Role: Co-investigator, 5% effort
"*Marijuana Cue-Reactivity and Seeking Behavior in Regular Cannabis Users: Pilot Test of Glutamatergic Modulation*". Purpose: Determine whether: (1) marijuana cues increase marijuana puff-seeking behavior, and whether craving moderates this effect, (2) N-acetylcysteine, relative to placebo, attenuates marijuana cue-reactivity or drug seeking.
Source: NIH/NIDA R21 DA040770
08/15/16 – 07/31/18
Total direct costs = $247,000

Mark Greenwald [in-kind effort] and Angela Tiura, Project Co-PIs
"*Physical Activity in Minority Youth: Effects on Eating, Cognition, and Metabolism*". Purpose: Determine whether exercise (vs. sedentary condition) produces intensity-dependent alterations in: (1) sympathetic, metabolic, and inflammatory biomarkers, and appetite ratings; (2) executive function; (3) palatable food choices and rate of food intake; and (4) coupling between peri-exercise measures of metabolism and appetite and post-exercise measures of cognitive function,

food choice and intake.
Source: WSU Diabetes and Obesity Team Science (WSU-DOTS), funded by WSU Office of Vice President for Research
03/01/16 – 09/30/18
Total direct costs = $65,000

David Ledgerwood, PI
Role: Co-investigator, 5% effort
"*Behavioral Smoking Cessation Treatment for People Living with HIV/AIDS*". Purpose: This clinical trial will test the efficacy of prize-based contingency management for promoting smoking reduction and cessation, using urinary cotinine and expired carbon monoxide as behavioral targets.
Source: NIH/NIDA R01 DA034537
09/01/13 – 08/31/18
Total direct costs: $1,268,634

Eric Woodcock [PhD student], PI
Role: Mentor, in-kind effort
"*Neuropharmacological Investigation of Frontostriatal Network Function and Nicotine Seeking Behavior in Current Smokers*". Purpose: Determine whether a pharmacological stressor (yohimbine + hydrocortisone) relative to placebo will induce biobehavioral stress-responses, disrupt dorsolateral prefrontal cortical (dlPFC) control of reward-network regions during smoking cues, impair dlPFC-dependent memory, and increase nicotine-seeking/self-administration.
Source: NIH/NIDA F31 DA040369
04/01/16 – 03/30/18 (terminated earlier than original award end date, as Dr. Woodcock completed and left for postdoctoral fellowship at Yale starting 07/31/17).
Total direct costs: $39,988

Mark Greenwald [in-kind effort] and Sylvie Naar, Project Co-PIs
"*Relative Reinforcing Value (RRV) of Food in African American Adolescents: Behavioral Choices, Neurocognition, and BMI*. Purpose: Investigate behavioral economic determinants of overeating palatable foods by assessing: (1) parental food budgeting; (2) adolescent food choices as a function of stress; and (3) adolescent delay discounting of palatable food and brain circuitry (fMRI) involved in food choice.
Source: WSU Diabetes and Obesity Team Science (WSU-DOTS), funded by WSU Office of Vice President for Research
12/01/13 – 03/31/16
Total direct costs = $75,000

Jon-Kar Zubieta and Scott Peltier (Univ. of Michigan) and Mark Greenwald, Co-PIs, 10% effort in years 1-2 and 20% effort in years 3-5
"*Development and Use of rtfMRI for Self-Control of Nicotine Craving*". Purpose: Develop real-time functional MRI and analytical capability to evaluate nicotine-dependent subjects' ability to control cigarette craving.
Source: NIH/NIDA R21/R33 DA026077
10/01/08 – 06/30/14
Total direct costs for R21 portion (all revenue in years 1-2) and WSU subcontract, respectively: $400,000 and $27,000; total direct costs for R33 portion (all revenue in years 3-5) and WSU subcontract, respectively: $1,200,000 and $81,000.

Mark Greenwald, PI, 15% effort
"*Biobehavioral Studies of Opioid Seeking Behavior*". Purpose: In this 2nd funding cycle, determine the neurochemical mechanisms of stress-potentiated opioid-seeking and biobehavioral responses.
Source: NIH/NIDA 2 R01 DA015462
09/30/11 – 11/30/15
Total direct costs: $751,403

Mark Greenwald, PI, 20% effort
"*Behavioral Economic Analysis of Medical Marijuana Use in HIV+ Patients".* Purpose: Remediate knowledge and policy gaps related to medical marijuana use by studying subgroups of marijuana-using HIV/AIDS patients (certified medical users, non-certified therapeutic users and recreational users) in Michigan's largest HIV primary care clinic with a prospective mixed-method approach that uses behavioral-economic simulations of marijuana demand, longitudinal health monitoring, and probability survey procedures.
Source: NIH/NIDA R01 DA032678
09/15/11 – 06/30/16
Total direct costs: $1,019,851

Jon-Kar Zubieta, PI, University of Michigan
Role: Co-investigator, 5% effort
"*Predicting Placebo Responses Across Disease States*". Purpose: Determine the contribution of specific brain regions and neurotransmitter systems, measured with a combination of functional and molecular imaging techniques, to variation in placebo responses across disease processes (major depression and nicotine dependence).
Source: NIH/NIMH R01 MH086858
09/16/09 – 06/30/13
Total direct costs overall and WSU subcontract, respectively: $820,566 and $72,000

Jon-Kar Zubieta, PI, University of Michigan
Role: Co-investigator, 10% effort
"*Interaction of Smoking and Chronic Pain at Neurochemical & Phenotypic Levels*". Purpose: Determine the effects of chronic pain and nicotine dependence on neurochemical (endogenous opioid and dopamine release) and behavioral responses to experimental pain.
Source: NIH/NIDA R01 DA027494
09/01/09 – 02/28/13
Total direct costs overall and WSU subcontract, respectively: $2,682,000 and $137,297

Mark Greenwald, PI, 35% effort
"*Human Laboratory Model of Cocaine Treatment: Behavioral Economic Analysis*". Purpose: Determine the extent to which the magnitude and probability of non-drug positive reinforcement attenuates cocaine demand elasticity.
Source: NIH/NIDA R01 DA026861 (funded under the American Recovery and Reinvestment [ARRA] Act.)
08/01/09 – 10/31/12
Total direct costs: $890,000

Leslie Lundahl, PI
Role: Co-investigator, 5% effort
"*Smoked Marijuana Discrimination and Marijuana Choice in Humans: A Laboratory Model*". Purpose: Determine whether marinol (oral THC) dose-dependently reduces the discriminative stimulus effects of smoked marijuana in cannabis abusers.
Source: NIH/NIDA R01 DA026761
07/01/09 – 06/30/12
Total direct costs: $500,000

Virginia Delaney-Black, PI
Role: Co-investigator, 5% effort
"*Teens at Risk: Prenatal Cocaine and Postnatal Challenges*". Purpose: To continue a prospective, longitudinal study to measure the impacts of prenatal cocaine exposure, socio-environmental factors and emotional regulation on late-teen (16.5–18 years old) risky behaviors of drug use, sexual activity, and delinquency.
Source: NIH/NIDA R01 DA022419
07/01/08 – 06/30/14

Total direct costs: $2,309,751

Hilary Marusak, PhD

Active Research Support

K01 NIH MH119241 Marusak (PI) 07/01/2019-06/30/2024
Title: Endocannabinoids and the development of extinction recall neural circuitry in adolescents
This study characterizes age-related changes in extinction recall, frontolimbic activity, and
endocannabinoid signaling across adolescence (ages 10-17).
Amount: $871,180 (total costs)
Role in project: Principal Investigator

R01 NIH MH111682 Jovanovic (PI) 09/23/2016-6/30/2021
Title: Impact of Trauma Exposure on Critical Periods in Brain Development and Fear Processing in Children
This longitudinal study will examine the timing and duration of trauma exposure in children ages 9-11.
Role in project: Co-Investigator
Amount: $389,424 (R01 MH111682-01); $110,599 (Supplement: R01 MH111682_03S1)

R01 NIH DE031117 Seligman and Geers (Co-PIs) 07/01/2021-06/30/2024
Title: Mechanisms of latent inhibition as a proactive interference for preventing dental anxiety.
The purpose of this project is to identify the mechanism(s) underlying the latent inhibition of dental fear, allowing for more precise engagement of these target(s).
Role in project: Site Lead and Study Co-Investigator
Amount: $249,529 (WSU Subcontract)

The Children's Foundation Pediatric Research Grant R1-2021-31 Marusak (PI) 02/08/2021-12/31/2021
Title: Effects of cannabidiol on anxiety and behavioral problems among children with epilepsy
This prospective observational study will track seizure frequency, anxiety symptoms, and behavioral problems among pediatric epilepsy patients who are newly started on CBD (Epidiolex).
Role in project: Co-Principal Investigator
Amount: $57,575 (total costs)

American Public Health Association NVDRS New Investigator Award Marusak (PI) 4/23/2021-4/30/2022
Title: Youth firearm-related deaths in the United States
Role in project: Principal Investigator
Amount: $6,500

WSU Dept. of Psychiatry and Behavioral Neurosciences New Investigator Grant Marusak (PI) 10/1/2020-8/31/2021
Title: Impact of adolescent cannabis use on endocannabinoid signaling and emotion regulation neural circuitry
Role in project: Principal Investigator
Amount: $25,000

WSU Office of the Provost Social & Behavioral Determinants of Health Research Stimulus Program Marusak and Barcelona (Co-PIs) 07/01/2021-06/30/2022
Title: Behind the "runner's high": Endocannabinoid levels as a potential mediator of the

beneficial effects of exercise on cognitive performance and mental health in youth
Role in project: Co-Principal Investigator
Amount: $20,000

Completed Research Support

Kids Kicking Cancer Marusak (Local PI) 11/01/2019-10/31/2020
Title: The Heroes Circle – Children Healing Children
This project examines the impact of a novel martial arts-based school curriculum (vs. a standard control socioemotional development curriculum) on stress, anxiety, and behavioral problems in elementary school children (Year 2).
Role in project: Local Principal Investigator
Amount: $68,819 (WSU subcontract)

State of Michigan Opioid Management Project Award to Kids Kicking Cancer Goldberg (PI), Greenwald (local PI) 08/01/2018-07/31/2019
Title: The Heroes Circle Opioid Project 2018
This project evaluates a novel martial arts-based virtual reality intervention for individuals with opioid use disorder who are on methadone maintenance treatment.
Role in project: Co-Investigator
Amount: $90,836 (WSU subcontract)

Kids Kicking Cancer Marusak (local PI) 07/01/2018-12/31/2019
Title: The Heroes Circle – Children Healing Children
This project examines the impact of a novel martial arts-based school curriculum (vs. a standard control socioemotional development curriculum) on stress, anxiety, and behavioral problems in elementary school children (Year 1).
Role in project: Local Principal Investigator
Amount: $33,325 (WSU subcontract)

American Cancer Society Postdoctoral Fellowship PF-16-057-01-PCSM Marusak (PI) 07/01/2016-06/30/2019
Title: Neurobehavioral correlates of learning and memory in child cancer survivors
This project compares brain and behavioral responses during implicit and explicit learning and memory paradigms in child cancer survivors vs. controls.
Role in project: Principal Investigator
Amount: $163,500

St. Baldrick's Foundation Supportive Care Research Grant 523497 Marusak (PI) 07/01/2017-02/28/2019
Title: Martial arts therapy and brain mechanisms for cancer-related pain
This study examines the impact of a novel martial arts-based intervention on pain, quality of life, and neural activity in the pain neuromatrix in children with cancer.
Role in project: Principal Investigator
Amount: $45,015.93

Barbara Ann Karmanos Cancer Institute, Pilot Project Grant from the American Cancer Society 14-238-04-IRG Rabinak (PI) 09/01/2016-08/31/2017
Title: Understanding emotional brain network organization in survivors of childhood cancer
This project examines emotion processing neural circuitry in pediatric cancer survivors, and correlates with anxiety and posttraumatic stress symptoms.
Role in project: Co-Investigator
Amount: $30,000

END APPLICANT RESPONSE

V-G Personnel

Selected applicant(s) must be able to staff a project team that clearly possesses skill and experience in coordinating clinical trials. In the narrative, identify the authorized contact person and key personnel to be involved with this project by name and title and provide a brief summary of their experience, qualifications, and the work to be performed.

If other organizations will be playing a role in the proposed project, provide sufficient background information that will give the Issuing Office a reasonable understanding of each organization's qualifications.

Include a detailed organizational chart including names, titles, and geographic location of all individuals that will contribute to the project.

Attach a copy of your confidentiality agreement and provide a list of personnel and the date that the confidentiality agreement was signed.

BEGIN APPLICANT RESPONSE

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Leslie H. Lundahl, PhD. Dr. Lundahl is an Associate Professor in the Department of Psychiatry and Behavioral Neurosciences at Wayne State University who has been conducting clinical human behavioral pharmacology studies for over two decades. Her expertise is in developing and refining efficient and rigorous human laboratory models to study factors involved in drug seeking and drug taking, such as drug abuse liability, drug-drug interactions, effects of stress and environmental cues on choice to use drugs, and subjective and physiological responses to drugs administered in the laboratory. She has been the Principal Investigator on six federal (NIH/NIDA) cannabis-related grants and several university grants, and served as Co-Investigator on many other federal and private grants examining alcohol, nicotine, cocaine, opiates, methamphetamine, and MDMA. Dr. Lundahl holds an IND that allows cannabis and cannabinoid administration to humans. Her current projects include evaluating the potential therapeutic efficacy of cannabidiol (CBD), alone and in combination with low doses of morphine, for treating pain, investigating the effects of stress and marijuana cue exposure on marijuana craving and self-administration, and establishing the pharmacokinetic profile of CBD. Dr. Lundahl's research is funded by the National Institute on Drug Abuse (NIDA), where she serves on several grant review committees. She is also a clinical psychologist with over 25 years of experience in the assessment and treatment of psychiatric and substance use disorders, and she has served as diagnostician and clinician on multiple randomized clinical trials of substance use disorders. In her clinical practice she specializes in depression, anxiety, and substance use issues. Thus, she has the necessary scientific, administrative, and clinical experience to lead this important work, along with Co-PI, Dr. Norrholm. She has enjoyed a long and successful history of collaboration with Drs. Ledgerwood and Greenwald, and they have worked closely with the rest of the team to develop this exciting proposal.

David Ledgerwood, PhD. Dr. Ledgerwood is a clinical psychologist and Professor studying various aspects of substance use, including cannabis, tobacco, opioids, and others. He has expertise in conducting clinical trials for treatment efficacy and effectiveness. Dr. Ledgerwood has conducted research in several areas that complement the proposed work, including examining trauma, post-traumatic stress disorder and suicidality among individuals with gambling disorder, and individuals receiving treatment for opioid use disorder. He is currently co-Principal Investigator of a tele-health trial examining the efficacy of Seeking Safety for co-occurring trauma and gambling problems. Additionally, Dr. Ledgerwood worked on the Vietnam Era Study, a longitudinal cohort study at Washington University that examines PTSD, suicidality, and other co-occurring conditions among Vietnam era veterans originally recruited in 1971. Dr. Ledgerwood's research has been funded by NIH and foundation grants. He serves on a number of editorial and grant review boards. His funded research involves primarily conducting clinical trials for behavioral interventions for individuals with nicotine use disorder, substance use disorder, and gambling disorder. Currently, Dr. Ledgerwood is conducting clinical trials and other clinical research with colleagues at several universities across North America including Medical University of South Carolina, Baylor University, University of Massachusetts Medical School, University of Windsor, and Yale University.

Seth D. Norrholm, PhD. Dr. Norrholm is an Associate Professor in the Department of Psychiatry and Behavioral Neurosciences at Wayne State. He is a translational neuroscientist whose work spans from the animal laboratory to the human clinical arena. With training in both the basic neurosciences and clinical psychology, Dr. Norrholm is a leading expert on posttraumatic stress disorder (PTSD) and the psychiatric conditions with which it is comorbid (namely substance/alcohol use and depression). He has spent over 20 years studying the neurobiology of these disorders using innovative physiological and technological approaches. A particular area of expertise for Dr. Norrholm is how individuals, both combat veteran and civilian, exposed to traumatic stress acquire new fears, maintain these fears, and ultimately attempt to overcome them. In addition, Dr. Norrholm is trained in neuropsychopharmacology and has led investigations of drugs such as MDMA (ecstasy) and d-cycloserine as potential facilitators of extinction, the fear reduction learning process upon which exposure therapies for fear and anxiety are based. Dr. Norrholm has been continuously funded by the Brain and Behavior Foundation, the Congressionally Directed Medical Research Program through the Department of Defense (DoD), NATO, the DoD-funded Pharmacotherapies for Alcohol and Substance Abuse (PASA) Consortium, and the VA Merit Program. In addition, he leads a team of translational, clinical researchers at the Neuroscience Center for Anxiety, Stress, and Trauma (NeuroCAST) on a program of studies that examine the multi-dimensional aspects of trauma-, stressor-, and anxiety-related symptomatology with an overarching goal of informing emerging clinical interventions for combat and civilian-related PTSD. Dr. Norrholm has been recognized internationally for his expertise in PTSD and Fear and collaborates with clinicians and scientists worldwide. For example, the protocols proposed here have been implemented at over 30 sites by Drs. Norrholm and Jovanovic including Harvard, Yale, Cornell, Brown, Stanford, Emory, and the Max Planck Institute (Munich, Germany).

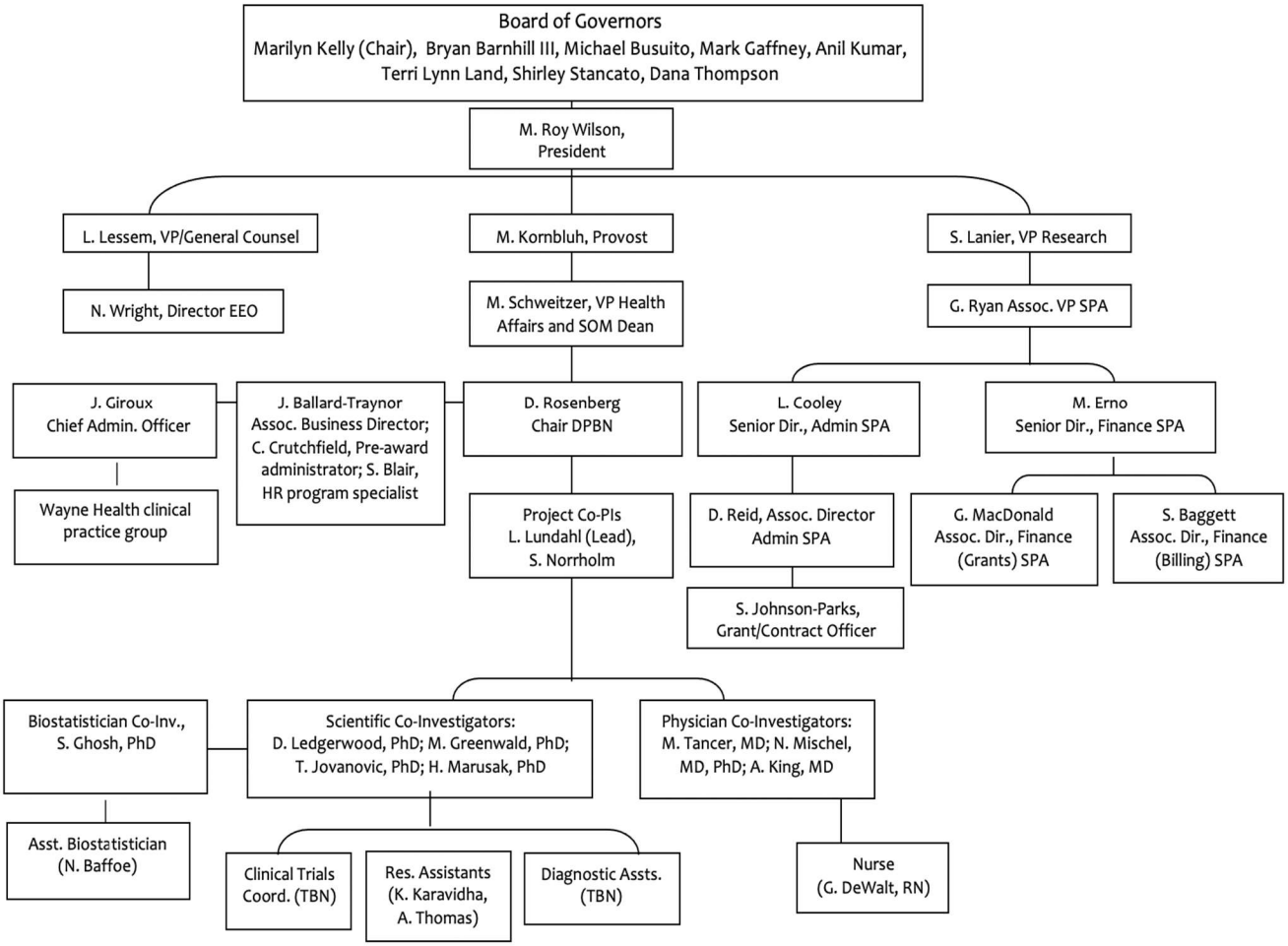
Mark K. Greenwald, PhD. Dr. Greenwald is Professor, the Gertrude Levin Endowed Chair in Addiction and Pain Biology, Associate Department Chair, and Director of the Substance Abuse Research Division in the Department of Psychiatry and Behavioral Neurosciences at Wayne State. His expertise is in the field of substance use disorders (SUDs), particularly opioid, cocaine and marijuana/cannabis. He conducts broad programmatic research in addiction and pain biology and therapies, directs the Human Pharmacology Laboratory (site of the proposed studies), and oversees a SUD treatment research clinic. His research foci include: (a) investigating individual-difference (e.g. genetics, affective states), environmental (e.g. cues, drug availability, response requirements), and pharmacological (PD and PK) determinants of drug seeking/use and its psychobiological consequences; (b) using behavioral, brain imaging and biomarker approaches to improve understanding of mechanisms of action; and (c) leveraging this knowledge to develop effective treatments for these conditions. Dr. Greenwald has broad training in clinical and experimental psychology, behavioral pharmacology, and neuroscience. Dr. Greenwald holds DEA Schedule I and Schedule II-V Researcher Licenses and State of Michigan Board of Pharmacy controlled substance and laboratory licenses, all of which are pivotal to performing this project. Dr. Greenwald has published more than 120 research papers, reviews and book chapters, and more than 200 research abstracts. His research has received continuous funding from the NIH since 1996. He has served on multiple national and international grant review committees and formerly chaired both NIH and US Veterans Affairs grant review committees. He collaborates with several industry partners involved in developing anti-addiction treatments. He is Past-President of the American Psychological Association Division 28, has served on many national, state and local committees, and advisory boards, related to substance use disorders. He is a leader in interdisciplinary research and education, especially mentoring junior faculty, postdoctoral fellows, medical students and graduate students, on topics related to substance use disorders.

Tanja Jovanovic, PhD. Dr. Jovanovic is a Professor and the David and Patricia Barron Endowed Chair in PTSD Neurobiology in the Department of Psychiatry and Behavioral Neurosciences at Wayne State. She is a leader in the field of trauma neurobiology and has directed two of the largest translational research projects focused specifically on traumatized urban populations. Her work incorporates cutting edge psychophysiological and neuroimaging techniques to better understand the relationship between genetic risk factors and human psychiatric conditions related to trauma, stress, anxiety, and depression. For several years, Dr. Jovanovic was the director of the Grady Trauma Project, a large study of trauma exposure and genetic risk factors in an urban population of primarily African American children and adults. In the Summer of 2018, she relocated from Emory University to Wayne State University to direct a PTSD and Trauma Neurobiology Program, which uses psychophysiological and neuroimaging methods to investigate biomarkers of posttraumatic stress symptoms. Dr. Jovanovic's work has been funded by multiple National Institutes of Health grants as well as by the Brain and Behavior Research Foundation. Her more recent work has included serving as the site PI for the AURORA

project which prospectively investigates risk for posttraumatic sequalae by recruiting Emergency Department patients and conducing intensive characterization of their biological and psychological responses immediately after experiencing a trauma. Dr. Jovanovic is actively collaborating with investigators across many institutions including Harvard, Emory, Brown, and the National Center for PTSD. Dr. Jovanovic sits on numerous journal editorial boards, grant review committees, and professional association Boards of Directors. Her peer-reviewed publications (>200) are widely cited and she has contributed significantly to the field of PTSD and trauma for over two decades.

Hilary A. Marusak, PhD. Dr. Marusak is a tenure-track Assistant Professor in the Department of Psychiatry and Behavioral Neurosciences at Wayne State University, and holds an adjunct position in the Merrill Palmer Skillman Institute for Child and Family Development. Dr. Marusak directs the Trauma History Investigation of Neurodevelopment in Kids (THINK) lab at Wayne State, which incorporates neuroimaging, behavioral, and physiological approaches to understand neurodevelopmental mechanisms leading to anxiety and other fear-based disorders (e.g., posttraumatic stress disorder, PTSD) in children and adolescents. In particular, Dr. Marusak is interested in the role of the endocannabinoid system in modulating frontolimbic brain development and risk of fear-based disorders, and has developed a novel line of research to examine behavioral (e.g., exercise, meditation) or pharmacological interventions (e.g., cannabidiol, CBD) that target the endocannabinoid system for the treatment and/or prevention of anxiety and PTSD in youth. An emerging area of interest is the impact of prenatal cannabis exposure and adolescent cannabis use on neurodevelopmental and mental health outcomes. Dr. Marusak is the PI of a currently funded NIMH K01 project (MH119241) that aims to characterize age-related changes in endocannabinoid signaling across adolescence (10-17 years), and associations with fear extinction, fear extinction neural circuitry, and anxiety and PTSD symptomology. Dr. Marusak is the Co-PI on a study funded by the Children's Foundation to examine the impact of CBD on stress and anxiety in children with epilepsy, and is the Co-PI of a recently funded internal award (WSU Office of the Provost) to examine the impact of exercise on endocannabinoid levels and cognitive and mental health in youth. Dr. Marusak also works closely with the other study personnel; Dr. Lundahl is a Co-I on Dr. Marusak's New Investigator Grant to study the impact of adolescent cannabis use on frontolimbic circuitry and fear regulation; Dr. Jovanovic has been Dr. Marusak's faculty mentor since 2019, and they are on two funded NIH grants together (K01MH119241, R01MH111682), co-authored 1 publication and 2 co-authored papers under review, co-mentor 4 students, and have 10+ co-authored conference abstracts; Dr. Greenwald is Dr. Marusak's co-mentor on her K award, and Drs. Greenwald and Marusak have co-authored 1 publication, 5+ conference abstracts, and co-mentor 3 students.

Organizational Chart: *WSU Warriors & US Veterans Marijuana Research Partnership*
July 14, 2021



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SIGNED CONFIDENTIALITY AGREEMENT GOES HERE

END APPLICANT RESPONSE

V-H Budget

To enable the Issuing Office to evaluate all project costs, **applicant(s) will submit a proposed budget and corresponding budget narrative.** Please see attachment A for the required budget format. The budget and narrative must include only VMR grant funds in the budget; do not include matching, leveraged, cost share or any other type of supplemental funds. The budget narrative must identify the budget line item and number, provide a detailed description for each line, and include individual unit

Representation Regarding the Prohibition on Using Funds under Grants and Cooperative Agreements with Entities that Require Certain Internal Confidentiality Agreements

By submission of its proposal or application, the applicant represents that it does not require any of its employees, contractors, or subrecipients seeking to report fraud, waste, or abuse to sign or comply with internal confidentiality agreements or statements prohibiting or otherwise restricting those employees, contractors, or subrecipients from lawfully reporting that waste, fraud, or abuse to a designated investigative or law enforcement representative of a Federal department or agency authorized to receive such information. Note that: (1) the basis for this representation is a prohibition in section 743 of the Financial Services and General Government Appropriations Act, 2015 (Division E of the Consolidated and Further Continuing Appropriations Act, 2015, Pub. L. 113-235) and any successor provision of law on making funds available through grants and cooperative agreements to entities with certain internal confidentiality agreements or statements; and (2) section 743 states that it does not contravene requirements applicable to Standard Form 312, Form 4414, or any other form issued by a Federal department or agency governing the nondisclosure of classified information.

Faith Simfukwe Mugala
Signature

07/16/2021
Date

prices.

Selected applicant(s) will be required to provide supporting documentation for all grant expenditures incurred during the term of the grant. Accounting records must be supported by source documentation including, but not limited to, general ledgers, time sheets, payroll registers, invoices, check copies and bank statements, or cancelled checks. Expenses will be verified based on actual expenditures incurred within the grant period that are supported by source documentation, not budgeted amounts.

(1) **Budget Changes** – Any changes to the budget must be pre-approved by the Grant Administrator. Changes in the budget of less than 5% of the total line item amount do not require a formal amendment; however, a revised budget should be submitted to the Grant Administrator for approval. The allowable transfer should be calculated as less than 5% of the total line item that the funds are being transferred from.

Cumulative changes in the budget equal to or greater than 5% of the total line item amount may be permitted only upon prior review and written approval by the Grant Administrator. A formal grant amendment must be signed by both the grantor and grantee.

(2) **Disallowed Costs** – Disallowed costs include but are not limited to the following: sick pay, vacation pay, holiday pay, bonuses, overtime, tuition reimbursement/remission, vehicle allowance, seminars, conferences, meetings, subscriptions, dues, and memberships.

(3) **Administrative Costs** – Administrative costs cover expenses related to general administrative functions and coordination of functions and oversight related to VMR administrative functions. Administrative costs should include costs of goods and services required for administrative functions of the program; travel costs incurred for official business in carrying out administrative activities or the overall management of the VMR; costs of information systems related to administrative functions; and contractual services related to sub-recipients or vendors that are solely for the performance of administrative functions. **Total administrative and indirect costs must be identified, labeled clearly, and may not exceed 10% of the overall grant.**

(4) **Budget Requirements** – the proposed budget will display three (3) headings identified as the: Line Item, Budget Category, and Total. The budget line items that need to be included, at a minimum, are listed below. The budget should reflect the best estimate of actual costs using whole numbers. Please refrain from using decimals or formulas. Refer to the budget example provided in Attachment D.

- **Personnel** – In the budget, include the name, job title, and salary for each staff position to be paid for by the grant. Time sheets and payroll registers must be submitted for each staff position, and hours worked must be grant related. Fringe benefits may not exceed 35% of each employee's salary. Fringe benefits will be reimbursed based on actual expenditures per employee up to 35%, not on budgeted amounts. Allowable benefits include: health, dental, and optical insurance, employer-paid Social Security and Medicare tax, Michigan and Federal unemployment tax, and other miscellaneous fringe benefits (life insurance, long- and short-term disability insurance, worker's compensation, and retirement program contributions up to 4%). Applicant(s) must provide details on the organization's method of calculating fringe benefit expenses that will be charged to the grant including whether fringe benefits are calculated on an annualized basis or based on the length of the grant term.

  The budget narrative must include the number of weeks the individual will work on the grant; number of hours per week a full time employee of the organization is expected to work; a description of the work to be performed by each individual; the estimated hours to be worked; actual pay rate; the fringe benefit percentage being charged to the grant for each employee; the percentage of the employee's time allocated to the grant;

whether each employee is salaried-exempt, salaried-non- exempt or hourly; and any other applicable information related to the individual's duties and responsibilities in connection with this grant.

Individuals that are not on selected applicant(s)'s payroll, e.g., independent contractors, individuals receiving a Form 1099, temporary workers, etc., must be placed under the Contractual Services budget category. Only employees on the selected applicant(s)'s payroll should be included in the Personnel budget category.

- **Supplies, Materials, & Equipment:** specify item(s) and cost. The budget narrative should include the anticipated cost of each item, a detailed explanation of the item's purpose, and how it relates to the project being funded. Be as detailed as possible.

- **Contractual Services:** these services must be competitively bid. Individuals that are not on selected applicant(s)'s payroll, e.g., independent contractors, individuals receiving a Form 1099, temporary workers, etc., must be placed under **Contractual Services**. When competitive selection is not feasible or practical, the selected applicant(s) agrees to obtain the written approval of the Grant Administrator before making a sole source selection. Selected applicant(s) must provide a copy of contracts, memoranda of understanding or agreements signed by selected applicant(s) and contractors.

  Selected applicant(s) assumes responsibility to select subcontractors on a competitive basis. A minimum of three (3) bids must be solicited and proposals must include, at a minimum: (1) name of selected applicant(s), grant number, and grant period; and (2) the type, number, and description of projects as described in the proposal.

  Selected applicant(s) must provide the Grant Administrator with the solicitation, list of vendor responses (including amounts), and name of the selected vendor. Selected applicant(s) must maintain bids on file at their place of business according to Section II-B, Records Maintenance, Inspection, Examination, Audit and Monitoring. The Grant Administrator will reserve the right to request a copy of all bids for services that are competitively bid.

  Selected applicant(s) must award the project to the lowest bid unless the Grant Administrator has given prior written approval for selection of a higher bid. Selected applicant(s) must provide a written justification for the selection of a higher bid. When awarding subcontracts, the selected applicant(s) must ensure that preference is given to products manufactured in or services offered by Michigan-based firms.

- **Travel:** in the budget include the name, job title and official workstation for each staff member that will be traveling. Selected applicant(s) must follow the State of Michigan Standardized Travel Regulations (www.michigan.gov/dtmb/0,5552,7-150- 9141_13132--,00.html). The State will reimburse for mileage, lodging, and meals, refer to the current State travel rates. Meals and lodging must be supported by itemized, legible receipts and reasons for travel. Itemized meal receipts must include a list of each item purchased; receipts for payments made by credit card that are not itemized will not be accepted.

  Mileage must be supported by travel log(s) with beginning and ending addresses, mileage total, and reason for travel. Grantees will be provided a travel log example. Out-of-state travel must be directly related to the grant project and approved by the Grant Administrator prior to travel. Travel expenses listed in the travel budget category are strictly for individuals listed on the budget under Personnel. Per Diem payments and alcoholic beverage reimbursements are not allowed.

- **Other Expenses:** This category is solely for use by organizations charging a per-case fee for work performed by subunits or internal agencies within the organization that do not require a competitive bid, i.e. contract, memorandum of understanding or any other type of signed agreement.

- **Indirect Costs:** Indirect costs are costs not directly or specifically related to the grant program. Indirect costs are costs of administering the organization and must be spread over a number of products, services, or grant programs proportionately. Examples include office supplies and equipment, utilities, rent, maintenance and repair, insurance, accounting and bookkeeping services, and legal services. Non-cash expenses like depreciation, amortization, and depletion are not allowable indirect costs under this grant. **Total administrative and indirect costs must be identified, labeled clearly, and may not exceed 10% of the overall grant.**

  Selected applicant(s) will be reimbursed for its proportional share of indirect costs. This means the MRA should be allocated a portion of the selected applicant(s)'s indirect costs and not 100% of the organization's total indirect cost.

  Indirect costs should be displayed on the face of the budget on a single line item and the indirect rate should be rounded to six (6) decimal places. The budget narrative should contain a list of indirect costs, how the selected applicant(s) determined its indirect costs, and the percentage rate calculation for reimbursable indirect costs. Selected applicant(s) is not required to provide documentation supporting indirect costs; however, documentation verifying the costs must be retained by the selected applicant(s).

(5) To ensure efficient review and approval of grant expenditures, selected applicant(s) will be provided additional guidelines to assist with calculating and determining accurate and appropriate grant expenditures.

(6) Each budget category should have a subtotal displaying the total anticipated amount to be expended, and the budget should include a subtotal for total direct project costs and a sum of total project costs.

(7) After grants are approved by the MRA, modifications of proposals and budgets may be necessary. If the MRA does not approve the total amount requested in the original proposal, selected applicant(s) will be required to submit a revised proposal, budget and budget narrative for the purpose of entering into a Grant Agreement. New line items to the revised budget are not allowed.

(8) Selected applicant(s) assumes the responsibility of ensuring all unexpended grant funds are returned to the State of Michigan at the end of the grant period. Failure to do so may render selected applicant(s) ineligible for future grant awards and/or subject to legal action.

(9) Selected applicant(s) may not commingle grant award funds with current or future grant awards. All funding sources must be managed and accounted for separately.

BUDGET NARRATIVE

BEGIN APPLICANT RESPONSE

Budget Justification

Key Personnel (All personnel work 40-hr work weeks)

Leslie Lundahl, Ph.D., Lead Principal Investigator (Associate Professor, tenured) is a licensed clinical psychologist and an experienced psychopharmacologist in the Human Pharmacology Laboratory within the Substance Abuse Research Division. Dr. Lundahl has over 20 years of extensive experience in designing, conducting, and publishing behavioral pharmacology clinical research studies, including the procedures proposed in this application. She will provide overall scientific direction and coordinate the design, implementation and quality control of data collected for the studies in this application. She will be responsible for all communication with LARA/MRA, FDA, DEA, WSU IRB and compliance with their monitoring and reporting requirements, including filing protocols under her FDA IND for marijuana (#75,596). Dr. Lundahl will oversee all drug storage, preparation, administration, and accountability, as well as psychiatric screening and monitoring of participants in this trial. Along with Dr. Ledgerwood, she will train and supervise master's levels clinical students

and research assistants in the conduct of clinical interviews, and assessment of neurocognitive function, PTSD and suicidal ideation. She will oversee protocol and data integrity, analyses, interpretation, and publication of study results, and present these findings at scientific conferences. She will devote 40% effort, or 16 hours per week, to these clinical trials throughout the 5-year project period.

Seth Norrholm, Ph.D., Co-Principal investigator (Associate Professor) is a translational neuroscientist with over 20 years of research experience in furthering the understanding of the neurobiological mechanisms underlying fear-, anxiety-, trauma-, and stressor-related disorders and the psychiatric conditions with which these disorders are co-morbid. Dr. Norrholm will develop, install, and implement the fear learning paradigm to be used in the proposed project, and will oversee the training of staff in testing, data analysis, and quality control for the fear learning phases to be conducted at baseline, post-treatment, and follow-up time point. He will oversee training in the administration of the Clinician Administered PTSD Scale for DSM-5 (CAPS-5) and the PTSD Checklist for DSM-5 (PCL-5). He will also maintain the BIOPAC psychophysiological equipment for the fear learning aspects of the study tasks and oversee data processing, cleaning, and analysis. This will require 8 hr/week in order to prevent a backlog of data. He will devote 40% effort, or 16 hours per week, throughout the 5-year project period.

David Ledgerwood, Ph.D., Co-Investigator (Professor, tenured) a licensed clinical psychologist and experienced clinical scientist in the Substance Abuse Research Division. He is also the Director of the Nicotine and Tobacco Research Division in the Department of Psychiatry and Behavioral Neurosciences. Dr. Ledgerwood has extensive experience conducting studies that examine the efficacy and effectiveness of clinical interventions. He is skilled in clinical trial methodology and has published several behavioral trials over his career. He has also conducted and published numerous studies examining the etiology, mechanisms, treatment predictors and consequences related to substance use disorders and behavioral addictions. Dr. Ledgerwood will have several roles on the clinical trials, and will oversee the naturalistic observation study. Specifically he will work with Dr. Lundahl to: assist with recruitment; oversee intake assessments; review data for quality and safety; develop, provide training and supervision for the CM component; assist with data analysis; and assist with dissemination. He will devote 40% effort, or 16 hours per week, to these clinical trials throughout the 5-year project period.

Tanja Jovanovic, Ph.D., Co-Investigator (Professor, tenured) Dr. Jovanovic is a Professor in the Department of Psychiatry and Behavioral Neurosciences at Wayne State University, David and Patricia Barron Chair for PTSD Neurobiology, and Adjunct Professor in the Merrill Palmer Skillman Institute for Child and Family Development. Prior to relocating to WSU, Dr. Jovanovic was the Director of the Grady Trauma Project at Emory University in Atlanta. Dr. Jovanovic has significant expertise in psychophysiological research with PTSD patients, and for the last 10 years she has been investigating neurobiological mechanisms of trauma and PTSD in adults and children from inner-city populations. Dr. Jovanovic will assist on developing experimental design, training and supervision of psychophysiology research staff, interpretation of data, preparation of manuscripts for publication. She will devote 40% effort to this project, or 16 hours per week, for this 5-year trial.

Mark Greenwald, Ph.D., (Professor, tenured) is Director of the Substance Abuse Research Division, and Chief of its Human Pharmacology Laboratory, Dept. of Psychiatry and Behavioral Neurosciences, and will serve as co-investigator for this project. Dr. Greenwald is a leading expert in the design and conduct of behavioral pharmacology studies using methods similar to those proposed here. Dr. Greenwald routinely collaborates with the PI on laboratory-based studies of cannabinoids, cocaine, and opioids. He will assist with study design, implementation, data analysis, interpretation of results, and will co-author publications. Dr. Greenwald will maintain his current DEA Schedule I Researcher license (he also has DEA Schedules II-V licenses). He will assist the PI with drug preparation and accountability. He will contribute 15% effort, or 6 hours per week, throughout this 5-year project.

Hilary Marusak, Ph.D. (Assistant Professor, tenure-track) Dr. Marusak is a tenure-track Assistant Professor in the Department of Psychiatry and Behavioral Neurosciences at Wayne State University, and holds an adjunct position in the Merrill Palmer Skillman Institute for Child and Family Development. Dr. Marusak directs the Trauma History Investigation of Neurodevelopment in Kids (THINK) lab at Wayne State, and is interested in the role of the endocannabinoid system in modulating frontolimbic brain development and

risk of fear-based disorders. Given her expertise in the role of the endocannabinoid system in stress, anxiety, and PTSD, Dr. Marusak will lead all aspects of sample collection, design, analysis, and interpretation of endocannabinoid levels and will be responsible for coordinating with the WSU Lipidomic Core (Krishnarao Maddipati, PhD, Director) for sample collection, processing, storage, analysis, and interpretation. She will devote 10% effort to this project, or 4 hours per week throughout the 5-year project period.

Manuel Tancer, M.D. (Professor, tenured) is former Chair of the Dept. of Psychiatry and Behavioral Neurosciences and has often collaborated with Drs. Lundahl, Greenwald, and others on substance abuse research studies. He is a former Chair of a WSU Institutional Review Board medical committee, is an expert in the ethical and safe conduct of psychopharmacological studies, and currently is head of review of adverse events across all medical review committees of the WSU IRB. He is a board certified psychiatrist with expertise in anxiety and mood disorders, as well as psychostimulant abuse. Dr. Tancer will provide medical approval and monitoring, oversee the nurse (Ms. Gwen DeWalt), and assist with interpretation of findings (including co-authoring). He will contribute 5% effort, or 2 hours per week, throughout this 5-year project.

Nick Mischel, M.D., Ph.D. (Assistant Professor)
Dr. Mischel provides outpatient psychiatric consultation for patients in medication-assisted treatment (MAT) with suboxone and methadone, and has also treated patients with alcohol, opiate, tobacco, cocaine, benzodiazepine, cannabis, other stimulant, and other psychedelic use disorders in both acute inpatient detoxification and rehabilitation centers. Dr. Mischel will review EKGs, labs, and perform physicals to determine study eligibility, as well as provide medical coverage during cannabis administration sessions and oversight throughout the trial. Dr. Mischel will be involved in interpretation of findings and manuscript preparation and publication. He will commit 10% effort, or 4 hours per week, to this 5-year project.

Andy King, M.D. (Assistant Professor)
Dr. King is an Emergency Department physician who also sees patients in our on-site methadone clinic. He will provide backup to Dr. Tancer and Dr. Mischel for medical monitoring and oversight, oversee the nurse (Ms. Gwen DeWalt), and assist with interpretation of findings and manuscript preparation. He will contribute 5% effort, or 2 hours per week, throughout this 5-year project.

Biostatistics Core.
Samiran Ghosh, Ph.D. (Professor, tenured)
Dr. Ghosh is a Biostatistician with significant experience in designing and running randomized intervention trial. He has experience writing and supporting trials similar to the proposed project and has also actively developed novel statistical methods for adaptive and Bayesian RCT. For this particular project, a repeated measure design is proposed which will be modeled via linear mixed effect model. As a core leader of Biostatistics, Epidemiology and Research Design (BERD a core facility) at WSU, he will work with the Co-PIs and their team for successful completion of the project. He is currently working with Drs. Lundahl and Ledgerwood on more than one NIH funded project and serves as a mentor for Dr. Marusak on her K-award. Hence, he knows our team well and has engaged with multiple grant activities from the department of Psychiatry at Wayne State University. He will commit 5%, or 2 hours per week, in Year 1 and then 10%, or 4 hours per week, for Years 2-5.

Nana Ama Baffoe, M.S. (Biostatistician)
Ms. Baffoe has a Master's Degree in Biostatistics. She will assist the team in setting up databases, performing manipulation checks, and conducting preliminary analyses. Ms. Baffoe will also provide MS Level statistical support to Dr. Ghosh and oversee the RedCap data cleaning and maintenance. She will commit 10%, or 4 hours per week, in Years 1-5.

Other Personnel
Clinical Trials Coordinator, **TBN.** The coordinator will be responsible for managing all day-to-day project needs, helping develop and implement protocols for collecting biological, behavioral, and questionnaire data, overseeing recruiting and scheduling of screening and baseline sessions, and enrollment, and randomization procedures. S/he will help complete IRB paperwork, maintain agency records, oversee scheduling of phone interviews and follow-ups, and coordinate data entry and management with the research assistants. The coordinator will meet regularly with the PI to assure quality control and maintenance of study records, provide summaries, and assist in preparing data for presentations and publications. S/he will devote 100% effort, or 40 hours per week, throughout this 5-year project.

Professional Research Assistant. Mr. Klevis Karavidha is a Professional Research Assistant in the Human Pharmacology Laboratory. He will create advertisements for various print and social media, establish contact with veterans organizations, conduct initial telephone screens, schedule and coordinate psychiatric/medical screening visits, provide phlebotomy services, and assist the coordinator in running experimental sessions, set up and manage the Qualtrics questionnaire data with assistance from Ms. Baffoe, and conduct the phone interview assessments. He will also assist Dr. Lundahl with study drug custodial record keeping. He will devote 100% effort, or 40 hours per week, throughout this 5-year project.

Professional Research Assistant. Ms. Anju Thomas is a Professional Research Assistant in the Human Pharmacology Laboratory. She will be responsible for collecting and processing biomarker (saliva, blood, urine) samples for this project, and will provide backup phlebotomy services for MR. Karavidha. Ms. Thomas will also be responsible for conducting informed consent procedures with participants, and maintaining contact tracking and follow-up calendar to make sure that all assessments are completed and on time. She will devote 75%, or 30 hours per week, to this 5-year project.

Professional Research Assistant. **TBN.** Full-time Professional Research Assistant will be responsible for implementing and executing aspects of the study that occur in the Detroit Trauma Project Lab, including but not limited to, participant screenings, scheduling participant assessment appointments, making pre-assessment reminder phone calls to maximize participation rates, and conducting study psychophysiological procedures and neuropsychiatric questionnaires and interviews. The Research Assistant will be responsible for accurate and timely upkeep of the project data and day-to-day operation of the project with supervision from PIs and Coordinator. This staff member will work on a day-to-day basis with study PIs at Wayne State University School of Medicine, Department of Psychiatry and Behavioral Neurosciences. This is a 100% effort position, for 40 hours per week throughout the 5-year project period.

Clinical diagnostic assistants. We request funds for two, half-time M.S.-level clinical psychology graduate practicum students (we routinely have 3-4 per year in our laboratory, who start in the Fall semester). They will have day-to-day responsibilities for conducting clinical interviews (SCID for DSM-5), PTSD and suicidal ideation assessments, and neurocognitive testing. They will each devote 50% effort, or 10 hours per week, throughout the 5-year project, and will be supervised by Dr. Lundahl and Dr. Ledgerwood.

Administrative Personnel

Jennifer Ballard-Traynor (Administrative Director)
Jennifer will provide financial oversight on this study. She will review all personnel charges and expenses on this study for compliance. She will monitor expenditures and report to the PI on a regular basis. Review and coordinate close out documents with the Sponsored Program Administrative Office. She will contribute 15% effort, or 6 hours per week throughout this 5-year project.

Cordell Crutchfield (Grants and Contracts Administrator)
Cordell will coordinate the pre-award aspects for this project to ensure compliance with University and sponsor. He will review budget proposals and justifications each award period and coordinate documentation required by granting agency. His will contribute 5% effort, or 2 hours per week, throughout this 5-year project.

Sonya Blair (HR Program Specialist)
Sonya will manage the human resource functions for this study. She will post all open TBN positions in coordination with the PI. She will be in charge of onboarding all new personnel for this process including gathering necessary documentation, working with HR on the hiring documents, submitting background check information, and coordinating new employee training. She will also be adding effort to the grant and reviewing effort certifications on a bi-annual basis. She will contribute 5% effort, or 2 hours per week, throughout this 5-year project.

Caroline Zajac-Benitez (Senior Research Assistant)
Caroline has over 20 years' experience with administering IRB related issues. For this proposal, she will be the key person generating and submitting the IRB application and consent forms as well as amendments and annual recruitment reports and renewals. She will contribute 5% effort, or 2 hours per week throughout this 5-year

project.

Fringe Benefits

Fringe benefits are calculated on requested salary per the University's policy. The fringe rates are set and charged by the University based on pay classification. These amounts are subject to change on a fiscal year basis (Oct to Sep). The current rate for faculty is 25.6% (Lundahl, Ledgerwood, Norrholm, Jovanovich, Marusak, King, Mischel), the rate for research personnel is 31.2%, and the rate for administrative personnel is 28.8% (Greenwald, Tancer).

Other Direct Costs

Computer Equipment

We will obtain two (2) MacBook Pro laptop computers with 15" monitors and four (4) computing tablets to be used for day-to-day tasks and data collection in the pharmacology laboratory vans as well as in the Human Pharmacology Laboratory. All will be dedicated to this study. Cost = $2000 each x 2 computers = $4000, $800 each x 4 tablets = $3200; total of $7200.

The 2 laptop computers and 2 tablets will be purchased in Year 1 ($5600), the other 2 tablets will be purchased in Year 4 ($1600) to replace the original ones bought in Year 1.

Laptop Computers**: ($2,400)** In year one, we will need to equip the BIOPAC MP160 system with two laptop computers ($1200 x 2) necessary to operate the lab components specific to stimulus presentation (dedicated laptop 1) and real-time psychophysiological data collection (dedicated laptop 2) as part of the system to be installed in the PVL. These computers will collect psychophysiology data pertinent to the specific aims of this proposal.

Vitals Monitor: In Year 1 we will purchase a Welch-Allyn 300 Series Vital Signs Monitor (All States Med) to monitor participants' heart rate, blood pressure, and skin temperature during cannabis administration session at baseline. Vitals monitoring is both for safety and to assess physiological responses to cannabis conditions. Cost: $875

Portable Vitals Monitors: In Year 1 we will purchase 2 Omron Intellisense Blood Pressure Monitors (OmronHealthcare.com) which are portable and will be used to assess heart rate and blood pressure during the weekly PLV visits. This monitoring is both for safety and to assess changes in physiological function over treatment and time. Cost: 2 at $675 = $1350.

Screening Related Supplies

These items represent costs for minor medical and nursing items regularly used during study screening. They include costs for hypodermic syringes, alcohol pads, band-aids, gauze pads, thermometer probe covers, gloves, examination table paper, examination gowns, sterile saline, peroxide, ace wraps, bacitracin, and tape. These are necessary items for conducting screening evaluations (e.g., blood withdrawal, physical) with a population that can have significant associated morbidity rates. Costs for these items have been budgeted at $12 per candidate for screening and $5 per participant for the Baseline session. We estimate these costs will increase 3% per year in years 2-5.

750 participants screened x $12/participant = $9000, or $1800/yr
500 participants enrolled x $5/participant = $2500, or $500/year
Total = $11,500 total or $2300/yr

Research/Data Handling Supplies

Supply costs associated with daily operation of the research include notebooks to maintain records, USB drives, printer paper for hard-copy records of data and graphs, laser writer toner cartridges, fax cartridges, post-it notes, pens/pencils for data recording, staples and paper clips to organize data, notepads, and clipboards. The budget for these costs is $70 per enrollee. We estimate enrolling an average of 500 participants x $70/participant = $35,000 or $7000/yr. We estimate that these costs will increase 3% per year in years 2-5.

Supplies for Participants During Laboratory Sessions

While volunteers are in the laboratory on Baseline and follow-up assessment sessions, there are costs associated with snacks and lunches. We allow participants to select these items up to the amount of $10/day. Completers will each spend 5 session weekdays in the laboratory (x $10/day = $50), whereas we estimate that non-completers will each spend 2 weekdays in the laboratory (x $10/day = $20).

Study 1: (200 complete x $50) + (85 non-complete x $20) = $11,700
Study 2: (150 complete x $50) + (65 non-complete x $20) = $8,880
Total costs of (350 complete x $50) + (150 non-complete x $20) = $20,500 or $4100/yr

HEPA filters (portable air cleaners)
The Human Pharmacology Laboratory is equipped with a negative pressure ventilation system that funnels air out of this building area to the external environment. Nonetheless, we routinely use filters to augment this system to promote the health and safety of our participants and staff members. As participants will be smoking cannabis we will need to outfit two testing rooms with HEPA filters to capture marijuana smoke so it does not filter into other rooms of the building and reduce the burden to the ventilation system. Each unit costs $300 and lasts approximately 2 years, thus we are requesting 6 units in total for $1800.

Cannabis Administration Expenses

Cannabis: THC and Cannabidiol (CBD)
We will purchase cannabis flower in bulk (preferably from one batch) from a local metro Detroit dispensary. The 4 THC:CBD conditions will be purchased: High THC:Low CBD (15-20%THC:8% CBD); High THC:High CBD (15-20% THC:15% CBD); Low THC:High CBD (8%THC:15%CBD), and Low THC:Low CBD (8%THC:8%CBD). Participants will be randomized into each of these conditions, with 50 participants in each condition. We estimate that 285 participants in Study 1 and 108 participants from Study 2-B will complete the Baseline session, in which they will undergo an acute cannabis administration of 300 mg of cannabis flower (equivalent to one joint, or marijuana cigarette) via vaporizer. Study 1 participants will receive the dose condition to which they are randomized (i.e.; 71 will receive High THC:Low CBD; 71 will receive High THC:High CBD; 71 will receive Low THC: High CBD, and 72 will receive Low THC:Low CBD). Study 2-B participants (n=108) who are heavy cannabis users (as determined by substance evaluation during screening) will receive High THC:Low CBD, and lighter users will receive Low THC:Low CBD. During the 12-week treatment phase, participants in Study 1 will receive 1 g/day of their assigned dose condition per week for 12 weeks (84 g per participant). We expect that of the 285, Study 1 participants who enroll and complete the baseline session, 200 (50 in each cannabis condition) will complete the trial (and thus we need 200 x 84g = 16,800 g), and approximately 85 will complete 25% of the study before dropping out (85 x 21 g = 1785 g). (Study 2-B participants supply their own product during the 12-week treatment phase, thus no cannabis flower is being purchased for them.)

Studies 1 and 2-B: (Baseline session 393 enrolled x 0.3 g) = 117.9 g
Study 1: (Completers 200 x 84 g = 16,800 g) + (non-completers 85 x 21 g = 1785 g) = 18,585 g

Total cannabis needed: 117.9 g + 18,585 g = 18,703 g or 660 ounces, at $250/oz = $165,000 over 5 years, or $33,000/year

Cannabis Vaporizers and Accessories: We will purchase 5 Medic 2® Certified Vaporizers from Storz & Bickel for cannabis administration. One will be used in each year of the 5-year study, at a cost of $709 each, for a total of $709/yr or $3545 over 5 years. We will also order 400 lip valves (a new one needs to be used for each participant for sanitary reasons) at a cost of $960 and 390 valve and balloon packs (each participant receives one for sanitary reasons) at a cost of $5200.
Thus, $3545 + $960 + $5200 = $9720 total for cannabis administration supplies.

Independent Laboratory Testing of Cannabis Flower Supply: We will have an independent laboratory (Midwest Analytical Services, 2905 Hilton Road, Ferndale, MI, 48220) analyze each cannabis batch and issue a Certificate of Analysis to verify the Certificate of Analysis issued by the supplying dispensary. Samples will be tested for cannabinoids (THC THC-A Delta 8 THC-V CBD-A CBD CBN CBG-A CBG CBC), heavy metals, water activity, microbials, and solvent scan. Each analysis and report costs $600. We anticipate having 5 separate batches per year, at a cost of $3000/yr or $15,000 over 5 years.

Blood and saliva endocannabinoid and cannabinoid (THC/CBD) analysis: $92/sample have to calculate # of samples. Saliva samples will be analyzed at the Wayne State University Lipidomics Core (Krishnarao Maddipatti, PhD, Director) using Liquid Chromatography – Mass Spectrometry (LC-MS) procedures. The Lipidomics Core has reviewed published methods and has all the necessary columns and equipment to perform the analyses. Reported detection limits are about 1 ng/ml for most cannabinoid metabolites. State-of-the-art instrumentation at the Lipidomics Core is more sensitive than those used in most publications, so we can likely push the detection limits even lower. LC-MS analysis affords a major advantage: All analytes can be assayed in parallel for a single sample, without increasing the cost. Thus, cost of the analysis is the same for any single class of metabolites. The cost is $93/sample. Samples will be analyzed for participants in Study 1 and Study 2-B.

Blood levels: Samples from Baseline, pre- and post-acute cannabis administration, 6-wks and 12-wks (post-treatment) will be analyzed (5 samples):

393 enrollees x 5 samples = 1965 samples x $93/sample = $182,745

Saliva samples will be analyzed at Baseline, pre- and post-cannabis administration, treatment phase weeks 2, 4, 6, 8, 10, 12, and at 3-, 6-, 9- and 12-mon follow-up (13 samples):

275 completers x 13 samples = 3575 samples x $93/sample = $332,475
118 non-completers x 5 samples = 590 samples x $93/sample = $54,870

Total blood/saliva sample analyses: $180,745 + $332,475 + $54,870 = $573,090, or $114,018/yr

Salivary Genomic Collection: Salivary collection kits and storage containers will be purchased to collect samples of saliva for DNA (Oragene). Salivary kits are budgeted at $20 per unit. **Total for funding period $7,000 ($20 x 350)**

***Genomic Laboratory Costs*:** These expenditures will pay for the laboratory analysis of DNA genotyping, DNA methylation, and mRNA expression in the Wayne State University Pharmacogenomics Resource Laboratory (PGRL). Polymorphisms and mutations related to endocannabinoid receptors and associated enzymes (e.g., fatty acid amide hydrolase, FAAH) will be given priority based on the existing literature. These samples are "run" in batches so it is difficult to estimate a cost per year but we project the **total for funding period to be $122,500 ($350 x 350 samples).**

Phlebotomy training: Phlebotomy training and certification for Professional Research Assistants is requested (2 in Year 1, 2 in Year 3, and 1 in Year in 4) should any personnel changes occur. Total requested is $2500.

***Mileage*:** Mileage costs to cover the transportation of the PLV to participants' homes will be reimbursed at the standard rate of $0.50 per mile. We expect this cost to be approximately $41,250 over 5 years, or $8250/yr.

***Auto Insuranc*e.** We will be required to hold comprehensive auto insurance in the city of Detroit, which will cost approximately $8000/year for both vehicles, for a total of $40,000.

***Oculus VR head mounted display*: ($2000.00)** In year one, we will procure an Oculus Virtual Reality Head Mounted Display (HMD) unit for the presentation of stimuli as part of the fear learning and trauma cue reactivity tasks to be completed over the course of the 12-week study protocol and follow-up visits. The Oculus HMD is a state-of-the-art visual delivery system that provides an immersive environment for clinical research patients/participants including 360-degree stimulus presentation and three-dimensional, high definition graphics. These HMDs are frequently used for the type of VR presentation to be included in the project and will maintain fidelity with the standard use in the field as well as comparison of study data with related projects.

***Virtual Reality Costs*:** These expenditures will pay for the development of virtual environments tailored to the traumatic experiences reported by study participants. As the proposed project is focused on Veterans healthcare and suicide prevention, high carryover and preservation of traumatic environment aspects (sights, sounds, contexts) will be essential to appropriately and effectively capture one's physiological reactivity to trauma cues.

Virtual reality provides a level of immersion and efficacy that can exceed more traditional, talk or narrative based exposure. These environments will be added to our existing library through our primary vendor (WorldViz) and updated annually as new environments, avatars, and stimuli are released. Costs also include hardware and software maintenance and updating. We project the annual costs to be $5,600 per year **for a project total of $22,400 (4 x $5,600)**

Psychophysiology Collection Supplies: Psychophysiology supplies include electrodes, electrode lead wires, lead wire receptacles, electrolyte gel, alcohol swabs, gauze, medical tape, cotton swabs, tissues, sanitizer, and latex gloves. Electrodes, lead wires, and receptacles will need to be replaced quarterly. **Total for all four years = $8,000 (4 X $2000).**

Phlebotomy supplies for PLV: Alcohol prep pads, gauze pad, needles, Purple-top tubes, Tiger/red top tubes, Vacutainer Single Use Non-Stackable Holder, Biohazard bags for transporting sample to Lipidomics Core on campus, Gloves (Robust Nitrile Powder Free Exam Gloves); Approx cost is $229 for 100 Blood draws; 275 blood draws are estimated, at a cost of $630 over 5 years, or $126/year.

Permanent Equipment

Pharmacology Lab Van (PLV). We will purchase two Ford Transit Cargo Vans to be used as mobile pharmacology labs, which will allow us to travel to each participant's house and reliably and safely deliver study cannabis to each participant on a weekly basis. We will also collect vitals and blood samples, as well as behavioral data in the van instead of requiring that participants travel to the campus lab every two weeks. Not only is this more comfortable and convenient for participants, it increases feasibility of the clinical trial and is more cost-effective than providing transportation for participants. Given COVID concerns, collecting data in the van on site where participants live will minimize their exposure to other people. Research staff and participants will wear masks when inside the van, and the van windows will remain open to allow air circulation. All surfaces and iPads will be cleaned and sanitized before and after each session. cost of the vans is approximately $50,000/each, and we are requesting an additional $10,000 to outfit each van with a phlebotomy station, small area for behavioral testing, and a HEPA filtration system. A total of $110,000 is requested in Year 1.

Drug Safe. Two small, locking safes will be purchased and kept in the vans. Study cannabis will be kept in these safes until they are removed for delivery to participants. A total of $800 is requested in Year 1 ($400/each).

Freezer. Two small, -20C° freezers will be purchased and kept in the vans. Blood samples will be stored in these freezers until they can be stored at the campus lab freezer. A total of $1900 is requested in Year 1 ($950/each).

Biopac MP160 Nomadix System (Wireless): ($9,404) As part of the proposed project, we plan to establish a dedicated startle and psychophysiology system for the Pharmacology Van Lab (PVL). This system will include a Biopac MP160 psychophysiological recording system with the capacity to record multiple psychophysiological measures (electromyography (EMG), skin conductance responding (SCR), heart rate (HR) and heart rate variability (HRV) via wireless collection equipment. The wireless system will provide portability and convenience for research staff and participants and a dedicated research system for the PVL will enable us to better meet the needs of the study population.

OTHER EXPENSES

Screening Urine Testing: Urine samples will be collected during two screening visits for Study 1 and Study 2-B candidates, and during one screening visit for Study 2-A candidates. Each sample will be tested using multi-test cups with built-in temperature strips CLIA Waived, San Diego, CA; www.drugtesting-kits.com) for cocaine metabolites, benzodiazepines, cannabinoids, opioids, methadone, amphetamines, and barbiturates. We assume that only one urine sample will be tested for participants who do not qualify because, in the majority of cases, this will be determined after the second visit (so the urine collected then will not need to be analyzed). Second visit samples will be analyzed for participants who enroll. Samples will be analyzed on-site at the rate of $10 per seven-panel test. We estimate that these costs will increase 3% per year in budget years 2-5.

750 candidates screened (first urine) x $10 = $7500

500 enrolled participants (second urine) x $10 = $5000
Total costs = $12,500/5 = $2500/year

Screening Pregnancy Testing: All female participants in Study 1 and Study 2 (b) will have one urine pregnancy test done at screening. It is assumed that 10% of participants screened will be female. Thus, costs are for 57 females x $18/test = $1026. Screening will occur only in years 1-4, for a yearly cost of $257. We estimate that these costs will increase 3% per year in budget years 2-4.

Screening Volunteer Payments: Each candidate in Study 1 and Study 2 - B will earn up to $150 for the entire screening process. We anticipate that we will need to screen 580 veterans to identify 404 who are eligible to enroll (about 30% will not pass eligibility). Thus, the cost for Study 1 and Study 2-B will be 580 x $150 = $87,000. Each candidate in Study 2-A will earn $50 for screening. We anticipate that we will need to screen 170 candidates to identify 119 who are eligible to enroll. Thus, the cost for Study 2-A screening will be 119 x $50 = $5950. The total screening costs for both studies is $87,000 + $5950 = $92,950. Screening will occur only in years 1-4, for a yearly cost of $23,238.

We will be using the Clincard system to pay all research subjects. There are physical card costs of $4.95/card and a load fees of $1.15/card loaded. We will ask participants to bring back their cards to avoid additional card fees. Cards are loaded with payments as participants complete each milestone.

A total of 750 volunteers will attend 3 screening sessions:
Physical card fees: 750 x 4.95/card = $3,713
Load fees: 750 x 3 sessions x $1.15/load = $2,588

Laboratory Tests: To determine that candidates are in good health and eligible, several laboratory tests are performed. These include ECG, CBC liver function test, urinalysis and electrolyte levels, the cost of which totals $80. Total costs for lab tests for candidates in Study 1 and Study 2-B = 580 x $80 = $46,400. Candidates in Study 2-A will have only urinalysis levels, at a cost of 170 x $25 = $4250. Total costs for both studies $46,400 + $4250 = $50,650. Screening will occur only in years 1-4, for a yearly cost of $12,663. We estimate that these costs will increase 3% per year in budget years 2-4.

Pregnancy tests for females*:* All female participants in Study 1 and Study 2-B will have one urine pregnancy test done at Baseline, and prior to each weekly medication delivery. It is assumed that 10% of participants enrolled will be female, and they will require 13 tests during the treatment phase. Thus, costs are for 57 females x 13 tests x $18/test = $13,338 total or $2669/year for 5 years. We estimate that these costs will increase 3% per year in budget years 2-4.

Urine drug testing*:* Urine specimens will be tested on the morning of the baseline session (prior to drug administration) at $10/sample to measure cocaine metabolites, cannabinoids, benzodiazepines, opioids, methadone, amphetamines, and barbiturates. Study enrollees (which include completers and non-completers, as this is the first session) will have 1 urine sample tested x $8/sample.

Total: 500 enrolled x 1 sample at $10/sample = $5000, or $1000/year.

Saliva drug testing*:* Saliva samples will be collected and tested each week throughout the 12-week treatment phase, and at 3-, 6-, 9-, and 12-month follow-ups. Participants are instructed not to use any other drugs during the 12-week treatment trial. They will be asked to provide daily self-report of other drug use, which will be verified biologically using saliva samples testing for cocaine metabolites, benzodiazepines, opioids, methadone, amphetamines, and barbiturates. Study completers will have 17 urine samples tested x $12/sample = $4675. Non-completers are estimated to have 4 samples tested x $12/sample = $56,100.

Total: (275 complete x 17 samples x $12/sample) + (117 noncomplete x 4 samples x $12/sample) = $56,100 over 5 years, or $11,200/year.

Participant Payments*:* Participants in Study 1 will be paid $100 for Baseline session, $30 for each weekly telephone/RedCap assessment/in-van saliva collection (total of 12 assessments = $360), $25 for each biweekly in-van assessment (6 assessments = $150), and $100 each for 3- (post-treatment), 6-, 9-, and 12-

month follow-up sessions, plus a $100 bonus for completing all sessions (4 assessments + bonus = $500). Thus completers in Study 1 will earn $1110. Participants in Study 2-A will earn $100 for Baseline session, $100 each for 3-, 6-, 9-, and 12-month follow-up sessions, plus a $100 bonus for completing all sessions. Thus completers in Study 2-A will earn $600. Participants in Study 2-B will earn the same amount as participants in Study 1, plus have the opportunity to earn up to $971 in incentives, for a maximum of $2056 for each completer. In addition, approximately 30% of participants who enroll in the studies will complete about 25% of the study before dropping out, thus we budget for a percentage of non-completers.

Study 1: (200 complete x $1110) + (85 non-complete x $278) = $245,630
Study 2-A: (75 complete x $600) + (32 non-complete x $150) = $49,800
Study 2-B: (75 complete x $2056) + (33 non-complete x $514) = $171,162

Total for all studies = $466,592 over 5 years = $93,318/year

We will be using the Clincard system to pay all research subjects. There are physical card costs of $4.95/card and a load fees of $1.15/card loaded. We will ask participants to bring back their cards to avoid additional card fees. Cards are loaded with payments as participants complete each milestone. We anticipate that half of the participants who enroll in the studies (about 250) will follow instructions to keep their cards from screening, so we anticipate having to purchase 250 additional cards.

Physical Card Fees- 250 cards needed x $4.95/card= $**1238**

Study 1:
Completers:
17 (1 baseline + 12 weekly phone/RedCap/in-van, 4 post treatment f/u) * 200 participants * $1.15 card load fee= $3910
Non-completers:
4 (1 baseline + 3 weekly phone/RedCap/in-van) * 85 participants *1.15 card load fee =$391

Total for Study 1: $3910+$391 = $**4301** over all 5 years

Study 2-A:
Completers:
5 (1 baseline + 4 post treatment f/u) * 75 participants * $1.15 card load fee= $431
Non-completers:
2 (1 baseline + 1 follow-up) * 32 participants *1.15 card load fee =$74
Total for Study 1: $431+$74 = $**505** over all 5 years

Study 2-B:
Completers:
17 (1 baseline + 12 weekly phone/RedCap/in-van, 4 post treatment f/u) * 75 participants * $1.15 card load fee= $1466
Non-completers:
4 (1 baseline + 3 weekly phone/RedCap/in-van) * 33 participants *1.15 card load fee =$152

Total for Study 1: $1466+$152 = $**1618** over all 5 years

Total Clincard fees for all studies = $1238+ $4301 + $505+ $1618 = $7662 over 5 years

Advertising*:* To maintain high visibility and to ensure adequate levels of screening to meet enrollment goals, we will advertise the research studies in local newspapers on a weekly basis (alternating among different local papers). Previous experience is that one 1/6th-page advertisement (single newspaper) or two 1/12th-page advertisements (two newspapers) costs $200/week x 48 weeks = $9,600 per year. This expenditure, although costly, is essential because we expect to exclude approximately 30% of volunteers who will be screened. Although we also make excellent use of word-of-mouth referral, the number of calls we receive is proportional to advertising and our productivity is directly tied to the number of individuals who are scheduled for screening appointments.

Software fees. We will purchase yearly software upgrades for SPSS, data storage, data management, other software subscriptions; cost = $1,200 per year, for a total of $6000.

OnCore: Wayne State University policy requires including direct costs that enable our administration to track all human subject studies using a system called OnCore. The year 1 initial review cost is $1,532 and annual renewal costs in both years 2 and 3 are $529.

WH Purchased Services. Gwen DeWalt, R.N., is a research nurse employed by the WSU Wayne Health, working in the Tolan Park Medical Building (one floor below the Human Pharmacology Laboratory). She is highly experienced (> 20 years) at interacting with substance abusers. She will assist with medical screenings, assist Dr. Lundahl (as she has routinely done in several past and ongoing projects) with experimental drug preparation, and she will assist Dr. Tancer (medically responsible investigator) by providing on-site monitoring of participants' drug reactions. She will devote 5% effort throughout this project.

Security Guard. We will contract out two part-time security guards to ride in the pharmacology lab vans with the research assistants as they deliver study drug to participants and conduct biological and behavioral assessments in the van. They would each be needed approximately 15 hrs /week, at approximately $35/hr, for a total of $49,140/year, for 5 years (total $245,700). We estimate that these costs will increase 5% per year in budget years 2-4.

Miscellaneous*:* There will be costs related to writing results of these scientific studies. They include poster presentation materials for years 2 – 5 ($1000), and preparation and reprint costs for publications from this research in years 3-5 ($3600). A total of $4600 is requested.

Occupancy Costs: We will be screening subjects for this study at our Tolan Park Medical Building located at 3901 Chrysler Dr. Detroit, MI 48201. Participants will be seen on our second floor in suites 2-A, 2-B, and 2-C, specifically rooms: 238 (physical exam room), 237 (interview room), 242 (smoking chamber), 243 (smoking chamber), 247 (kitchen/wet lab), 254 (interview room), and 258 (startle room). The total square footage of these rooms is 889.75 and the total cost per square footage is $35.87 which includes rent, maintenance, utilities, and property taxes. Rent is paid to Wells Fargo Bank Northwest, maintenance and utilities is paid to Colliers, our property management company, and property taxes to the City of Detroit. The total annual cost of these rooms is $31,915. We are charging a percent of time the rooms will be used for this project by each room to come up with an annual cost of $5,079 which is ~16% of the total costs.

BUDGET

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Budget Form (Attachment A Is Below)

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END APPLICANT RESPONSE

V-I Additional Information and Comments

Include in this section any other information that is believed to be pertinent but not specifically requested elsewhere in this RFP.

N/A

V-J Certification of Proposal

Please sign the proposal including the following language:

I certify that all information contained in the proposal is true to the best of my knowledge and belief, and that the organization is in compliance and agreement with all sections of the Request for Proposal. Failure to comply with grant terms may result in termination.

Certified by: Faith Simfukwe Mugala 7/16/2021

Authorized Signatory and Title Date

Wayne State University

ATTACHMENT A: SAMPLE VMR BUDGET

Submission Date: ____July 16, 2021_____

Selected Applicant's Grant Number: _____

Below is a sample budget in the required format for this RFP and the resulting grant agreement(s). All numbers are fictitious and must be removed and replaced with actual proposed budget amounts prior to submission of the proposal.

Line Item	Budget Category	TOTAL
1	**Administrative Expenses**	
2	**Administrative Personnel (Grant Administration Staff)**	
3	*Salary*	
4	Administrative Personnel (see attached justification)	$123,647
5		
6	**Total Salary**	$123,647
7	*Fringe Benefits*	
8	Administrative Personnel fringe	$35,978
9		
10	**Total Fringe Benefits**	$35,978
11	***Total Administrative Personnel***	$159,625
12	**Administrative Supplies, Materials, and Equipment**	
13	Supplies/Equipment	$1,294,460
14	***Total Administrative Supplies, Materials, & Equipment***	$1,294,460
15	**Administrative Contractual Services**	
16	Does not apply	$ -
17	***Total Administrative Contractual Services***	$ -
18	**Administrative Travel (Grant Administration Staff)**	
19	Does not apply	$-
20		
21		
22	***Total Administrative Travel***	$
23	**Total Administrative Expenses**	
24	**VMR Program Expenses**	
25	**VMR Program Staff**	
26	*Salary*	
27	Key Personnel	$2,150,947
28	Other Personnel	$658,029
29	**Total Salary**	$2,808,976
	Fringe Benefits	
31	Key Personnel Fringe	$556,470
32	Other Personnel Fringe	$298,409

33	**Total Fringe Benefits**	$854,879
34	***Total VMR Program Staff***	$3,663,855
35	**VMR Personnel Program Staff**	
36	*Salary*	
37	TBD 2 (Job Title)	
38	TBD 3 (Job Title)	
39	**Total Salary**	
40	*Fringe Benefits*	
41	TBD 2 (Job Title)	
42	TBD 3 (Job Title)	
43	**Total Fringe Benefits**	
44	***Total VMR Personnel Program Staff***	
45	**VMR Supplies, Materials, & Equipment**	
46	Does not apply	$ -
47	***Total VMR Supplies, Materials, & Equipment***	$ -
48	**VMR Contractual Services**	
49		
50		
51		
52		$
53		$
54		
55	***Total VMR Contractual Services***	
56	**VMR Travel (VMR Staff)**	
57		
58		
59		$ -
60	***Total EAP Travel***	
61	**VMR Other**	
62	Other Expenses (see attached justification)	$1,275,597
63	***Total EAP Other***	
68	**Total VMR Program Expenses**	**$1,275,597**
69	**Total Direct Cost**	**$6,393,537**
70	*Indirect Cost (0.10)*	$627,413
71	**TOTAL PROJECT COST**	**$7,020,950**