State of Michigan
Department of Licensing and Regulatory Affairs
Marijuana Regulatory Agency

VETERAN MARIJUANA RESEARCH (VMR) GRANT PROGRAM

2022

REQUEST FOR PROPOSALS

VETERAN MARIJUANA RESEARCH (VMR) GRANT

RESPONSE DOCUMENT

ESTIMATED TIMELINE	
Issue Date	April 1, 2022
Inquiries Due	April 15, 2022
Inquiries Response Posted	May 1, 2022
Proposals Due	June 1, 2022
Anticipated Start Date	July 30, 2022

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

Regents of the University of Michigan
3003 S. State Street, SPC 1274
Ann Arbor, MI 48109
P: 734-936-1361
F: 734-764-8510
EIN: 38-6006309

The organization is located 100.0% 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

Daniela Marchelletta
Sr. Project Representative, ORSP
P: 764-936-1296
F: 734-764-8510
E: dcmarch@umich.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

EXECUTIVE SUMMARY

In 2018, the voters of the State of Michigan passed the Michigan Regulation and Taxation of Marihuana Act. A provision of this law provides funding for research on the effectiveness of marijuana (hereafter, cannabis) for treating "*medical conditions of United States Armed Services Veterans and preventing Veteran suicide*". More than 6,400 military Veterans committed suicide in 2018, and chronic, non-cancer pain (henceforth, chronic pain) conditions such as back pain and migraine are associated with higher risks of dying by suicide among Veterans. Nearly a quarter of Veterans have chronic pain and many use cannabis for chronic pain management, due in part to the limited effectiveness and substantial harm (including lethal overdose) associated with some conventional pain medications, such as opioids. Unfortunately, despite chronic pain being the most common reason for medical cannabis use in the US, therapeutic cannabis research in this area is severely impeded by cannabis's Schedule I status under the Controlled Substances Act, leading to limited clinical trial literature to inform Veterans and clinicians about how to properly use medical cannabis products. We believe that the Request for Proposals put forth by the Marijuana Regulatory Agency is a critical step towards understanding how cannabis products could help improve symptom management among Veterans with chronic pain and thus contribute to the ultimate goal of reducing suicide among Veterans.

Our investigative team is led by researchers from the University of Michigan Anesthesiology department, which has been ranked #1 nationally in NIH funding among anesthesiology departments for seven consecutive years as of 2021. Our team is led by Drs. Kevin Boehnke, Amy Bohnert, and Rachel Bergmans, who are nationally and internationally recognized as experts in cannabis, Veteran health issues including pain and suicidality, community-based participatory research, clinical trials, and chronic pain. In addition, our team includes numerous experienced researchers with existing collaborative relationships who have appointments throughout Michigan Medicine (Anesthesiology, Physical Medicine and Rehabilitation, Psychiatry), the School of Public Health (Biostatistics), and the Veteran's Affairs Ann Arbor Healthcare System, leveraging further expertise in conducting impactful patient-centric trials and applying principles of community-based participatory research among Veterans. Our team is supported by the strong research and fiduciary infrastructure at the University of Michigan Office of Research and within the Anesthesiology Department, which has a proven track record of: 1) obtaining and managing large intramural and extramural grants; 2) conducting ethical human subjects research with oversight of the University of Michigan Institutional Review Board (IRB) and federal regulatory bodies such as the Food and Drug Administration (FDA) and Drug Enforcement Administration (DEA); 3) publishing highly impactful research in top medical journals, and; 4) disseminating results that change clinical practice, demonstrated by the Michigan Opioid Prescribing Engagement Network (Michigan OPEN), which has published and implemented clinical guidelines for opioid prescribing throughout the state.

With the support of this collaborative and the University of Michigan, we propose two randomized controlled trials (RCTs) to investigate the effectiveness of cannabis-based therapies to treat Veterans with chronic pain, towards the goal of reducing Veteran suicide risk. Both trials will obtain appropriate regulatory approval from the FDA, DEA, and IRB. Both studies were developed with input from a Veteran advisory panel and will employ community-engaged approaches through our existing, NIH-funded Health Equity Core to partner with Veteran groups and develop a Community Advisory Board to help oversee the study, aid with recruitment, investigate barriers to participation and help overcome them, and disseminate results.

In **study 1**, we will conduct an RCT to investigate whether CBD is effective in managing pain symptoms among n=455 Veterans with chronic pain. CBD is a strong candidate for a first-line cannabis-based analgesic as it is very well-tolerated across many medical conditions, is non-intoxicating and has no abuse potential, and has shown promising anxiolytic, anti-inflammatory, sleep-enhancing and analgesic effects in preclinical research and small clinical trials. Our approach will provide much-needed clinical data to understand whether Veterans with chronic pain respond positively to CBD and pain characteristics that underly clinical response – critically important questions that could immediately and positively impact Veteran health.

In **study 2**, we will conduct an RCT to investigate whether evidence-based, tailored guidance on how to appropriately use available cannabis products affects chronic pain symptoms among n=422 Veterans with chronic pain. We and others have shown that use patterns are out of line with what available evidence and expert guidance suggests might be

safest and most effective, potentially leading to unwanted side effects that may reduce benefit. Participants will work with a trained cannabis coach to learn how to methodically use cannabis for pain management. This intervention will provide personalized, scientifically guided structure to the current landscape in which people generally self-direct their cannabis use without physician oversight or guidance.

Impact on Veteran Health: Designed with input from Veterans in Michigan, our proposal investigates two critically important questions that may improve Veteran health: 1) Does CBD reduce chronic pain symptoms relative to placebo, and does this lead to a signal suggesting that suicide risk may be lower? 2) Does scientifically-informed cannabis use guidance improve chronic pain symptoms relative to unguided use, and thus potentially reduce the risk of suicide? Our studies would overcome many limitations of existing RCTs (e.g., not using available products) and provide actionable data that can positively shape public health outcomes and policy for Veterans by: 1) offering clinicians much-needed empirical data on CBD and a useful template for guiding Veterans and other patients who use cannabis for chronic pain, which is special importance given the pressing need for alternative, lower risk pain medications; 2) leveraging the collective voices of our Community Advisory Board to effectively disseminate results to varied audiences, including Veterans, healthcare providers, the cannabis industry, and policymakers; 3) improving outcomes for Veterans and others using cannabis for chronic pain. If funded, this proposal would lay the groundwork not only for the proposed studies but also for our collaborative to conduct many future RCTs that investigate the therapeutic potential of cannabis products among Veterans in Michigan. Our findings will catalyze the critical work of minimizing harm and maximizing benefit from widely available cannabis products for chronic pain management, which may also ultimately lower incidence of Veteran Suicide.

Obstacles to coordinating and managing clinical trial research:
We have identified several obstacles to appropriately conducting clinical trials with medical cannabis products that we have encountered and plan to address through our proposed program. These include:

(1) The 2017 National Academies of Sciences, Engineering, and Medicine report on the Health Effects of Cannabis and Cannabinoids concluded, "There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabis and cannabinoid research".[1] Our investigative team has encountered and overcome these barriers in our NIH-funded research studies over the past 5 years, in which we have obtained FDA, NIH, DEA, and IRB approvals to investigate therapeutic effects of CBD and THC in clinical trials conducted among individuals with knee osteoarthritis and multiple sclerosis. We are purchasing our descheduled CBD study drug from a company whose products are already being use in active FDA-approved clinical trials, easing regulatory burden using a product that is already available to consumers over-the-counter.

(2) Funding to conduct pragmatic, community-engaged research with cannabinoid products has been extremely limited. As such, while there is a considerable amount of preclinical research investigating mechanistic effects of cannabis and cannabinoids, large-scale studies using commercially available medical cannabis products are largely non-existent. If our project is selected, the Veteran Marijuana Research Program will support the first set of randomized, controlled trials examining the efficacy of commercially available CBD and cannabis products on chronic pain and suicidality among US armed forces Veterans.

(3) Research participation by Veterans in clinical research studies, especially among Veterans living in low-income and marginalized communities, is often impeded by structural and institutional barriers. Our investigative team has considerable expertise engaging Veterans across the state of Michigan in clinical trials, including behavioral interventions for pain management. Further, our home department of Anesthesiology at the University of Michigan has obtained extramural NIH funding and dedicated significant resources to developing infrastructure to conduct community-engaged pain research. We will employ and advance this infrastructure to build strong community engagement and partnership with Veterans groups to enhance recruitment, reduce barriers to participation, and improve retention among Veteran communities typically under-represented in research studies.

(4) While many Veterans use cannabinoids to treat chronic pain symptoms, many healthcare providers and the Department of Veteran Affairs (VA) do not support use of cannabinoid therapies nor trials of cannabinoid products or educational interventions meant to optimize therapeutic cannabis use. Our

proposed studies would thus fill an unmet need for research on cannabinoid therapies to manage chronic pain symptoms. Further, by using descheduled CBD products as our study medication in Study 1, we will avoid concerns associated with use of Schedule I drugs among Veterans receiving VA benefits.

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

Management Summary

(1) Management procedures

Established in 1817, the University of Michigan (U-M) is one of the world's largest public universities, and it has long been considered one of the major research institutions in the United States. It is an internationally recognized research university with a broad spectrum of expertise in biomedical research. Research is conducted within the nineteen academic schools and colleges, as well as within several large-scale research institutes, which emphasize interdisciplinary work. Teaching and research often cross traditional Departmental and School boundaries, especially because of the University's impressive set of interdisciplinary research centers and institutes. U-M's dedicated departmental and institutional staff ensure appropriate disbursement and management of funds, regulatory issues, and research conduct, with a long history of successfully managing large grants and awards from the Michigan state government, foundations, industry, and government agencies.

The management procedures will: 1) aligns the program with goals of the research and program partners; 2) ensure that project tasks and deliverables are achieved; 3) monitors project performance; and 4) closes out the project. The most efficient and cost-effective way to manage a program of this size is to work within a foundation of robust project management practices. The Leadership Team and Program Manager will develop the master project management plan and track progress. Other core directors are responsible for developing functional project plans in support of the overall master plan. Regular meetings will be held to review progress and the status of deliverables.

Administration will be supported by a cadre of highly capable faculty and staff that already successfully administer several large center and other grants and state contracts. Overarching programmatic administration will be coordinated by a lead project manager, Laura Thomas, who will work with Amy Harms, our grants administrator in Anesthesiology. Ms. Harms will be principally responsible for the fiscal administration of the projects and working with both institutional and sponsor organizations to establish necessary contracts, managing budgets, procurement, and coordinating any intellectual property or materials transfer matters that may arise over the course of the program period.

Key Management Protocols

Formulation of a monitoring and reporting plan that documents the necessary information required to effectively manage the data from study start-up to delivery of study outcome analysis is required. Here we describe how the Leadership Team will oversee monitoring and reporting.

Leadership Meetings. The Leadership Team, Team Leads, and key staff will have a weekly conference call to discuss progress of the project, including recruitment, retention, and any other challenges.

Document and Record Control. Documents and records will be reviewed by the leads according to role function. Any changes to Standard Operating Procedures (SOPs) due to modifications for this project will require a formal approval by the Co-PIs. Records will be retained for all protocol data, quarterly reviews, and approvals. Study data will be entered in the secure research site portal.

Tracking. In our prior studies, we developed participant recruitment electronic "dashboards" that contain tracking information for each individual's progress through recruitment and study protocols. The dashboard generates automated weekly reports of the participant recruitment activities, randomization, and survey completion.

Hiring and Supervision of Staff. We will engage Michigan Medicine Human Resources to post and fill positions on the research team. Staff will have annual performance appraisals and be encouraged to develop performance goals using the SMART (Specific, Measurable, Achievable, Relevant, Time bound) process. Policies are described in detail here: https://hr.medicine.umich.edu/pay-benefits/employment-policies

Training Program. All key personnel will be required to complete a training program at the start of the study to align the team to the overall goal and task deliverables. Tests may include their proficiency to follow internal documented procedures. Also, we will ensure that all personnel involved in handling research subjects are trained according to University of Michigan human subjects research standard practices. Training will be documented, verified for its effectiveness, and reviewed annually. If needed, we will provide repeat and continued education training. Training specific to the cannabis coaching will be overseen by the directors of the Cannabis Coaching and Manualization Core.

Quality Control Inspection. Monitoring and quality control will be overseen by the director of the Data Collection, Management, and Privacy Core. These inspection requirements and check-points will be tailored to the methods by which the data will be handled, processed, stored and transferred. The inspection process includes confirmation of data accuracy and completeness.

(2) Quality Control Measures, compliance, and eligibility determination

The following protocols will be undertaken to ensure high quality control procedures are used throughout the conduct of the study.

Hiring

We will follow all University of Michigan policies to ensure that well-qualified candidates are selected, using a fair and rigorous process.

Training

Staff and investigators associated with the project will undergo appropriate annual training for project-specific procedures (see details below). In addition, all staff and investigators have received appropriate training per institutional guidelines, including training on Humans Subjects research, HIPAA, and Good Clinical Practices.

Adverse Reporting

All adverse event reporting will be done in accordance with institutional guidelines per IRBMED.

Data Monitoring Plan

Interim monitoring will be conducted monthly by the study coordinator and/or investigators

1. Observe enrollment calls and assess staff adherence to study protocol and scripts
2. Random "spot checks" of participants' data within the study participant tracking database and the MyDataHelps data collection application to ensure data completion and accuracy. Monitor data quality through routine review of submitted data to identify and follow-up on missing data.

a. Consent form completion
b. Survey responses
c. Fitbit Data: heart rate, physical activity, geospatial location, sleep

3. Review risk assessments, AEs, and subject withdrawals to verify proper reporting and measures were completed.
4. Review protocol deviations to verify completion of corrective action and to verify proper recording and reporting.
5. Submission and tracking of protocol amendments. Documentation of IRB approvals.
6. Study team will review in team meetings the weekly "participant retention and activity engagement" reports generated from the study dashboard

Compliance

IRB and ethics

The study will be reviewed and approved by the Institutional Review Board (IRBMED, University of Michigan, Ann Arbor, MI). Before implementing this study, the protocol, the proposed informed consent form and other information to be provided to subjects, will be reviewed by a properly constituted Institutional Review Board (IRB). Any amendments to the protocol must be reviewed and approved by IRBMED. This study will be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described below:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.

2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

3. Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects)

(3) Fiscal Control

The University of Michigan Office of Research (UMOR) financial management and oversight activities align with the requirements laid out in the University of Michigan Statement on Stewardship and the Fiscal Responsibilities Standard Practice Guide (SPG) 500.1. Within UMOR, financial management and oversight is viewed as a shared responsibility between the Office of the Vice President of Research and its reporting departments, programs, and initiatives, which comprise the entirety of UMOR.

- University of Michigan uses Oracle's PeopleSoft (M-Pathways) which integrates financials and physical resources, human resource management and student administration.
- Sponsored Programs manages the financial post-award activities of the University of Michigan's research enterprise and other sponsored activities to ensure compliance with applicable federal, state, and local laws as well as sponsor regulations.
- Sponsored funds (grants) are accounted for individually and assigned their own chartfields, the building blocks of the University of Michigan financial reporting structure, whose elements provide a common framework for internal and external financial reporting and analysis.
- An external audit of the consolidated financial statements is conducted annually. The current independent

auditing firm is PriceWaterhouseCoopers. University of Michigan Audit Services conducts an annual risk assessment and develops an audit plan for the fiscal year based on Input from more than 150 university leaders, across all areas of the university, during annual risk assessment meetings; benchmarking with peer institutions to understand their significant and emerging risks; and alignment with the university's enterprise strategic risks. Copies of the FY2020 Audited Financial Statement and FY20 Report on Federal Awards in Accordance with the Uniform Guidance are included under separate cover, as specified in Section V-F.

(4) Data security plan

All data collected on study participants will be obtained and managed specifically for research purposes and will follow best practices in data collection and protections. The types of data to be collected in aggregate across projects include medical status and history; self-report questionnaires that assess physical and psychological symptoms and life functioning; data from electronic monitors. The data file containing the linkage of subject identity to study ID number and any group assignments will be maintained using a limited access, password-protected database on a password-protected desktop maintained by Michigan Medicine's Health Information Technology and Services (HITS), a unit of the University of Michigan. All other data will be contained in datasets without identifying information. Study personnel and appropriate oversight organizations (e.g., IRBMED) will have access to the study databases when necessary. All assessment forms will be collected either via a web-enabled Electronic Data Capture System (EDC). The EDC website will be available via secure access and security will be implemented using firewalls, unique user IDs and passwords, secure socket level (SSL) encryption, trusted third party certificates, and standard operating system maintenance, backups and patches. Any paper forms will be kept in a secure, locked filing cabinet located at the University of Michigan's Chronic Pain and Fatigue Research Center (CPFRC) in Ann Arbor, MI, USA. The Michigan EDC system for this study will be a protected, industry-leading survey system, MyDataHelps, which follow all regulatory requirements regarding subject confidentiality and human subject safety and backs up all data every 24 hours. All MyDataHelps data is stored on secure, protected servers, and a copy is sent via a secure file transfer mechanism across the UM firewall to be stored on HITS servers at UM. A study team member will serve as the database manager and, along with the PIs will be responsible for the development of electronic case report forms, data entry modules, the study websites, data quality control, and beta testing of all forms before placing the study into production.

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.
8) Publish the results of the clinical trials.

BEGIN APPLICANT RESPONSE

We have provided a summary of the items 1-8 below. In addition, see a detailed description of the proposed project in the work plan below.

Items 1-3 are covered in detail in the **Work Plan** below as well in our description of our investigative team.

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.

Our group has extensive experience in managing large grants and contracts through both the State of Michigan (Dr. Bohnert) and the National Institutes of Health (Drs. Bohnert and Boehnke) which have resulted in high-quality, impactful science that has shaped both policy and clinical care. Our budget has dedicated **$10,788,901** to covering costs of the proposed project (e.g., study drug, participant compensation), salary for project leads, research staff, and analytical support personnel, and partnerships with Veteran organizations with only **$1,198,764 (9.99% of the total budget requested)** going towards administrative and indirect costs.

5) Work with organizations closely tied to veterans and veterans' programs.

As described below, three members of our research team have appointments in the Ann Arbor Veteran Affairs Healthcare system in Ann Arbor and have existing collaborations with Veterans Affairs Healthcare systems throughout Michigan. Further, our study design was developed in collaboration with the Veteran Engagement Research Council (VREC) at the Ann Arbor VA and we will employ community-based participatory research approaches to prioritize Veteran voices through all stages of the study, as described in the Community Outreach and Recruitment sections of our **Work Plan**.

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.

Please see the attached budget provided by the grant administrator for our department.

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

In the table below, we have outlined the proposed goals of our research activities. In the first stage of the project, we will refine these goals based on feedback from stakeholders and partners and from regulatory reviews (e.g., FDA, DEA, IRB). We will seek all necessary regulatory approval as part of this process. The final, approved protocol will be implemented as soon as possible.

We will use established University of Michigan protocols for financial oversight of the project, as detailed elsewhere. The PIs have continuous access to financial reporting and all charges to the project through the M-Reports software. The University Human Subjects Incentive Program (HSIP) ensures fair, timely, and accurate accounting for payments to participants throughout the state and avoiding the potential for waste or fraud.
We will specify clinical trial analyses via clinicaltrials.gov once all protocols have been approved through the appropriate regulatory bodies. The biostatistics and analytics co-investigators will develop code for analyzing results before data are fully collected, and then analyze results, which will be reviewed by the study team and the Data Safety and Monitoring Board for the study. See additional details in the **Work Plan** below.

Table 1. PROJECT TIMELINE	Project period									
	08/22 - 1/23	02/23 - 07/23	8/23 - 1/24	2/24 - 07/24	8/24 - 1/25	2/25 - 07/25	8/25 - 1/26	08/26 - 01/27	08/26 - 01/27	08/27 - 1/28
Hire/train staff; Develop study materials; Design study database	X	X								
Regulatory requirements: Obtain Investigational new drug license from FDA, IRB approval	X	X								
Operationalize therapy intervention	X	X								
Build community partnerships and awareness	X	X	X	X	X	X	X	X	X	X
Community advisory board meetings	X	X	X	X	X	X	X	X	X	X
Data collection (RCTs)		X	X	X	X	X	X	X	X	
Data entry and cleaning		X	X	X	X	X	X	X	X	X
Dissemination: publications and presentations		X	X	X	X	X	X	X	X	X

8) Publish the results of the clinical trials.

Our research team has considerable experience and an established publication record in: 1) studying naturalistic trends in medicinal and recreational cannabis use for pain[2-13], 2) studying pain and related symptoms[2-6,8-10,13-105] 3) studying risks of suicide among Veterans and in the broad population,[65,69,71,77,90,95,106-125] 4) performing research with Veterans, both in the Veteran's Administration healthcare system and in the community,[65-70,72-78,80-97,99,106-108,110-112,114-156] and 5) collecting rich patient-reported symptoms and passively-collected health data.[65-70,72-78,80-97,99,106-108,110-112,114-157] This experience influences our belief that it is practical and important to study cannabis effects on chronic pain as it increases suicide risk among veterans. We have also had significant success conducting both classic clinical trials and pragmatic designs and publishing our results in high impact journals, including the Journal of the American Medical Association, the New England Journal of Medicine, and JAMA Psychiatry.[21,22,58,66,69,76,78,84,90,94,102,141,145,147,153,158-165] As such, we are confident of our ability to perform the proposed studies.

WORK PLAN

Specific Aims

Background and Rationale

More than 6,400 military Veterans committed suicide in 2018. This high suicide rate is likely due to numerous psychological and physical factors, including chronic, non-cancer pain (henceforth, chronic pain) conditions such as back

pain and migraine, which are associated with higher risks of dying by suicide among Veterans.[65,69,71,90] Chronic pain is common among Veterans (24.7%),[166] up to 12% of Veterans use cannabis,[167] and the prevalence of cannabis use is higher among Veterans with chronic pain than those without (8.8% vs. 6.2%).[166] Chronic pain is by far the most common reason for medical cannabis use in the US, accounting for >60% of all licenses issued in state registries[6] and reflecting the immense societal burden of chronic pain, which affects tens of millions of Americans.[168] Among people using cannabis for chronic pain, many report doing so for harm reduction reasons, i.e., as a substitute or alternative to opioids and other pain medications[2,3,11,105] because of cannabis's favorable safety profile, which includes negligible risk of overdose. Unfortunately, therapeutic cannabis research is severely impeded by cannabis's Schedule I status under the Controlled Substances Act, leading to clinical trial literature that is widely acknowledged as inadequate, with outstanding issues including poor characterization of how cannabis affects different pain phenotype, small sample sizes, short follow up.[169] In this application, we propose two randomized controlled trials (RCTs) that will overcome many limitations of the previous literature and investigate the effectiveness of cannabis-based therapies to treat Veterans with chronic pain, towards the goal of reducing Veteran suicide risk.

Our team at the University of Michigan is well poised to conduct such studies, with three members of our investigative team (Drs. Bohnert, Silveira, and Hosanagar) having salaried appointments in the Ann Arbor Veteran's Affairs Healthcare System and experience working with Veteran populations.[66,75,86,107,111,112,114,117,127,128,142,156,170,171] We have proven ourselves able to overcome federal barriers to cannabis research, as we are conducting large NIH-funded projects for FDA-approved RCTs that elucidate analgesic and sleep impacts of Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) among people with knee arthritis and multiple sclerosis (MS), as well as CBD's opioid-sparing potential following surgery. In these studies, we are investigating how CBD and THC affect people with different chronic pain phenotypes, i.e., with contribution from varied underlying pain mechanisms: nociceptive pain (caused by tissue damage and/or inflammation), neuropathic pain (caused by nerve damage), and nociplastic pain, which is thought to be due to central nervous system (CNS) dysfunction and results in widespread pain and a cluster of co-occurring symptoms such as fatigue and mood issues.[28,29,33,56,58,172] Nociplastic pain occurs across numerous chronic pain diagnoses[173-175], and individuals with nociplastic contributions are less responsive to traditional analgesic interventions (e.g. opioids, surgery) compared to those with nociceptive pain alone.[28,29,56,173] This experience has informed our proposed approach here to examine the potential for variation in cannabis or CBD effectiveness by pain phenotype. We also have experience conducting large, national observational studies of people using cannabis and CBD that have revealed important naturalistic trends, including: 1) chronic pain is the most common reason for cannabis use nationwide, 2) many people substitute cannabis products for opioids and pain medications, and 3) naturalistic use regimens differ substantial from those used in clinical trials.[2-4,6,9-11,13,105,176]

In this application, we propose two pragmatic RCTs that utilize telehealth and app-based approaches to minimize participant burden and be as geographically inclusive as possible within the state of Michigan. Our design is informed by lessons from our past and ongoing RCTs, observational studies, and our experience and partnerships with Veteran populations, making the proposed study highly feasible. In addition, we will employ community-engaged approaches through our existing Chronic Pain and Fatigue Research Center Health Equity Core (housed in the Anesthesiology Department) to partner with Veteran groups and developed our research plans with input from a Veteran advisory panel.

In **study 1**, we will conduct a 12-week long RCT to investigate whether commercially available CBD products are effective in managing pain symptoms among Veterans with chronic pain who have not used cannabis products more than 4 times in the past month. CBD is a strong candidate for a low-risk cannabis-based analgesic as it is very well-tolerated across many medical conditions,[177] is non-intoxicating and has no abuse potential,[178] and has shown promising anxiolytic, anti-inflammatory, sleep-enhancing and analgesic effects in preclinical research and small clinical trials.[179-188] Further, CBD products are not regulated by the Controlled Substances Act, making them more efficient to investigate in clinical trials than Schedule I cannabis products. However, despite considerable naturalistic use of CBD for pain of many etiologies,[10,189] CBD's effects have not yet been rigorously evaluated in large, well-designed clinical trials nor by pain phenotype – two key limitations of the existing literature.[169] Thus, for this study we will keep our inclusion criteria broad to include Veterans with a non-cancer, chronic pain diagnosis because: 1) Chronic pain mechanisms (e.g., nociceptive and nociplastic pain) often co-occur in the same individual or across chronic pain conditions,[172-175,190] so diagnosis often

reflects training biases of the healthcare provider rather than underlying cause, and; 2) we and others have shown that pain phenotype is predictive of clinical response regardless of clinical diagnosis (e.g., in studies of surgical outcomes)[28,29,56,173,191] We expect different pain phenotypes will be differentially responsive to CBD, and will embed simple, survey-based phenotyping measures in the study will allow us to investigate pain characteristics that underly clinical response. In so doing, we will be able to investigate which Veterans with chronic pain may benefit from CBD and why – critically important questions that could immediately impact patient care.

In **study 2**, we will use a 12-week long, wait-list RCT to investigate whether evidence-based, tailored guidance on how to appropriately use available cannabis products affects chronic pain symptoms among 422 Veterans with chronic pain. Participants would be Veterans who have used cannabis in the past 3 months for pain management and wish to optimize their cannabis use to improve treatment outcomes. This study intervention would provide education on how to methodically approach cannabis for pain management, including information on routes of administration (e.g., effect onset and harms), symptom tracking, cannabinoid content, known negative side effects, and cannabinoid doses that have been investigated in the scientific literature and suggested by expert panels of physicians and scientists for managing symptoms of pain.[102,192,193] This intervention has great potential to provide personalized, scientifically-guided structure to the current landscape in which people generally self-direct their cannabis use without physician oversight or guidance. It would also act as a scalable template to inform training of both healthcare providers and dispensary employees who provide care for Veterans and other people with chronic pain. As in study 1, we will recruit Veterans with chronic pain of any etiology. Participants who complete study 1 will also be eligible for study 2 if they wish.

In both studies, our **primary outcome measure** is the patient global impression of change. This outcome aligns with patient-centric approaches to pain studies and with large network studies funded by the National Institutes of Health, such as the Back Pain Consortium Research Program. Our **secondary outcome measures** include assessments of safety, suicidality, pain interference, anxiety, insomnia, post-traumatic stress disorder symptoms, and sleep. We will also monitor activity characteristics continuously, objectively, and unobtrusively using a wearable device (e.g., FitBit). The **specific aims** of this proposal are to:

Specific Aim 1 (Both Studies): Using community-engaged research approaches, build upon and enhance our existing partnerships with Veteran's groups to ensure robust recruitment, Veteran and other stakeholder input on this project, and results dissemination that influences policy and clinical care.

Specific Aim 1a: We will create a community advisory board (CAB) composed of Veteran partners, healthcare providers, researchers, and policy makers, including the Ann Arbor VA Medical Center's Veteran Research Engagement Committee, which has already provided input on our proposal's design and protocols. The CAB will aid with recruitment, provide insight on results dissemination, and build and maintain community partnerships.

Specific Aim 1b: We will hire a Veteran Recruitment Ambassador (e.g., community health worker or community organizer) to conduct recruitment, education, and outreach regarding this study. This individual will maintain community relationships, oversee the CAB, and help enrolled participants navigate barriers that arise, thus enhancing study retention.

Specific Aim 1c**:** Once our studies have commenced, we will share progress and results through the CAB and our Recruitment Ambassador. To iteratively improve our approach as well as inform future therapeutic cannabis research among Veterans, we will qualitatively assess the impact of our studies, reasons for participation, and barriers to participation among study participants.

Specific Aim 2 (Study 1): Determine whether 12 weeks of daily use of CBD (60-120mg/day) improves pain and related functioning among Veterans with chronic pain. Participants will be randomized to receive placebo, broad-spectrum CBD (includes other plant excipients but no THC), or full-spectrum CBD (same as broad-spectrum CBD but with <0.3% THC). In our meetings with Veteran groups, some expressed concerns about drug testing requirements (e.g., for the VA compensated work therapy program) that might be affected by ingesting even small quantities of THC, so we will use a modified equipoise stratified design that allows participants to be randomized across all three choices or to opt out of the THC choice and be randomized between placebo and broad-spectrum CBD.[194] We include broad and full-spectrum products as both are widely available, but despite extensive marketing there is no scientific consensus of which may be

more effective. As such, consumers may be uncertain about which should be preferred – a question that we can empirically answer with this proposed study design. Doses will be 60mg of CBD for 4 weeks, followed by 90mg of CBD for 4 weeks, followed by 120mg of CBD for 4 weeks. Participants who report satisfaction with their symptom control after each dosing period will be allowed to stay at their desired dose for the remainder of the trial. *We hypothesize that participants receiving CBD (either broad or full-spectrum) will report greater improvements via the Patient Global Impression of Change and across secondary outcomes compared to those who receive placebo.*

Specific Aim 2a**.** In addition to the overall effects of CBD on our primary and secondary outcomes, we will investigate and explore relationships between participant characteristics (e.g., pain phenotype, co-morbid anxiety) and response to CBD.

Specific Aim 3 (Study 2): Evaluate whether 12 weeks of an evidence-based, tailored educational program on appropriate medical cannabis use improves treatment outcomes among Veterans with chronic pain. Participants will be randomized to immediately receive 4 sessions of tailored guidance or to receive it after 12 weeks, as a waitlist control condition. All educational sessions may be conducted virtually or via phone to remove barriers to participation. *We hypothesize that participants immediately receiving the educational intervention will report greater improvements via the Patient Global Impression of Change and across secondary outcomes compared to participants at the end of the waitlist condition.* Specific Aim 3a**.** Characterize and explore relationships between symptom and use trajectories of naturalistic cannabis use among participants during and following participation in Study 2.

Impact and Potential Benefits: Designed with input from Veterans in Michigan, our proposal investigates two critically important questions that may improve Veteran health: 1) Does CBD reduce chronic pain symptoms relative to placebo, and does this lead to a signal suggesting that suicide risk would be lower? 2) Does scientifically-informed cannabis use guidance improve chronic pain symptoms relative to unguided use, and thus reduce the risk of suicide? Our pragmatic approach will overcome many limitations of existing RCTs, such as small sample size and use of products unavailable to consumers. Our results will inform use of cannabis products as a potential alternative to opioids and other conventional pain medications for chronic pain management. Veterans will also have the support of our dedicated Community Advisory Board and Health Equity Core, which will help overcome barriers to participation, thus improving recruitment and retention. Further, our design lowers risks and healthcare disruptions to study participants, who will not be dispensed Schedule I drugs by the study team and who will be able to easily access study drug (either federally descheduled CBD or products from their local dispensary) after the intervention, ensuring continuity of care. Moreover, our educational intervention is easily scalable, and has the potential to inform healthcare practice and dispensary employee training, benefitting not only Veterans but also people with chronic pain issues in Michigan and other states with medical cannabis laws. Our findings will catalyze the critical work of minimizing harm and maximizing benefit from widely available cannabis products, which may also ultimately lower incidence of Veteran Suicide.

Innovation: Our proposal addresses critical knowledge gaps in the cannabinoid and chronic pain literature through rigorously designed pragmatic clinical trials that will help keep pace with quickly changing cannabis policy. Our CBD clinical trial will be the first human study to rigorously investigate how commercially available CBD products affect pain and related symptoms among Veterans with varying pain etiologies, and further be able to determine whether the small amounts of THC in hemp-derived CBD products impact effectiveness or safety outcomes. Our educational clinical trial will be the first to empirically test guidance proposed by experts on appropriate use of cannabis products for chronic pain.[192,193,195] By prioritizing Veteran perspectives into our proposed studies, conduct of research, and results dissemination through the CAB and Health Equity Core, our trials will be more successful at recruiting and retaining participants (including from underrepresented communities) than traditional RCTs and have a more immediate effect on policy and patient outcomes. If successful, the findings from this trial would help standardize how both healthcare providers and the medical cannabis industry approach use of cannabis products for pain management. Importantly, implementation of the findings from both trials do not rely upon the approval of a new drug from a pharmaceutical company, instead “meeting people where they are” to help encourage judicious use of currently available medical cannabis and CBD products.

Research Team

Principal Investigators

Our team of co-Principal Investigators (co-PIs) has complementary expertise to ensure that all aspects of the study can be carried out. They are Drs. Kevin Boehnke, Amy Bohnert, and Rachel Bergmans, all three of whom are faculty members at the University of Michigan (UM). Drs. Bohnert and Boehnke have successfully managed very large grants and contracts at the state (State of Michigan) and federal level (CDC, NIH).

- Dr. Boehnke is a Research Investigator in the Department of Anesthesiology Chronic Pain and Fatigue Research Center (CPFRC) at the University of Michigan and a nationally renowned cannabis expert. He is currently leading and involved in several NIH-funded clinical trials investigating effects of cannabinoids on pain and sleep. He has led numerous studies showing that people with chronic pain substitute cannabis for opioids and other pain medications, mostly without clinician oversight.[2-6,8-13] Dr. Boehnke has provided guidance on CBD for the Arthritis Foundation[196] and is currently a Technical Expert Panel member for two national committees on cannabinoid use for pain, including a collaboration between the office of Veterans Affairs and Oregon Science and Health University. He has published numerous articles about chronic pain as well as cannabis, including in *JAMA, Annals of Internal Medicine* and *Journal of Pain.*[2-6,8-13,101,102,104,105,176,197-200] Dr. Boehnke will be the contact PI for this proposal, helping oversee all proposed studies with a particular focus on the CBD trial.
- Dr. Bohnert is a Professor in the Departments of Anesthesiology, Psychiatry and Epidemiology at the University of Michigan and a researcher with the Department of Veterans Affairs Center for Clinical Management Research (CCMR). She is an internationally renowned epidemiologist whose research team has been very involved in studying Veterans, mental health, and the risk of suicide She is Co-Director of the Division of Mental Health Innovations, Services, and Outcomes. She leads a number of NIH-, CDC-, and VA-funded projects to identify paths for reducing the burden of opioid use disorders, opioid misuse, and overdose using randomized controlled designs and electronic health records databases. Her projects include a trial of a mobile behavioral intervention to reduce opioid misuse and a State of Michigan DHHS-partnered project, the Michigan Opioid Collaborative, to provide technical assistance and peer mentoring to physicians providing medications for opioid use disorders. Dr. Bohnert has published over 100 articles related to mental health, opioids, pain, and addiction, including papers in *NEJM, JAMA*, *BMJ*, *Annals of Internal Medicine*, *JAMA Psychiatry*, and the *American Journal of Psychiatry*. [66,68-70,72-78,80-93,95-97,99,107-128,130-142,144-156,201] Her research, funded by NIH, CDC, and the VA, has been foundational in understanding the balance of benefits and harms of opioid analgesic use, and she has content expertise in pain and substance use disorders. She has also served in a scientific advisory role to the Centers for Disease Control and Prevention, to the Food and Drug Administration, and the Michigan Prescription Drug and Opioid Abuse Task Force. With Dr. Boehnke, Dr. Bohnert will help oversee the proposed clinical trials in this study, with a focus on the educational intervention.
- Dr. Bergmans is a Research Investigator in the Department of Anesthesiology Chronic Pain & Fatigue Research Center (CPFRC), a T32 trainee (AR007080, 9/01/21-8/31/22), and the faculty co-leader for the CPFRC Health Equity Core. As a social epidemiologist and community-engaged researcher, Dr. Bergmans uses quantitative and qualitative approaches to advance equity in chronic pain and related health outcomes.[202-224] Her program of work is focused on putting permanent infrastructure in place to increase diversity, equity, and inclusion within chronic pain research at the University of Michigan; establishing sustainable academic-community partnerships; and privileging the priorities and perspectives of representatives from Black and African American communities in the development of non-pharmaceutical therapies and interventions for pain management. Dr. Bergmans has over 7 years of experience implementing community-engaged approaches to partner with key representatives in addressing social and environmental determinants of health. Dr. Bergmans will primarily oversee Aim 1, supervising the formation of the patient/community advisory board, and the work of the Recruitment Ambassador, Research Specialist Associate, and the postdoctoral research fellow. Dr. Bergmans will oversee the development of new materials and other strategies to boost Veteran recruitment and retention (including of underrepresented minorities), as decided on by the CAB and/or as requested by the Recruitment Ambassador.

Co-Investigators

We have assembled an exceptional team of co-Investigators (co-Is) with extensive experience in the following areas: clinical expertise in veteran health; clinical and research expertise insomnia/sleep disturbances, chronic pain, and anxiety; health assessments (patient-reported and ambulatory measures); social determinants of health; data

management; clinical trial design and statistical methods/analyses, and cannabis (medical and problematic use). These co-investigators, their expertise, and contributions to the current project are listed in section V-G under Personnel.

Methods Common to both Clinical Trials

Regulatory Oversight and Support for Clinical Trials (FDA, IRB, DEA)

We will work with the UM Michigan Investigator Assistance Program (MIAP), which is a sponsored UM program that assists with FDA submissions for Investigation New Drug and Investigation Device Exemption (IND and IDE) applications. MIAP provides comprehensive regulatory support, guidance, and education services to investigators involved in Food and Drug Administration (FDA) regulated clinical research. MIAP's primary focus is providing regulatory assistance to sponsors and investigators of drugs, biologics, and medical devices. This includes IND services such as: regulatory needs assessments; exemption rationale development; assistance with FDA meeting preparation; assistance with IND application submissions, including protocol and informed consent development; assistance with regulatory compliance, document preparation, and FDA contact and correspondence; sponsor investigator training; and ongoing study assistance, including safety reporting, FDA annual report preparation, protocol amendments, and IND closeout. We have used this service in the past, obtaining IND approval through FDA for clinical trials using compounds including dronabinol (synthetic THC), Epidiolex (CBD), milnacipran, and duloxetine.

Data Safety and Monitoring Board

The PIs will designate a Data Safety Monitoring Board (DSMB) to perform an independent review of ongoing study progress and safety. The DSMB for this study will comprise of experts who are not associated with this research project and thus work independently of the PIs, with the Chairperson of the Board having experience monitoring safety issues in large clinical trials. The DSMB will be assembled before the start of the trial recruitment period. DSMB members will not be part of the key personnel involved in this grant and each are qualified to review the patient safety data generated by this study because of their unique areas of expertise. The DSMB will meet every six months to review safety assessments and study progress. One member of the DSMB will be the Medical Monitor, a licensed physician who will promptly evaluate participants and initiate emergency or non-emergency treatment, if needed. Any adverse events (AEs) evaluated by the Medical Monitor will be reported to the IRBs, regardless of whether treatment is necessary. The DSMB will also report its findings of any adverse events or decisions regarding modification of the protocol to the University of Michigan IRB committee.

Study Physicians: Clinical Monitoring and Oversight

Co-Investigators Drs. Avinash Hosanagar and Maria Silveira are both board certified physicians with appointments at the VA Ann Arbor Healthcare System. As part of their role in this study, Drs. Hosanagar and Silveira will provide medical assessments at enrollment, prescribe study medications, help monitor participant safety, conduct risk assessments and risk management (e.g., in case of a participant becoming suicidal), and provide requisite treatment referrals should the need arise. Both study physicians have many years of experience working with Veterans and will bring this knowledge and practical expertise to ensuring participant safety.

Data Collection

Once participants are screened for either study, they will begin using a smartphone app called MyDataHelps, which can also be used on any internet-enabled device if an individual does not have a smartphone. (Note: Our team may provide smartphones or devices to participants who do not have them.) MyDataHelps was developed by a Michigan-based firm to enables new types of pragmatic digital health trials such as the ones we propose. This app is currently used in several large well-known studies, including the NIH All of Us study and the eFramingham study.[157,225-227] This app will ask participants a series of validated self-report Patient Reported Outcomes (PROs) that will track each participant's individual symptoms. Our prior studies using the MyDataHelps app with Michigan residents to deploy these surveys has resulted in survey completion rates >90%. Daytime activity data and sleep characteristics will be continuously and unobtrusively collected with wrist-worn devices (e.g., FitBit). Use of these technology-enabled data collection methods offer a number of benefits. They are accessible to participants, who can complete PROs when and where they choose. Further, we will be able to collective continuous and objective data on physical activity and sleep (directly related to pain and pain-related functioning) with no burden to participants beyond wearing the activity monitor. Automated data collection, scoring, and storage of MyDataHelps is uniquely scalable for large studies such as those proposed herein.

Additionally, real-time data collection shows superior sensitivity to change relative to traditional "recall" surveys that are biased by memory heuristics that favor recent and extreme experiences. Therefore, our choice of assessment methodology has both pragmatic and scientific advantages.

Recruitment: Building a Registry of Veterans with Chronic Pain

Participants will be recruited through: 1) Our Community Outreach Core, as described in detail below; 2) Dr. Bohnert's existing research and community outreach infrastructure, which is geographically distributed throughout the state; and; 3) leveraging our existing relationships with Veteran Affairs medical centers (VA) in Michigan, as three members of our investigative team (Drs. Bohnert, Hosanagar, and Silveira) have salaried appointments in the VA and have conducted studies recruiting Veterans in Michigan. This recruitment infrastructure includes access to the VA Ann Arbor and Central VA IRBs and Research and Development Committees, and partnerships with ongoing, large scale research recruitment efforts (e.g., the Million Veterans Project). In preparation for this project, we have already obtained input on our proposed research programs from the Veteran Engagement Research Council (VREC) at the Ann Arbor VA, which has considerably influenced and strengthened our study design. VREC members have expressed excitement about our proposed projects (see their attached letter of support) and will provide continued support in helping with project recruitment and participating in our community advisory board.

We will invite all screened participants to enroll in a registry regardless of whether they decide to participate in Study 1 or Study 2. Those who enroll in the registry (estimated 2000 Veterans over the course of the project) will complete measures of pain and related functioning 1 month after enrollment and then at subsequent 6-month intervals. These participants will be able to contact study team members about participation in either Study 1 or Study 2 at any point if they would like to enroll.

Drawing from the Registry to Account for Regression-to-the-Mean Effects

In addition to helping with recruitment, having participants enroll in the registry after screening will strengthen the findings from the clinical trials by accounting for regression-to-the-mean effects. These effects refer to the commonly observed phenomenon that simply enrolling in a study often results in substantial reductions in symptom severity, even if no treatment is provided.[228,229] This may be due to factors such as participants feeling heard, having attentive trained medical staff closely pay attention to their symptoms,[230] or having their symptoms validated, which is of special importance for people with intractable chronic pain, who may be told by healthcare providers that symptoms are "all in their head". Our group has shown that regression-to-the-mean occurs among people with chronic pain in the Multidisciplinary Approach to Chronic Pelvic Pain (MAPP) study, which has been funded by the National Institutes of Health since 2009. As part of the MAPP study, we asked individuals with urinary chronic pelvic pain syndromes to be in a 3-year longitudinal study where we collected clinical outcome data at regular intervals to track symptom progression. Even though this study offered no treatment, participants generally reported a substantial improvement in pain in the first 4 weeks of the study, followed by relative stability of symptoms on average for the subsequent three years. Had these first 4 weeks of the study been included in analyses, more than one third of those showing "improvement" would be due to this regression-to-the-mean effect.[231] As such, we will ensure that all participants in studies 1 and 2 are enrolled in the registry for at least 4 weeks prior to starting active interventions to avoid confounding our study results.

Taken together, we believe that including the registry adds substantial value, both enhancing recruitment efforts for the proposed and future studies and allowing us to more accurately measure the true treatment effects of our proposed intervention.

Registry Inclusion Criteria:

- Ability to read and speak English sufficiently to allow for written informed consent and patient-reported outcomes measures;
- Adult (aged 21 years or older);
- Armed Services Veteran;
- Willingness to attend all study visits (may be done virtually);
- Willingness to fill out periodic assessments via smartphone to assess symptom status and cannabis use. (Note: The study team has budgeted appropriately to procure smartphones and data plans for study participants if needed).

Registry Exclusion Criteria:

- Inability to provide informed consent (e.g., cognitive impairment, unable to sufficiently communicate in English);
- If participant volunteers that they are pregnant;
- Unable to attend study visits or planning to move out of the state of Michigan during course of study;
- Risk for eminent harm - Suicidal ideation or wish to die as assessed with the PANSI (Positive and Negative Suicide Ideation) questionnaire and further risk assessment by study team members. This risk assessment will only apply to (anticipated to be rare) instances were ensuring participant immediate safety supersedes all other treatment needs, as determined by the study psychiatrist (Dr. Hosanagar).
- Any impairment, activity, behavior, or situation that in the judgment of the study team would prevent satisfactory completion of the study protocol.

Remuneration for Registry Participation

Participants will be compensated for their participation in the registry with $25 at baseline and per 6-month assessment, up to $150 total.

Community Outreach – Building a Strong Basis for Recruitment and Retention for Clinical Trials

The Chronic Pain and Fatigue Research Center (CPFRC) Health Equity Core at the University of Michigan aims to increase diversity, equity, and inclusion in clinical research. Activities of this NIH-funded core include (1) partnering with underrepresented and diverse groups across the research life-cycle; (2) recruiting more representative populations; (3) ensuring ethical recruitment through enhanced training of study staff; and (4) sharing findings in ways that effectively reach underrepresented and marginalized groups. Indeed, increasing the racial/ethnic diversity of participants in clinical pain research and including community partners in the design and conduct of research are intertwined goals that are essential to increasing the rigor and relevance of the resulting findings. Structural factors like discrimination and bias have disadvantaged communities of color in healthcare systems and research,[232-234] decreasing both the opportunities for and willingness of individuals from these communities to participate in research.[235] Thus, for our studies, we will leverage and build upon the CPFRC Health Equity Core's existing infrastructure to enhance engagement with Veteran communities and the communities where they live, particularly those from underrepresented racial/ethnic groups and rural areas. These efforts will include:

The creation of a Community Advisory Board (CAB) to Oversee and Aid with the Proposed Studies.

Composed of Veteran partners, healthcare providers, and policy makers, the CAB will communicate directly with research leadership to shape research priorities, including aiding with recruitment, building and maintaining community partnerships, and providing insight on study design and results dissemination. Meetings will be held every other month for the first 2 years of the program, and quarterly for the remaining 2 years. Meetings will be co-planned and co-led by CPFRC Health Equity Core faculty co-leaders (including Bergmans, PI), Ms. Chambers-Peeple (Community-Engaged Research Coordinator), as well as a community co-lead (to be determined). At least two meetings per year will have an in-person option, if feasible; the remaining meetings will be virtual. Table 1 describes the proposed structure of the CAB.

Table 2. Proposed Structure of Community Advisory Board (CAB) for Studies 1 and 2 (8-12 members)

Community type	Member/Organization
Veterans living with chronic pain (VLCPs)	We will seek to include at least 4 VLCPs on the CAB and will ensure that they represent a diverse range of experiences. VLCPs who are being considered for the CAB include members of the Veteran's Research Engagement Committee at Veteran's Affairs Ann Arbor Healthcare System and will also be drawn from partnerships with other Veteran groups.
Veteran and community-based organizations	Organizations we may partner with include but are not limited to: Veterans Research Engagement Committee, Veterans Affairs Healthcare System Ann Arbor, No Veteran Left Behind
Providers	Avinash Hosanagar, MD, University of Michigan Medicine (Psychiatry) and Veteran's Affairs Ann Arbor Healthcare System; Maria Silveira, MD, Michigan Medicine (Family

	Medicine) and Veteran's Affairs Ann Arbor Healthcare System; Dana Horowitz, MSW, Veteran's Affairs Ann Arbor Healthcare System
Ad-hoc consultants or presenters	We plan to invite individuals with specific expertise on an as-needed basis to participate in one or more meetings. Examples include topical experts to help emerging or specific issues with Studies 1 or 2.
Pain researchers	As needed from the CPFRC and broader UM pain researcher community for topical expertise
Other members	Policy makers, such as a representative from the Marijuana Regulatory Agency

CAB Process.
In addition to CAB members, at least one of the project MPIs will attend each meeting, as well as the project manager and the Research Ambassador. Subcommittees will be formed as needed to address specific issues that arise; (e.g., developing marketing materials, planning educational events), and will meet separately from the main group. CAB members will be asked to make initial, renewable commitments of one year. In recognition that members may need to step down from the Board during the project, the CAB's governance documents will include a plan for identifying and approving new members as needed. Table 2 provides examples of how the CAB will take part in decision-making at each phase of the research project.

Table 3: Expected CAB Tasks, by Study Phase.

Study Phase	Tasks
Study Design and Recruitment	1. Ensure relevance and tailor recruitment materials to Veteran communities. 2. Ensure that design and procedures are responsive to Veteran participant needs. 3. Discuss how to adapt workflows if needed to ensure greater eligibility among Veterans and minimize barriers to participation. 4. Tailor retention strategies to Veterans. 5. Design recruitment strategies and messages and review recruitment materials. Includes addressing concerns about the trustworthiness of the research team, safety, and stigma. 6. Ensure informed consent procedures are broadly accessible and acceptable.
Data Collection & Measures	1. Ensure that demographic measures are inclusive and relevant. 2. Ensure that factors relevant to stigma, discrimination, and access are adequately measured. 3. Determine domains and create guidance for qualitative assessment of patient experiences. 4. Ensuring that study outcomes are meaningful to patients. 5. Devise plan for capturing participant vignettes, ensuring representation of diverse participants.
Data Analysis & Interpretation	1. Use data dashboard for analysis and interpretation throughout projects. 2. Perform qualitative analysis using RADaR (rapid-, team-based analysis).[236]
Dissemination & Sustainability	1. Identify channels and events for community dissemination and dissemination events (e.g., town halls). 2. Give input into the design of communication materials (e.g., factsheets, brief videos, policy briefs). 3. Participate in academic dissemination activities, including publications and presenting at conferences. 4. Generating future research questions based on study findings to pursue as part of the ongoing clinical-community partnership.

Research Ambassador (RA): an Active Extension of the CAB
The Research Ambassador will be a health worker or community organizer who works on Veteran issues and has a personal connection to Veterans (e.g., is a Veteran themselves, has Veterans in their family, or works with organizations that center Veteran priorities). The RA will focus on recruitment and outreach, including hosting educational seminars at public and private housing buildings, recreation centers, churches and other community spaces; establish rapport with

local Veteran organizations where study recruitment materials could be disseminated; and engage with Veteran organizations to disseminate study information. The RA will also facilitate bidirectional communication and knowledge transmission between researchers and Veterans, including establishing an ongoing conversation to inform research development and disseminate study findings. Further, the RA will assist enrolled participants so that they can navigate challenges of participation, including answering questions and concerns, helping participants navigate access to resources that support participation (e.g., transportation, overnight accommodation). Because the RA will possess local knowledge and context within Veteran communities, they will be well-poised to participate in these roles and will also be "ears on the ground" to inform any adaptions of the protocol needed to enhance recruitment or retention.

Evaluation of Challenges and Barriers to Research Participation among Veterans with Chronic Pain

Overview

Our evaluation using qualitative approaches will improve study design and contribute to community engagement science. We will invite both study participants and those who decline to participate in studies 1 and 2 to complete semi-structured, open-ended interviews to evaluate the challenges and barriers to study participation.

Evaluation of Challenges to Participation

In a sub-sample of the study population in both studies (*n* = 80) we will conduct in-depth interviews at the conclusion of their participation in the study. This evaluation will assess perceptions of study participation, what it was like to participate in the study, the reasons why individuals decided to participate in the study, what participants liked about the study, and what were the biggest challenges of participation.

Evaluation of Barriers to Participation

We will recruit participants (*n* = 50) who are eligible for studies 1 or 2 but do not participate in the study. In-depth interviews will assess perceptions of clinical research, barriers to study participation, and opportunities to increase community interest and engagement in clinical research for chronic pain.

Data Collection and Analysis

Data collection in interviews

Interviews will be conducted remotely over the computer or telephone using U-M Zoom, which is HIPAA compliant for collecting protected health information. The interview guide will include questions like, "*What was it like to participate in this intervention?*", "*How do you feel like your symptoms changed over the course of the study?*", "*What did you like about this study?*", "*What were the biggest challenges of adhering to the study protocol?*", "*Why didn't you participate in the study?*", and "*What would have helped you participate in the study?*"

Qualitative analysis

We will analyze the data using an inductive, thematic analysis approach,[237] that consists of 4 phases. After extracting descriptive information (e.g., demographics, social determinants of health, symptoms), we will open code the transcripts and generate memo diagrams that present and categorize the relationships between quotes within participants. Next, we will develop a coding scheme that focuses on three questions: what was the experience of participating in the RCT for CBD, what was the experience of participating in the RCT for tailored guidance on how to appropriately use available cannabis products, and what were barriers and facilitators to participation? We will apply the coding scheme in MAXQDA 2022 (VERBI Software, 2021) to ensure the capture of all coded segments related to participant experiences. We will then create themes by grouping related codes and coded segments into categories that represent common experiences across participants. This is an iterative process where we will repeatedly compare the data with the specified categories to refine and finalize the theme development.

Community engagement: Interpretation of findings

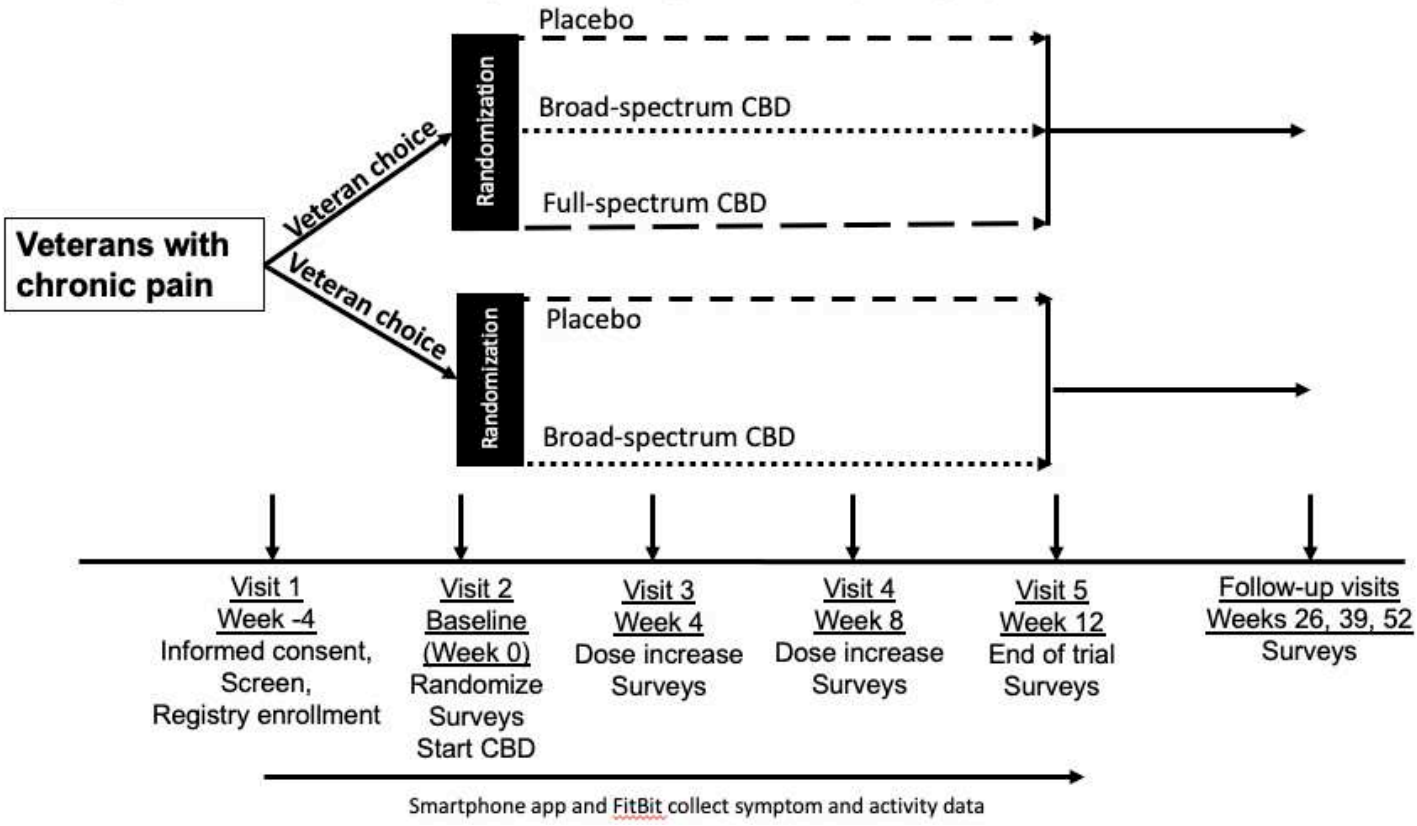
This proposed study prioritizes community engagement throughout the project timeline to obtain community representative input on interpretating study findings and disseminating results. We will present preliminary findings to the CAB once the first coding scheme is developed. During this initial meeting, CAB members will provide their interpretation of the data and in what ways the findings may be most meaningful to Veterans and their communities. We will then return to the CAB meetings periodically to review and refine the theme development.

Proposed Clinical Trial 1 – CBD for Chronic Pain among Veterans: Methods

Overview of Study Design.
Our proposed study consists of a randomized, double-blind, placebo-controlled clinical trial to determine whether 12 weeks of daily use of CBD (60-120mg/day) improves pain intensity and related functioning among n=455 Veterans with chronic pain. Participants will be randomized to receive placebo, broad-spectrum CBD (includes other plant excipients but no THC), and full-spectrum CBD (same as broad-spectrum CBD but with <0.3% THC). In our meetings with Veteran groups, some Veterans expressed concerns about drug testing issues or legal consequences from ingesting even small quantities of THC.[238] To address this concern, we will use a modified equipoise stratified design that allows participants to be randomized across all three choices or to opt out of the full-spectrum product (with THC) choice and to be randomized between only placebo and broad-spectrum CBD.[194] We include broad and full-spectrum products as both are widely available, but despite extensive marketing, there is no scientific consensus of which may be more effective for treating chronic pain. As such, consumers may be uncertain about which should be preferred – a question that we can empirically answer with this proposed study design. To enhance recruitment and reduce participant burden, all study visits will be conducted via video conference or phone call unless the participant wishes to do in person study visits.

The study design is overviewed in figure 1. At the screening visit, participants will complete informed consent documents electronically or in person. Those who qualify will enroll in the study and registry and start completing study assessments via MyDataHelps for a period of at least 4 weeks prior to taking study medication. They will also indicate whether they are willing to be randomized to receive a product with THC (full-spectrum). Those who are not will be randomized to receive gel capsules with either broad-spectrum products or placebo (carrier oil), while those who are will be randomized to receive placebo, broad-spectrum CBD, or full-spectrum CBD. Broad and full-spectrum products will be identical excepting the presence of THC (in full-spectrum products only). Doses will increase at visits 3 and 4 if participants are not obtaining sufficient pain relief (determined by participant). Throughout the study, participants will wear a Fitbit or other wearable device to unobtrusively measure activity and sleep data and complete daily assessments of pain level, anxiety level, sleep quality, and adverse events. After the study intervention is complete, participants will be informed what treatment they received. They will then be followed at 26, 39, and 52 weeks (measured from baseline) to investigate patterns of pain symptoms and continued CBD/cannabis use.

Figure 1. CBD for chronic pain among Veterans (Study 1)



Inclusion Criteria:

- Ability to read and speak English sufficiently to allow for written informed consent and patient-reported outcomes measures;
- Adult (aged 21 years or older);
- Armed Services Veteran;
- Willingness to attend all study visits (may be done virtually);
- Willingness to wear Fitbit or other similar sensor for passive-data collection;
- Willingness to fill out daily diary via smartphone to assess symptom status and CBD use (Note: The study team has budgeted appropriately to procure smartphones and data plans for study participants, if needed).

Exclusion Criteria:

- Inability to provide informed consent (e.g., cognitive impairment, unable to sufficiently communicate in English);
- If participant volunteers that they are pregnant;
- Use of cannabis products more than 4 times in the past month;
- Planning to move out of the state of Michigan during course of study;
- Risk for eminent harm - Suicidal ideation or wish to die as assessed with the PANSI (Positive and Negative Suicide Ideation) questionnaire and further risk assessment by study team members. This risk assessment will only apply to (anticipated to be rare) instances were ensuring participant immediate safety supersedes all other treatment needs, as determined by the study psychiatrist (Dr. Hosanagar).
- Self-reported allergies cannabis/cannabinoids;
- Any impairment, activity, behavior, or situation that in the judgment of the study team would prevent satisfactory completion of the study protocol.
- Participation in other clinical trials over the course of this study.

Setting

As described in the Recruitment and Community Outreach sections above, we will recruit participants from throughout the state of Michigan. To aid with geographic inclusivity, all assessments with the study team at the University of Michigan and Ann Arbor Veteran Affairs Medical Center may be done virtually. Because our CBD study medication is descheduled, temperature stable, and can be ordered online from the manufacturer in naturalistic settings, we intend to ship it to study participants to both reduce participant burden and pragmatically mimic the real-world environment.

Dosing and Study Drug

The 12-week dosing duration was selected in accordance with the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations on defining the clinical importance of treatment outcomes in studies of chronic pain.[239,240] Study drug will be provided by Ananda Professional, a hemp CBD company that is sponsoring ongoing clinical trials for chemotherapy induced peripheral neuropathy and agitation/aggression among people with dementia and Alzheimer's disease. These trials have IND approval through the FDA. Per their letter of support, we will purchase study drug in standardized lots from Ananda Professional throughout the duration of the study, and their team will provide all necessary manufacturing documentation required by the FDA for the IND process. CBD will be provided as 15mg gel capsules for ease of dosing, and capsules in all study arms will be visually identical. Broad- and full-spectrum products will be identical excepting that full-spectrum products will contain a standard amount of THC that is below the <0.3% threshold required for descheduled, hemp-derived CBD products. Doses will be 60mg of CBD for 4 weeks, followed by 90mg of CBD for 4 weeks, followed by 120mg of CBD for 4 weeks. Participants who report satisfaction with their symptom control after each dosing period will be allowed to stay at their desired dose for the remainder of the trial. These doses align with those seen among our studies of people using CBD products naturalistically for chronic pain,[13] guidance from cannabinoid experts on appropriate dosing with CBD for chronic pain,[192,193,195] and pragmatic economic reasons. Indeed, because there are no CBD products that have been FDA-approved for pain, understanding whether doses that are economically feasible (in this case, $3-$6 per day) is of great import.

Remuneration for Study 1 Participation

Screening: $20
Baseline visit: $30
Visit 3: $30
Visit 4: $30

Visit 5: $30
Visit 6: $30
Follow ups 1-3: $30 each ($90 total)
Total: $260

In total, participants can receive up to $260 for participating, as well as free study drug throughout the course of the trial. In addition, we have budgeted sufficiently for all study participants to receive a one-month supply of either broad or full-spectrum CBD after they complete the intervention if they so wish. Participants will also be able to keep the Fitbit provided for the study.

Proposed Randomization Scheme.

All eligible patients who agree to be randomized across all three options will be randomized using random blocks of size 3 and 6. All eligible patients who opt out of full-spectrum CBD will be randomized between placebo and broad-spectrum CBD using random blocks of size 2 and 4. We will conceal allocation to groups in the following manner. First, all included patients will be given unique identifiers by the investigative team. Next, an independent data analyst will then assign patient identifiers to groups relative to the block randomization procedure. The randomization code will be then kept confidential by this individual until the follow-up period is completed or in the event of the need to reveal randomization (e.g., repeated adverse events as deemed by the DSMB). The study investigators and personnel, data analysts, physicians, and the included patients will be blinded to the allocation.

Assessment and Outcome Measures.

The schedule of events for study 1 is in table 4, with details of assessments and outcome measures below.

Table 4. Schedule of Events for CBD Clinical Trial (Study 1)

Assessment	1	2	3	4	5	6-8
Visit Description	Screening	Baseline	Dose escalation 1	Dose escalation 2	End of treatment	Virtual follow-ups 1-3
Time point	Week -4 or earlier	Week 0	Week 4	Week 8	Week 12	Weeks 26, 39, and 52
Informed Consent	X					
Demographics	X					
Eligibility	X					
Medical History	X					
STOP-BANG	X					
Randomization	X					
Taking Study Medication (starting after visit)		X	X	X	X	
Concomitant Medication Review	X	X	X	X	X	X
PROMIS 29+2[a]	X	X	X	X	X	X
PGIC					X	
2016 fibromyalgia survey criteria, painDETECT	X	X	X	X	X	X
Sleep-related impairment	X	X	X	X	X	X
Catastrophizing	X	X	X	X	X	X

PC-PTSD-5	X	X	X	X	X	X
PANSI	X	X	X	X	X	X
Adverse Events		X	X	X	X	X
Daily assessments[b]	X	X	X	X	X	X
Adherence Assessment			X	X	X	
Blinding assessment[c]			X	X	X	

Notes: STOP-BANG: Snoring, Tiredness, Observed Sleep Apnea, Blood Pressure, Body Mass index, Age, Neck Circumference, and Gender; PANSI: Positive and Negative Suicide Ideation; PGIC: Patient Global Impression of Change; PROMIS: Patient Reported Outcome Measurement Information System. PC-PTSD-5: Primary Care Post-Traumatic Stress Disorder Screen for DSM-5.

a) PROMIS 29+2 will also be administered every week during the CBD intervention.
b) Daily assessments include pain, timing of dose, anxiety, and sleep measures.
c) We will ask participants to identify what group they are in.

Primary Outcome Measures: Our primary outcome will be the Patient Global Impression of Change (PGIC), a 1-item survey that measures patient perceptions of intervention success.[241] This will be measured at the end of the active intervention (12 weeks on treatment).

Secondary Outcome Measures: We selected secondary outcomes in accordance with the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations on defining the clinical importance of treatment outcomes in studies of chronic pain.[239,240]

1. *Safety (self-reported).* Over the 12 weeks of active treatment, we will capture AEs at study visits (online, phone, and/or in-person) and as needed by participant request per institutional and FDA guidelines. The study team will assess causality and severity using the Common Terminology Criteria for Adverse Events v.5.0.[242]
2. *Pain.* The assessment of CBD analgesic effectiveness will be a longitudinal comparison of trends in pain intensity (0-10 numerical rating scale, NRS) in 7-day epochs between baseline and end of intervention using aggregated data from the daily pain diary. Pain assessment points are 7-day epochs throughout the drug intervention. Patients will be asked to complete pain diaries each evening over the course of the trial to measure their "worst pain" rating (on an NRS) the previous day.
3. *Physical Function.* We will measure physical function using the physical function subscale from the PROMIS-29+2 Profile v2.1 (PROPr), and will assess longitudinal trends in physical function from baseline until the end of intervention.[243] We will also measure physical activity as daily step counts and total daily active minutes from Fitbit data from baseline to end of the intervention.
4. *Pain Interference*. We will measure pain interference using the pain interference subscale from the PROMIS-29+2 Profile v2.1 (PROPr), and will assess longitudinal trends in pain interference from baseline until the end of intervention.[244]
5. *Anxiety.* We will measure anxiety using the anxiety subscale from the PROMIS-29+2 Profile v2.1 (PROPr),[244] and will assess longitudinal trends in anxiety from baseline until the end of intervention.
6. *Sleep time and disturbance.* We will measure sleep disturbance using the sleep disturbance subscale from the PROMIS-29+2 Profile v2.1 (PROPr),[244] and will assess longitudinal trends in sleep disturbance from baseline until the end of intervention. We will also assess total sleep hours each night of the study using Fitbit-based metrics across the length of the intervention.
7. *Suicidal Ideation.* Suicidal ideation or wish to die as assessed with the PANSI (Positive and Negative Suicide Ideation)[245] questionnaire and further risk assessment by study team members. The 14 items of the PANSI separate to 8 items of vulnerability to suicidality and 6 items of protective factors. We will use the vulnerability sub-scale as our secondary outcome from baseline to end of the intervention.
8. *Post-traumatic stress disorder (PTSD)*. PTSD symptoms will be briefly assessed using the Primary Care Post-

Traumatic Stress Disorder (PTSD) Screen for DSM-5 (PC-PTSD-5), which consists of five questions and can be used to identify individuals with probable PTSD.[246] We will assess changes in PTSD symptoms from baseline to end of the intervention.

9. *Wearable Data.* Despite lower precision overall, wearables such as Fitbits have several advantages over laboratory gold standard measures for this study. Notably, mobile technology can assess patients continuously in the real world, outside of the laboratory setting. With their relative ease of use and scalability, commercial mobile devices are ideally suited for large-scale clinical studies. Further, newer generation of commercial wearables, such as the Fitbit Charge 5, have demonstrated improved accuracy in measuring parameters of sleep and activity, relative to research grade actigraph devices. In this study, all participants will be provided a Fitbit Charge 5 device and coached to wear the device continuously and charge the battery during the day to ensure collection of sleep data. We will be able to generate a number of objective biometrics from Fitbit data, as we have done for other studies using the MyDataHelps data collection system. Some of these measures are detailed in Table 5. These changes will be measured from baseline to end of the intervention.

Table 5. Detailed List of Available Fitbit-Based Measures

Domain	Minute-by-Minute Data	Constructed Measures
Activity	Steps	-daily step count **-daily exercise minutes** -activity type (e.g., running, walking, biking, swimming)
Sleep	Sleep Status	**-daily Total Sleep Time (TST), minutes and variability** -sleep time in specific sleep stages (light, deep and REM) -sleep onset time, mid-point, and wake time and variability of each -circadian phases (based on sleep and heart rate) (55) -sleep efficiency (REM+Light+Deep minutes)/ (REM+Light+Deep+Awake minutes)
Heart Rate	Heart Rate	-heart rate variability -maximum heart rate -resting heart rate
Skin Conductance	Multipath electric sensor	Continuous electrodermal activity (EDA)

Table 5. Bolded measures (daily exercise minutes and total sleep time) are secondary outcome measures. The rest will be exploratory.

Additional Proposed Patient Reported Outcomes.

At study visits and follow up phone calls, participants will complete questionnaires to measure pain, psychosocial status, and numerous validated quality of life indicators relevant to pain.[26,28,29,247,248] The instruments below represent those that we may use at different points during the proposed clinical trial.

Medication Consumption: We will measure changes in medication consumption throughout the trial and after the trial to see if there are any changes that may occur in response to taking CBD.

Pain and Pain Quality: We will use the 2016 FM survey criteria, a combined measure of widespread pain (body map[249] with number of painful sites 0-19) and symptom severity (e.g., fatigue, subjective cognitive problems, headache, poor mood, scores range 0-12), as a continuous measure of the degree of nociplastic pain, with scores ranging from 0-31.[56,173] In addition, we will use validated self-report measures to examine pain intensity (Brief Pain Inventory (BPI)[250]) and pain quality, e.g., neuropathic pain (PainDETECT[251]).

Psychosocial Status: We will use questionnaires that measure clinically relevant physical and mental traits associated with chronic pain.[84,252] These will include:

1) The PROMIS-29+2 Profile v2.1 (PROPr),[244] will be used to assess multiple domains: Physical function, Anxiety, Depression, Fatigue, Sleep Disturbance, Ability to participate in social roles, Pain interference, Cognitive function, and Pain intensity. The addition of the 2 cognitive functioning items differentiates this instrument from its parent the PROMIS Profile 29.[253] The PROMIS29+2 can also be used to calculate a preference score (PROMIS Preference, PROPr).[254-256] Preference-based scores provide an overall summary of health-related quality of life

on a common metric. Preference-based scores summarize multiple domains on a metric ranging from 0 (as bad as dead) to 1 (perfect or ideal health).

2) We will augment the PROMIS-29+2 with the PROMIS Sleep-Related Impairment scale (Short Form 4a), so as to better assess non-restorative sleep – thought to be characteristic of nociplastic pain.[257]
3) The catastrophizing scale from the Coping Strategies Questionnaires Pain,[258] which assesses pain catastrophizing, a thinking style associated with poorer outcomes generally among people with chronic pain.[259]

Demographics and Group Assignment: We will use standardized case report forms to collect sex, age, race/ethnicity, marital status, education level, body mass index (BMI), disability status, social determinants of health, and a family history of pain. We will also collect basic medical data such as current and new diagnoses, and current interventions for pain (e.g., physical). This collection may be done via medical records review as well as through participant self-report. At each time point, we will also ask participants to guess which treatment group they are in and their reasoning for their guess. This information will be used to detect and control for demand characteristics and unblinding related to potential side effects from CBD. We will compare patient characteristics between "equipoise strata": those who chose to be randomized across all options versus those who opted out of full-spectrum CBD. In all analyses, a variable indicating the strata of whether individuals chose to be randomized across all options vs. opted out of full-spectrum will be included to account for possible differences in the patients associated with the decision to receive broad vs. full-spectrum products.

Anticipated Results: We hypothesize that Veterans receiving CBD (broad or full-spectrum) will have greater improvement in PGIC scores and secondary outcomes compared to those receiving placebo. We further hypothesize that Veterans with lower nociplastic pain contributions (i.e., lower FM survey scores) will have greater improvement CBD products than those with greater nociplastic pain contributions (i.e., higher FM survey scores). However, we expect that participants with greater nociplastic pain contributions who are taking full-spectrum CBD products will respond preferentially compared to those taking placebo or broad-spectrum products. We expect that all products will causes similar levels of AEs (typically minor, e.g., dizziness, somnolence, dry mouth).[260]

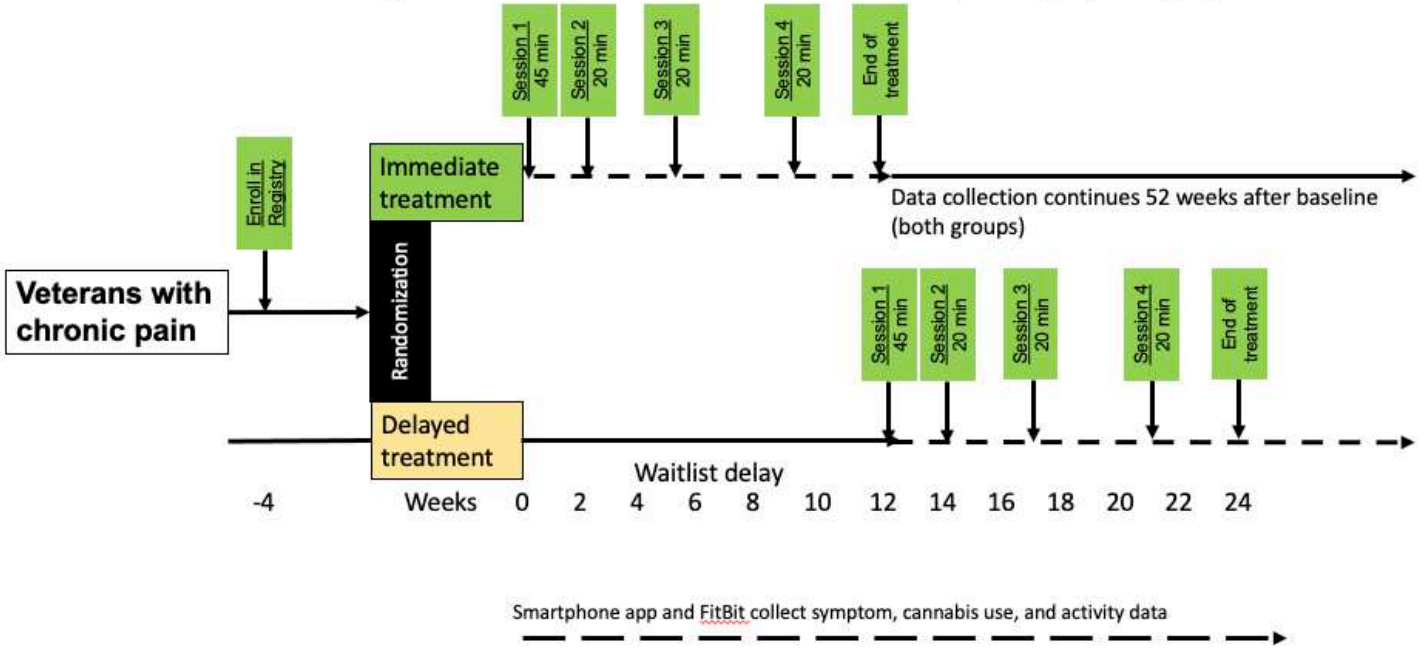
Proposed Clinical Trial 2 – Tailored Guidance Educational Intervention

Overview of Study Design.

In this study, we will use a 12-week long, wait-list RCT to investigate whether evidence-based, tailored guidance on how to appropriately use available cannabis products affects chronic pain symptoms among 422 Veterans with chronic pain. In this design, half of participants will be randomized to receive treatment immediately while the other half will have a 12-week delay before undergoing treatment, which will help distinguish between the effects of our educational intervention and spontaneous symptom improvement. Participants would be Veterans who have used cannabis in the past 3 months for pain management and wish to optimize their cannabis use to improve treatment outcomes. The tailored educational guidance will draw from the scientific literature and clinical expertise of scientists and physicians who work directly with medical cannabis patients to develop best practices for use based on: 1) individual symptoms and priorities; 2) recommended cannabinoid content (THC vs. CBD); 3) therapeutic levels of cannabis or cannabinoids according to the scientific literature, and; 4) route of administration (e.g., smoking, edibles, tinctures, etc…).[192,193,195] The tailored guidance cannabis coaching intervention will also draw from the extensive clinical experience of Dr. Evan Litinas, who has worked with medical cannabis patients for nearly a decade. Dr. Litinas and other investigators will manualize the intervention and train study staff to deliver the intervention. Participants randomized to receive "tailored guidance" will be assigned to four manualized educational sessions (options of in person, video conference or teleconference) with a trained behavioral health consultant (i.e., cannabis coach). These cannabis coaches will have a background in research and social work as well as expertise and training on appropriate medical cannabis use for these conditions.

During screening visit, participants will complete informed consent documents electronically or in person. Those who qualify will enroll in the study and registry and start completing study assessments via MyDataHelps for a period of at least 4 weeks prior to the first intervention. Participants randomized to receive immediate treatment will then have educational sessions at baseline, 2 weeks, 5 weeks, and 9 weeks after initiation; a total of 4 sessions total over the course of the intervention. Participants randomized to the waitlist control will be assessed periodically during the waitlist period and then undergo the same intervention (Figure 2). Participants will also complete follow up surveys 26, 39, and 52 weeks from baseline to investigate patterns of pain symptoms and naturalistic medical cannabis use patterns.

Figure 2. Educational intervention study design (Study 2)



The **Inclusion and Exclusion criteria** for this study are identical to Study 1 except that participants in Study 2 must be currently using cannabis products for treatment of chronic pain symptoms (defined as any medical use in the past 3 months). Participants who are not eligible for Study 1 because of frequent cannabis use would be immediately invited to enroll in Study 2, allowing for more efficient recruitment efforts.

Setting

As described in the Recruitment and Community Outreach sections above, we will recruit participants from throughout the state of Michigan. To aid with geographic inclusivity, all assessments with the study team at the University of Michigan and Ann Arbor Veteran Affairs Medical Center may be done virtually.

Remuneration for Study 2 Participation

Screening: $20
Baseline visit: $50
Visit 3: $40
Visit 4: $40
Visit 5: $40
Visit 6: $50
Follow ups 1-3: $30 each ($90 total)
Total: $330

In total, participants can receive up to $330 for participating, as well as free educational sessions on optimizing cannabis use with a cannabis coach. Participants will also be able to keep the Fitbit provided for the study.

Proposed Randomization Scheme.

All eligible participants will be randomized between the waitlist control and intervention using random blocks of size 2 and 4. Given the nature of the intervention, study investigators and personnel, data analysts, physicians, and the included participants Study 2 will not be blinded.

Details of Study Intervention

Prior to the educational sessions, study participants will be given access to educational materials (e.g., handouts, videos) that provide an overview of information regarding cannabis products, effects, and pain. In tailored guidance sessions, the cannabis coach will assess pain, other symptoms related to pain (e.g., sleep, anxiety), and current use patterns. These materials will be developed with insight from the study team and the CAB. The cannabis coach will then share information with participants on routes of administration, cannabinoid content, and appropriate therapeutic levels of

cannabis or cannabinoids according to the scientific literature for managing symptoms of pain. Educational content will also include known side effects of cannabis (e.g., common effects like dizziness or sedation, rare side effects like hallucinations or vomiting[261]) as well as specific risks associated with administration routes, such as respiratory harm from smoking or unregulated vaporized concentrate products,[262] and the delayed onset of edible products.[192] Cannabis coaches will also share information on ways to avoid side effects based on the scientific literature, such as starting with low doses and increasing slowly and that intoxication is not always necessary for a therapeutic effect.[192,193,195]

The first session will largely focus on: 1) understanding which symptoms are most important to the participant to manage; 2) characterizing current use patterns; 3) safety and side effects; 4) differential effects of THC and CBD; 5) the effect onset and duration of effects of each administration route (i.e., smoking, vaporizing, eating, topicals, tinctures); 6) how to methodically approach quantity used; 7) effectively tracking symptoms when using cannabis; and; 8) making suggestions of first steps to optimize medical cannabis use. Symptom and cannabis tracking will be easily facilitated through use of the MyDataHelps app used for data collection in this study as described above. The following sessions will focus on suggestions of how participants might consider adjusting their use patterns to minimize negative side effects while maximizing benefit, taking into account clinical changes, cannabis side effects, and harm reduction.

<u>Example of Educational Intervention</u>

Case Study: A 52-year-old male Veteran has chronic knee osteoarthritis pain and shoulder pain from an old injury. The knee pain is most painful when he is walking, and his shoulder pain is most painful after a day of computing at his job as an IT consultant. He also has trouble falling asleep and staying asleep. To manage his symptoms, he currently smokes THC-dominant joints five times per day, including one right before bed and one when he wakes up in the middle of the night and cannot fall back asleep. He has been using cannabis to manage pain symptoms for 9 months. His primary concerns are: inadequate pain relief, wanting to avoid being "high" at work, feeling drowsy in the mornings and in between smoking sessions, and not wanting to hurt his lungs with smoking.

Proposed response from cannabis coach

To help facilitate more skillful cannabis use, the coach would suggest tracking symptoms so the participant can better understand patterns of and triggers for symptoms, e.g., sitting for a long time at work. This will be facilitated via use of the MyDataHelps app, in which the participant will be able to review their past symptom checks and use patterns. The coach would recommend adding sublingual CBD-dominant tincture or capsules during the workday with a 1:1 THC:CBD tincture or vaporizer (if required) available for breakthrough pain. For sleep, the coach would propose taking a 1:1 CBD:THC tincture at night rather than smoking, and to use this same tincture at night if the participant wakes up and has trouble falling back asleep. The coach would also recommend reducing smoking, both generally and also if symptoms improve with these suggestions.

Rationale for response

1) *Routes of administration*: Smoking damages the lungs, so avoiding smoking is important for harm reduction. Tinctures typically take effect within 15-45 minutes – a time scale that helps more quickly with breakthrough pain.[192] Tinctures and capsules also last for 6-8 hours vs. 2-4 hours for smoking, providing a more stable level of pain control rather than a quick spike in effect followed by a quick taper.[192] If the participant does not wish to take a tincture or capsules instead of smoking, the coach may offer education about alternative inhalation routes such as vaporization of cannabis flower, as vaporization results in less exposure to combusted material and carcinogens.

2) *Cannabinoid content*: THC and THC analogs are effective in reducing pain symptoms in some people, but use during the day can be problematic as THC-related intoxication can increase the risk of vehicle accidents and may cause cognitive effects that reduce productivity at work or endanger employment.[261,263] Thus, CBD or CBD-dominant products would be ideal to use during this time if they were sufficient on their own. THC use after work or at night may has positive effects on insomnia and sleep issues, especially in the context of chronic pain or PTSD (which many participants may have),[1,264-269] so continuing use then is supported by the evidence. CBD can reduce anxiety associated with THC,[270] so co-administration may be useful to help reduce side effects generally, but especially when taken during the day.

3) *Doses*: Given that the study participant has largely been smoking, they may be unused to effects of edible or tincture cannabis products. As such, the coach would suggest starting with 2.5mg of THC and 2.5mg of CBD at

night (tincture or capsule) to help with sleep. This starting dose is equivalent to the lowest dose for FDA-approved dronabinol (synthetic THC, brand name Marinol). From there, the participant could slowly titrate up if needed. During the day, the coach would suggest starting with 15-25mg of a CBD-dominant tincture or capsule in the morning, and then taking another 15-25mg at lunch. If the participant requires THC for pain relief during these times and has built up comfort with tinctures (i.e., not having significant side effects), adding 1-2mg of THC and titrating up from there as necessary. If the participant still wishes to smoke or vaporize after the suggested changes, the coach may also advise taking only 1-2 puffs at a time to see if that provides adequate pain relief, especially given that the participant is also concerned about drowsiness between smoking sessions. Use of fewer puffs may also be possible for similar pain relief given that there may be additive effects between the inhaled THC and the CBD from the tincture or capsules.

In subsequent sessions, the coach would meet with the participant, review changes that the participant had made, and provide further guidance as needed and solicited.

Quality Control

Educational sessions will be recorded so that we can ascertain whether the educational sessions elicit behavior change and enhance the effectiveness of using cannabis to manage pain symptoms. Investigators will also review 10% of these sessions to monitor that the intervention is faithfully delivered according to the manual. Adherence to intervention components or fidelity will be checked with each cannabis coach, who will be asked to refrain from delivering the educational intervention with participants until after the fidelity check is "passed." Initial intervention fidelity will be assessed through audio recording with standardized participants, which will be coded by two independent coders with the MITI43 and content adherence. All cannabis coaches must achieve an average Global Rating score of 3 and an 80% content adherence to pass initial fidelity checks. If this intervention is found to improve outcomes, the coaching model and training materials will facilitate speedy dissemination.

Assessment and Outcome Measures.

Our primary, secondary, and exploratory outcome measures will largely be the same as those used in Study 1. Please see description of assessments above and the schedule of events in Table 6 (below). We will also measure aspects of actual cannabis consumption during the trial using a customized module in MyDataHelps in which participants will enter data on these use parameters each time they use cannabis.

Table 6. Schedule of Events for Educational Clinical Trial (Study 2)

Assessment	1	2	3	4	5	6	7-9
Visit Description	Screening	Baseline and educational visit 1	Educational visit 2	Educational visit 3	Educational visit 4	End of Intervention	Virtual follow-ups 1-3
Time point	Week -4 or earlier	Week 0	Week 2	Week 5	Week 9	Week 12	Week 26, 39, and 52
Informed Consent	X						
Demographics	X						
Eligibility	X						
Medical History	X						
STOP-BANG	X						
Randomization	X						
Coaching sessions		X	X	X	X		
Concomitant Medication Review	X	X	X	X	X	X	X
PROMIS 29+2[a]	X	X	X	X	X	X	X

PGIC						X	
2016 fibromyalgia survey criteria, painDETECT	X	X	X	X	X	X	X
Sleep-related impairment	X	X	X	X	X	X	X
Catastrophizing	X	X	X	X	X	X	X
PC-PTSD-5	X	X	X	X	X	X	X
PANSI	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X
Daily assessments[b]	X	X	X	X	X	X	

Notes: Participants who are waitlisted will complete periodic assessments during the waitlist period (12 weeks) and then complete the schedule of events as described above. STOP-BANG: Snoring, Tiredness, Observed Sleep Apnea, Blood Pressure, Body Mass index, Age, Neck Circumference, and Gender; PANSI: Positive and Negative Suicide Ideation; PGIC: Patient Global Impression of Change; PROMIS: Patient Reported Outcome Measurement Information System. Primary Care Post-Traumatic Stress Disorder Screen for DSM-5.

a) PROMIS 29+2 will also be administered every week during the educational intervention.
b) Daily assessments include pain, anxiety, sleep, and cannabis use characteristics (route of administration, dose, cannabinoid content).

Anticipated Results: We hypothesize that participants immediately receiving the educational intervention will report greater improvements via the Patient Global Impression of Change and across secondary outcomes compared to participants at the end of the waitlist condition. We further hypothesize that participation in the tailored guidance intervention will result in a trajectory of fewer side effects as the intervention progresses.

Data Analysis Plan.

Studies 1 and 2

Primary analysis will use an intent-to-treat analysis and include all randomized participants regardless of their completion of the protocol. The distribution of variables will be examined along with their univariate association with the primary and secondary outcomes. Transformations will be applied if necessary. Descriptive statistics such as means, medians, standard deviations, range, frequencies, and percentages will be generated overall, by "equipoise strata" and by intervention assignment, conditional on the scale of measurement, respectively. We will compare patient characteristics between "equipoise strata": those who chose to be randomized across all options versus those who opted out of full-spectrum CBD. In all analyses, a variable indicating the strata of whether individuals chose to be randomized across all options vs. opted out of full-spectrum will be included to account for possible differences in the patients associated with the decision about if THC is an acceptable option to receive.

Descriptive statistics and univariate comparisons will be applied to test the equality of means or conditional proportions between intervention arms within strata to check the randomization process, however no formal p-values will be reported. If assumptions are not met, we will instead use non-parametric methods such as Wilcoxon two-sample test and Fishers Exact test. Missingness will be examined by "equipoise strata" and randomization arm to determine whether there is a differential drop-out. Using two-sample t-tests, chi-square tests, and potentially their non-parametric equivalents, we will compare the characteristics of completers and drop-outs. We will examine patterns of missing data and use multiple imputation methods for missing outcome measures under appropriate missingness assumption. If there are any differences between completers and drop-outs, we will account for those variables in our imputation models. We will use regression-based imputation methods to account for uncertainty in data and generate unbiased estimates and their variances. All statistical hypothesis tests will use two-sided $\alpha = 0.05$ for significance testing.

Study 1. The primary hypothesis is to investigate the difference in PGIC at 12 weeks between those who receive CBD versus those on placebo. The PGIC outcome from participants who received any CBD, regardless of whether they opted

out of full-spectrum CBD, will be pooled and compared to those who received placebo. If we observe a significant effect of CBD vs. placebo, exploratory analysis will consider all pairwise comparisons of broad-spectrum CBD vs. placebo, full-spectrum CBD vs. placebo and broad-spectrum CBD vs. full-spectrum CBD with emphasis on point estimates of the difference and corresponding 95% confidence intervals. Linear regression with PGIC at 12 weeks and the variable of interest as an indicator of CBD vs placebo and control for "equipoise strata" via an indicator of randomized including full-spectrum CBD, or not will be used. Covariates such as age, sex, race/ethnicity, comorbid symptoms (e.g., anxiety, sleep disturbance), pain phenotype (nociplastic vs. nociceptive vs. neuropathic vs. pain of various etiologies), will be included in secondary analyses.

Secondary outcomes, including both PROs and Fitbit-derived objective measures, will be analyzed using linear mixed effects models (with any transformation necessary) to explore longitudinal changes. Mixed effects models will compare the pooled CBD vs. placebo groups with a random intercept for the participant and random slope of time and fixed effects of CBD vs. placebo, "equipoise strata", time, and the interaction between time and treatment. The covariates described above will be included. As sensitivity analyses, we will conduct per protocol analyses considering the (dose of) treatment consumed, as opposed to only the assigned intervention group.

Study 2. As the primary and secondary outcomes are the same for each study, analyses will be similar. Primary analysis will compare PGIC in the tailored guidance vs. usual practice groups at end of treatment using a two-sample t-test, with secondary analysis employing linear regression controlling for covariates such as age, sex, race/ethnicity, comorbid symptoms (e.g., anxiety, sleep disturbance), pain phenotype (nociplastic vs. nociceptive vs. neuropathic vs. pain of various etiologies). Secondary analyses will use linear mixed effects models as explained above in study 1, only without the equipoise strata. We will also use the same approach for secondary outcomes.

As we will collect detailed cannabis use data among those in the tailored guidance vs. usual practices groups, we will be able to adjust for individuals in the usual practices who may already be using products in a way that is consistent with the best practices from the educational intervention in per protocol analyses. We will also explore trajectories in use patterns after the intervention.

Safety outcomes. In both studies, continuous safety monitoring will occur for each treatment arm employing Bayesian toxicity monitoring.[271]

Sample Size

Study 1

This sample size calculation depends on the ratio of participants who receive placebo versus broad + full-spectrum CBD and given the modified equipoise stratified design, these are unlikely to be equal numbers. We anticipate at most 85% of participants allowing randomization to full-spectrum CBD, leading to a maximum imbalance ratio between the CBD and placebo groups of 1.73. For 80% power to detect a relatively small, or specifically, a Cohen's d effect size of 0.30 in PGIC between those who receive CBD vs. placebo, we require 240 participants receiving CBD and 139 receiving placebo assuming a two-sided type I error of 5% and a two-sample t-test. To account for 20% attrition (either through screen fails or loss to follow up), we plan to enroll 455 participants. We based our estimate of retention from two recent studies led by Dr. Bohnert: one of Veterans with chronic pain, which had follow-up rates exceeding 95% over 1 year, and another ongoing study using MyDataHelps to remotely recruit and follow patients with mental health symptoms, which has follow-up rates exceeding 90% over 6 months.

Study 2

We have selected our sample size to ensure we are sufficiently powered (i.e., 80%) to detect an effect size that is relatively small, or specifically, a Cohen's d effect size of 0.30 in PGIC between individuals who received immediate treatment vs. those at the end of the waitlist control period. Assuming a two-sample t-test, a two-sided $\alpha = 0.05$ assuming 20% attrition as in Study 1, this translates to our selected sample size of 352/.8= 422 total participants or 211 per arm.

Future Directions and Conclusions

Taken together, the proposed studies will provide a strong foundation for pragmatically using cannabis products for pain management among Veterans and thus reduce downstream risk of Veteran suicide. Our approach will provide vital, actionable data on the therapeutic potential of cannabis products for pain management, which is of great importance given cannabis's negligible overdose risk and the limited effectiveness and concerning side effect profile of many conventional chronic pain medications (e.g., lethal overdose risk from opioids).[272] Our rigorous assessment of whether available CBD products improve pain will provide much needed data on whether this remarkably safe compound has a place in the analgesic pharmacopeia. Through our educational intervention, we will provide considerable scientific structure to already-occurring personal experiments with cannabis, which will yield particularly useful information for Veterans and beyond since Michigan and many of states and countries have legalized or decriminalized cannabis, but not given patients nor providers guidance on appropriate cannabis use. Our ability to investigate pain phenotype and symptom clusters that may predict responsiveness to cannabinoids will inform precision analgesia approaches to determine when and in whom these compounds are most effective. Finally, our community-engagement core will allow for rapid dissemination to Veterans, healthcare providers, and policy makers to promote more sensible use and regulation of these products.

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

Current and Prior Experience and Funding Disclosure

(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.

The resources and robust infrastructure available at the University of Michigan will ensure the success of the proposed study and will provide the research team with a rich environment for conducting research examining buprenorphine initiation. The University of Michigan is one of the best public research universities in the U.S and ranks second in federal research and development funding among all colleges and universities. The intellectual environment at U-M fosters rigorous interdisciplinary research, and views creating an environment for excellence in interdisciplinary research as among its signal achievements. This work will draw on the collaborative resources from several established areas of excellence at U-M.

The University of Michigan

U-M is located on a 3,244-acre campus in Ann Arbor, Michigan, with branch campuses in Flint and Dearborn, Michigan. U-M is ranked first by the National Science Foundation in research and development spending among public universities (second overall) and listed as the top U.S. public university in the QS World Ranking. U-M is also ranked 21st out of 800 ranked universities in the 2016 annual Times Higher Education World Reputation Rankings. The university has top-ten ranked professional schools across the spectrum of health sciences, including Medicine, Dentistry, Nursing, Pharmacy, and Public Health, and >100 graduate programs ranked in the top 10 by U.S. News and World Report total. The U-M College of Literature, Science, and the Arts, the primary undergraduate academic unit, boasts a large number of top ranked academic departments in the natural and social sciences and in the humanities. U-M, and its 19 schools and colleges, supports a student body of >43K with a faculty of >7.5K and a total operating budget of >$6.8B. Annual research expenditures are approximately $1.5B per year. U-M has >90 core facilities that support faculty in the conduct of their research, and the university has >2.8M square feet of lab space for research and teaching. The university was rated the 8th most innovative university in the world by Reuters in 2018. U-M is a national leader in securing private sector support from its friends and alumni; it has >500K living alumni around the world. An elected Board of Regents, of which each member is elected to an 8-year term without term limits, governs the university. U-M is committed to expanding and deepening biomedical research. One strength of U-M is the North Campus Research Complex, which is devoted primarily to interdisciplinary health-related research. This 30-building research campus includes the Institute for Healthcare Policy and Innovation (which hosts Michigan OPEN) as well as research laboratories, research and administrative office space, collaboration and training venues, and MCity, a 32-acre outdoor laboratory with the world's first full- scale simulated city designed for testing the performance of connected, automated, and autonomous vehicles. The environment at North Campus Research Complex is translational in nature, housing U-M resources and crucial scientific core facilities specifically designed to foster collaboration and innovation with the goal to move scientific discoveries from the lab to the marketplace and clinic.

The University of Michigan Medical School

The U-M Medical School (UMMS), a leading partner of MICHR and part of Michigan Medicine, is one of the nation's powerhouses of biomedical research. The rich history of firsts and bests in medicine helped make UMMS a leader in healthcare research. Accomplishments include generous and consistent support from the National Institutes of Health (NIH), collaborations with U-M's preeminent professional programs, and a track record of engagement in the world's most important clinical trials. In FY 2021, faculty from UMMS received $720M in awards from a large portfolio of external sponsors. Annual NIH grant funding awarded to the school's clinical researchers and biomedical scientists reached $443M in FY 2021. According to data gathered in FY 2021, faculty were engaged in >1,890 active clinical trials and authored 8,951 publications. In FY 2021, UMMS researchers filed 205 reports of new inventions with U-M Office of Technology Transfer. UMMS has also implemented a Strategic Research Initiative, which has resulted in groundbreaking, innovative science and is "fast forwarding" biomedical research at U-M and shaping the future of human health and global healthcare policy.

Michigan Medicine and Department of Anesthesiology

Based in Ann Arbor, Michigan, Michigan Medicine is a premier academic medical center made up of patient care, education, and research facilities that are among the most comprehensive and sophisticated in the nation and the world. In addition, Michigan Medicine is composed of a network of specialty care centers and clinics throughout Michigan. Michigan Medicine includes three major hospitals and 40 outpatient locations with >150 clinics. The physical plant is composed of 124 buildings (including 30 at the North Campus Research Complex), encompassing >11M square feet. Patient care at Michigan Medicine is carried out by 3,160 physicians and faculty members and nearly 5,000 nurses. Michigan Medicine provided 2.1M outpatient visits and >48K inpatient stays in Fiscal Year (FY) 2016. The U.S. News and World Report ranked Michigan Medicine 6th in their 2017-2018 U.S. News Best Hospitals Honor Roll, #9 for research medical schools, and #5 for primary care medical schools. The University of Michigan ranks second in the United States in federal research and development funding amongst all colleges and universities. Specifically, the Department of Anesthesia has a strong commitment to academic excellence. The Department of Anesthesiology is ranked #1 in the nation for NIH funding for the last several years. These statistics reflect the institutional commitment to academic scientific endeavors, including the resources and protected time necessary for successful research. Drs. Boehnke, Bohnert, Bergmans, Clauw, Williams, Kheterpal, Shah, and McAfee have primary appointments in the Department.

Chronic Pain and Fatigue Research Center (CPFRC) – *Daniel J. Clauw, M.D., Director, David A. Williams, Ph.D. Associate Director*

Located in Lobby M - Suite 3100 of the Domino's Farms Office Complex, the UM CPFRC is comprised of an investigative team of over 30 individuals with considerable experience in conducting clinical research in the areas of cognitive/behavioral, observational, functional imaging (fcMRI, ^{1}H-MRS, etc.), and drug trials, both federally and non-federally sponsored.

Office: The Center is comprised of 12 offices, 20 staff cubicles, a kitchenette, and storage space. All offices are equipped with high-speed internet connectivity, and all offices and cubicles are equipped with desktop computers and phones. CPFRC has standard and color laser printers as well as copier, fax and scanning capabilities and several small conference/meeting rooms and one large conference room equipped with a state-of-the-art audio-video system for large group video conferencing. The location and configuration of the space promotes collaboration among the CPFRC faculty and clinical researchers from across campus.

Michigan Anesthesiology Informatics and Systems Improvement Exchange (MAISE)

The Michigan Anesthesiology Informatics and Systems Improvement Exchange (MAISE) is part of the University of Michigan Department of Anesthesiology. This unit is comprised of software developers, desktop support specialists, project managers, system and applications analysts, database experts, data scientists, nurses, and physicians, whose mission is to improve the care of our patients through the development of novel software, facilitation of research, service of innovative technologies, and support of department as well as enterprise operations

Under the leadership of Sachin Kheterpal, MD, MBA, Professor and Associate Dean for Research IT, Nirav Shah, MD, Associate Professor and Director, Informative and System Improvement, and Peter Bow, Director, Anesthesiology Informatics, MAISE collaborates with colleagues at University of Michigan and hospitals across the country to enable research and quality initiatives, develop software with deep expertise in managing PHI, web development database integration, user interfaces, and big data, and helps optimize business and clinical workflow.

Research Pharmacy

The Research Pharmacy (RP) ensures that clinical trials involving medications, including investigational drugs, are conducted safely, efficiently, and in compliance with study protocols and applicable regulations. In doing so, the RP participates on the UM Medical School Institutional Review Board (IRB) by reviewing protocols for approval and continuing review. The RP will only handle protocols that have been IRB approved. Additionally, the RP adheres to federal law, study sponsor protocols, the Joint Commission regulations, and University of Michigan Health System policies in conducting its work.

Experience of Study Team

Our team has relevant expertise in clinical trials, health effects of cannabis, and recruiting veterans and studying veteran-specific health concerns, indicated in part by published work in each of these areas by our co-PIs. These studies have utilized a variety of study designs for delivering useful educational interventions as well as using cutting-edge techniques for measuring symptom burden and drug use, including patient-reported outcomes, neuroimaging, virtual and in-person therapy, educational interventions, and FDA-approved drug studies.

Clinical Trials. The principal investigators of this proposal have extensive experience in leading and managing clinical trials, including with veterans.[21,55,57,62,76,78,145,153,159,160,165,201,273-293] Of relevance to the current project, we have shown that: 1) educational interventions show clinical and statistically significant effects on chronic pain symptoms, 2) brief virtual visits with health counselors can reduce risk of drug overdose and non-medical drug use; 3) we have the proven ability to design and complete complex interventional studies with FDA approval. The investigative team has successfully recruited, randomized, and retained thousands of participants in medication and behavioral clinical trials to date, including using remote/digital recruitment methods. The team is also able to engage support, if needed, specifically for trials management from the Clinical Trials Support Unit of the University of Michigan Medical School.

Health Effects of Cannabis. The principal investigators of this proposal have extensive experience in performing cannabis research - both examining potential benefits as well as harms of cannabis products.[2-9,11,12,156,294,295] Of relevance

to the current project, we have shown that naturalistic cannabis product use is associated with positive clinical impacts, including improved symptom management and substitution of cannabis for medications with greater risk profiles (e.g., opioids). However, this use is typically not overseen by medical providers, leaving many patients without clear guidance on how to appropriately use these products for their health conditions, potentially leading to harmful or suboptimal outcomes.

Recruiting Veterans and Studying Veteran-specific Health Concerns. Our study team has extensive experience in recruiting and studying veterans as well as conducting impactful research aimed at understanding and improving Veteran health.[65-70,72-78,82,83,107-117,123,126-142,144] In particular, we have elucidated many risk factors associated with Veteran suicide (including pain of various etiologies, anxiety, benzodiazepine, and opioid use) and conducted clinical trials to develop innovative ways of improving Veteran healthcare.

(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.

Of our team, Dr. Bohnert has been continuously funded as the principal investigator of contracts totaling over $4 million from the State of Michigan since 2017. Specifically, Dr. Bohnert leads the Michigan Opioid Collaborative, which is supported by contract from the Michigan Department of Health and Human Services, with funds originating from SAMHSA under the State Targeted Response and State Opioid Response federal initiatives. Blue Cross Blue Shield of Michigan became an additional sponsor and partner in 2020.

The Michigan Opioid Collaborative provides support to clinicians with the goal of expanding access to medications for opioid use disorders. Behavioral Health Consultants located in each region of the state conduct outreach to clinicians in their area to assess interest in medications for OUD, provide information about training opportunities, and address myths about addiction and OUD medications. They participate in community organizations (e.g. county Opioid Task Forces), and address other barriers in each community, (e.g., identifying pharmacies willing to carry buprenorphine). For interested clinicians, the program offers same-day consultation on patient issues from addiction-boarded physicians located at the University of Michigan and Michigan State University. Program team members also provide technical assistance to clinics determining care processes and staff training gaps. In 2020, services expanded to include consultation of Hepatitis C Virus pharmacotherapy, stigma training led by a peer support specialist, and expanded training on co-occurring substance use disorders. In 2021 alone, the program has delivered the “x-waiver” training necessary to prescribe buprenorphine outside of opiate treatment programs to 390 clinicians. These efforts have resulted in the formation of a state-wide network of over 481 clinics.

State-wide Pilot of Remote Behavioral Care. As part of the Michigan Opioid Collaborative program, we conducted a single arm clinical pilot study of remote counseling that has prepared us for statewide-recruitment efforts. We recruited 43 patients from 13 clinics, representing a mix of geographic regions. In this sample, 95% of patients were being treated with buprenorphine, and 56% reported chronic pain, defined as a mean of 5 or greater of the worst and average pain in the last 3 months on the Numeric Rating Scale.[94] The average number of years of chronic pain was 9.3. The sample was 52% female, 34% employed, 9% Hispanic, 19% Black, 77% White; one NA/AI person was recruited. Participants were offered 8 tele-counseling sessions delivered by therapists, with 57% completing all 8 sessions, and 80% completing at least 4. Of those with follow-up data, collected 2-7 months post-baseline, 91% were still prescribed buprenorphine. This study established the feasibility of state-wide recruitment clinics and the acceptability of remote recruitment and care to the participants through our research infrastructure.

The Michigan Opioid Collaborative has been successful in meeting its objectives and in developing and maintaining partnerships. Dr. Bohnert is also a co-investigator of the Michigan Opioid Prescribing Engagement Network (M-OPEN), a University of Michigan program that seeks to improve opioid analgesic prescribing and related opioid safety practices at hospitals throughout Michigan, also funded through contracts with state government. Collectively, the two programs establish our team’s capacity to responsibly manage State of Michigan funding and produce deliverables in a timely manner.

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

Current Support and Support over the Past Ten Years has been provided for the Principal Investigators and Co-Investigators at the University of Michigan on pages 35-78.

BOEHNKE, KEVIN F. PH.D.

Current

K01 DA049219 (Boehnke, K) 07/15/20 – 06/30/24
NIH/NIDA $569,355 Total Award Amount
Cannabinoid Effects on Central and Peripheral Pain Mechanisms in Osteoarthritis of the Knee
The primary goal of this K01 award is to provide me with additional training that will allow me to unify chronic pain and cannabinoid mechanisms as an independent researcher.
Role: Principal Investigator

R01 AT010381 (Harris, RE / Harte, SE) 08/01/20 – 07/31/25
NIH/NCCIH $3,489,509 Total Award Amount
Cannabinoid interactions with central and peripheral pain mechanisms in osteoarthritis of the knee
The studies proposed herein are the first attempt to understand how THC and CBD affect different chronic pain mechanisms in humans by examining the effects of these compounds on knee OA in individuals with varying degrees of pain centralization.
Role: Co-Investigator

R34 AR078435 (Boehnke, K-Contact/Gagnier, J)07/01/21 – 12/31/23
NIH/NIAMS $274,560 Total Award Amount
Planning Grant for a Clinical Trial of Cannabidiol for Postoperative Opioid Reduction in Primary Total Knee Arthroplasty
In this study, our aim to is develop study procedures for a randomized, double-blinded, controlled trial to characterize the opioid-sparing effects of cannabidiol (CBD) administered postoperatively following total knee arthroplasty.
Role: Principal Investigator

R01 AT011341 (Braley, T-Contact / Kratz, A) 08/15/21 – 05/31/26
NIH/NCCIH $3,351,287 Total Award Amount
NSS Mechanisms of cannabidiol in persons with MS: the role of sleep and pain phenotype
Major Goals: Changes in sleep microstructure (Aim 1; including sleep stage bout length, sleep stage transition probability, and entropy) and macrostructure (Aim 2; including sleep regularity, rhythmicity, timing and duration) will be compared between cannabinoid and placebo groups, and pain phenotype will be assessed as a predictor of CBD-related changes in sleep. Aim 3 will assess the measures of sleep microstructure and macrostructure as mediators of analgesic response to CBD. Data generated from this study will inform CBD research, across a spectrum of neurological and other chronic conditions, that can be applied to the development of precision-medicine approaches for chronic pain.
Role: Co-Investigator

Past Support

K12 DE023574 (Clauw, DJ-Contact/Kapila, S) 07/01/13 – 06/30/19
NIH/NIDCR $172,800 Total Award Amount
University of Michigan's TMJD and Orofacial Pain Interdisciplinary Consortium
The goal of this K12 program is to train a cadre of high caliber clinician scientists and basic scientists to enhance the number and quality of interdisciplinary researchers that can appropriately unravel the mechanisms and most effective treatments for TMJD/OP.
Role: Postdoctoral Fellow, *support 09/01/17 – 06/30/19

Dow Sustainability Fellow (Boehnke, K) 09/01/15 – 08/31/17
Graham Institute of Sustainability $25,000 Total Award Amount
Risk of infection from waterborne Helicobacter pylori in Lima, Peru: Examining sustainable solutions through an integrated assessment approach
The purpose of this project is to train the individual to develop an interdisciplinary approach to thinking about science in society, and to bring this approach to research on characterizing risk from waterborne *Helicobacter pylori*.
Role: Principal Investigator

BOHNERT, AMY S.B., PH.D.

Current Support

E20221440-00 / H79TI083298 (Bohnert/Lin) 10/01/2021-09/30/2022
MDHHS/SAMHSA $750,000 Total Award Amount
The Michigan Opioid Collaborative: State Opioid Response 2
This project will use telementoring and consultant services to increase access to medication assisted therapy (MAT) for individuals with Opioid Use Disorders (OUD). Specifically, the program will help to increase the workforce of physicians prescribing medications used in MAT, increase clinician access to training on counseling services that accompany those medications in MAT, and provide a process for linkages to other OUD treatment in the community.
Role: Principal Investigator

E20221872-00 (Englesbe/Brummett/Waljee) 10/01/2021 – 09/30/2022
Medicaid/MDHHS - MA-2021 Master Agreement Program $2,156,243 Total Award Amount
Michigan Opioid Prescribing Engagement Network (M-OPEN)
The overall goal of this initiative is to reduce the amount of opioids prescribed to surgical patients by 50%, reduce new chronic postoperative opioid use by 50%, and reduce opioid diversion into our communities.
Role: Co-Investigator

R01 DA039159 (Bohnert, A) 05/01/2016-01/31/2023 (NCTX)
NIH-NIDA $2,817,357 Total Award Amount
Reducing Non-Medical Opioid Use: An automatically adaptive mHealth Intervention
This study is a phase - III clinical trial of the intervention compared to an enhanced usual care condition with 600 ED patients. This study will also involve focus groups of patients and ED clinicians in order to understand issues related to implementation of the intervention.
Role: Principal Investigator

Bohnert, A / Sen, S 01/01/2019-12/31/2022
Internal/Precision Health $1,081,717 Total Award Amount United States
Precision Health: Enhancing Mental Health Care through Mobile Technology
The overall goal of this project is to reduce the burden of depression by two means: first, by increasing capacity in the mental health care system through expanding use of mobile technology–delivered interventions, and second, by accelerating recovery from mental illness by better matching pharmacological, psychological, and mobile-based treatments to patients. Researchers will use machine learning to identify key predictor of treatment response from mobile technology, genomic, and environmental data collected from patients.
Role: Co-Director

OPD-1511-33052 (Krebs, E) 11/01/2019-10/31/2022
University of Minnesota/PCORI $354,604 Total Award Amount
Veterans Pain Care Organizational Improvement Comparative Effectiveness (VOICE) Trial
This study will test which of two pain treatment strategies is better for managing pain and helping patients improve safety of opioid medication. For patients on high opioid doses who want to reduce, this study will also test whether

offering an extra option for tapering (buprenorphine-naloxone) helps them succeed. Finally, the study will examine patients' and clinicians' experiences with the interventions.
Role Co-Investigator

Brummett, C 01/01/2017 – 12/31/2022
University of Michigan $959,572 Total Award Amount
Institute for Health Policy and Innovation (IHPI)
Precision Health Opioid Use Case
The overall goal of this project is to test and test and refine the resources and infrastructure most useful to researchers relating to opioid prescribing in the pre-surgical setting.
Role: Associate Director

Agreement (Bohnert, A) 01/01/2020-12/31/2022
Blue Cross Blue Shield of Michigan $3,639,345 Total Award Amount
Michigan Opioid Collaborative
The primary goal of this service project is to provide mentoring to BCBS network providers related to prescribing medications to treat opioid use disorder. Target rural Michigan counties to help engage providers with medication assisted treatment with mentoring support. This includes partnering with other BCBS grantees/partners to help support PQI/PGIP.
Role: Principal Investigator

R49 CE03085 (Carter, P) 08/01/2019 – 07/31/2024
DHHS / CDC $7,347,477 Total Award Amount
University of Michigan Injury Prevention Center 2019-2024
The University of Michigan Injury Prevention Center provides the infrastructure to coordinate a collaborative injury prevention agenda focused on the prevention of opioid misuse/overdose, suicide, youth/sexual violence, concussion, motor vehicle crash, and are beginning a portfolio in older adult falls. Adverse childhood experiences are a crosscutting and underlying risk factor for all of focus areas.
Role: Co-Investigator

UH3 DA050173 (Walton, M / Bonar, E) 09/30/2019-08/31/2024
NIH/NIDA $5,870,743 Total Award Amount
Optimized Interventions to Prevent Opioid Use Disorder among Adolescents and Young Adults in the Emergency Department
This project will adapt promising remote health coach-delivered interventions, and pilot test feasibility/acceptability among adolescents and young adults. Then, we will evaluate the efficacy of interventions and their combinations to prevent/reduce opioid misuse among adolescents and young adults in the emergency department. Finally, we conduct an economic evaluation to identify the most efficacious intervention combination for preventing opioid misuse and implement it in the emergency department among adolescents and young adults.
Role: Co-Investigator

SDR 21-107 (Lagisetty/Bohnert) 01/01/2022-12/31/2025
VA Health Administration–HSR&D $1,188,045 Total Award Amount
Diagnosing and Treating Veterans with Chronic Pain and Opioid Misuse
Using an automated identification chart review algorithm, the project will compare effectiveness of readily available treatments for Veterans with chronic pain and opioid misuse.
Role: Co-Principal Investigator

IIR 19-431 (Wachterman/Bohnert (LSI)) 07/01/2021-06/30/2025
VA Health Administration–HSR&D $1,195,847 Total Award Amount
Optimizing Pain Management in End-Stage Renal Disease Among Veterans (OPERA-Vets): Balancing Benefits and Harms of Opioids

To evaluate potential implications of VA's system-wide opioid safety initiatives on patient-centered outcomes among Veterans with end-stage renal disease.
Role: Co-Investigator

C19 21-278 (Ioannou, Bohnert, Boyko, Maciejewski)
C19 21-279 (Iwashyna, O'Hare, Hynes, Bowling)
VA Health Administration–HSR&D 05/01/2021-04/30/2024
$3,369,599 Total Award Amount
COVID-19 Observational Research Collaboratory (CORC) Coordinating Center (C19 21-278) and Long-term Outcomes Study (C19 21-279)
This project will establish a Collaboratory aiming to study the long-term adverse outcomes of COVID-19 infection in the VA using a variety of experimental approaches.
Role: Co-Investigator

Past Support

IIR 16-235 (Blow) 06/01/2018-05/31/2022
VA Health Administration–HSR&D $1,446,071 Total Award Amount
Improving Outcomes for Emergency Patients with Alcohol Problems
This study is a randomized controlled trial to facilitate reductions in alcohol use and to link Veterans with alcohol problems to needed primary and specialty care including other needed services such as homeless outreach and case management where needed.
Role: Co-Investigator

IIR 16-210 (Maust) 02/01/2018-01/31/2022
VA Health Administration–HSR&D $1,097,796 Total Award Amount
Addressing inappropriate benzodiazepine prescribing among older Veterans
The aims of this project are: 1) identify high- and low-performing facilities on acute and chronic BZD prescribing among those facilities that prioritized the BZD≥75 measure; 2) assess facility-level strategies to address BZD≥75 prescribing, the associated barriers and facilitators, and acceptability of these strategies to older Veterans through semi-structured interviews and site visits; and 3) identify and pilot test context-sensitive strategies for facilities to successfully reduce acute and chronic BZD use among older adults.
Role: Co-Investigator

COR 19-490 (Ilgen) 07/01/2019-06/30/2021
Suicide Prevention Research Impact NeTwork (SPRINT)
Suicide prevention is VHA's number one clinical priority, and multiple, important suicide prevention research gaps need to be addressed. The mission of the "Suicide Prevention Research Impact NeTwork (SPRINT)" is to accelerate health services suicide prevention (SP) research that will improve care and result in reductions in suicide behaviors among Veterans.
Role: Co-Investigator

IIR 16-078 (Olivia) 12/01/2018-11/30/2021
VA Health Administration–HSR&D
Effectiveness of a Rescue Medication in Preventing Opioid Overdose in Veterans
The aims of this project are: 1) Characterize naloxone distribution within VA and patient-, prescriber-, and setting-related factors associated with distribution. 2) Assess whether naloxone distribution to at-risk Veterans compared to similar at-risk Veterans who did not receive naloxone is associated with reduced fatal and non-fatal opioid overdose.
Role: Co-Investigator

U01 CE002780 (Bohnert) 09/01/2017-08/31/2020
CDC-DHHS $799,823
Heroin use and overdose following changes to individual-level opioid prescribing

Heroin-related overdose deaths more than tripled between 2010 and 2014 in the United States. Emerging evidence has identified nonmedical use of prescription opioids as a risk factor for heroin initiation. Some have observed that the spike in heroin overdose deaths has overlapped with efforts to reduce the nonmedical use of prescription opioids; however, a causal link has not been established. Using analysis of medical records for over 50 million Americans and in-depth interviews with patients, this study will seek to inform prevention efforts by examining the association between individual-level opioid prescribing patterns – in particular tapering or discontinuation of opioids – and the risk of heroin use and overdose.
Role: Principal Investigator

R01 DA042859 (**Brummett, C / Waljee, J)** 07/01/2017-04/30/2022
oPIOIDS: Prevention of Iatrogenic Opioid Dependence after Surgery
The purpose of this study is to better understand the factors that put people at risk of long-term opioid use so that these patients can be prescribed alternative pain management strategies when having surgery. This study will examine new prescription drug claims data with existing clinical and genetic data as well as the opioid prescription fulfillment data to assess patient characteristics associated with greater opioid ascertainment.
Role: Co-Investigator

Grant Agreement (Lagisetty, P) 11/12/2018-01/14/2022 NCTE
Michigan Health Endowment Fund $498,596 Total Award Amount
Enhancing Treatment Access for Abandoned Chronic Pain Patients
This project aims to quantify primary care access for patients on long-term opioid therapy (LTOT) for their pain utilizing an audit, 'secret shopper' methodology. In addition, qualitative interviews will elicit feedback from providers, office staff, and patients on their experiences with treating pain and opioid prescribing. These findings will be used to convene a Delphi panel of experts to create recommendations to the State of Michigan for how to best care for this patient population.
Role: Co-Investigator

E20213472-00 / H79TI081712 (Bohnert/Lin) 10/01/2020-09/30/2021
MDHHS/SAMHSA $400,000 Total Award Amount
Michigan Opioid Collaborative - State Opioid Response FY21
This project will build upon the connections of the Michigan Opioid Collaborative with physicians in areas of Michigan with limited access to MAT to provide telehealth support for opioid use disorders.
Role: Principal Investigator

E20213600-00 / H79TI083298 (Bohnert/Lin) 10/01/2020-09/30/2021
MDHHS/SAMHSA $1,290,728 Total Award Amount
The Michigan Opioid Collaborative: State Opioid Response 2
This project will use telementoring and consultant services to increase access to medication assisted therapy (MAT) for individuals with Opioid Use Disorders (OUD). Specifically, the program will help to increase the workforce of physicians prescribing medications used in MAT, increase clinician access to training on counseling services that accompany those medications in MAT, and provide a process for linkages to other OUD treatment in the community.
Role: Principal Investigator

E20213443-00 (Englesbe/Brummett/Waljee) 10/01/20 – 09/30/21
$2,156,243 Total Award Amount
Medicaid/MDHHS - MA-2021 Master Agreement Program
Michigan Opioid Prescribing Engagement Network (M-OPEN) (AWD16455-SUB030)
The overall goal of this initiative is to reduce the amount of opioids prescribed to surgical patients by 50%, reduce new chronic postoperative opioid use by 50%, and reduce opioid diversion into our communities.
Role: Co-Investigator

(Bohnert/Lin) 10/01/2019-09/30/2020

MDHHS/SAMHSA $1,950,479 Total Award Amount
Michigan Opioid Collaborative - State Opioid Response FY20
To provide this type of support to clinics in rural area of Michigan, we propose to engage in the following activities: 1. Over a period of 3 months, conduct a needs and capacity assessment with clinics and providers currently offering MAT or interested in offering MAT to their patients, and also interested in using telehealth to support MAT. 2. Provide nurse care manager-led telehealth for MAT, following the Collaborative Care Model of Office-Based Opioid Treatment developed in Massachusetts, which has been found to be effective for in-person MAT. The telehealth program will also be supported by a team of addictions psychiatrists and other University clinical staff, consistent with this model. In compliance with telehealth laws related to controlled substances, prescribers local to the patient will be a member of the collaborative care team and retain primary responsibility for prescribing. 3. Also as part of the collaborative care team. we will offer telehealth-based psychotherapy to clinics that identify this as a gap to their ability to provide MAT. 4. We will create a dissemination toolkit to ensure that the program can be replicated.
Role: Principal Investigator

IIR 13-322-2 (Bohnert) 07/01/2015-03/31/2021
VA Health Administration-HSR&D $324,372 Total Award Amount
Primary Care Intervention to Reduce Prescription Opioid Overdoses: Prescription Opioid Safety Trial (POST)
This project aims to determine the safety of high-dose opioid use among Veterans presenting to primary care and mental health clinics, it is of critical importance to involve researchers who have expertise in overdose risk, opioid use, primary care and mental health care settings, pharmacoepidemiology, and longitudinal data analysis, as well as sufficient support staff.
Role: Principal Investigator

R03 AG042899 (Bohnert, A) 08/01/12 – 07/31/14
NIH/NIA $155,500 Total Award Amount
Safety of Opioids for Older Adults: Determinants of Opioid Overdose Risk
The primary specific aims will be to examine the relationship of specific opioid formulations, interactions with other medications (particularly other central nervous system depressants), and the timing of treatment (length of continuous opioid treatment, number of days supplied at once) in relation to the outcomes of interest.
Role: Principal Investigator

R34 DA0358331 (Bohnert, A) 03/01/2014 – 08/31/2017
NIH/NIDA $677,747 Total Award Amount
Developing a Prescription Opioid Overdose Prevention Intervention
The purpose of this project is to refine a three-session brief intervention focused on reducing personal overdose risk and improving response to witnessed overdoses among individuals in substance use disorder treatment reporting recent non-medical prescription opioid use and to pilot test randomized controlled procedures comparing the intervention to a control condition. Study findings will inform a full-scale randomized controlled trial of an intervention with the potential to reduce overdose mortality associated with prescription opioid use.
Role: Principal Investigator

BERGMANS, RACHEL, PH.D.

Current

U19 AR076734-01S4 (Clauw, D/Hassett, A) 09/01/2021 – 05/31/2024
Supplement PIs: (Bergmans, R/Janevic, M) $583,491 Total Supplement Award Amount
NIH/NIAMS $8,969,433 Total Award Amount
University of Michigan BACPAC Mechanistic Research Center – Supplement
This is a supplement to an ongoing study of the mechanisms underlying treatments for chronic low back pain (cLBP). As part of the BACPAC initiative, the mechanistic research center at the University of Michigan aims to be a team member in realizing the vision of personalized medicine for individuals with cLBP. This project will support a robust effort to

enhance patient and other stakeholder engagement, particularly that of underrepresented minorities, and to implement a sustained outreach effort to the historically underserved Black and Hispanic communities in and around Detroit and Flint, Michigan, and a Stakeholder Advisory Board will be established to provide input across all phases of the main study.
Role: Supplement Principal Investigator, *support begins 7/1/22

No. 2022-1648 (Gudjonsson/Bergmans/ et al) 12/01/2021 – 11/30/2024
University of California-Irvine $831,549 Total Award Amount
Ancestry Dependent Mapping of Skin at a Single Cell Level UCI-CZI
The objective of the Michigan "Single-cell Mapping of Skin across Ethnically and Spatially Diverse Scales" application for the Chan Zuckerberg Initiative, and the Human Cell Atlas is to: 1) Build an effective Community Engagement Approach within minority populations in the greater Detroit Area, 2) Collect skin biopsies from scalp, sun-protected and sun-exposed skin from 100 healthy individuals who belong to specific minority groups. This work will provide information about biological processes in the skin and serve as a foundation for elucidation of
pathogenic mechanisms for skin diseases that predominantly affect minority populations, such as SLE in African American populations
Role: Co-Principal Investigator, *support begins 7/1/22

T32 AR007080 (Knight, J) 07/01/1976-06/30/2023
NIH/NIAMS $1,405,625
The goal of this application is to provide comprehensive training for future independent researchers who will lead the efforts to better understand the mechanisms underlying human rheumatic autoimmune diseases and improve patient care and outcomes.
Role: Postdoctoral Research Fellow, *support ends 06/30/2022

(Bergmans, R) 08/29/18 – 08/28/20
UM Comprehensive Depression Center $25,000 Total Award Amount
The Influence of Climatic Factors and Air Quality on Depression Severity and Suicidality
The objective of this study was to specify the acute impact of speciated aeroallergens and other environmental factors on suicide.
Role: Principal Investigator

R01 AG051142 (Smith, J) 09/15/15 – 06/30/24
NIH/NIA $5,925,104 Total Award Amount
Enhancing Retrospective Life History Data in the Health and Retirement Study
This project will enrich the stock of retrospective information about the lives of participants in the Health and Retirement Study (HRS) from childhood to study entry. We will produce user-friendly aggregated files of partnership, fertility, employment, and health histories and early-life traumatic events that have been collected in different waves of HRS since 1992. Gaps in these data will be supplemented by a Life History Mail Survey (LHMS) which we will design, test, and field in 2017.
Role: Postdoctoral Research Fellow

Past Support

P30 ES017885 (Loch-Caruso, R) 04/01/16 – 03/31/21
NIH/NIEH $25,000 Pilot Project Total Award Amount
Michigan Center of Lifestage Environmental Exposures and Disease
Pilot Project *Linking atmospheric pollen and air pollution to suicide* (6/01/20 – 02/28/21)
This project links environmental data with mortality records to determine whether atmospheric concentrations of speciated aeroallergens increase the risk of suicide.
Role: Pilot Project PI

R01 AG051142 (Smith, J) 09/15/15 – 06/30/24

NIH/NIA $5,925,104 Total Award Amount

Enhancing Retrospective Life History Data in the Health and Retirement Study

This project will enrich the stock of retrospective information about the lives of participants in the Health and Retirement Study (HRS) from childhood to study entry. We will produce user-friendly aggregated files of partnership, fertility, employment, and health histories and early-life traumatic events that have been collected in different waves of HRS since 1992. Gaps in these data will be supplemented by a Life History Mail Survey (LHMS) which we will design, test, and field in 2017.

Role: Postdoctoral Research Fellow

T32 MH073553 (Bruce, M) 09/01/05 – 06/01/21

NIH/NIMH $405,762 Direct Award Amount

Training Geriatric Mental Health Services Researchers

This training program responds to a nationally recognized urgent need to develop new researchers who have the necessary skills to inform the development, dissemination, and implementation of future mental health and substance abuse services for a rapidly growing older population.

Role: Postdoctoral Research Fellow, *support 05/01/19 – 04/30/20

UL1 TR002240 (Mashour, G) 09/17/07 – 02/28/22

NIH/NCATS $48,448,400 Total Award Amount

$150,000 Total Pilot Award Amount

Michigan Institute for Clinical and Health Research (MICHR)

Pilot Project: *Targeting the Gut Microbiome to Improve Psychiatric Treatment Paradigms*

The objective of this pilot project was to determine how specific dietary control alters the microbiome composition to effect clinical outcome measures in a longitudinal study of individuals with bipolar disorder. Our central hypothesis is that a low carbohydrate (CHO) / high polyunsaturated fat (PUFA) diet will increase the fractional representation of specific butyrate producing members of the Firmicutes phylum in the gut microbiome, which will attenuate host inflammation, improve sleep quality, and reduce anxiety in bipolar disorder.

Role: Post-doctoral Fellow, *Support 07/01/18 – 05/31/19

CLAUW, DANIEL J., M.D.

Current Support

U19 AR076734 (Clauw, DJ/Hassett, AL) 09/26/19 – 05/31/24

NIH/NIAMS $8,969,433 Total Award Amount

University of Michigan BACPAC Mechanistic Research Center

As part of the BACPAC initiative, the mechanistic research center at the University of Michigan aims to be a team member in realizing the vision of personalized medicine for individuals with cLBP.

Role: Contact Principal Investigator (MPI)

U01 DK082345 (Clauw, DJ/Clemens, JQ) 09/15/18 – 06/30/22

NIH/NIDDK $1,172,455 Total Award Amount

University of Michigan MAPP Research Network Discovery Site

The goal this project is to study the etiology and treated natural history of UCPPS, to inform better treatments and management of symptoms through improved designs of clinical trials, and to identify clinical factors and research measurements to define clinically relevant sub-groups of these patients. The proposed three-year extension will allow the participating institutions to obtain an additional 12 months of follow-up in the MAPP-II Symptom Patterns Study (SPS), observe additional ATLAS (Analysis of Therapies during Longitudinal Assessment of Symptoms) events in the MAPP-II SPS, and analyze MAPP-II data.

Role: Contact Principal Investigator (MPI)

R01 DA038261 (Clauw, DJ/Brummett, CM) 09/01/15 – 07/31/22 (NCTE)

NIH/NIDA $2,871,151 Total Award Amount
Centralized Pain Phenotype as a Predictor of Opioid Non-responsiveness
The goal of this project is to test if the degree of pain centralization as measured on a simple self-report measure strongly predicts acute opioid pain responsiveness by providing a surrogate measure of endogenous opioid function.
Role: Contact Principal Investigator (MPI)

P50 AR070600 (Clauw, DJ/Brummett, CM) 09/20/16 – 08/31/22 (NCTX)
NIH/NIAMS $7,415,237 Total Award Amount
University of Michigan Fibromyalgia CORT
The goal of this program of research is to understand how fibromyalgia and other rheumatic diseases affect patients, better understand the underlying mechanisms of their pain, and personalize analgesic treatment.
Role: Contact Principal Investigator (MPI) - Program Director

UM1 NS118922 (Brummett/Chang/Clauw/Waljee) 08/01/20 – 07/31/23
NIH/NINDS $6,598,505 Total Award
Transition from Acute to Chronic Pain After Thoracic Surgery
The successful completion of the proposed study and supplement would provide an unparalleled resource for understanding the factors associated with CPSP and will allow for more efficient and personalized trials to prevent the development of chronic pain after thoracotomy and other thoracic surgeries.
Role: Principal Investigator (MPI)

R01 AT010381 (Harris, RE/Harte, SE) 08/01/20 – 07/31/25
NIH/NCCIH $3,489,509 Total Award Amount
Cannabinoid interactions with central and peripheral pain mechanisms in osteoarthritis of the knee
The studies proposed herein are the first attempt to understand how THC and CBD affect different chronic pain mechanisms in humans by examining the effects of these compounds on knee OA in individuals with varying degrees of pain centralization.
Role: Co-Investigator

R01 AT011341 (Braley, T-Contact / Kratz, A) 08/15/21 – 05/31/26
NIH/NCCIH $3,351,287 Total Award Amount
NSS Mechanisms of cannabidiol in persons with MS: the role of sleep and pain phenotype
Major Goals: Changes in sleep microstructure (Aim 1; including sleep stage bout length, sleep stage transition probability, and entropy) and macrostructure (Aim 2; including sleep regularity, rhythmicity, timing and duration) will be compared between cannabinoid and placebo groups, and pain phenotype will be assessed as a predictor of CBD-related changes in sleep. Aim 3 will assess the measures of sleep microstructure and macrostructure as mediators of analgesic response to CBD. Data generated from this study will inform CBD research, across a spectrum of neurological and other chronic conditions, that can be applied to the development of precision-medicine approaches for chronic pain.
Role: Co-Investigator

R01 NR017096 (Hassett, AL/Williams, DA) 05/09/17 – 02/28/23 (NCTE)
NIH/NINR $2,549,712 Total Award Amount
Resilience Skills Self-Management for Chronic Pain
The objective of this application is to evaluate the general effectiveness and impact on telomere health of a resilience-based self-management intervention, the CBT self-management with resilience-enhancing activities (CBTRE) program.
Role: Consultant

UL1 TR002240 (Mashour, GA) 09/17/07 – 02/28/23 (NCTE)
NIH/NCATS $48,448,400 Total Award Amount
Michigan Institute for Clinical and Health Research (MICHR)
The UM CTSA, housed in the Michigan Institute of Clinical and Health Research (MICHR), was created to provide robust infrastructure and support based on strong existing units and programs, as well as academic programs in key clinical and

translational disciplines in order to provide faculty leadership, expertise, and consultation as well as high quality services.
Role: Sr. Associate Director; Co-Director, Research Development Core; Education and Mentoring Core – Predoc Programs Leader

R01 HD088712 (As-Sanie, S/Clauw, DJ) 06/01/17 – 02/28/23 (NCTE)
NIH/NICHD $3,028,770 Total Award Amount
Peripheral and Central Nervous System Correlates of Persistent Post-Hysterectomy Pain
The objective of this study is to characterize role of peripheral and central sensitization among women undergoing hysterectomy for CPP and to explore the utility of preoperative measures of PNS and CNS factors to predict the likelihood of persistent post-hysterectomy pain.
Role: Principal Investigator (MPI)

R01 AR077418 (Sluka, K/Law, L/Schrepf, AE) 09/01/20 – 08/31/25
University of Iowa / NIH Prime $396 646 UM Subco Total Award Amount
Metabolic Biomarkers for Fibromyalgia
The goal of this R01 is to validate a new metabolic biomarker of fibromyalgia and determine its relationship to established mechanisms of the disease.
Role: Co-Investigator

U24 AR076730 (LaVange, LM) 10/01/21 – 05/31/24
University of North Carolina / NIH/NIAMS $691,493 Total Award Amount
BACPAC - Biomarkers for Evaluating Spine Treatments (BEST) Study
This multi-site precision health clinical trial strives to better understand which Chronic low back pain (cLBP) patients respond best to a collection of non-opioid, evidence-based treatments by directly taking into account patient-specific information, including those from racially and ethnically diverse backgrounds.
Role: Co-Investigator

ME-2020C3-20925 (Kidwell, K) 11/01/21 – 01/31/25
PCORI $998,998 Total Award Amount
Design and Methodological Development for a Patient Preference SMART
This project will combine SMART and PRPP designs to produce a PRPP-SMART design, for which we will develop Bayesian statistical methods to estimate treatment effects and tailored sequences of treatments or dynamic treatment regimens (DTRs) using data from all individuals and compare to frequentist methods.
Role: Co-Investigator

D43 TW012027 (Musch, D) 08/17/21 – 07/31/22
H. Lundbeck A/S $86,642 Total Award Amount
Building Non-Communicable Eye Disease Research Capacity in India
The goal of this project is to build on a longstanding partnership between the University of Michigan and Aravind Eye Care System (AECS) in South India. This multifaceted research capacity building program will provide graduate training in epidemiology to faculty at AECS, develop a supportive research ecosystem, and result in a long-term sustainable training program that will make vital contributions to vision research and to addressing the large burden of blindness and vision related disability among older adults in India and beyond.
Role: Co-Investigator

Clinical Trial 19365B (Kaplan, C) 09/20/21 – 07/31/26
NIH/FIC $1,155,469 Total Award Amount
Role: Co-Investigator
Interventional, randomized, double-blind, crossover, placebo-control
This clinical trial includes the following: Initial qualification of individual imaging sites; Perform validation of MRI equipment and facility to ensure the quality of the imaging and quantitative sensory testing (QST) data output.
Role: Co-Investigator

R01 DE024450 (Cevidanes, L) 09/13/19 – 05/31/24
NIH/NIDCR $2,545,710 Total Award Amount
Integrative Predictors of Temporomandibular Osteoarthritis
The goal of this project is to develop efficient web-based data management, mining, and analytics, to integrate and analyze clinical, biological, and high dimensional imaging data from TMJ OA patients.
Role: Co-Investigator

Past Support

R01 AT007550 (Harris, RE-Contact/Napadow, V) 05/01/13 – 10/31/20
NIH/NCCIH $117,474
Neuroimaging Approaches to Deconstructing Acupuncture for Chronic Pain
Our overall goal is to evaluate the impact of acupuncture-induced somatosensory afference on altered neurobiology and analgesia in FM.
Role: Co-Investigator

SAV-MD-09 (Clauw, D.) 04/22/10 – 05/31/12
Forest Laboratories, Inc. $592,470
A single-center, randomized, double-blind, placebo-controlled, two-way crossover study to evaluate the effect of milnacipran on pain processing and functional magnetic resonance imaging activation patterns in patients with Fibromyalgia.
The objective of this study is to evaluate the effect of milnacipran on pain processing in patients with fibromyalgia and to assess the correlation between this effect and neural activation patterns during functional magnetic resonance imaging.
Role: Principal Investigator

R01 AR057808 (Lumley, M. – Wayne St. Univ.) 08/15/10 – 06/30/15
NIH/NIAMS $204,037 (UM Subcontract Dir Costs)
Emotional Exposure and Cognitive Behavioral Therapies for Fibromyalgia
This application combines the clinical research, pain, and FMS expertise of two research teams to conduct a 2-site, randomized, controlled trial of emotional exposure therapy (EET) against both a standard cognitive-behavioral therapy (CBT; pain coping skills training) and control condition (FMS education and support) in a design that controls for the importance of exercise, non-specific factors, and experimenter allegiance to the different treatments.
Role: Co-Investigator

R01 AR060392 (Clauw, D./Brummett, C.-MPI) 08/01/11 – 05/31/16
NIH/NIAMS $437,235
Central Nervous System Mechanisms in Knee Osteoarthritis (KOA)
The goal of this project is to show that simple clinical testing easily performed at the point-of-care can reliably segment chronic pain patients into those with prominent central components to their pain, that are likely to need different pharmacologic (i.e. centrally acting analgesics) and non-pharmacologic approaches (not surgery). Moreover this study has tremendous potential to help improve broaden our understanding of the underlying mechanisms that may lead to pain and other symptoms in OA.
Role: Contact Principal Investigator

R24 DK094583 (Clemens/Clauw/Reed-MPI) 09/15/11 – 08/31/12
NIH/NIDDK $225,000
Sensory Sensitivity and Urinary Symptoms in the Female Population
This project will examine for clinical evidence of global pain hypersensitivity in these patients. If a global pain abnormality is identified, additional studies can be done to examine the etiology of these symptoms and design novel treatments that are focused on central, rather than peripheral, pathophysiology.
Role: Principal Investigator (MPI)

Services Agreement (Clauw, D.) 01/01/12 – 12/31/12
Pfizer, Inc. $402,572
Development of a Web-based Patient Engagement Tool for Chronic Low Back Pain
The goal of this project is to develop the Patient Engagement Platform (PEP), an integrated and interactive eHealth product developed for physician and patient engagement surrounding the pain management of chronic low back pain. The PEP contains 5 categories and functions (clinic assessment, guidance, tracking/reporting, self-management modules, and motivational tools).
Role: Principal Investigator

K12 DE023574 (Kapila, S-Contact/Clauw, DJ) 07/01/13 – 06/30/18
NIH/NIDCR $385,538
University of Michigan's TMJD and Orofacial Pain Interdisciplinary Consortium
The goal of this K12 program is to train a cadre of high caliber clinician scientists and basic scientists to enhance the number and quality of interdisciplinary researchers that can appropriately unravel the mechanisms and most effective treatments for TMJD/OP.
Role: Principal Investigator (MPI)

GM103730 (Clauw, DJ-Contact/Mashour, GA) 07/01/14 – 06/30/19
NIH/NIGMS $79,124
University of Michigan Anesthesiology Post-Doctoral Research Training Program
This proposed new *NIGMS T32 Postdoctoral Training Program in Anesthesiology* will provide support to post-doctoral trainees interested in careers in academic anesthesiology, and who embrace the interdisciplinary nature of our institution.
Role: Contact Principal Investigator (MPI)

R01 DK100368 (Tu, F) 04/01/14 – 03/31/19
Northshore University Healthcare System $317,056
Research Institute (NIH Prime)
Deciphering the hormonal and nociceptive mechanisms underlying bladder pain
The objective of this proposal is to identify the hormonal, nociceptive, and psychological mechanisms responsible for COS of the bladder and determine the mechanisms underlying the ability of oral contraceptives to improve bladder pain.
Role: Co-Investigator

U01 DK082345-10 (Clemens/Clauw-Contact) 09/18/2014 – 06/30/2019
National Institutes of Health $4,293,441/total award amount
University of Michigan MAPP Research Network Discovery Site
The NIDDK supplement to MAPP will modify the CMSI that is currently in use within the MAPP network. This involves expert consensus building regarding the best diagnostic criteria for each condition, cognitive interviews (focus groups) with patients to determine item relevance and understandability, and preliminary psychometric analysis of the instrument. The CMSI screener will also be updated to include trigger items for the 4 new conditions not currently in the MAPP version of the CMSI.
Role: Principal Investigator

WILLIAMS, DAVID A., PH.D.

Current Support

R01 NR017096 (Hassett, AL/Williams, DA) 05/09/17 – 02/28/23 (NCTE)
NIH/NINR $2,549,712 Total Award Amount
Resilience Skills Self-Management for Chronic Pain
The objective of this application is to evaluate the general effectiveness and impact on telomere health of a resilience-

based self-management intervention, the CBT self-management with resilience-enhancing activities (CBTRE) program.
Role: Principal Investigator (MPI)

UL1 TR002240 (Mashour, GA) 09/17/07 – 02/28/23 (NCTE
NIH/NCATS $48,448,400 Total Award Amount
Michigan Institute for Clinical and Health Research (MICHR)
The UM CTSA, housed in the Michigan Institute of Clinical and Health Research (MICHR), was created to provide robust infrastructure and support based on strong existing units and programs, as well as academic programs in key clinical and translational disciplines in order to provide faculty leadership, expertise, and consultation as well as high quality services
Role: Co-Director, Research Development Core / Director, Network-based Research Unit

U19 AR076734 (Clauw, DJ/Hassett, AL) 09/26/19 – 05/31/24
NIH/NIAMS $8,969,433 Total Award Amount
University of Michigan BACPAC Mechanistic Research Center
As part of the BACPAC initiative, the mechanistic research center at the University of Michigan aims to be a team member in realizing the vision of personalized medicine for individuals with cLBP.
Role: Co-Director, Behavioral Phenotyping Core

U19 AR076734-01S2 (Clauw, DJ/Hassett, AL) 06/01/21 – 05/31/22
Supplement PIs: (Williams, DA/Schrepf, AE) $113,9821 Total Award Amount
NIH/NIAMS $8,969,433 Total Award Amount
University of Michigan BACPAC Mechanistic Research Center – Supplement
Conversion of the COPC screener into REDCap: a supplement to the NIAMS HEAL BACPAC study
The goal of this supplement is to convert the Chronic Overlapping Pain Conditions (COPCs) classification tool into the REDCap format so that it will be more broadly accessible by research, including those involved in the HEAL Initiative, and conduct a small validation study.
Role: Supplement Principal Investigator (MPI)

P50 AR070600 (Clauw, DJ/Brummett, CM) 09/20/16 – 08/31/22 (NCTX)
NIH/NIAMS $7,415,237 Total Award Amount
University of Michigan Fibromyalgia CORT
The goal of this program of research is to understand how fibromyalgia and other rheumatic diseases affect patients, better understand the underlying mechanisms of their pain, and personalize analgesic treatment.
Role: Co-Director, Phenotyping and Outcomes Core (POC)

U01 DK082345 (Clauw, DJ/Clemens, JQ) 09/15/18 – 06/30/22
NIH/NIDDK $1,172,455 Total Award Amount
University of Michigan MAPP Research Network Discovery Site
The goal this project is to study the etiology and treated natural history of UCPPS, to inform better treatments and management of symptoms through improved designs of clinical trials, and to identify clinical factors and research measurements to define clinically relevant sub-groups of these patients. The proposed three-year extension will allow the participating institutions to obtain an additional 12 months of follow-up in the MAPP-II Symptom Patterns Study (SPS), observe additional ATLAS (Analysis of Therapies during Longitudinal Assessment of Symptoms) events in the MAPP-II SPS, and analyze MAPP-II data.
Role: Co-Investigator

R01 DK123164 (Harte, SE/Schrepf, AE) 01/22/20 – 11/30/24
NIH/NIDDK $2,594,063 Total Award
Neuroimmune Interface in Urological Chronic Pelvic Pain Syndrome
Our primary goal is to identify how inflammation interacts with the CNS to promote chronic pain and other debilitating symptoms in UCPPS.
Role: Co-Investigator

ME-2020C3-20925 (Kidwell, K) 11/01/21 – 01/31/25
PCORI $998,998 Total Award Amount
Design and Methodological Development for a Patient Preference SMART
This project will combine SMART and PRPP designs to produce a PRPP-SMART design, for which we will develop Bayesian statistical methods to estimate treatment effects and tailored sequences of treatments or dynamic treatment regimens (DTRs) using data from all individuals and compare to frequentist methods.
Role: Co-Investigator

OT2 HL161847 (Forrest, C) (Site PI: Williams, DA) 10/01/21-05/31/25
Childrens Hospital of Philadelphia / NIH/NHLBI $810,799 Total Award Amount
COVID-19: The PCORnet Pediatric Study of Post-Acute Sequelae of SARS-CoV-2 Infection in Children and Adolescents
U-M will contribute to PASC clinical data on a regular schedule for all patients meeting the eligibility criteria. While details of the cohort will be defined by the consortium after it is established, we are taking as an estimation for application purposes the cohort definition currently used by the PCORnet CDC COVID-19 surveillance network, which approximates the inclusion criteria used by N3C.
Role: Site Principal Investigator

RI-PITT-01-PS1 (McTigue, K) (SitePI: Williams, DE) 01/01/21 – 12/31/24
University of Pittsburgh/PCORI $834,218 Total Award Amount
PaTH to Health: PCORnet Clinical Research Network
In Phase 3 of PCORnet, this "network of networks" is intended to optimize its capacity to serve as a national resource for conducting rapid, efficient, patient-centered comparative clinical effectiveness research (CER) that improves healthcare delivery and health outcomes. CRNs will ensure the continuity and optimization of critical CRN resources and operations developed in prior phases to facilitate implementation of definitive research studies that are national in scope and align with PCORI's Strategic Research Priorities and other priorities stemming from PCORI's ongoing strategic planning efforts (e.g., intellectual and developmental disabilities, maternal morbidity and mortality, and COVID-19).
Role: Site Principal Investigator

NU38 OT000316 (Site PI: Williams, DA) 10/01/20-07/31/22
Task Force for Global Health / CDC $129,000 Total Award Amount
Task Force for Global Health – COVID-19 Electronic Health Data Initiative
The COVID-19 electronic healthcare data initiative project will demonstrate PCORnet sites ability to collect information on COVID data through the implementation of a nationally distributed data infrastructure. The collection of these COVID-19 data will help to answer critical questions to assist in the emergency response to the COVID-19 pandemic.
Role: Site Principal Investigator

Past Support

RI-CRN-2020-006 (714976-3) (Site PI: Williams, DA) 01/01/20 – 07/31/21
University of Pittsburgh/PCORI $541,104 Total Award Amount
University of Pittsburgh Clinical and Translational Science Institute - ACT Network Supplement
As a site in the network, the Michigan Institute for Clinical and Health Research will support maintenance and updates of the informatics platform and data harmonization schema for the ACT network.
Role: Co-Investigator, Site Principal Investigator

UL1 TR001857 (Hanauer, D) 06/01/19 – 05/31/21
University of Pittsburgh/NIH $129,000 Total Award Amount
University of Pittsburgh Clinical and Translational Science Institute - ACT Network Supplement
As a site in the network, the Michigan Institute for Clinical and Health Research will support maintenance and updates of the informatics platform and data harmonization schema for the ACT network.
Role: Co-Investigator

CNVA00062316 (713948-5) (McTigue, K) 03/30/19 – 09/30/20
University of Pittsburgh / People Centered Research Foundation $90,740
PaTH Network
The goal of this agreement is for UM to actively and collaboratively participate in the development of PCORnet governance, including development of PCORnet-wide policies and standards and ad hoc working groups or teams for the governance of PCORnet. The UM PI will attend and contribute to PCORnet-wide meetings, ad hoc groups and teams that support the operations, management, improvement and sustainability of PCORnet. **Role:** UM Site Principal Investigator

UL1 TR001857 (Ries, SE) 06/01/19 – 05/31/20
University of Pittsburgh / NIH Prime $75,000
University of Pittsburgh Clinical and Translational Science Institute - ACT Network Supplement
As a site in the network, the Michigan Institute for Clinical and Health Research will support maintenance and updates of the informatics platform and data harmonization schema for the ACT network.
Role: Co-Investigator

R21 NR016930 09/26/18 – 08/31/20
Burgess, H $137,500 Annual Direct Costs
NIH / NINR $421,751 Total Award Amount
Bright Light Treatment at Home to Improve Symptom Management of Fibromyalgia Syndrome
Our pilot data suggests that morning bright light treatment can meaningfully reduce FMS symptoms. In the proposed study, we will reduce subject burden and increase innovation by testing a wearable light device (bright vs. dim Re-timer®) with objective measures of treatment compliance.
Role: Co-Investigator

(Piette, J) 10/01/14 – 06/30/19
VA Ann Arbor Healthcare System $2,451
Patient-Centered Pain Care Using Artificial Intelligence and Mobile Health Tools
As a member of the Expert Panel, Dr. Williams will contribute expertise on delivering CBT using m-Health technologies.
Role: Expert Panel Member

RSG-13-240-01-PCSM (Henry, NL) 08/01/13 – 07/31/17
American Cancer Society (ACS) $150,000
Centralization of pain in breast cancer survivors
The primary goals of this proposal are to investigate markers of centralization of pain and to evaluate potential predictors of response to the predominantly centrally-acting analgesic duloxetine in breast cancer survivors with chronic, treatment-related pain.
Role: Co-Investigator

R01 AR060392 (Clauw, D./Brummett, C.–MPI) 08/01/11– 05/31/16
NIH/NIAMS $437,235
Central Nervous System Mechanisms in Knee Osteoarthritis (KOA)
The goal of this project is to show that simple clinical testing easily performed at the point-of-care can reliably segment chronic pain patients into those with prominent central components to their pain, that are likely to need different pharmacologic (i.e. centrally acting analgesics) and non-pharmacologic approaches (not surgery). Moreover this study has tremendous potential to help improve broaden our understanding of the underlying mechanisms that may lead to pain and other symptoms in OA.
Role: Co-Investigator

R01 AR057808 (Lumley, M. – Wayne St. Univ.) 08/15/10 – 06/30/15
NIH/NIAMS $566,563
Emotional Exposure and Cognitive Behavioral Therapies for Fibromyalgia

This application combines the clinical research, pain, and FMS expertise of two research teams to conduct a 2-site, randomized, controlled trial of emotional exposure therapy (EET) against both a standard cognitive-behavioral therapy (CBT; pain coping skills training) and control condition (FMS education and support) in a design that controls for the importance of exercise, non-specific factors, and experimenter allegiance to the different treatments.
Role: Site Principal Investigator

U01 DK082345-10 (Clemens/Clauw-Contact) 09/18/14 – 06/30/19
National Institutes of Health $4,293,441/total award amount
University of Michigan MAPP Research Network Discovery Site
The NIDDK supplement to MAPP will modify the CMSI that is currently in use within the MAPP network. This involves expert consensus building regarding the best diagnostic criteria for each condition, cognitive interviews (focus groups) with patients to determine item relevance and understandability, and preliminary psychometric analysis of the instrument. The CMSI screener will also be updated to include trigger items for the 4 new conditions not currently in the MAPP version of the CMSI.
Role: Co-Investigator

VA Merit Grant E7557R (Murphy, S.) 10/01/10 – 09/30/13
U.S. VA Rehabilitation Research & Development $40,000
Effectiveness of Tailored Activity Pacing for Symptomatic Osteoarthritis
The goal of this project is to examine the effectiveness of tailored activity pacing, compared to general activity pacing and usual care, on pain, fatigue, and physical function for veterans with knee or hip osteoarthritis.
Role: Co-Investigator

U01 AR55069 (Williams, D.) 08/01/07 – 02/28/12 (NCTX)
NIH/NIAMS $128,388
A Fibromyalgia-Specific Extension of the PROMIS Network
The overall goal of this project is the development, testing and integration of a disease-specific measurement instrument to use in clinical trials for the assessment of multiple domains of relevance for fibromyalgia.
Role: Principal Investigator

Services Agreement (Clauw, DJ) 01/01/12 – 12/31/12
Pfizer, Inc. $402,572
Development of a Web-based Patient Engagement Tool for Chronic Low Back Pain
The goal of this project is to develop the Patient Engagement Platform (PEP), an integrated and interactive eHealth product developed for physician and patient engagement surrounding the pain management of chronic low back pain. The PEP contains 5 categories and functions (clinic assessment, guidance, tracking/reporting, self-management modules, and motivational tools).
Role: Co-Investigator

JANEVIC, MARY R., PH.D.

Current Support

R01 NR020442 (Janevic, M) 09/24/2021 – 06/30/2026
NIH $2,809,500 Total Award Amount
Improving Physical and Psychosocial Functioning in Underserved Older Adults During the COVID-19 Pandemic: A Community Health Worker-Led Intervention
Improving Physical and Psychosocial Functioning in Underserved Older Adults During the COVID-19 Pandemic: A Community Health Worker-Led Intervention
Role: Principal Investigator

R01 AG071511 (Janevic, M) 09/15/2021 – 08/31/2026
NIH $2,910,374 Total Award Amount
An Efficacy Trial of Community Health Worker-Delivered Chronic Pain Self-Management Support for Vulnerable Older Adults
The major goal of this project is to conduct a randomized controlled trial of chronic pain self-management intervention delivered by community health workers, with support from mobile health tools to primarily African American older adults in an underserved urban community.
Role: Principal Investigator

U19 AR076734-01S4 (Clauw, D/Hassett, A) 09/01/2021 – 05/31/2023
Supplement PIs: (Bergmans, R/Janevic, M) $583,491 Total Supplement Award Amount
NIH/NIAMS $8,969,433 Total Award Amount
University of Michigan BACPAC Mechanistic Research Center – Supplement
This is a supplement to an ongoing study of the mechanisms underlying treatments for chronic low back pain (cLBP). As part of the BACPAC initiative, the mechanistic research center at the University of Michigan aims to be a team member in realizing the vision of personalized medicine for individuals with cLBP. This project will support a robust effort to enhance patient and other stakeholder engagement, particularly that of underrepresented minorities, and to implement a sustained outreach effort to the historically underserved Black and Hispanic communities in and around Detroit and Flint, Michigan, and a Stakeholder Advisory Board will be established to provide input across all phases of the main study.
Role: Supplement Principal Investigator

U01 TR003409-01-S1 (Murphy, S) 08/15/2020 – 07/31/2024
NIH $2,279,760 Total Award Amount
Training Promotoras/Community Health Workers Using Culturally and Linguistically Appropriate Best Practices
Project (supplement) goals are to: 1) update the current Best Practices for Social and Behavioral Research Course to account for the latest regulatory requirements and scientific and technological advancements; 2) enable clinical research professionals to partner with community-based stakeholders more readily by developing a community-engagement module as part of the best practices training; and 3) evaluate the updated training course with users. This project is expected to yield a robust update to the Best Practices for Social and Behavioral Research Course which will be readily available through the array of dissemination outlets the current course utilizes.
Role: Co-Investigator

U45 ES006180 (Sivin) 08/01/2020 – 07/31/2025
NIH/NIEHS / UAWI $3,176,405 Total Award Amount
Hazardous Materials Worker Health and Safety Training
The University of Michigan (U-M) activities will emphasize newer aspects of the proposed training programs including continued development of innovative approaches to evaluation of both the specific training and the overall worker-trainer program. At the same time U-M will continue to provide ongoing monitoring and evaluation of the existing programs and modules provided by the UAW.
Role: Co-Investigator

Past Support

R01 AG047203 (Connell) 06/15/2015 – 03/31/2022
NIH/NIA $2,889,567 Total Award Amount
A partnership to translate an EBI for vulnerable older adults with heart disease
The goal of this project is to adapt and implement an evidence-based program for older adults with heart disease for a vulnerable older, primarily African American population, in Detroit, Michigan, and to assess its effectiveness and cost-effectiveness in this setting, as well as factors affecting the translation process. The study will be conducted in partnership with the Rosa Parks Geriatric Center at the Detroit Medical Center (RPC) and the Detroit Area Agency on Aging (DAAA).
Project/Proposal Start and End Date:

Role: Co-Investigator

K01 AG050706 (Janevic, M) 04/01/2016 – 03/31/2021
NIH/NIA $580,361 Total Award Amount
A Low-intensity, Cognitive-Behavioral Self-Management Intervention for Chronic Musculoskeletal Pain in Older Adults
This mentored career development grant has provided me with training in the areas of cognitive-behavioral approaches to pain management, physical activity monitoring, and emerging study designs. Research aims center on the development and testing of a guided internet-based intervention for older chronic pain patients. This is enabling me to launch a research program in the area of scalable non-pharmacological interventions to support chronic pain self-management among older adults.
Role: Principal Investigator

MOU (Janevic, M) 01/01/2019 – 03/31/2021
Detroit Area Agency on Aging/ $50,000 Total Award Amount
Michigan Health Endowment Fund
Passport to Health
The goal of this project is to increase the use of health and wellness services among Detroit seniors and improve their physical and psychosocial health outcomes.
Role: Principal Investigator

P30 AG022845 (Janevic, M) 09/15/2019 – 10/31/2020
Weill Cornell Medical College / NIH/NIA $63,960 Total Award Amount
Feasibility of a Technology-Enabled Chronic Pain Self-Management Intervention Delivered by Community Health Workers
This Stage 1 pilot study will test a Positive Psychology intervention for chronic pain management ("Positive STEPS") to enhance psychological resilience and pain coping. The intervention is community health worker (CHW)-delivered and technology-enabled via a website and wearable activity trackers. The priority population is older African American adults in an underserved urban community (Detroit, MI).

R21 MH109932 (Piette, J) 09/25/2015 - 03/31/2019
NIH/Fogarty International Center $387,500 Total Award Amount
AniMóvil: mHealth Support for Depression Management in a Low-Income Country
The goal of this study is to develop and evaluate an mHealth intervention for depression management that incorporates Interactive Voice Response calls, SMS text messages, and community health workers. It is hoped that this model can increase the reach and effectiveness of mental health care in LMICs.
Role: Co-Investigator

Grant Agreement (Janevic, M) 01/01/2019 – 05/31/2020
American Pain Society $25,000 Total Award Amount
A new model to reach vulnerable older adults with pain self-management support
The goal of this project is to adapt an existing guided internet program for chronic pain self-management support so that it is responsive to the needs of older African American adults and can be delivered by community health workers.
Role: Principal Investigator

P30 AG022845 (Reid, MC/Wethington, E) 01/01/2019 – 05/31/2021
190635-5 Pilot Project PI: (Janevic, M) $73,903 Total Pilot Award Amount
Weill Medical College of Cornell University / NIH/NIA
Cornell Roybal Center-Translational Research Institute on Pain in Lather Life
Feasibility of a Technology-Enabled Chronic Pain Self-Management Intervention Delivered by Community Health Workers
This Stage 1 pilot study will test a community health worker (CHW)-delivered, technology-enabled chronic pain self-management (CPSM) intervention that integrates positive psychology activities to enhance psychological resilience. The priority population is older African American adults in an underserved urban community (Detroit, MI)
Role: Pilot Project Principal Investigator

R75535 (Antonucci, T) 01/01/2019 – 06/30/2021
Eastern Mich Univ/Michigan Health Endowment Fund $102,569 Total Award Amount
A Family Centered Approach to Dementia Caregiving in Cultural Context
The overarching goal of the proposed study is to develop and pilot test an AD caregiver support intervention that is directed at multiple family caregivers and is culturally-responsive to the needs of the Arab American community.
Role: Co-Investigator

None (Janevic, M) 06/01/2019 – 05/31/2021
Edward Ginsberg Center, University of Michigan $10,000 Total Award Amount
Re-imagining the Senior Center: Advancing Equity among Older Adults in Detroit
The goal of this project is to develop a community-academic partnership between the Detroit-based Community Social Services of Wayne County and researchers at the University of Michigan, and to conduct an evaluation of the Virtual Senior Center program, an innovative program that delivers telephone-based classes to older adults in Detroit.
Role: Principal Investigator

None (Janevic, M) 07/01/2015 – 06/30/2020
Claude D. Pepper Older Americans Independence Center, the Michigan Institute for Clinical and Health Research, and the University of Michigan Geriatrics Center $22,500 Total Award Amount
Promoting Physical Activity for Chronic Pain Management among Older Adults in Detroit: Comparing Technology-Based Strategies
This mixed-methods pilot-trial will assess barriers and facilitators to using wearable activity monitors among older adults with chronic pain living in Detroit, and will test the feasibility and validity of various technology-based strategies for reporting daily step count data for a six-week period. Changes in self-reported functioning compared to a control group will also be assessed.
Role: Principal Investigator

None (Janevic, M)
09/01/2017 – 08/31/2018
Michigan Institute for Clinical and Health Research (MICHR) $4,792 Total Award Amount
the Michigan Institute for Clinical and Health Research, and the University of Michigan Geriatrics Center
Michigan Institute for Clinical and Health Research – The role of companion animals in chronic pain management among community-dwelling adults aged 70+
This small qualitative study consists of four focus groups with pet owners aged 70 and over who have pain due to osteoarthritis or other musculoskeletal conditions that limits full participation in everyday activities. We will collect in-depth data on how pets are perceived to impact chronic pain and its management. Findings will serve as a basis for the design of larger observational studies focusing in more detail on the benefits and potential harms of pets for older people with pain, as well as on the design of potential intervention components leveraging pets' role in chronic pain management.
Role: Principal Investigator

None (Janevic, M) 09/01/2010 – 11/04/2015
Merck Childhood Asthma Network, Inc. (MCAN) $616,327 Total Award Amount
Evaluation of the MCAN Care Coordination Initiative
Cross-site Evaluation of the MCAN Care Coordination Initiative. The major goal of this project is to conduct a cross-site qualitative and quantitative evaluation to assess both processes and outcomes associated with the work.
Role: Principal Investigator

None (Janevic, M/Zanley) 01/01/2015 – 12/31/2015
Detroit Community-Academic Urban Research Center $3,936 Total Award Amount

Forming a Collaborative Health Research Partnership to Increase Effectiveness and Reach of Chronic Disease Prevention and Management Services among Detroit's Elderly (small planning grant)
The goal of this project is to build a strong partnership between the Detroit Area Agency on Aging (DAAA) and the Center for Managing Chronic Disease (CMCD) at the University of Michigan. The purpose of this partnership, once established, would be to engage in collaborative research to address one or more pressing needs related to chronic illness prevention and management among older adults in the city of Detroit.

U48 DP001901 (SIP12-057) (Janevic, M) 09/30/2012 – 09/29/2014
DHHS/CDC $240,000 Total Award Amount
MEW Network and FOCUS on Epilepsy
The goal of this project is to engage in the activities of the Network of Managing Epilepsy Well (MEW) Collaborating Centers that contribute to the Network's mission: sharing research challenges, solutions, findings, and other information with Network members to enrich the development and implementations of research studies and conduct a randomized controlled trial of FOCUS on Epilepsy, a promising community- and home-based intervention employing a model developed by the Center for Managing Chronic Disease designed to enhance self-regulation skills among adults with epilepsy and the significant other persons assisting them to manage the condition.
Role: Principal Investigator

MCAFEE (GOESLING), JENNA, PH.D.

Current Support

U24 AR076730 (Lavange, LM) (Site PI: Hassett, AL) 10/2021 – 05/2024
University of North Carolina / NIH/NIAMS $800,114 Total Award Amount
BACPAC- Biomarkers for Evaluating Spine Treatments (BEST) Study
The BEST-BACPAC neuroimaging group will collect brain neuroimaging metrics on all participants that undergo deep phenotyping. This will include T1, DTI, and resting state scanning sequences. We will harmonize across platforms and pre-process and analyze all brain imaging data.
Role: Co-Investigator

U19 AR076734 (Clauw, DJ-Contact / Hassett, AL) 09/26/19 – 05/31/24
NIH/NIAMS $8,969,433 Total Award Amount
University of Michigan BACPAC Mechanistic Research Center
As part of the BACPAC initiative, the mechanistic research center at the University of Michigan aims to be a team member in realizing the vision of personalized medicine for individuals with cLBP**.**
Role: Co-Investigator; Clinical Core, Behavioral Phenotyping Core, Research Project

Past Support

K23 DA038718 (Goesling, J) 05/01/16 – 04/30/21
NIH/NIDA $690,841 Total Award Amount
Advancing the Treatment of Chronic Pain through Individualized Opioid Cessation

The goal of this mentored career development award is to better understand why patients continue taking opioids and incorporate theory-based models of behavior change into the development of interventions for individuals who would benefit from opioid cessation.
Role: Principal Investigator

U01 CE002780 (Bohnert, AB) 09/01/17 – 08/31/20 NCTX
CDC $799,823 Total Award Amount
Heroin use and overdose following changes to individual-level opioid prescribing
Heroin-related overdose deaths more than tripled between 2010 and 2014 in the United States. Emerging evidence has

identified nonmedical use of prescription opioids as a risk factor for heroin initiation. Some have observed that the spike in heroin overdose deaths has overlapped with efforts to reduce the nonmedical use of prescription opioids; however, a causal link has not been established. Using analysis of medical records for over 50 million Americans and in-depth interviews with patients, this study will seek to inform prevention efforts by examining the association between individual-level opioid prescribing patterns – in particular tapering or discontinuation of opioids – and the risk of heroin use and overdose.
Role: Co-Investigator

KHETERPAL, SACHIN, MD, MBA

Current Support

Research Agreement #042230 (Kheterpal, S) 08/17/18 – 03/31/23
Apple, Inc. Contract Amount Confidential per Signed Agreement
Michigan Predictive Activity and Clinical Trajectories Study (MiPACT)
The interplay between genomics, activity, lifestyle, family history, and clinical care upon long term outcomes is poorly understand. By enrolling patients and providing them with mobile wearable devices combined with electronic health record, genotyping, clinical laboratory, and electronic health record data, we will be able to advance our understanding of the value of each data stream and potential predictors of poor outcomes.
Role: Principal Investigator

T32 GM1037 (Mashour, GA / Kheterpal, S) 07/01/19 – 06/30/24
NIH/NIGMS $814,861 Total Award Amount
University of Michigan Anesthesiology Post-Doctoral Research Training Program
The *NIGMS T32 Postdoctoral Training Program in Anesthesiology* provides support to post-doctoral trainees interested in careers in academic anesthesiology, and who embrace the interdisciplinary nature of our institution.
Role: Principal Investigator (MPI)

UL1 TR002240 (Mashour, GA) 09/17/07 – 02/28/23 (NCTE)
NIH/NCATS $48,448,400 Total Award Amount
Michigan Institute for Clinical and Health Research (MICHR)
The UM CTSA, housed in the Michigan Institute of Clinical and Health Research (MICHR), was created to provide robust infrastructure and support based on strong existing units and programs, as well as academic programs in key clinical and translational disciplines in order to provide faculty leadership, expertise, and consultation as well as high quality services.
Role: Faculty Support; Informatics Core

PLACER 2020C3-21106 (Kheterpal, S/Avidan,M) 01/01/2022-06/30/2028
PCORI $32,945,950 Total Award Amount
THRIVE: "Ttrajectories of Recovery after Intravenous propofol vs inhaled VolatilE anesthesia"
We hypothesize that participants receiving PROPOFOL will demonstrate clinically and statistically significant improvement in quality of recovery the evening of surgery and POD 1 without an increase in intraoperative awareness with recall.
Role: Principal Investigator

R61 HL155498 (Brahmajee, N, Dorsch, M) 09/15/2021 – 08/31/2022
NIH/NHLBI $1,552,228 Total Award Amount
A Just-In-Time Adaptive Mobile Application Intervention to Reduce Sodium Intake
And Blood Pressure in Hypertensive Patients
Our overall objectives are to: (1) evaluate the efficacy of a dietary sodium mobile application intervention on reducing BP, (2) establish that the improvement in BP is directly related to the change in diet and body weight, and (3) optimize the intervention to demonstrate sustained effects on BP.
Role: Co-Investigator

20SFRN35360220 (Brahmajee, N) 04/01/2020 – 03/31/2024
American Heart Association $2,500,000 Total Award Amount
Wearables In Reducing risk and Enhancing Daily Life-style (WIRED-L) - SFRN
The long-term goal of our research is to develop successful strategies driven by adaptive technologies that support self-management in common cardiovascular conditions.
Role: Co-Investigator

COVID-19 Rapid Response (Shah, N/Brahmajee, N) 06/01/2020 – 12/31/2021
American Heart Association $20,000 Total Award Amount
COVID-19 Health Evaluation & Cardiovascular Complications (CHECC) Study; COVID-19 Rapid Response
To better understand the pathobiology and the clinical implications of the viral infection that leads to the morbidity and mortality seen with COVID-19. We propose leveraging data from two ongoing U-M mHealth studies: (1) the Michigan Predictive Activity & Clinical Trajectories (MIPACT) study of nearly 7,000 diverse participants in Ann Arbor (21% African American, 18% Asian, 12% Hispanic) and (2) the REACH-OUT Blood Pressure study of over 450 largely African-American participants in Flint.
Role: Co-Investigator

UM1 NS118922 (Brummett/Clauw/Waljee/Chang) 08/01/2020 – 07/31/2023
NIH/NINDS $6,598,505 Total Award
Transition from Acute to Chronic Pain After Thoracic Surgery
The successful completion of the proposed study would provide an unparalleled resource for understanding the factors associated with CPSP and will allow for more efficient and personalized trials to prevent the development of chronic pain after thoracotomy and other thoracic surgeries.
Role: Co-Investigator

R01 DA042859 (**Brummett, C / Waljee, J)** 07/01/2017 - 04/30/2022
NIH/NIDA $3,137,204 Total Award Amount
oPIOIDS: Prevention of Iatrogenic Opioid Dependence after Surgery
The purpose of this study is to better understand the factors that put people at risk of long-term opioid use so that these patients can be prescribed alternative pain management strategies when having surgery. This study will examine new prescription drug claims data with existing clinical and genetic data as well as the opioid prescription fulfillment data to assess patient characteristics associated with greater opioid ascertainment.
Role: Consultant

Past Support

Master Vendor Agreement #12600 (Kheterpal,S) 01/01/2019 – 12/31/2022
Blue Cross Blue Shield of Michigan $2,350,691 Total Award Amount
Anesthesiology Performance Improvement and Reporting Exchange (ASPIRE) / MPOG
Integrating electronic health record data across dozens of centers, we are able to provide near real-time feedback to providers and hospitals regarding their adherence to accepted standards of care.
Role: Principal Investigator/Executive Director, APSIRE

(Boehnke, M / Kheterpal, S / Wiens, J) 01/01/2017 – 12/31/2021
University of Michigan $236,750 Total Award Amount
Precision Health
The goal of Precision Health is to 1) develop fundamental social, medical, computational, and engineering science; 2) translate these basic science discoveries into promising treatments that are evaluated in partnership with Michigan Medicine patients and regional health systems; and 3) evaluate and increase the public health impact of effective therapies, working with community health systems, policy makers, and payers to implement these therapies nationally.
Role: Co-Director

Protocol #28431754HFA3002 (Brahmajee, N) 03/27/2020 – 06/30/21
Janssen Research & Development, LLC $379,215 Total Award Amount
Canagliflozin: Impact on Health Status, Quality of Life, and Functional Status in Heart Failure
This randomized study is designed to assess whether canagliflozin therapy improves HF symptoms as assessed by the Total Symptom Score (TSS) of the Kansas City Cardiomyopathy Questionnaire (KCCQ) patient-reported outcome (PRO) scale in participants with HF and with or without T2DM in a real-world setting.

Agreement (Kheterpal, S) 4/27/2020-10/31/2020
Becton, Dickinson and Company $120,000 Total Award Amount
Analysis of Anesthesia Medications Delivered in Acute Care Hospitals
The goals of this statement of work are the following: **1.** Develop report table shells, finalize patient inclusion criteria, confirm data quality limitations, establish project timeline; **2.** Develop, refine, execute on dose and unit of measure database queries across all MPOG sites for patients; **3.** Develop, refine, execute on medication concentration database queries for top 25 medications across MPOG sites using Cerner electronic health record; **4.** Review query results, establish plausibility, iterate on queries as needed; **5.** Collate query results into report package for sponsor.
Role: Principal Investigator

Service Agreement (Colquhoun, D) 04/24/2020 – 10/23/2020
Merck Sharp & Dohme Res Labs $194,275 Total Award Amount
Pulmonary complications and mortality among high risk patients and surgical procedures; evaluating the impact of sugammadex
This study evaluates the impact of sugammadex use, compared to neostigmine, among patients exhibiting one or more of these surgical (major abdominal, thoracic, emergency, or prolonged procedure) or underlying risk factors (advanced age, morbid obesity, sleep apnea, or pulmonary disease).
Role: Co-Investigator

E20192408-00 (Englesbe/Brummett/Waljee) 10/01/19 – 09/30/20
Medicaid/MDHHS - MA-2020 Master Agreement Prog $1,625,737 Total Award Amount
Michigan Opioid Prescribing Engagement Network (M-OPEN) (AWD16455-SUB030)
The overall goal of this initiative is to reduce the amount of opioids prescribed to surgical patients by 50%, reduce new chronic postoperative opioid use by 50%, and reduce opioid diversion into our communities.
Role: Co-Investigator

Role: Co-Investigator
R21 HS024581 (Avidan, M) Site PI (Kheterpal, S) 04/01/2017-3/31/2019
Washington University / AHRQ $103,078 Total Award Amount
Anesthesiology Control Tower: Feedback Alerts to Supplement Treatment (ACTFAST)
This pilot study will institute an air-traffic control-like command center to facilitate increased adherence to best-practice principles and superior intraoperative care, ultimately improving postoperative quality of recovery and patient outcomes.

PO810225 (Kheterpal, S) 04/18/2017 – 11/31/2018
Merck and Company, Inc. $1,860,000 Total Award Amount
National Trends and Variation in the Reversal of Perioperative Neuromuscular Blockade -A Comparison of Cholinesterase Inhibitors and Selective Relaxant Binding Agents
The goal of the proposed study is to use a broadly representative observational dataset to compare patterns of care in the reversal of non-depolarizing neuromuscular blockade, comparing patients receiving neostigmine and sugammadex. Next, using administrative data, we will compare the impact of sugammadex use on pulmonary complications and resource utilization.
Role: Co-Investigator

SHAH, NIRAV, M.D.

Current Support

R01 LM013894 (Landis-Lewis, Z) 09/01/2021 – 08/31/25
NIH $1,326,000 Total Award Amount
A scalable service to improve health care quality through precision audit and feedback
We propose to build a software service that customizes feedback for healthcare professionals based on their requirements and preferences, and to evaluate the effect of using the service on care quality.
Role: Co-Investigator

E20221872-00 (Englesbe/Brummett/Waljee) 10/01/2021 – 09/30/2022
Medicaid/MDHHS - MA-2021 Master Agreement Program $2,156,243 Total Award Amount
Michigan Opioid Prescribing Engagement Network (M-OPEN)
The overall goal of this initiative is to reduce the amount of opioids prescribed to surgical patients by 50%, reduce new chronic postoperative opioid use by 50%, and reduce opioid diversion into our communities.
Role: Co-Investigator

R01AG 059607 04/01/2019 – 01/31/2023
Yale University / NIH/NIA $450,590 Total Award Amount
Anesthetic Induction Overdose Among Elderly Surgical Patients
University of Michigan researchers provide data for this project via data abstraction from the MPOG research database. An analysis-ready dataset will be extracted and used for the aims of the project.
Role: Co-Investigator, Site Principal Investigator

Master Vendor Agreement #12600 (Kheterpal,S) 01/01/2019 – 12/31/2022
Blue Cross Blue Shield of Michigan $2,350,691 Total Award Amount
Anesthesiology Performance Improvement and Reporting Exchange (ASPIRE) / MPOG
Integrating electronic health record data across dozens of centers, we are able to provide near real-time feedback to providers and hospitals regarding their adherence to accepted standards of care.
Role: Quality Improvement Director, MPOG

Research Agreement #042230 (Kheterpal, S) 08/17/18 – 08/31/21
Apple, Inc. Contract Amount Confidential per Signed Agreement
Michigan Predictive Activity and Clinical Trajectories Study (MiPACT)
The interplay between genomics, activity, lifestyle, family history, and clinical care upon long term outcomes is poorly understand. By enrolling patients and providing them with mobile wearable devices combined with electronic health record, genotyping, clinical laboratory, and electronic health record data, we will be able to advance our understanding of the value of each data stream and potential predictors of poor outcomes.
Role: Co-Investigator

PLACER 2020C3-21106 (Kheterpal, S/Avidan,M) 01/01/2022-06/30/2028
PCORI $32,945,950 Total Award Amount
THRIVE: "Ttrajectories of Recovery after Intravenous propofol vs inhaled VolatilE anesthesia"
We hypothesize that participants receiving PROPOFOL will demonstrate clinically and statistically significant improvement in quality of recovery the evening of surgery and POD 1 without an increase in intraoperative awareness with recall.
Role: Co-Investigator

Past Support

SOW#2 (Shah, N) 03/01/2021 – 02/28/2022

Edwards Lifesciences, LLC $225,000 Total Award Amount
Association between Intraoperative Hypotension and Patient Outcomes: A Multicenter Retrospective Observational Study
This study will analyze the relationship between several commonly used definitions of intraoperative hypotension and post-operative outcomes. Our primary hypothesis is that as the burden of hypotension increases, rates of AKI will increase as well.

COVID-19 Rapid Response (Shah, N/Brahmajee, N) 06/01/2020 – 12/31/2021
American Heart Association $20,000 Total Award Amount
COVID-19 Health Evaluation & Cardiovascular Complications (CHECC) Study; COVID-19 Rapid Response
To better understand the pathobiology and the clinical implications of the viral infection that leads to the morbidity and mortality seen with COVID-19. We propose leveraging data from two ongoing U-M mHealth studies: (1) the Michigan Predictive Activity & Clinical Trajectories (MIPACT) study of nearly 7,000 diverse participants in Ann Arbor (21% African American, 18% Asian, 12% Hispanic) and (2) the REACH-OUT Blood Pressure study of over 450 largely African-American participants in Flint.
Role: Co-Investigator

E20213443-00 (Englesbe/Brummett/Waljee) 10/01/20 – 09/30/21
Medicaid/MDHHS - MA-2021 Master Agreement Prog $2,156,243 Total Award Amount
Michigan Opioid Prescribing Engagement Network (M-OPEN) (AWD16455-SUB030)
The overall goal of this initiative is to reduce the amount of opioids prescribed to surgical patients by 50%, reduce new chronic postoperative opioid use by 50%, and reduce opioid diversion into our communities.
Role: Co-Investigator

PO810225 (Kheterpal, S) 04/18/2027 – 11/31/2028
Merck and Company, Inc. $1,860,000 Total Award Amount
National Trends and Variation in the Reversal of Perioperative Neuromuscular Blockade -A Comparison of Cholinesterase Inhibitors and Selective Relaxant Binding Agents
The goal of the proposed study is to use a broadly representative observational dataset to compare patterns of care in the reversal of non-depolarizing neuromuscular blockade, comparing patients receiving neostigmine and sugammadex. Next, using administrative data, we will compare the impact of sugammadex use on pulmonary complications and resource utilization.
Role: Co-Investigator

Trial # 20181-15 (Kumar, S) 8/20/2019 - 12/31/2020
Edwards Lifesciences $378,654 Total Award Amount
Prospective, Single-Arm, Open-Label, Multicenter Study of Hypotension Prevention and Treatment in Patients Receiving Arterial Pressure Monitoring with Acumen Hypotension Prediction Index Feature Software
The objective of the study is to determine whether use of the AcumenTM HPI Feature Software to guide intraoperative hemodynamic management in non-cardiac surgery reduces the duration of intraoperative hypotension (defined as MAP < 65 mmHg for at least 1 minute) as compared with a historic retrospective control group.
Role: Co-Investigator

E20192408-00 (Englesbe/Brummett/Waljee) 10/01/19 – 09/30/20
Medicaid/MDHHS - MA-2020 Master Agreement Prog $1,625,737 Total Award Amount
Michigan Opioid Prescribing Engagement Network (M-OPEN) (AWD16455-SUB030)
The overall goal of this initiative is to reduce the amount of opioids prescribed to surgical patients by 50%, reduce new chronic postoperative opioid use by 50%, and reduce opioid diversion into our communities.
Role: Co-Investigator

Service Agreement (Colquhoun, D) 04/24/2020 – 10/23/2020
Merck Sharp & Dohme Res Labs $194,275 Total Award Amount
Pulmonary complications and mortality among high risk patients and surgical procedures; evaluating the impact of sugammadex

This study evaluates the impact of sugammadex use, compared to neostigmine, among patients exhibiting one or more of these surgical (major abdominal, thoracic, emergency, or prolonged procedure) or underlying risk factors (advanced age, morbid obesity, sleep apnea, or pulmonary disease).
Role: Co-Investigator

KIDWELL, KELLEY, PH.D.

Current Support

75F40120C00195 09/2020-09/2023
FDA **(Kidwell)** Total Award Amount: $799,670
Innovative randomized trial designs and Bayesian analyses for registration of a drug for rare diseases in small samples
We will develop Bayesian methods to estimate and compare the mean outcome for placebo, low and high doses sharing information across the two stages of the design. We can also estimate the mean outcome of the five embedded fixed or dynamic treatment regimens that consider an initial treatment followed by a treatment for responders and a treatment for non-responders. We will describe the assumptions required to implement the snSMART design (e.g. a rare disease that waxes and wanes or progresses relatively slowly compared to potential treatment efficacy) and assumptions required to implement the analyses. We will critically evaluate the violation of assumptions via simulations. Moreover, we will test the sensitivity of our proposed approach to determine minimal sample sizes required for robust results. We believe development and dissemination of this snSMART design will stimulate more randomized trials of drugs for rare diseases and provide examples of appropriate Bayesian inference in small sample clinical trials.

ME-2020C3-20925 11/2021-01/2025
PCORI **(Kidwell)** Total Award Amount: $998,998
Design and Methodological Development for a Patient Preference SMART
We seek to incorporate the idea of a partially randomized patient preference (PRPP) design into SMARTs that will allow participants with a preference to be assigned to the treatment they prefer, and those without a preference to be randomized to a treatment. By allowing for patient preference, PRPP designs may allow for a more representative participant sample, better treatment adherence, and higher retention than standard RCTs or SMART designs.

UL1-TR-002240 06/2017-02/2023
NIH **(Mashour)** Total Award Amount: $48,548,399
Michigan Institute for Clinical and Health Research (MICHR) U-award
MICHR will further this transformation by pursuing 4 overarching objectives: 1) Create the next generation of clinical and translational researchers and interdisciplinary teams, 2) Develop and enhance capacity-building services that add value, remove barriers, and maximize productivity across the translational research continuum, 3) Create new collaborations and novel approaches to accelerate the pace of driving discoveries to application that impacts health, and 4) Actively lead and contribute to national CTSA consortium activities.

P30CA046592 07/2018-05/2023
NIH **(Fearon)** Total Award Amount: $36,749,525
Cancer Center Support Grant 2018-2023
The core grant supports the senior leadership, programs and shared facilities of the Rogel Cancer Center. The Center provides the organizational framework to promote interdisciplinary research through the development of defined clinical, basic science and prevention programs in cancer research, and the development and support of shared resources.

R01AA024755 08/2016-07/2022
NIH/NIAAA **(Walton)** Total Award Amount: $2,947,570
Adaptive Interventions to Reduce Risky Drinking and Violent Behaviors among Adolescents
This project will test adaptive interventions for risky drinking and violent behaviors among adolescents using a SMART design.

R01MH122636 04/2020-02/2023
NIH/Henry Ford Health System Total Award Amount: $34,293
Sleep to Reduce Incident Depression Effectively (STRIDE)
A proposed large-scale clinical trial that will take place in primary care utilizing a stepped-care model to determine the effectiveness of digital cognitive behavioral therapy for insomnia (dCBT-I) alone or in combination with face-to-face CBT-I and the effects of these sleep interventions for the prevention of depression in vulnerable populations (elevated sleep reactivity, minority, low income).

UG3 DA050173 09/2019-08/2024
NIH **(Walton/Bonar)** Total Award Amount: $6,455,593
Optimized Interventions to Prevent Opioid Use Disorder among Adolescents and Young Adults in the Emergency Department
This project will adapt promising remote health coach-delivered interventions, and pilot test feasibility/acceptability among adolescents and young adults. Then, we will evaluate the efficacy of interventions and their combinations to prevent/reduce opioid misuse among adolescents and young adults in the emergency department. Finally, we conduct an economic evaluation to identify the most efficacious intervention combination for preventing opioid misuse and implement it in the emergency department among adolescents and young adults.

R01 CA125577 07/2019-06/2024
NIH **(Kleer)** Total Award Amount: $1,852,500
Role of CCN6 (WISP3) in the progression and metastasis of breast cancer
To understand the tumor suppressor function of CCN6 in the development and progression of metaplastic breast carcinomas

U19-AR076734 09/2019-05/2024
NIH **(Clauw/Hassett)** Total Award Amount: $9,268,467
University of Michigan BACPAC Mechanistic Research Center
The evidence-based treatments for cLBP typically include a combination of pharmacologic, non-pharmacologic and procedural treatments. However, none of these treatments works well in more than a fraction of patients, and at present there is little guidance regarding what treatment should be used in which patients (i.e. precision medicine). Our central hypothesis is that an Interventional Response Phenotyping study can identify individuals with different underlying mechanisms for their pain who thus respond differentially to evidence-based interventions for cLBP. To address this hypothesis, we will conduct a randomized controlled SMART study of cLBP (n=500) considering 4 treatments.

R01CA237046 12/2019-11/2024
NIH **(Hawley)** Total Award Amount: $2,196,889
Improving Patient-Centered Communication in Breast Cancer: A RCT of a Shared Decision Engagement System (ShaDES)
This project is a multi-level, factorial study that crosses a patient-level RCT of 700 newly-diagnosed breast cancer patients within 25 breast surgical oncology practices to evaluate a shared decision engagement system (ShaDES) to support PCC. In collaboration with the Alliance NCORP Research Base and its Statistics and Data Core, the trial will: 1) evaluate the impact of the emotional support enhancements to iCanDecide on primary and secondary outcomes measuring patient appraisal of PCC, 2) evaluate the impact of the Clinician Dashboard on patient appraisal of PCC, 3) examine potential mediators of the patient and clinic interventions, and 4) conduct a process evaluation of the two intervention components to inform revision and future widespread implementation of ShaDES.

U01-CA232827 06/2020-05/2025
NIH **(Stoffel/Resnicow/Griggs)** Total Award Amount: $3,955,535
Innovative Approaches to Expand Cancer Genetic Screening and Testing for Patients & Families in a Statewide Oncology Network through Community, State, & Payer Partnerships

The goals of this project are to use novel methods to expand the reach of genetic services to diverse populations across the state of Michigan and to increase the proportion of potentially affected family members who seek genetic services.

R01-MD-015024 09/2020-03/2025
NIH **(Zimmerman)** Total Award Amount: $3,270,177
Youth Empowerment Solutions: Engaging Youth for Anti-Racism And Cultural Equity (YES-ERACE)
Our specific aims for this project are: 1) adapt the YES curriculum to include the Teaching Tolerance curriculum and study the adaptation and implementation process for the new curriculum; 2) test the efficacy of the YES-ERACE curriculum in a randomized design on empowered outcomes which will mediate the effects of YES-ERACE on perpetration of racist attitudes and behavior; 3) test the efficacy of the YES-ERACE curriculum on a model that predicts empowered outcomes will mediate perpetration of racism, and that YES-ERACE effects on aggressive and violent behavior (especially those motivated by racism) will also be mediated by reducing perpetration of racism over time and; 4) study the effects of dose received and sustainability of change on the outcomes from AIMS 2 and 3.

R21-CA251343 04/2021-03/2023
NIH **(Henry)** Total Award Amount: $427,833
Inflammatory oxylipins and aromatase inhibitor toxicity in breast cancer
Our overall goals are to obtain a greater understanding of the etiology of aromatase inhibitor -associated musculoskeletal symptoms by examining the effects of estrogen deprivation on oxylipins, and evaluating associations between genetic alterations related to metabolism of oxylipins and patterns of oxylipin metabolites in AI treated patients.

10/2020-09/2024
ASCO **(Henry/Grogan)** Total Award Amount: $184,200
Grogan ASCO: A Single Center Phase 2 Trial to Evaluate Use of Cannabidiol (CBD) to Treat Aromatase Inhibitor-Associated Musculoskeletal Symptoms (AIMSS) in Early Stage Breast Cancer Patients
The overall goal is to evaluate safety and efficacy of CBD in treating AIMSS.

DT2019-012B 09/2019-08/2022
V Foundation **(Henry)** Total Award Amount: $600,000
Inflammatory lipid mediators and aromatase inhibitor-associated arthralgias in breast cancer
Our overall goals are to obtain a greater understanding of the etiology of AIMSS, and to examine the effects of omega-3 fatty acids on prevention of aromatase inhibitor-associated musculoskeletal symptoms.

CSDG-21-177-01-CDP 01/2022-12/2024
American Cancer Society **(Cobain)** Total Award Amount: $437,400
Tumor/normal genomic profiling to identify and characterize pathogenic germline variants in metastatic cancer
To leverage the somatic genomic and transcriptomic profiles of tumors to understand if identified germline variants play a direct role in tumor pathogenesis and assess the clinical impact of pathogenic germline variant detection.

R01 MH126871 09/2021-06/2026
NIH/NIMH **(Czyz)** Total Award Amount: $3,123,955
Adaptive intervention to prevent adolescent suicidal behavior following psychiatric hospitalization: A Sequential Multiple Assignment Randomized Trial
Leveraging a novel sequential multiple assignment randomized trial (SMART) design, the project will identify an effective technology-augmented intervention package that will guide the adaptive delivery of post-discharge support—provided via text messages, asynchronous portal communication, and booster calls—in a tailored and resource-efficient way.

K23 HD099283 09/2020-082025
NIH **(Till)** Total Award Amount: $837,000
An Intervention for Chronic Pelvic Pain

The proposed research will generate the preliminary data to provide the foundation for an R01 application to advance our long-term goal of designing and performing large-scale intervention studies to develop effective personalized treatment strategies for chronic pelvic pain.

CCR19606584 06/2019-06/2022
Susan G. Komen for the Cure **(Morikawa)** Total Award Amount: $450,000
Personalized drug screening platform for breast cancer brain metastasis
Aim 1: Conduct drug sensitivity testing of breast cancer brain metastasis PDOs using a customized panel of single concentration drugs selected based on the genomic profiling, the clinical drug exposure history, frequently observed alterations in metastatic breast cancer and brain metastasis from solid tumors, and standard of care drugs used to treat metastatic breast cancer treatment. Retrospectively correlate predicted drug response using PDO testing with clinical response of drugs administered during routine clinical care for the PDO source subject. Aim 2: Determine the gene expression profile of cells resistant to a customized panel and test drug- drug combinations (or sequential use of drugs) based on the resistance profile.

K23 DK118179 07/2019-02/2024
NIH **(Kurlander)** Total Award Amount: $973,500
Using Intervention Mapping and the Multiphase Optimization Strategy to develop multilevel interventions to prevent upper GI bleeding
Develop an in-depth understanding of patient-, provider-, and system- level barriers and facilitators to appropriate PPI gastroprotection by conducting semi-structured interviews with patients, providers, and other key informants. Design and produce a theory-based multilevel intervention that targets patients, providers, and the health system. Assess the feasibility, appropriateness, and efficacy of the multilevel intervention in a single-site pilot study.

K01 AG062754 01/2020-11/2024
NIH **(Webster)** Total Award Amount: $632,391
Leveraging social networks: a novel physical activity intervention for senior housing
Regular physical activity is one of the most important predictors of healthy independent living, but the number of older adults meeting recommended guidelines remains low, especially in lower income communities. This project proposes career development to assist the candidate in developing and testing feasibility of a social network-based physical activity intervention in an affordable (HUD subsidized) senior housing community. This project is the first step in developing a novel low-cost intervention that will work with naturally occurring social resources to increase physical activity in lower income communities and reduce health disparities.

R01 DK128179 04/2022-02/2027
NIH **(Telem)** Total Award Amount: $3,244,184
Combining Policy and Implementation Science to Optimize Clinical Practice
The major goals of this project are to improve adherence to preoperative patient preoptimization for improved clinical outcomes and costs of care. The proposed study will bring together financial incentives and adaptive implementation to develop and validate practical, effective and scalable strategies to achieve clinical practice change.

UG1CA189823 03/2022-07/2025
NIH/Alliance NCTN Foundation **(Kidwell)** Total Award Amount: $14,383
Alliance NCORP Research Base (SHaRES Study)
This effort is aligned with the SHaRES study so I have become the primary statistician within the Alliance NCORP Research Base and Statistics and Data Core. Thus I, along with the Alliance team trial will: 1) evaluate the impact of the emotional support enhancements to iCanDecide on primary and secondary outcomes measuring patient appraisal of PCC, 2) evaluate the impact of the Clinician Dashboard on patient appraisal of PCC, 3) examine potential mediators of the patient and clinic interventions, and 4) conduct a process evaluation of the two intervention components to inform revision and future widespread implementation of ShaRES, while monitoring the accrual, provide DSMB reports, and provide oversight on the trial design and analyses.

R01AA029808 05/2022-02/2027
NIH **(Lin/Bonar)** Total Award Amount: $3,445,401
Leveraging virtual care strategies to improve access and treatment for individuals with alcohol use disorders
The goal of this project is to test the most effective combination of interventions to engage adults with alcohol use disorders in reducing their drinking and engaging with care.

R01AA029666 05/2022-02/2027
NIH **(Fernandez)** Total Award Amount: $2,989,356
Reducing Alcohol use among Elective Surgical Patients using Adaptive Interventions
The specific aims are: 1) to determine the efficacy of preoperative telehealth-based 'Virtual Coaching' relative to Enhanced Usual Care for reducing alcohol use and surgical complications among elective surgical patients; and 2) to identify the most efficacious postoperative intervention for those who initially respond and for those who do not.

Past Support

5-UL1-TR-000433-07 06/2012-05/2017
NIH **(Shanley/Mashour)** Total Award Amount: $49,911,994
Michigan Institute for Clinical and Health Research (MICHR) - U-award
MICHR will further this transformation by pursuing 4 overarching objectives: 1) Create the next generation of clinical and translational researchers and interdisciplinary teams, 2) Develop and enhance capacity-building services that add value, remove barriers, and maximize productivity across the translational research continuum, 3) Create new collaborations and novel approaches to accelerate the pace of driving discoveries to application that impacts health, and 4) Actively lead and contribute to national CTSA consortium activities.

R01 AR057808 07/01/13-06/30/14
NIH/NIAMS **(Lumley, M)** Total Award Amount: $1,223,460
Emotional Exposure and Cognitive Behavioral Therapies for Fibromyalgia
This application combines the clinical research, pain, and FMS expertise of two research teams to conduct a 2-site, randomized, controlled trial of emotional exposure therapy (EET) against both a standard cognitive-behavioral therapy (CBT; pain coping skills training) and control condition (FMS education and support) in a design that controls for the importance of exercise, non-specific factors, and experimenter allegiance to the different treatments.

KG111063 01/31/12-01/30/15
Komen Foundation **(Wicha)** Total Award Amount: $104,751
Targeting Stem Cells in Triple-Negative Breast Cancer (TNBC) in Different Racial Populations
We propose to develop a strategy to target TNBC by attacking the pathways which drive self-renewal and survival in BCSCs. Developing effective strategies to target BCSCs may help reduce racial disparities in outcome, as well as benefit all women with TN disease.

10/2013-08/2016
MedImmune, LLC **(Wicha)** Total Award Amount: $350,000
Cytokine Inhibition and CTC Assay Development in Breast and Lung Xenograft Models
Our ultimate goal is to demonstrate that successful targeting of BCSCs improves outcome for patients with breast and lung cancers.

53-10 07/2013-12/2015
Damon Runyon Foundation **(Henry)** Total Award Amount: $300,000
Pain processing pathway analysis in aromatase inhibitor-associated musculoskeletal syndrome
The overall goal of this proposal is to conduct multidisciplinary studies designed to determine the genesis and basis for development of treatment-related pain in breast cancer.

1-R01-HL-119542-01-A1 04/2014-05/2018
NIH/HHS **(Fu)** Total Award Amount: $2,690,641
Microfluidic Functional Immunophenotyping of Pediatric Patients Following Cardiopulmonary Bypass (CPB)

Our central objective of this research is to develop an integrated microfluidic immunosensing platform for efficient isolation, enrichment, enumeration, and sensitive multiplexed functional immunophenotyping of subpopulations of immune cells from blood specimens. To extend our research to make clinical impact, we propose to implement our microfluidic immunomonitoring technology to further determine the incidence and impact of immunosuppression in critically ill children and its functional connection to post-operative infections.

R01DA041032 09/2015-05/2022
NIH/NAHDAP **(Stephenson/Bauermeister)** Total Award Amount: $4,039,542
Optimizing HIV counseling testing and referral through an adaptive drug use intervention
The four main project goals are: to determine the efficacy of a sequence of interventions including Test Counselor (TC) delivered Substance Use Brief Intervention (SUBI) in promoting and sustaining "successful engagement", as defined by repeat HIV-testing behaviors among HIV-negative YMSM and linkage and retention in care among incident HIV+ cases, to test the differential efficacy across a 4-arm test-counselor delivered intervention (CTR-CTR, SUBI-CTR, CTR-SUBI, or SUBI-SUBI) in reducing sexual risk and drug use outcomes, to compare intervention effectiveness on risk reduction outcomes based on agency (TC characteristics, site fidelity, acceptability, satisfaction) and area indicators (socioeconomic disadvantage, HIV prevalence) and to assess agencies' acceptability and satisfaction of the intervention and its potential for sustainability as measured by a cost-effectiveness analysis.

R21DK106647 04/2016-03/2018
NIH **(Dimagno)** Total Award Amount: $439,886
Acute Pancreatitis Alert & Decision Support Improves Care & Cuts Length of Stay
The long-term goal of this research is to develop a portable, scalable software tool to improve treatment for patients with acute pancreatitis (AP).

ME-1507-31108 08/2016-08/2020
PCORI **(Kidwell)** Total Award Amount: $892,696
Design and Methodological Improvements for Patient-Centered Small n Sequential Multiple Assignment Randomized Trials (snSMARTs) in the Setting of Rare Diseases
The project goal is to improve existing methods in small sample size trial research, particularly for rare diseases, and we will innovatively combine and modify statistical methods from standard clinical trials and SMARTs. We will develop statistical methods to optimize efficiency and decrease bias in analysis that pools together information from separate stages within one trial, incorporates flexibility by the addition of adaptive components, and produces utility models that integrate a developed patient reported outcome tool to demonstrate the risk-benefit tradeoff of treatment effectiveness with tolerability and quality of life.

4UL1TR001079-04 08/2016-03/2018
NIH/NCATS **(Ford)** Total Award Amount: $61,316
Institute for Clinical and Translational Research
This project is focused, through collaboration among methodologists at four CTSA hubs, on enhancing network capacity by disseminating state-of-the-art methods and tools for the design and analysis of randomized clinical trials. Topics will include: (1) Sequential, multiple assignment randomized trial (SMART) designs, (2) Leveraging baseline covariates to improve the efficiency of randomized trials, (3) Causal analysis of pragmatic trials, (4) Sensitivity analysis for randomized trials with missing outcome data, and (5) Heterogeneity of treatment effects and individualized treatment effects.

1 R34 HL130738-01A1 08/2016-05/2020
NIH **(Neumar)** Total Award Amount: $697,500
Extracorporeal CPR for Refractory Out-of-Hospital Cardiac Arrest (EROCA) Trial Planning Grant
The goal of this NHLBI Clinical Trial Pilot Studies application is to generate the preliminary feasibility and efficacy data necessary and sufficient to design a full-scale clinical trial that will provide definitive guidance on the value of ECPR for refractory OHCA.

No sponser # 09/2016-10/2019
AstraZeneca **(Busui)** Total Award Amount: $407,056
Dapagliflozin and measures of cardiovascular autonomic function in patients with type 2 diabetes (T2D)
Evaluate the effects of dapagliflozin on measures of cardiovascular autonomic function as assessed by changes in heart rate variability (HRV), changes in cardiovascular autonomic reflex tests and resting heart rate to assess as measures of sympathetic/parasympathetic balance.

No Sponser # 07/2016-06/2019
BCRF **(Hayes/Morikawa)** Total Award Amount: $200,000
Predicting brain metastases in breast cancer patients through molecular profiling
The result of study will lead to the identification of a molecular pathway across different breast cancer subtypes and a development of novel BM predictive model. The proposed research has a potential clinical impact on future preventive and/or therapeutic strategies for breast cancer patients with brain metastasis (BM).

R01CA107469 09/26/16-08/31/21
NIH **(Kleer)** Total Award Amount $190,000
Role of EZH2 in Breast Cancer Progression
The project goal is to determine how EZH2 enhances ER- breast progression and translate biologic findings into clinical utility

R01MD011516 07/2017-02/2022
NIH **(Meurer, Skolarus**) Total Award Amount: $3,298,337
Reach Out: Randomized Clinical Trial of Emergency Department-Initiated Hypertension Behavioral Intervention Connecting Multiple Health Systems
Department-Based Hypertension Management. Emergency department visits present an opportunity to find people with untreated or uncontrolled hypertension and provide tools to help them manage their disease; this project will help us learn the best way to accomplish this.

06/01/19-05/31/21
HOPE Foundation for Cancer Research **(Speers)** Total Award Amount $202,825
Derivation of endocrine and chemotherapy resistance gene signatures and evaluation of previously developed molecular signatures as prognostic and predictive biomarkers in SWOG 8814
In Aim 1 we will assess the performance of 5 previously derived molecular signatures for chemotherapy response (OncotypeDx, MammaPrint, ProSigna, EndoPredict, Zhao metastasis signature) in the SWOG 8814 ER+, LN+ cohort. In Aim 2, we will determine if our previously identified lncRNAs associated with breast cancer treatment resistance are predictive of chemotherapy resistance and if their inclusion in molecular signatures improve their performance. In Aim 3 we will train and cross-validate a novel coding and non-coding gene signature to predict response to adjuvant chemotherapy designed specifically for patients with ER+, LN+ breast cancer.

UMCC 2018.108 03/06/19-03/05/27*
AstraZeneca Pharmaceuticals **(Reichert)** Total Award Amount: $961,903
A Multi-Center Phase II Study Testing the Activity of Olaparib and AZD6738 (ATR Inhibitor) in Metastatic Castration-Resistant Prostate Cancer (UMCC 2018.108)
To determine the response rate of the combination of olaparib and AZD6738 in mCRPC patients who are DNA repair proficient (DRPro, e.g. intact ATM, BRCA1 or BRCA2).
*Effort for Dr. Kidwell has ended

UMCC 2017.163 12/01/18-09/01/23*
UM Rogel Cancer Center **(Reichert)** Total Award Amount: $49,372
FOcal Radiation for Oligometastatic Castration-rEsistant Prostate Cancer (FORCE): A Phase II Randomized Trial

This clinical trial will determine whether the addition of radiotherapy to standard of care early systemic therapy improves objective progression-free survival rate (combined radiographic and clinical) at 18 months, compared to systemic therapy alone in patients with oligometastatic castration-resistant prostate cancer.
*Effort for Dr. Kidwell has ended

Career Catalyst Research Grant 10/2017-10//2021
Susan G. Komen for the Cure **(Burness)** Total Award Amount: $450,000
Role of Cancer Stem Cells in Mediating Resistance to DNA Repair Targeting Therapy
To target cancer stem cells via DNA damage.

07/2017-06/2018
Plastic Surgery Educational Foundation **(Momoh)** Total Award Amount: $10,000
Upper Extremity Biomechanics Following Breast Reconstruction
There are over 250,000 new cases of breast cancer diagnosed in the United States each year. In women pursuing post-mastectomy breast reconstruction, an implant-based technique is commonly used requiring disinsertion of either the pectoralis major muscle or latissimus dorsi muscle to provide soft tissue coverage of the breast prosthesis. These muscles are principal stabilizers of the shoulder girdle and their disinsertion has been shown to increase shoulder instability with short- and long-term functional deficits. We hypothesize that alterations in muscle length following disinsertion of either the pectoralis major muscle or latissimus dorsi muscle at the time of implant-based breast reconstruction will result in a reduction in the stiffness capacity and force generation of the donor muscle leading to increased shoulder instability. The proposed work is the first attempt to characterize physiological changes within both the donor muscle and the shoulder following implant-based breast reconstruction. Our study will utilize a cross-sectional design to identify the effects of two different implant-based breast reconstruction techniques on upper extremity biomechanics using objective functional measures. Additionally, patient reported outcomes measures utilizing validated questionnaires will characterize the reliability of the biomechanical assessments in predicting a patient's upper extremity dysfunction post-operatively. By understanding the mechanisms of why certain patients develop post-reconstruction shoulder disability, we hope to develop prospective strategies to identify and rehabilitate at-risk patients to improve the quality of life in cancer survivors.

1 K23 DK118179-01A1 04/01/19-03/31/24
NIH **(Saini)** Total Award Amount: $973,500
Using Intervention Mapping and the Multiphase Optimization Strategy to develop multilevel interventions to prevent upper GI bleeding
Develop an in-depth understanding of patient-, provider-, and system- level barriers and facilitators to appropriate PPI gastroprotection by conducting semi-structured interviews with patients, providers, and other key informants. Design and produce a theory-based multilevel intervention that targets patients, providers, and the health system. Assess the feasibility, appropriateness, and efficacy of the multilevel intervention in a single-site pilot study.

04/2014-08/2015
Verastem, Inc. **(McDermott)** Total Award Amount: $$174,889
Investigation of VS-4718 and VS-6063 in pre-clinical breast cancer models
Preliminary studies from Verastem have demonstrated that VS-4718 targets cancer stem cells (CSC) in vitro and in vivo using breast cancer cell lines. This proposal will further extend the studies to patient-derived xenograft (PDX) models using our MC1 primary human breast cancer cells. We will assess if VS-4718 and a related compound VS-6063 (compared with Paclitaxel) as well as combined therapy using Paclitaxel and VS-4718 (or VS-6063) affect the maintenance of CSCs in PDX models of breast cancer using established CSC assays, including the ALDEFLUOR+ and Lin-CD44+CD24–CSC content, tumorsphere formation and ALDH1, CD44, CD24 immunofluorescence in frozen tumor sections.

08/2014-07/2016
Cormorant Pharmaceuticals AB Total Award Amount: $232,251
Assessment of the Biologic Effects of IL-8 Inhibition in Triple Negative and Her2+ Breast Cancer Stem Cells and Therapy Responsive Circulating Tumor Cells

To measure the biologic effects of IL-8 inhibition on CSCs and in vivo tumor growth in TN and Her2 positive BC.

01/2015-12/2015
The Hope Foundation **(Schott)** Total Award Amount: $36,560
Neutrophil Extracellular DNA Traps and Breast Cancer Metastasis
To determine if the presence of NETs in primary tumor tissue and in plasma samples obtained from breast cancer patients correlates with disease stage and risk of metastasis.

UMCC 2017.002 09/2019-08/2021
Univ. of Michigan Rogel Cancer Center **(Burness)** Award Amt to Department: $17,585
A Phase 1 Multi-center trial of Trastuzumab and Pertuzumab in Combination with Tocilizumab in Subjects with Metastatic HER2 Positive Breast Cancer Resistant to Trastuzumab
To determine the highest dose level of tocilizumab (up to 8 mg/kg every 3 weeks) that, when given in combination with trastuzumab and pertuzumab every three weeks in subjects with HER2 positive metastatic breast cancer, will result in less than 25% incidence of DLT. This dose level will be the Recommended Phase 2 dose (RP2D).

DEMPSEY, WALTER, PH.D.

Current Support

R61 HL155498 (Brahmajee, N, Dorsch, M) 09/15/2021 – 08/31/2022
NIH/NHLBI $1,552,228 Total Award Amount
A Just-In-Time Adaptive Mobile Application Intervention to Reduce Sodium Intake And Blood Pressure in Hypertensive Patients
Our overall objectives are to: (1) evaluate the efficacy of a dietary sodium mobile application intervention on reducing BP, (2) establish that the improvement in BP is directly related to the change in diet and body weight, and (3) optimize the intervention to demonstrate sustained effects on BP.
Role: Co-Investigator

P50 DA054039 (Nahum-Shani/Almirall) 09/01/21-06/30/26
NIH/NIDDK Total Award Amount $13,208,081
Methodologies for Adapting and Personalizing Prevention, Treatment and Recovery Services for SUD and HIV (MAPS Center)
Project 2: Methods for Optimizing the Integration of Adaptive HumanDelivered and Digital SUD/HIV Services
This research center proposed to develop novel experimental and data analytic methods to optimize the adaptation of SUD/HIV services across different levels (e.g., individual, clinic), modalities, and time scales; serve as a national resource by placing the innovative methods developed in the MAPS Center directly into the hands of SUD/HIV scientists; and to nurture and build capacity among scientists to design experiments and analyze data to inform the development of adaptive SUD/HIV services. The MAPS Center will pave the way for a new generation of highly effective and scalable interventions that will reduce the prevalence and incidence of SUD and HIV infection.
Role: Co-Investigator, Project 2:

R01 DA039901 (Nahum-Shani/Almirall) 08/01/20-05/31/25
NIH Total Award Amount $2,913,828
Novel Longitudinal Methods for SMART Studies of Drug Abuse and HIV
The treatment of drug use and HIV often requires sequential, individualized decisions concerning the type or delivery of treatments. The methods developed in this project will improve clinical and public health outcomes by enabling drug use and HIV scientists to develop more potent approaches to guide the sequential, individualization of drug use and HIV treatments.

20SFRN35370008/20SFRN35360220 (Nallamothu/Skolarus) 04/01/20-03/31/24

American Heart Association Total Award Amount: $2,500,000
Wearables in Reducing Risk and Enhancing Daily Life-style (WIRED-L) – SFRN
The long-term goal of our research is to develop successful strategies driven by adaptive technologies that support self-management in common cardiovascular conditions.

R44 CA236557 (Walch) (Site PI: Tewari, M) 09/01/20-08/31/22
Arascope, LLC / NIH/NCI Total Award Amount: $800,031
Assessing the effects of lighting interventions on fatigue in three populations of cancer patients
The goal of this project is to carry out a clinical trial to test the effects of a mobile app that recommends lighting interventions on fatigue and other quality of life metrics in a population of cancer patients.
Role: Co-Investigator

Past Support

None

KRATZ, ANNA L., PH.D.

Current Support

R01 HD102337 (Kratz, A-Contact / Fritz, N) 08/01/2021 – 07/31/2026
NIH $3,009.381//total award amount
Optimizing detection and prediction of changes in cognitive function in multiple sclerosis with novel ambulatory assessment methods
In this study, we will use multiple complementary ambulatory assessment strategies to better understand cognitive dysfunction in MS. This project is designed to better characterize the natural history of cognitive dysfunction in MS, to identify factors that contribute to cognitive functioning in daily life, and to highlight functional domains that might be impacted by changes in cognitive function.
Role: Principal Investigator

R01 AT011341 (Braley, T-Contact / Kratz, A) 08/15/2021 – 05/31/2026
NIH/NCCIH $3,351,287 Total Award Amount
NSS Mechanisms of cannabidiol in persons with MS: the role of sleep and pain phenotype
Major Goals: Changes in sleep microstructure (Aim 1; including sleep stage bout length, sleep stage transition probability, and entropy) and macrostructure (Aim 2; including sleep regularity, rhythmicity, timing and duration) will be compared between cannabinoid and placebo groups, and pain phenotype will be assessed as a predictor of CBD-related changes in sleep. Aim 3 will assess the measures of sleep microstructure and macrostructure as mediators of analgesic response to CBD. Data generated from this study will inform CBD research, across a spectrum of neurological and other chronic conditions, that can be applied to the development of precision-medicine approaches for chronic pain.
Role: Principal Investigator (MPI)

U44 NS122002 (Kruger, G) (Site PIs: Harte/Schrepf) 09/10/2021 – 08/31/2026
Arbor Medical Innovations / NIH/NINDS $750,549 /total subcontract amount
Actigraphy Enhanced Pain Management
This project will use a combination of actigraphy, lab-based performance measures, and self-report of symptoms and functioning to develop and validate a whole-person measure of physical fatigability in MS.
Role: Co-Investigator

Innovative Research Award (Murphy, S/Khanna, D) 07/01/2021 – 06/30/2023
Rheumatology Research Foundation $399,999/total award amount
Resilience-based, Energy Management to Enhance Wellbeing in Scleroderma (RENEW): Testing of a Peer-Mentored Web-based Intervention

This project will examine the content validity of the website by engaging patient and peer-mentor stakeholders to assess whether the current RENEW program is appropriate to address the problem of fatigue and resilience in people with scleroderma, and determine whether the peer-mentored, RENEW intervention is more effective at achieving a clinically significant reduction in fatigue and performance outcomes compared to a waitlist control condition.
Role: Co-Investigator

724175 (Kratz, A) 04/30/2021 – 04/29/2024
Craig H. Neilsen Foundation $400,000//total award amount
Acceptance and Commitment Therapy for Chronic Pain in SCI: Development and Testing of an eHealth Program
The overall objectives of this study are to develop and test the efficacy of an Acceptance and Commitment Therapy (ACT)-based eHealth intervention to manage chronic pain in persons with SCI. This intervention will leverage the content of an existing and proven efficacious ACT intervention for chronic pain as well as the investigator's existing eHealth platform of a web-based multiple symptom self-management program that was designed for multiple sclerosis (my MS Toolkit (www.mymstoolkit.com).
Role: Principal Investigator

U19 AR076734 (Clauw, DJ/Hassett, AL) 09/26/2019 – 05/31/2024
NIH/NIAMS $8,969,433/total award amount
University of Michigan BACPAC Mechanistic Research Center
As part of the BACPAC initiative, the mechanistic research center at the University of Michigan aims to be a team member in realizing the vision of personalized medicine for individuals with cLBP.
Role: Co-Investigator

UG3 HL145269 (Meurer, W) 09/19/2019 – 08/31/2024
NIH/NHLBI $27,515,029/total award amount
½ ICECAP: Influence of Cooling duration on Efficacy in Cardiac Arrest Patients
The overarching goal of this project is to identify clinical strategies that will increase the number of patients with good neurological recovery from cardiac arrest. We hypothesize that longer durations of cooling may improve either the proportion of patients that attain a good neurological recovery or may result in better recovery among the proportion already categorized as having good outcome.
Role: Co-Investigator

90ARC90003-01-00 (Murphy/Kratz) 10/01/2019 – 09/30/2024
$840,223/total award amount
Administration for Community Living, National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR)
University of Michigan Advanced Rehabilitation Research Training Program in Community Living and Participation
This 5-year, University of Michigan Advanced Rehabilitation Research Training Program in Community Living and Participation (ARRTP-CP) will train postdoctoral fellows to advance the rehabilitation field by embracing community-based and person-centered research methods.
Role: Co-Principal Investigator

MB-1706-27943 (Kratz) 07/01/2019 – 06/30/2024
National Multiple Sclerosis Society $430,255/total award amount
Training to Advance Rehabilitation Research in Multiple Sclerosis
The goal of this project is to train postdoctoral research fellows in rehabilitation research. The aim is to produce highly-competent and innovative researchers who can launch independent research programs that advance the goal of optimizing quality of life for those living with MS.
Role: Principal Investigator

U01 HL123009-06S2 (Iwashyna) 05/01/2020 – 04/30/2022
Massachusetts General Hospital /NIH $386,107/total award amount

COVID-19: PETAL COVID-19 Observational Study
This project will conduct the 1, 3, and 6 month post-admission follow-ups for a national cohort of patients with COVID-19 recruited from within the more than 40 hospitals in the NIH/NHLBI's Prevention and Early Treatment of Acute Lung Injury Network. These follow-up surveys will be conducted over the phone from a centralized location.
Role: Co-Investigator

(Murphy/Khanna) 07/01/2021 – 06/30/2023
Rheumatology Research Foundation $399,999/total proposed amount
Resilience-based, Energy Management to Enhance Wellbeing in Scleroderma (RENEW)
We hypothesize that participants in the RENEW intervention will have a clinically meaningful improvement in fatigue as well as other symptoms and psychosocial issues (pain interference, depression, and resilience). We will also explore whether self-efficacy, a potential mediator of effects, is increased for participants in the RENEW intervention.
Role: Co-Investigator

MS-1610-36980 (Braley, T, / Kratz, A) 04/01/2018 – 04/01/2023
PCORI $3,362,330 Total Award Amount
A randomized controlled trial of telephone-delivered cognitive behavioral-therapy, modafinil, and combination therapy of both interventions for fatigue in multiple sclerosis
This clinical trial compares the effects of CBT monotherapy, modafinil monotherapy, and CBT+modafinil combination therapy on fatigue impact, fatigue severity, and fatigability in MS.
Role: Principal Investigator (MPI)

Past Support

WSU21009 (Fritz) (Site PI: Kratz, A) 10/01/2020 – 09/30/2021
Wayne State Univ / Natl Multiple Sclerosis Society $25,455/total award amount
Ambulatory Measurement of Perceived and Performance Fatigability
This project will use a combination of actigraphy, lab-based performance measures, and self-report of symptoms and functioning to develop and validate a whole-person measure of physical fatigability in MS.
Role: Site Principal Investigator, Co-Investigator

42114 (Tate, D) 04/30/2018 – 04/29/2021
Craig H. Neilsen Foundation $200,000//total award amount
Phenomenology of Chronic Pain After Spinal Cord Injury: Experience, Adaptation and Quality of Life
The overall objectives of this study are to develop and test the efficacy of an Acceptance and Commitment Therapy (ACT)-based eHealth intervention to manage chronic pain in persons with SCI. This intervention will leverage the content of an existing and proven efficacious ACT intervention for chronic pain as well as the investigator's existing eHealth platform of a web-based multiple symptom self-management program that was designed for multiple sclerosis (my MS Toolkit (www.mymstoolkit.com).
Role: Co-Investigator

RG5280-A-2 (Braley) 04/01/2015 – 03/31/2021
National Multiple Sclerosis Society (NMSS) $827,967/total award amount
A randomized trial of positive airway pressure therapy to treat cognitive dysfunction in MS patients with obstructive sleep apnea
Project Goals: The goals of this project are to examine the effects of OSA (obstructive sleep apnea), and its treatment - positive airway pressure therapy - on cognitive performance in MS patients who suffer from OSA.
Role: Co-Investigator

542114 (Tate/Rohn) 04/30/2018 – 04/29/2021
Craig H. Neilsen Foundation $200,000/total award amount
Phenomenology of Chronic Pain After Spinal Cord Injury: Experience, Adaptation and Quality of Life

The goal of the proposed study is to characterize the factors that contribute to the day-to-day experience of and adaptation to chronic pain and examine the relationship of those factors to QOL for those with SCI.
Role: Collaborator

W81XWH-17-1-0367 (Kratz) 09/15/2017 – 03/14/2020
Department of Defense $209,556/total award amount
Development of a Web-Based Symptom Self-Management Program for Individuals with Multiple Sclerosis
The primary objective of the proposed research is to improve management of pain, fatigue, and depressed mood through an online platform that provides education, guidance, and skills-building exercises that are specifically tailored for people with MS. Access to rehabilitation care that focuses on symptom self-management is seriously limited for many individuals with MS due to geographical location, limited resources (e.g. financial, transportation), and/or disability. The objective of this proposal is to expand access to symptom self-management care to all patients with MS, with particular focus on those under-served patients with limited access to symptom management care.
Role: Principal Investigator

R21 AG053186 (Kratz) 09/01/2016 – 04/30/2020
National Institutes of Health $426,250/total award amount
Development of a conceptual model of subjective physical and mental fatigability: the MI-FI study
Project Goals: The goal of this study is to address these limitations through a two-phase study to develop a foundational conceptual model of fatigability and lay the ground work for a state-of the art self-report measure of fatigability, the Michigan Fatigability Inventory (MI-FI).
Role: Principal Investigator

440343 (Carlozzi) 04/30/2017 – 10/30/2020
Craig H. Neilsen Foundation $399,187/total award amount
The Impact of Sleep Quality on Symptoms, Cognition, and Functioning in SCI
Project Goals: Using this multi-method measurement approach, we will conduct a novel study of how adults with SCI experience sleep, symptoms and cognition across a seven-day period. This study will focus on four common and troubling SCI symptoms – fatigue, pain, depression, anxiety, and cognitive concerns – assessed by self-report at five intervals each day throughout the week. We will evaluate functioning over the week through objective physical activity, assessed continuously by wrist-worn accelerometer, and by subjective report of daily participation in activities. We will also evaluate objective cognitive status through an in-person neurocognitive assessment completed at the end of the seven-day period.
Role: Collaborator

K01 AR064275 (Kratz) 04/01/2014 – 06/30/2019
National Institutes of Health $652,785/total award amount
Characteristics and Mechanisms of Cognitive Problems in Fibromyalgia
The overarching goal of this proposal is to provide education and training to the Principal Investigator (PI), Anna Kratz, PhD, so that she has the requisite knowledge and skills to address these limitations in the scientific evidence on fibrofog.
Role: Principal Investigator

RG4986A 1/1 (Kratz) 04/01/2014 – 06/30/2019
University of Washington/NMSS $52,441/total award amount
Life after MS diagnosis: a biopsychosocial assessment of symptom trajectory
Project Goals: Year 1: Dr. Kratz will provide the PI consultation on the selection and administration of outcomes measures and study design. She will establish data collection and data monitoring protocols and will see to it that research staff are following protocols. Once data collection has begun, she will conduct monthly data quality checks for the first three months of the study to assure adherence to study data collection protocols. Years 2 and 3: Dr. Kratz will conduct quarterly data quality checks and troubleshoot problems with data collection and/or entry. She will also conduct quarterly data analyses to ensure that study recruitment is meeting sample requirements in terms of

participant demographic and clinical characteristics (e.g. to assure that appropriate numbers of racial minority participants are being recruited) and advise the research team for the need for targeted recruitment efforts. Year 4: Dr. Kratz will ensure that all data are adequately cleaned and conduct standard data integrity analyses. She will complete all primary study statistical analyses (to test the primary aim hypotheses) and will disseminate study findings through peer-reviewed manuscripts and scientific conference presentations.
Role: Site Principal Investigator

U01 DK082345-10 (Clemens/Clauw) 09/18/1999 – 06/30/2019
National Institutes of Health $4,293,441/total award amount
University of Michigan MAPP Research Network Discovery Site
The NIDDK supplement to MAPP will modify the CMSI that is currently in use within the MAPP network. This involves expert consensus building regarding the best diagnostic criteria for each condition, cognitive interviews (focus groups) with patients to determine item relevance and understandability, and preliminary psychometric analysis of the instrument. The CMSI screener will also be updated to include trigger items for the 4 new conditions not currently in the MAPP version of the CMSI.
Role: Co-Investigator

WSU16102 (Kratz) 04/30/2016 – 05/30/2018
Wayne State University/Craig H. Neilsen Foundation $53,634/total award amount
Positive Psychological Traits and Psychological Flexibility in a Model of SCI Rehabilitation and Adjustment
Project Goals: 1. The University of Michigan will cover the recruitment of 80 participants for the survey portion of the study and 10 participants for the pilot intervention portion of the study. 2. The University of Michigan will collect data from the participants it recruits. 3. The University of Michigan will process participant compensation for the participants it collects data from. 4. The University of Michigan will program data collection web-sites and manage the data collected through these sites. 5. The University of Michigan will be engaged in subject recruitment, data collection, data processing and transfer, and dissemination activities. 6. The University of Michigan will engage in data analysis and dissemination activities.
Role: Site PD/PI/Collaborator

R01 NR013658 (Carlozzi) 09/27/2012 – 06/30/2018
NIH $3,112,023/total award mount
Quality of Life in Caregivers of Traumatic Brain Injury: The TBI-CareQOL
The purpose of this study is to develop and validate a sensitive caregiver-specific measure of HRQOL (the "TBI-CareQOL"). Ultimately, the findings from this study will provide clinically relevant information to providers, allow for more sensitive assessment of intervention-related change, and maximize the efficiency of clinical interventions.
Role: Co-Investigator

R01 NS077946 (Carlozzi) 05/15/2012 – 04/30/2018
NIH $3,123,236/total award amount
Validation of the HD-HRQOL (Huntington disease quality of life measure)
This project proposed to validate the HD-QOL and other relevant, newly developed PROs in a diverse sample of individuals with HD. Specifically, a state-of-the-art approach employing both classical and contemporary methods of test construction and validation - including Item Response Theory and computerized adaptive testing technology - will be used to develop a computerized adaptive test that permits brief and precise measurement of clinically relevant symptoms and functional limitations. In addition, this study will examine these measures' sensitivity and responsiveness to change over time.
Role: Co-Investigator

R03 NR014515 (Kratz) 07/01/2014 - 05/31/2016
National Institute of Nursing Research (NIH/NINR) $95,130/total award amount
Characteristics of Symptoms and Functioning in Multiple Sclerosis

Project Goals: The goal of this study is to examine the day-to-day variability and interactions between various symptoms in multiple sclerosis and the impact of symptom burden on functioning.
Role: Principal Investigator

287372 (Kratz) 04/01/2014-03/31/2016
Craig H. Neilsen Foundation $299,282/total award amount
The Dynamics of Pain Acceptance, Well-Being, and Functioning in SCI
Project Goals: This study examines the role of pain acceptance in the day to day functioning and well-being of individuals with chronic pain secondary to spinal cord injury.
Role: Principal Investigator

WHIBLEY, DANIEL, PH.D.

Current Support

R01 HD102337 (Kratz, A-Contact / Fritz, N) 08/01/2021 – 07/31/2026
NIH $3,009.381//total award amount
Optimizing detection and prediction of changes in cognitive function in multiple sclerosis with novel ambulatory assessment methods
In this study, we will use multiple complementary ambulatory assessment strategies to better understand cognitive dysfunction in MS. This project is designed to better characterize the natural history of cognitive dysfunction in MS, to identify factors that contribute to cognitive functioning in daily life, and to highlight functional domains that might be impacted by changes in cognitive function.
Role: Co-Investigator

R01 AT011341 (Braley, T-Contact / Kratz, A) 08/15/21 – 05/31/26
NIH/NCCIH $3,351,287 Total Award Amount
NSS Mechanisms of cannabidiol in persons with MS: the role of sleep and pain phenotype
Major Goals: Changes in sleep microstructure (Aim 1; including sleep stage bout length, sleep stage transition probability, and entropy) and macrostructure (Aim 2; including sleep regularity, rhythmicity, timing and duration) will be compared between cannabinoid and placebo groups, and pain phenotype will be assessed as a predictor of CBD-related changes in sleep. Aim 3 will assess the measures of sleep microstructure and macrostructure as mediators of analgesic response to CBD. Data generated from this study will inform CBD research, across a spectrum of neurological and other chronic conditions, that can be applied to the development of precision-medicine approaches for chronic pain.
Role: Co-Investigator

(Murphy/Khanna) 07/01/2021 – 06/30/2023
Rheumatology Research Foundation $399,999/total proposed amount
Resilience-based, Energy Management to Enhance Wellbeing in Scleroderma (RENEW)
We hypothesize that participants in the RENEW intervention will have a clinically meaningful improvement in fatigue as well as other symptoms and psychosocial issues (pain interference, depression, and resilience). We will also explore whether self-efficacy, a potential mediator of effects, is increased for participants in the RENEW intervention.
Role: Co-Investigator

724175 (Kratz, A) 04/30/2021 – 04/29/2024
Craig H. Neilsen Foundation $400,000//total award amount
Acceptance and Commitment Therapy for Chronic Pain in SCI: Development and Testing of an eHealth Program
The overall objectives of this study are to develop and test the efficacy of an Acceptance and Commitment Therapy (ACT)-based eHealth intervention to manage chronic pain in persons with SCI. This intervention will leverage the content of an existing and proven efficacious ACT intervention for chronic pain as well as the investigator's existing eHealth platform of a web-based multiple symptom self-management program that was designed for multiple sclerosis (my MS Toolkit (www.mymstoolkit.com).

Role: Co-Investigator

U19 AR076734 (Clauw, DJ/Hassett, AL) 09/26/19 – 05/31/24
NIH/NIAMS $8,969,433 Total Award Amount
University of Michigan BACPAC Mechanistic Research Center
The NIH BACPAC initiative is designed to address the need for effective and personalized therapies for chronic low back pain (cLBP). Within the initiative, we are conducting a research project that uses a patient-centric, SMART design study to follow people with cLBP longitudinally to generate new knowledge regarding phenotypes, endotypes, mechanisms, diagnostics, trial outcomes, and therapeutic responsiveness.
Role: Co-Investigator

Past Support

(Whibley) 06/02/2019 – 05/29/2020
Michigan Medicine Dan Barry Grant $2500/total award amount
Harnessing Participatory Action Research to guide the design of a sleep and physical activity improvement intervention for adults with osteoarthritis
This grant funded a longitudinal qualitative focus group study to explore target user motivations, expectations, and attitudes toward a newly developed digitally delivered hybrid sleep and physical activity improvement intervention.
Role: Principal Investigator

(Whibley) 03/05/2018 – 06/04/2021
Versus Arthritis (Foundation Fellowship) £178,377.00/total award amount
Investigating the role of exercise and sleep in the management of chronic pain
This grant funded an investigation of the interlinkages between chronic pain, exercise/physical activity and sleep among people living with chronic pain. Insights gained were then used to develop and feasibility test a new digital intervention that simultaneously targets exercise and sleep behaviors in people living with chronic pain.
Role: Principal Investigator

(Whibley) 08/01/2018 – 09/01/2018
Scottish Universities Life Sciences Alliance £4110/total award amount
The relationship between sleep, fatigue, cognitive dysfunction and chronic pain: Identifying temporal relationships and targets for treatment
This Postdoctoral and Early Career Research Exchange grant funded travel to work in the Kratz Lab at the University of Michigan to analyze actigraphy and ambulatory assessment data to enhance understanding of the temporal associations between sleep, fatigue, cognitive dysfunction and chronic pain.
Role: Principal Investigator

KRUGER, DANIEL, PH.D.

Current

Research Agreement (Kruger, D) 02/03/22 – 01/31/24
MoreBetter, Ltd $60,000 Total Award Amount
Assessing the efficacy of Cannabis compositions in providing chronic pain relief and improving overall quality of life
The goal of this project is to study the efficacy of different Cannabis chemical compositions in providing pain relief and improving overall quality of life for individuals with the following chronic pain conditions: fibromyalgia, rheumatoid arthritis, and osteoarthritis of the knee and/or hip.
Role: Principal Investigator

R01 HD096909 (Mendelsohn, A) (Site PI: Kruger, D) 03/01/19 – 02/28/24
New York University / NIH Prime $76,204 Total Subcontract Award

Universal Strengths-Based Parenting Support in Pediatric Health Care for Families with Very Young Children Following the Flint Water Crisis
The goals of this project are to characterize neighborhood-level stressors and resilience factors in relation to the disaster and to poverty more broadly using geocoded, census-linked Speak to Your Health survey data before, during, and in the aftermath of the disaster. Assess impacts of promotion of parenting on responsive parenting and child development in the aftermath of a disaster in a high poverty community.
Role: Site Principal Investigator, Co-Investigator

Past Funding

R01 HD062565 (Zimmerman, M) 09/01/10 – 07/31/17
NIH $3,183,711 Total Award Amount
Youth Empowerment Solutions for Positive Youth Development
The proposed study aims to implement and evaluate an empirically developed after school intervention for empowering youth (YES) using a randomized controlled trail design in a high risk, urban sample; to test a conceptual model that posits a causal relationship from youth empowerment processes to positive developmental outcomes; and, to follow youth over time to assess sustainability of gains in healthy development.
Role: Co-Investigator

RFP #09-013 10/01/11 – 09/30/12
Genesee County, MI $84,997 Total Award Amount
REACH US
The Genesee County REACH US project is designed to reduce disparities in perinatal health and infant mortality in Genesee County, MI. The project is funded by a grant from the Centers for Disease Control and Prevention to the Genesee County Health Department. The project follows Community Based Public Health principles and involves a partnership between local health infrastructures, community-based organizations and universities. The partnership promotes education and health promotion programs, community mobilization, healthcare advocacy, and other activities that address historical, cultural and structural aspects of racism.
Role: Principal Investigator

HOSANAGAR, AVINASH, M.D.

Dr. Hosanagar holds a dual appointment with the Department of Veterans Affairs (VA) and the University of Michigan (UM). Veterans Affairs 8/8 appointment and an adjunct University of Michigan appointment.

As his focus is clinical he is not listing research support.

SILVEIRA, MARIA J., M.D., M.P.H.

Dr. Silveira holds a dual appointment with the Department of Veterans Affairs (VA) and the University of Michigan (UM). Veterans Affairs 5/8 appointment and University of Michigan 6.0 calendar months.

Current

PLC-1609-35995 (Temel) (Site PI: Silveira, M) 1/1/2018-12/31/2022
PCORI Total Award: $338,800
Comparative effectiveness trial of early integrated telehealth vs in-person palliative care for patients with advanced lung cancer
Early and longitudinal involvement of palliative care (PC) in the outpatient management of patients with advanced cancer improves patient-reported and end of life (EOL) care outcomes. While recommended by national organizations as the standard of care, this early integrated care model utilizes substantial PC resources, which has limited its

dissemination across care settings. Telehealth (i.e., the use of information and communication technology in health care delivery) is an effective strategy to increase patients' access to health care services when the numbers of specialty-trained clinicians are limited. We seek to perform a multi-site comparative effectiveness trial of early integrated telehealth versus in-person PC in patients with advanced lung cancer. By demonstrating the equivalence of the telehealth delivery modality, we seek to define a role for this more accessible, scalable and patient-centered approach to PC.
Role: Co-Investigator, Site-Principal Investigator

Past Support

Pilot Grant (PI: Silveira) 6/1/2020-5/31/2022
University of Michigan Palliative Care $20,000 Total Pilot Award Amount
Centralized pain in lung cancer patients
Our objective is to measure the prevalence of central sensitization in a convenience sample of lung cancer patients in preparation for an R01 to examine central sensitization in chronic cancer pain.
Role: Pilot Project Principal Investigator

MCube (PI: Silveira) 6/1/2019-12/31/2021
University of Michigan $60,000 Total Award Amount
Electronic monitoring of opioid adherence among patients at risk for misuse
The primary goal of this project is to assess the ideal features of a program to electronically monitor patient opioid use among patients with cancer pain who have past histories of substance use or alcohol use disorder.
Role: Principal Investigator

IIR 13-322-2 (Bohnert) 07/01/2015-03/31/2021
VA Health Administration-HSR&D $324,372 Total Award Amount
Primary Care Intervention to Reduce Prescription Opioid Overdoses: Prescription Opioid Safety Trial (POST)
This project aims to determine the safety of high-dose opioid use among Veterans presenting to primary care and mental health clinics, it is of critical importance to involve researchers who have expertise in overdose risk, opioid use, primary care and mental health care settings, pharmacoepidemiology, and longitudinal data analysis, as well as sufficient support staff.
Role: Co-Investigator

SD 15-461 (Lorenz) 09/01/2016-08/31/2018
VA Health Administration-HSR&D $324,372 Total Award Amount
The Opioid Consent: Helping Optimize Information for Cancer and Effective (CHOICE) Pain Management
The Opioid CHOICE Study set out to evaluate the appropriateness of excluding Veterans with cancer from SOIC, and how the SOIC process impacted treatment decisions and communication for Veterans and providers. Opioids CHOICE aimed to assemble a nationally representative cohort of Veterans receiving LTOT stratified by cancer status to describe their demographic and clinical characteristics and treatment patterns, and compare those with and without cancer with regard to a) serious opioid-related adverse events, b) pain outcomes, and c) use of SOIC using iMED. We will then qualitatively evaluate provider and Veteran perceptions of SOIC for LTOT.
Role: Co-Investigator

(Silveira, M) 10/31/2012-10/30/2014
McKesson Foundation $250,000 Total Award Amount
Development of a mobile monitoring application for chemotherapy related toxicities for patients undergoing chemotherapy
This project will work toward advancing the science of cognitive behavioral interventions for managing symptoms in cancer. If successful, our application will help patients with cancer symptoms for whom self-care is a challenge and who experience preventable morbidity and health service use as a consequence.
Role: Principal Investigator

IIR 08-309 (Silveira, M) 10/01/2009-09/30/2014
VA HSR&D $1,100,000 Total Award Amount
Web-based support for caregivers of Veterans undergoing chemotherapy
This research represents the next step in advancing the science of cognitive behavioral interventions for managing symptoms in cancer. It is the first trial to address the difficulties many veterans face when attempting to manage their symptoms with inadequate support from social network members, by providing a mechanism so that any caregiver can be more informed about the patient's status and needs, and provide structured support in key areas over the phone. If successful, our program stands to help thousands of veterans with cancer symptoms for whom self-care is a challenge and who experience preventable morbidity and health service use as a consequence.
Role: Principal Investigator

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

PERSONNEL

Leadership Team
Our team of co-Principal Investigators (co-PIs) have complementary expertise to ensure that all aspects of the study can be carried out. They are Drs. Kevin Boehnke, Amy Bohnert, and Rachel Bergmans, all three of whom are faculty members at the University of Michigan. Drs. Bohnert and Boehnke have successfully managed very large grants and contracts at the state (State of Michigan) and federal level (CDC, NIH).

- Dr. Boehnke is a Research Investigator in the Department of Anesthesiology Chronic Pain and Fatigue Research Center (CPFRC) at the University of Michigan. and a nationally renowned cannabis expert. He is currently involved in several NIH-funded clinical trials investigating effects of cannabinoids on pain and sleep. He has led numerous studies showing that people with chronic pain substitute cannabis for opioids and other pain medications, mostly without clinician oversight.[2-6,8-13] Dr. Boehnke has provided guidance on CBD for the Arthritis Foundation[196] and is currently a Technical Expert Panel member for two national committees on cannabinoid use for pain, including a collaboration between the office of Veterans Affairs and Oregon Science and Health University. He has published numerous articles about chronic pain as well as cannabis, including in *JAMA, Annals of Internal Medicine* and *Journal of Pain.* Dr. Boehnke will be the contact PI for this proposal, helping oversee all proposed studies with a particular focus on the CBD trial.
- Dr. Bohnert is a Professor in the Departments of Anesthesiology, Psychiatry and Epidemiology at the University of Michigan and a researcher with the Department of Veterans Affairs Center for Clinical Management Research (CCMR). She is an internationally renowned epidemiologist whose research team has been very involved in studying Veterans, mental health and the risk of suicide She is Co-Director of the

Division of Mental Health Innovations, Services, and Outcomes. She leads a number of NIH-, CDC-, and VA-funded projects to identify paths for reducing the burden of opioid use disorders, opioid misuse, and overdose using randomized controlled designs and electronic health records databases. Her projects include a trial of a mobile behavioral intervention to reduce opioid misuse and a State of Michigan DHHS-partnered project, the Michigan Opioid Collaborative, to provide technical assistance and peer mentoring to physicians providing medications for opioid use disorders. Dr. Bohnert has published over 100 articles related to mental health, opioids, pain, and addiction, including papers in *NEJM, JAMA*, *BMJ*, *Annals of Internal Medicine*, *JAMA Psychiatry*, and the *American Journal of Psychiatry*. [66,68-70,72-78,80-93,95-97,99,107-128,130-142,144-156,201] Her research, funded by NIH, CDC, and the VA, has been foundational in understanding the balance of benefits and harms of opioid analgesic use, and she has content expertise in pain and substance use disorders. She has also served in a scientific advisory role to the Centers for Disease Control and Prevention, to the Food and Drug Administration, and the Michigan Prescription Drug and Opioid Abuse Task Force. With Dr. Boehnke, Dr. Bohnert will help oversee the proposed clinical trials in this study, with a focus on the educational intervention.

- Dr. Bergmans is a Research Investigator in the Department of Anesthesiology Chronic Pain & Fatigue Research Center (CPFRC), a T32 trainee (AR007080, 9/01/21-8/31/22), and the faculty co-leader for the CPFRC Health Equity Core. As a social epidemiologist and community-engaged researcher, Dr. Bergmans uses quantitative and qualitative approaches to advance equity in chronic pain and related health outcomes. Her program of work is focused on putting permanent infrastructure in place to increase diversity, equity, and inclusion within chronic pain research at the University of Michigan; establishing sustainable academic-community partnerships; and privileging the priorities and perspectives of representatives from Black and African American communities in the development of non-pharmaceutical therapies and interventions for pain management. Dr. Bergmans has over 7 years of experience implementing community-engaged approaches to partner with key representatives in addressing social and environmental determinants of health. Dr. Bergmans will primarily oversee Aim 1, supervising the formation of the patient/community advisory board, and the work of the Recruitment Ambassador, Research Specialist Associate, and the postdoctoral research fellow. Dr. Bergmans will oversee the development of new materials and other strategies to boost Veteran recruitment and retention (including of underrepresented minorities), as decided on by the CAB and/or as requested by the Recruitment Ambassador.

- *Project managers under leadership team*
    - Laura Thomas, MSW, MPH is a Project Manager at the VA and a Clinical Therapist in Anesthesiology at UM. Ms. Thomas has worked with Dr. Bohnert leading human subjects research for over eight years, including working with Veterans, and starting and closing projects. Ms. Thomas will assist in the day-to-day operations of the project and oversee IRB applications and other regulatory applications and amendments.
    - TBN: A senior level project manager will be hired with a background in social work and public health. The project manager will assist in the day-to-day operations of the project and oversee IRB applications and other regulatory applications and amendments for this project. Ms. Thomas will help train this program manager.

Clinical Oversight and Monitoring (all aims)

- Dr. Avinash Hosanagar, MD, is a Staff Psychiatrist at the Ann Arbor VA Medical Center and a Clinical Assistant Professor in the Department of Psychiatry at UM. Dr. Hosanagar is addiction medicine-boarded and provides addiction-related services to Veterans, as well as leading the ketamine clinic for severe depression at the Ann Arbor VA Medical Center. He will lead efforts to monitor and conduct risk assessments and treatment referrals in this project, and aid with Veteran outreach and engagement efforts.

- Dr. Maria Silveira, MD is an Associate Professor in Geriatric and Palliative Medicine at the University of Michigan, Research Scientist at the Ann Arbor VA Medical Center Geriatric Research Education and Clinical Center and Director of the Supportive Oncology Clinic at the Rogel Cancer Center. She has devoted the last 10 years to developing technology to improve patient and caregiver access to safe and effective symptom management advice, including trials of web-based support for caregivers. Dr. Silveira served on the VA's Expert Panel for Long-term Opioid Therapy Guidelines and am on NCCN's panel for Anti-emesis Guidelines. In addition to her research, she has treated hundreds over Veterans clinically over the course of her career. Dr. Silveira will provide risk management for enrollees in the study, insight on the web-based intervention, and aid with Veteran outreach and engagement efforts.

Outreach (Aim 1, recruiting for Aims 2+3)

- Dr. Janevic is an Associate Research Scientist in the Department of Health Behavior and Health Education in the University of Michigan School of Public Health, and the faculty co-leader for the CPFRC Health Equity Core. Dr. Janevic brings expertise in cognitive-behavioral approaches to chronic pain management in underserved populations, chronic pain disparities and social determinants of health, the influence of cultural factors on chronic disease management, and mixed methods analyses in behavioral trials. Dr. Janevic has over 10 years of experience working on community-engaged health research projects. She has led or co-led numerous studies and evaluations involving active community partnerships, has applied participatory approaches to ensure that key partners are represented in the research process and in the adaptation of evidence-based interventions to meet the needs of a given community. Dr. Janevic will assist Dr. Bergmans with the formation and conduct of the CAB, the hiring and job responsibilities of the Recruitment Ambassador, and the development of new materials and other strategies to boost recruitment and retention of underrepresented minorities, as decided on by the CAB and/or as requested by the Recruitment Ambassador.
- Keiyana Chambers-Peeples is a community outreach coordinator in Anesthesiology at the University of Michigan. She has extensive experience in administration as well as in outreach efforts among Black communities.
- TBN:
    - Recruitment Ambassador: We will hire a community health worker, community organizer, or individual with similar experience, with deep knowledge of local resources who can serve as a bridge between research and diverse communities as a recruitment ambassador. The recruitment ambassador will lead outreach efforts in Veteran communities, including in the Detroit and Flint areas, to support study recruitment efforts. This individual will also facilitate bidirectional communication and knowledge transmission between the CPFRC and community stakeholders by assisting enrolled participants navigate the challenges of participating in clinical trials, thereby enhancing retention. The recruitment ambassador will take part in biweekly meetings with the investigator team and will be actively engaged in community dissemination efforts.
    - Postdoctoral Research Fellow: We will hire a post-doctoral research fellow with expertise in qualitative research and mixed methods, including semi-structured interviewing and qualitative data analysis. This person's primary role will be assisting with qualitative analysis to advance community-engaged, Veteran-centered approaches for clinical application of cannabis and CBD. Under Drs. Bergmans' and Janevic's supervision, this person will collect and analyze data from those who are eligible for the proposed studies (both participants and those who declined study participation) to understand barriers to participation. This person will also assist with evaluating the processes and activities for the CAB.
    - Research Specialist: We will hire a research specialist with a background in Social work or public health (Master's level) to help with enrolling participants in the qualitative interviews, qualitative coding, data analysis, interviews, literature reviews, and oversight/assistance with CAB management.
    - We anticipate that most of the individuals will be located in Ann Arbor, MI, but are flexible in allowing some to work remotely as that may facilitate a broader pool of qualified applicants.

Clinical Trial Co-Investigators (Aims 2+3)

- Dr. Daniel J. Clauw, MD is a Professor of Anesthesiology, Rheumatology, and Psychiatry at UM. He serves as the Director of the Chronic Pain and Fatigue Research Center (CPFRC), which is one of the world's leading pain research groups. Dr. Clauw is an internationally renowned pain researcher and expert on centralized pain syndromes, and and currently leads or has previously led numerous federally funded projects related to chronic pain including the NIH-funded UM Fibromyalgia Center for Research Translation, the Back Pain Consortium Research Program, and the Multidisciplinary Approach to the Study of Chronic Pelvic Pain network. He has extensive experience in clinical trial administration, design, conduct, and interpretation, as well as considerable expertise in cannabinoids,[2-4,6,7,61,104,165,286,289,290,294,296-322] – all of which he will lend to this project.
- Dr. Sachin Kheterpal, MD, is a Professor of Anesthesiology and associate dean for research information technology at the Medical School at UM. He is an expert in information technology (IT) and directs the ongoing development IT infrastructure across multiple international sites using innovative techniques to integrate

administrative, electronic health records (EHR), and registry data across institutions. He is also the Principal Investigator of a study (MiPACT), funded via contract from Apple, that has recruited over 7,000 participants to use Apple Watch devices to track health outcomes longitudinally and developed methods to ensure a diverse sample. In this project, he will provide technical leadership to ensure that key delivery functionality of the mobile technology is operational and maintained.

- Dr. Nirav Shah, MD, is an Assistant Professor in the Department of Anesthesiology at the University of Michigan. Within Michigan Medicine, he is the Associate Chief Medical Information Officer – Perioperative Care, and Director of Anesthesia Informatics and Systems Improvement, where he leads a team that develops software solutions for perioperative quality improvement, research, clinical and business operations, and supports the hospital's perioperative electronic health record (EPIC). Dr. Shah has deep expertise in workflow optimization, data privacy, and data management, all of which he will bring to his role on this project.
- Dr. Evan Litinas, MD, is the co-owner of Om of Medicine and owner of Litinas LLC. He has spent the last 9 years focusing exclusively on optimizing the clinical use of medical cannabis. He has collaborated with study team faculty at UM on several cannabis projects and is a co-author on several resulting publications.[2-5,11] Dr. Litinas has extensive clinical experience working with patients from his time as the Chief Medical officer of Om of Medicine, developing patient education materials and individualized medical cannabis usage protocols based on his extensive knowledge of cannabinoid research, methods of administration, therapeutic levels of cannabis or cannabinoids according to the scientific literature, and available cannabinoid based medicines. Dr. Litinas will help lead the intervention development, manualization, and training for this project.
- Dr. Williams is a Professor in the Departments of Anesthesiology, Psychiatry, Rheumatology, and Psychology at the University of Michigan as well as the Associate Director of the Chronic Pain and Fatigue Research Center. Additionally, he serves as Co-Director of Research Development within the Michigan Institute for Clinical and Health Research (MICHR). He is both a pain psychologist and a researcher with publications in the areas of chronic illness management, mobile health services delivery for chronic pain, patient-reported outcomes instrument development and validation, and mechanisms of pain perception/modulation. He is the past President of the American Pain Society and serves on numerous scientific editorial boards and scientific review committees both nationally and internationally. In recognition of his commitment to students, he received the Distinguished Clinical and Translational Research Mentor Award from the University of Michigan. Dr. Williams has published over 100 articles related to pain and pain management. For the current application, Dr. Williams brings extensive experience in characterizing chronic illnesses and assessing outcomes of interventions. He also brings expertise in coaching, educational, and adherence methods associated with pharmacological and nonpharmacological interventions. With Drs. McAfee and Litinas, he will oversee intervention development and manualization as well as providing insight on outcome assessment.
- Dr. McAfee is a Clinical Associate Professor of Anesthesiology at the University of Michigan, who treats patients at the Department of Anesthesiology Back and Pain Center. Dr. McAfee recently completed a K23 (DA038718) that aimed to better understand why patients continue taking opioids and incorporate theory-based models of behavior change into the development of interventions for individuals who would benefit from opioid cessation. Such work included qualitative assessment including focus groups and semi-structured clinical interviews and the evaluation of related data. She is also leading a study at the Back & Pain Center exploring chronic pain patient's cannabis use patterns and attitudes towards medical cannabis and has co-authored numerous manuscripts on cannabis and chronic pain with members of the proposed study team.[4,8,9] Dr. McAfee will help oversee manualization of the educational intervention, training of behavioral health consultants (i.e., cannabis coaches), and ensuring the fidelity of the educational intervention.

- TBN:
    - We will hire a data manager who will oversee the project database and maintain data quality and consistency.
    - We will hire Help Desk Staff who will aid with maintaining the project database and providing as-needed support to study participants and the project team.
    - We will hire an Applications programmer will be responsible for development and maintenance of the database and data collection forms/applications. They will refine any data transfer processes, develop reports as needed, and specific narrative management functions within the application platform.

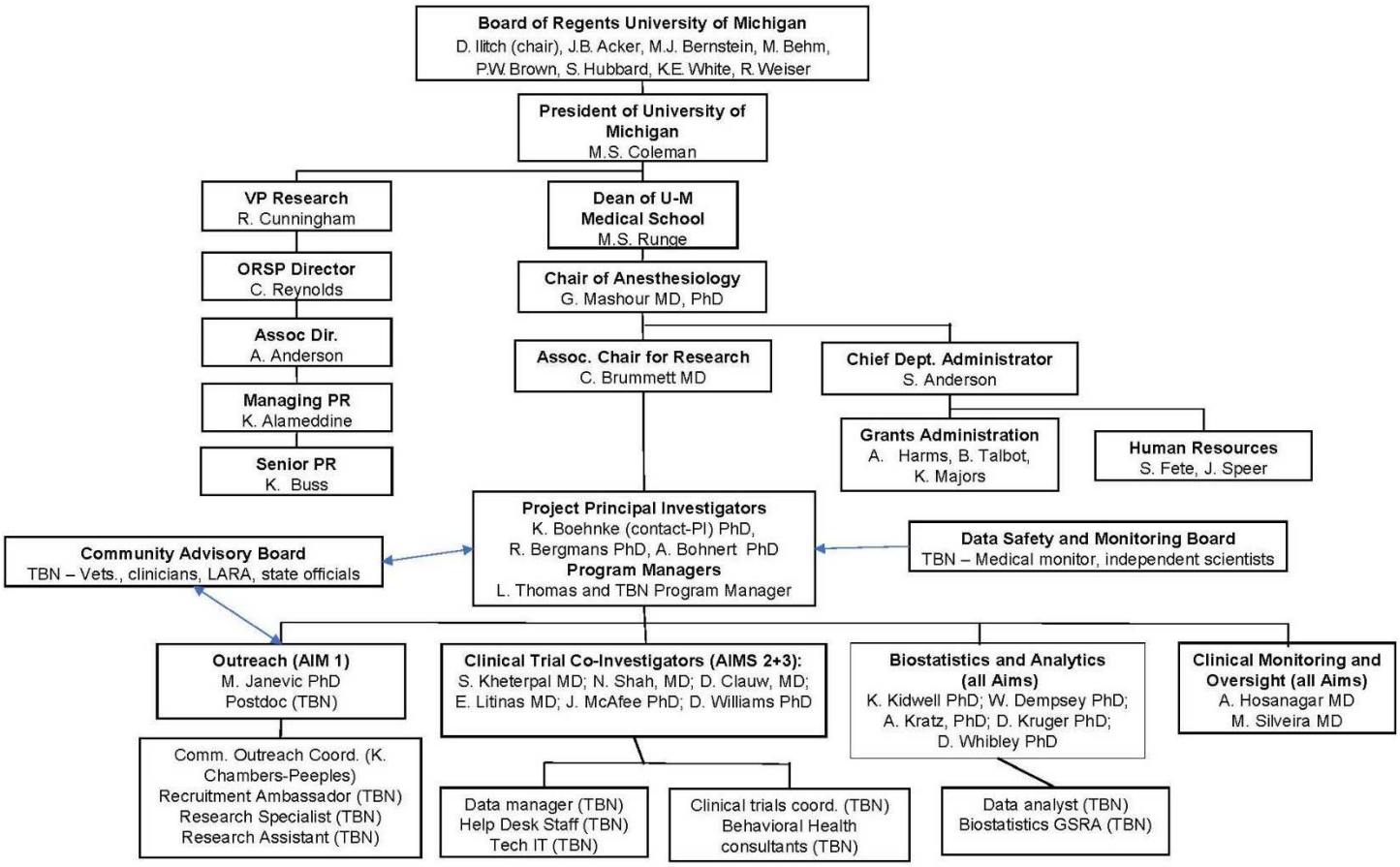
- We will hire clinical subject coordinators who will be charged with study coordination throughout all Aims of this program. In addition, these individuals will work closely with the investigator team regarding recruitment of participants for the registry (Aim 1) and Aim 2 & 3 clinical trials.
- We will hire behavioral health consultants (i.e., cannabis coaches) to help deliver the educational intervention. These behavioral health consultants will have a background in research and social work, and will be trained by Dr. Litinas, Dr. McAfee, and Dr. Williams in faithfully adhering to the educational intervention. Dr. Bohnert's lab has run multiple telemedicine intervention studies, and both Dr. Bohnert and Ms. Thomas have extensive experience overseeing and successfully completing such studies. Behavioral health consultants will also aid with retention and study coordination efforts related to the participants with whom they are directly working in this study.
- We anticipate that most of these employees will be located in Ann Arbor, MI, but are flexible in allowing some to work remotely as that may facilitate a broader pool of qualified applicants.

Biostatistics and analytics (all aims)

- Dr. Kidwell is an Associate Professor of Biostatistics in the School of Public Health, where she is also the Associate Chair for Academic Affairs. Her expertise in the design and analysis of innovative digital clinical trials, particularly in Sequential Multiple Assignment Randomized Trials (SMARTs). Her methodological focus is on the design and analysis of SMARTs, more recently in the area of rare disease or small samples. She was principal investigator (PI) of a PCORI funded contract developing SMART design and methods in small samples (2016-2019) and now is the PI of an FDA funded contract continuing that work. She recently received another PCORI methodology contract as PI to consider patient preferences in SMART design. Dr. Kidwell will be the lead statistician for the primary analysis of both clinical trials on this project.
- Dr. Walter Dempsey, PhD, is an Assistant Professor of Biostatistics and Assistant Research Professor at the Institute for Social Research at UM. His research focuses on statistical methods for digital mental health, with a particular interest in dynamic (i.e., longitudinal) treatment strategies and using sensor data to improve participant engagement and outcomes. In this project, he will guide statistical modeling decisions and oversee the activities of the project data analysts.
- Dr. Daniel J. Kruger, PhD is a Research Investigator in the Institute for Social Research at UM. He has extensive expertise in on-line survey research, program evaluation, and statistical analyses. Dr. Kruger has a collaborative research program on cannabis use and public health, focusing on the relationships and disconnects between medical cannabis use and mainstream health systems.[8,11,323-331] His work has been funded by federal and state agencies, as well as foundations. Dr. Kruger will provide insight on statistical analyses, survey design, data management, and manuscript preparation for this project.
- Dr. Daniel Whibley, PhD, is a UK-registered physiotherapist, a Research Assistant Professor in the Department of Physical Medicine and Rehabilitation at UM. His research is focused on the impact of sleep and physical activity on the symptoms pain, fatigue, and cognitive function. His expertise includes analysis of data collected using ambulatory assessment methods and actigraphy. He has published numerous studies in the sleep and pain fields and previously investigated cannabis use patterns among adults with Multiple Sclerosis and impacts on pain, anxiety, fatigue, and insomnia. He will provide support and expertise related to the sleep, pain, and measurement/analysis aspects of the project, building on prior collaborations with members of the research team.
- Dr. Anna Kratz, PhD, is a clinical psychologist and Associate Professor in the Department of Physical Medicine and Rehabilitation at UM. She leads a program of federally- and foundation-funded research that examines the characteristics, mechanisms, and treatment of chronic symptoms, including chronic pain and fatigue. Dr. Kratz has extensive expertise in ambulatory assessment techniques, including ecological momentary assessment (self-report in real time), actigraphy, app-based cognitive tests, and collection of physiological data using wearable devices. She has expertise in randomized as well as pragmatic and comparative effectiveness trial designs. She has developed digital educational and behavioral interventions for symptom management (e.g. MyMSToolkit, PainGuide). She will provide support and expertise on the areas described above for this project, which is a natural extension of her ongoing collaborations with the team.

- TBN:
  - We will hire a data analyst who will help conduct statistical analyses for the many manuscripts produced through this project.

- We will hire a biostatistics graduate student research assistant who will help oversee the data analysts and conduct high-level statistical analyses.



The figure above shows the organizational structure for the individuals who will contribute to this project. These individuals include the Leadership Team and Co-Investigators listed above, all of whom are based in Ann Arbor, MI. Our employees are bound through their employment with the University and our internal policies to comply with the terms and conditions of research agreements the University signs.

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 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.

(3) **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.

(4) **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.

(5) **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.**

(6) **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).

(7) 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.

(8) 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.

(9) 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.

(10) 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.

(11) 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.

BEGIN APPLICANT RESPONSE

BUDGET NARRATIVE

The University of Michigan (UM) calculates effort commitment for faculty based on either a 12-month calendar year (52 weeks / 2,080 hours), or 9-month academic year (38 weeks / 1,520) and 3 summer months (14 weeks / 560 hours) and FTE appointment. Staff effort is determined using a 12-month calendar year (52 weeks / 2,080 hours) and FTE appointment. Per University guidelines, all faculty and staff are required to review and certify their effort allocated to sponsored projects annually.

Fringe benefits (FB) are estimated using the University Costs for Benefits as a Percentage of Salary spreadsheet. It displays the benefits as percentages, and it is updated each year in July. As per the RFP, fringe benefits are capped at 35.0%. The only exception is the GSRA, who is eligible for gradcare at a cost of $326/month for 12 months. The cost is inflated 3.0% in out years. A fringe benefit rate of 32% is used for faculty, and a rate of 35% is used for staff.

Administrative Expenses

<u>Administrative Personnel</u> ($74,652 Salary + $26,131 FB + $22,980 Other = $123,763)

M. Kathleen Majors, Grant Administrator (10% effort)
Ms. Majors is a Research Administrator Senior in the department of Anesthesiology. She has a Bachelor of business administration degree and has over 15 years of experience managing grants. She will be responsible for establishing subawards, managing project expenses, and submitting financial reports as required by the sponsor. She will meet regularly with PIs to review finances and expenditures. Ms. Majors is a salaried-exempt-exempt Research Administrator Senior with a Y1 salary of $79,928.

Keiyana Chambers-Peeple, Project Coordinator for Community Engagement (12.5% effort)
Ms. Chambers-Peeple is a Project Coordinator for Community Engagement in the Department of Anesthesiology Chronic

Pain & Fatigue Research Center. She will be responsible for coordinating all meetings and maintaining strong lines of communication with the research team. She will provide administrative support as needed to the PIs and Project Leadership and will assist them in planning and meeting with community partners. Ms. Chambers-Peeple will coordinate and take part in take part in biweekly meetings with the Project Team. Ms. Chambers -Peeple is a salaried-exempt-non-exempt Project Coordinator with a Y1 salary of $48,547.

Daniel Kruger, PhD, UM ISR Service Personnel Fee ($22,980)
The University of Michigan institute for Social Research (UM ISR) charges a fee for contributions by their faculty and staff to sponsored projects. We are requesting the following: **Y1-$4,328; Y2-$4,458; Y3-$4,592; Y4-$4,730; Y5-$4,872**.

VMR Program Expenses (Y1-$2,139,916; Y2-$2,272,362; Y3-$2,296,541; Y4-$2,127,026; Y5-$1,953,056 = $10,788,901)

<u>VMR Program Staff</u> ($1,674,281 Salary + $535,772 FB = $2,210,053)

Kevin F. Boehnke, PhD, Contact Principal Investigator (50% Effort)
Dr. Boehnke is a Research Investigator in the Department of Anesthesiology Chronic Pain and Fatigue Research Center (CPFRC) at the University of Michigan. and a nationally renowned cannabis expert. He is currently involved in several NIH-funded clinical trials investigating effects of cannabinoids on pain and sleep. He has led numerous studies showing that people with chronic pain substitute cannabis for opioids and other pain medications, mostly without clinician oversight. Dr. Boehnke has provided guidance on CBD for the Arthritis Foundation and is currently a Technical Expert Panel member for two national committees on cannabinoid use for pain, including a collaboration between the office of Veterans Affairs and Oregon Science and Health University. He has published numerous articles about chronic pain as well as cannabis, including in *JAMA, Annals of Internal Medicine* and *Journal of Pain.* With Dr. Bohnert, Dr. Boehnke will oversee the proposed clinical trials in this study, with a focus on the cannabidiol trial. Dr. Boehnke is a salaried-exempt-exempt Research Investigator with a Y1 salary of $87,500.

Amy S.B. Bohnert, PhD, Co-Principal Investigator (20% FTE – UM Effort)
Dr. Bohnert is a Professor in the Departments of Anesthesiology, Psychiatry and Epidemiology at the University of Michigan and a researcher with the Department of Veterans Affairs Center for Clinical Management Research (CCMR). She is Co-Director of the Division of Mental Health Innovations, Services, and Outcomes. She leads a number of NIH-, CDC-, and VA-funded projects to identify paths for reducing the burden of opioid use disorders, opioid misuse, and overdose using randomized controlled designs and electronic health records databases. Her projects include a trial of a mobile behavioral intervention to reduce opioid misuse and a State of Michigan DHHS-partnered project, the Michigan Opioid Collaborative, to provide technical assistance and peer mentoring to physicians providing medications for opioid use disorders. Dr. Bohnert has published over 100 articles related to mental health, opioids, pain, and addiction, including papers in *NEJM, JAMA*, *BMJ*, *Annals of Internal Medicine*, *JAMA Psychiatry*, and the *American Journal of Psychiatry*. She has also served in a scientific advisory role to the Centers for Disease Control and Prevention, to the Food and Drug Administration, and the Michigan Prescription Drug and Opioid Abuse Task Force. With Dr. Boehnke, Dr. Bohnert will help oversee the proposed clinical trials in this study, with a focus on the educational intervention. Dr. Bohnert is a salaried-exempt-exempt Professor with a Y1 salary of $127,118.

Dr. Bohnert also has a VA appointment; however, all effort on this project will be from the University appointment. A Memorandum of Understanding is on file describing the relationship.

Rachel Bergmans, MPH, PhD, Co-Principal Investigator (25% Effort)
Dr. Bergmans is a Research Investigator in the Department of Anesthesiology Chronic Pain & Fatigue Research Center (CPFRC), a T32 trainee (AR007080, 9/01/21-8/31/22), and the faculty co-leader for the CPFRC Health Equity Core. As a social epidemiologist and community-engaged researcher, Dr. Bergmans uses quantitative and qualitative approaches to advance equity in chronic pain and related health outcomes. Her program of work is focused on putting permanent infrastructure in place to increase diversity, equity, and inclusion within chronic pain research at the University of Michigan; establishing sustainable academic-community partnerships; and privileging the priorities and perspectives of representatives from Black and African American communities in the development of non-pharmaceutical therapies and interventions for pain management. Dr. Bergmans has over 7 years of experience implementing community-engaged

approaches to partner with key representatives in addressing social and environmental determinants of health. Dr. Bergmans will supervise the formation of the patient/community advisory board, and the work of the Recruitment Ambassador, Research Specialist Associate, and the postdoctoral research fellow. Dr. Bergmans will oversee the development of new materials and other strategies to boost Veteran recruitment and retention (including of underrepresented minorities), as decided on by the CAB and/or as requested by the Recruitment Ambassador. Dr. Bergmans is a salaried-exempt-exempt Research Investigator with a Y1 salary of $74,000.

Daniel Clauw, MD, Co-Investigator (10% Effort)
Dr. Clauw is a Professor in the Departments of Anesthesiology, Psychiatry, and Rheumatology, as well as the Director of the Chronic Pain and Fatigue Research Center. He has been involved in the growth of clinical and translational research infrastructure and was the founding director of the unit at Michigan that supports translational research – the Michigan Institute for Clinical Health Research (MICHR). He is now the Senior Associate Director of MICHR and co-directs the Research Development Core and Pre-Doctoral Programs. He is currently co-PI of two NIH center grants studying the mechanisms underlying chronic pain in urological and musculoskeletal disorders and is an active mentor of clinical and pain researchers. Dr. Clauw is also a co-investigator on a NIAMS HEAL grant that aims to perform interventional response phenotyping in a cohort of chronic low back pain (cLBP) patients. Dr. Clauw has published over 400 articles related to chronic pain and pain management, including papers in *JAMA, Annals of Internal Medicine, Annals of Surgery, Journal of Pain, and Lancet.* Dr. Clauw will provide guidance and support on clinical trial management and in collaboration with the project PIs. Dr. Clauw is a salaried-exempt-exempt Professor with a Y1 salary of $279,403.

David A. Williams, PhD, Co-Investigator (8% Effort)
Dr. Williams a Professor in the Departments of Anesthesiology, Psychiatry, Rheumatology, and Psychology at the University of Michigan as well as the Associate Director of the Chronic Pain and Fatigue Research Center. Additionally, he serves as Co-Director of Research Development within the Michigan Institute for Clinical and Health Research (MICHR). He is both a pain psychologist and a researcher with publications in the areas of chronic illness management, mobile health services delivery for chronic pain, patient-reported outcomes instrument development and validation, and mechanisms of pain perception/modulation. He is the past President of the American Pain Society and serves on numerous scientific editorial boards and scientific review committees both nationally and internationally. In recognition of his commitment to students, he received the Distinguished Clinical and Translational Research Mentor Award from the University of Michigan. Dr. Williams has published over 100 articles related to pain and pain management. For the current application, Dr. Williams brings extensive experience in characterizing chronic illnesses and assessing outcomes of interventions. He also brings expertise in coaching, educational, and adherence methods associated with pharmacological and nonpharmacological interventions. With Drs. McAfee and Litinas, he will oversee intervention development and manualization as well as providing insight on outcome assessment. Dr. Williams is a salaried-exempt-exempt Professor with a Y1 salary of $239,908.

Mary R. Janevic, MPH, PhD, Co-Investigator (3% Effort)
Dr. Janevic is an Associate Research Scientist in the Department of Health Behavior and Health Education in the University of Michigan School of Public Health, and the faculty co-leader for the CPFRC Health Equity Core. Dr. Janevic brings expertise in cognitive-behavioral approaches to chronic pain management in underserved populations, chronic pain disparities and social determinants of health, the influence of cultural factors on chronic disease management, and mixed methods analyses in behavioral trials. Dr. Janevic has over 10 years of experience working on community-engaged health research projects. She has led or co-led numerous studies and evaluations involving active community partnerships, has applied participatory approaches to ensure that key partners are represented in the research process and in the adaptation of evidence-based interventions to meet the needs of a given community. Dr. Janevic will assist Dr. Bergmans with the formation and conduct of the Community Advisory Board (CAB), the hiring and job responsibilities of the Recruitment Ambassador, and the development of new materials and other strategies to boost recruitment and retention of underrepresented minorities, as decided on by the CAB and/or as requested by the Recruitment Ambassador. Dr. Janevic is a salaried-exempt-exempt Associate Research Scientist with a Y1 salary of $108,171.

Jenna (Goesling) McAfee, PhD, Co-Investigator (20% Effort Y1-Y2, 10% Effort Y3-Y5)

Dr. McAfee is a Clinical Associate Professor of Anesthesiology at the University of Michigan, who treats patients at the Department of Anesthesiology Back and Pain Center. Dr. McAfee recently completed a K23 (DA038718) that aimed to better understand why patients continue taking opioids and incorporate theory-based models of behavior change into the development of interventions for individuals who would benefit from opioid cessation. Such work included qualitative assessment including focus groups and semi-structured clinical interviews and the evaluation of related data. Dr. McAfee will help oversee manualization of the educational intervention, training of behavioral health consultants, and ensuring the fidelity of the educational intervention. Dr. McAfee is a salaried-exempt-exempt Clinical Associate Professor with a Y1 salary of $135,265

Sachin Kheterpal, MD, MBA Digital Coordinating Center Co-Director (5% Effort)
Dr. Kheterpal is a Professor in the Department of Anesthesiology and the Associate Dean for Research IT for the University of Michigan Medical School. Prior to a clinical anesthesiology career, he was the lead architect of a leading commercially available electronic health record — General Electric Centricity. He led the global clinical information system product development team at GE Healthcare IT. He brings nearly two decades of informatics, software development and business administration experience to perioperative outcomes research. He is a practicing anesthesiologist, focused on high acuity surgery, including adult liver transplantation and vascular. He is the founder and principal investigator of the Multicenter perioperative outcomes group (MPOG), a research and quality improvement consortium of more than 50 anesthesiology and surgical departments across the US. The MPOG centralized research database contains more than 15 million perioperative records with risk adjusted long term outcome data and detailed clinical intervention data. Dr. Kheterpal's current research focus is evaluating the comparative effectiveness of intraoperative anesthesiology interventions on long-term patient outcomes. Dr. Kheterpal also leads the MIPACT study, which used wearable sensors and the MyDataHelps app proposed here to collect long-term health outcomes on a diverse sample of 7,000 Michigan residents. Nationally, Dr. Kheterpal serves on the NIH Council of Councils and previously served on the Advisory Panel for the NIH Precision Medicine Initiative (All Of Us), focused on electronic health record data integration and multicenter collaboration. Dr. Kheterpal will bring this expertise to this project. Dr. Kheterpal is a salaried-exempt-exempt Professor with a Y1 salary of $243,853.

Nirav Shah, MD Digital Coordinating Center Co-Director (5% Effort)
Dr. Shah is an Associate Professor in the Department of Anesthesiology at the University of Michigan. Within Michigan Medicine, he is the Associate Chief Medical Information Officer – Perioperative Care, and Director of Anesthesia Informatics and Systems Improvement, where he leads a team that develops software solutions for perioperative quality improvement, research, clinical and business operations, and supports the hospital's perioperative electronic health record (EPIC). Dr. Shah's interests lie at the intersection of perioperative care, quality improvement, research, and information technology. As Program Director for the Quality Improvement arm of MPOG, his role is to lead collaborative quality improvement efforts across its 50+ member institutions, including 20 across the state of Michigan. As co-I of MIPACT, he has helped design the MQUARK features and workflow processes to enroll 7000 patients in 18 months. Dr. Shah has deep expertise in workflow optimization, which he will bring to this project. Dr. Shah is a salaried-exempt-exempt Associate Professor with a Y1 salary of $229,690.

Kelley Kidwell, PhD, Co-Investigator (20% Academic & 20% Summer Effort)
Dr. Kidwell is an Associate Professor of Biostatistics in the School of Public Health. Her expertise in the design and analysis of innovative digital clinical trials, particularly in Sequential Multiple Assignment Randomized Trials (SMARTs). Her methodological focus is on the design and analysis of SMARTs, more recently in the area of rare disease or small samples. She was principal investigator (PI) of a PCORI funded contract developing SMART design and methods in small samples (2016-2019) and now is the PI of a FDA funded contract continuing that work. She recently received another PCORI methodology contract as PI to consider patient preferences in SMART design. Dr. Kidwell will be the lead statistician for the primary analysis of both clinical trials on this project. Dr. Kidwell is a salaried-exempt-exempt Associate Professor with a Y1 salary of $175,316.

Walter Dempsey, PhD, Co-Investigator (10% Academic & 10% Summer Effort)
Dr. Dempsey is an Assistant Professor of Biostatistics (School of Public Health) and Assistant Research Professor at the Institute for Social Research (ISR) at the University of Michigan. He is a core faculty member of the D3 Lab at ISR, which

is made up of data scientists with expertise in adaptive mobile intervention designs and repeated randomizations (e.g., micro-randomized trials). His current work focuses on statistical methods and theory for digital and mobile health as well as more traditional areas of biomedical research involving (multi-state) survival analysis and temporal process regression. His work aims to inform decision making in health by aiding in intervention evaluation and development. His expertise in the design and analysis of innovative digital trials will be vital for the proposed project. Dr. Dempsey is a salaried-exempt-exempt Assistant Professor with a Y1 salary of $145,161.

Anna Kratz, PhD, Co-Investigator (10% Effort)
Dr. Anna Kratz is a clinical psychologist and Associate Professor in the Department of Physical Medicine and Rehabilitation at UM. She leads a program of federally- and foundation-funded research that examines the characteristics, mechanisms, and treatment of chronic symptoms, including chronic pain and fatigue. Dr. Kratz has extensive expertise in ambulatory assessment techniques, including ecological momentary assessment (self-report in real time), actigraphy, app-based cognitive tests, and collection of physiological data using wearable devices. She has expertise in randomized as well as pragmatic and comparative effectiveness trial designs. She has developed digital educational and behavioral interventions for symptom management (e.g. MyMSToolkit, PainGuide). She will provide support and expertise on the areas described above for this project, which is a natural extension of her ongoing collaborations with the team. Dr. Kratz is a salaried-exempt-exempt Associate Professor with a Y1 salary of $165,545.

Daniel Whibley, PhD, Co-Investigator (20% Effort)
Dr. Whibley is a Research Assistant Professor in the University of Michigan Department of Physical Medicine & Rehabilitation. He also has affiliations with the Epidemiology Group, University of Aberdeen (UK), and the Sleep and Pain Laboratory, University of Warwick (UK). He received his doctorate from the University of Aberdeen and has published in the areas of chronic pain, physical activity/exercise, and sleep health, including their intersection. Dr. Whibley is a registered physiotherapist in the UK and has clinical expertise in rheumatology and neuro-musculoskeletal rehabilitation. He was awarded a personal postdoctoral fellowship on completing his PhD from Versus Arthritis (formerly Arthritis Research UK), and was funded as Principal Investigator to develop and feasibility test a hybrid sleep and physical activity intervention for people living with chronic pain. He has undertaken extensive training in advanced statistical methods including modelling that uses momentary data collected using actigraphy, and has experience conducting qualitative research, all of which he will contribute to the current project. Dr. Whibley is a salaried-exempt-exempt Research Assistant Professor with a Y1 salary of $87,500.

Daniel J. Kruger, PhD, MS, Co-Investigator (20% Effort)
Dr. Kruger is a Research Investigator in the University of Michigan Institute for Social Research, Population Studies Center, whose research interests include community-based prevention research aimed at improving health status and reducing morbidity and mortality among populations experiencing a disproportionate share of poor health outcomes. He studies several areas from an evolutionary perspective and conducts basic research as well as implementing practical applications. His applied work includes community health surveys and program evaluations conducted in partnership with health departments and community-based organizations. Projects have focused on birth outcomes, risk-taking, violence, mortality patterns, neighborhood conditions, and outcomes of cannabis use. Dr. Kruger will help provide oversight for the data manager, aid with community outreach efforts, help with analyses of study outcomes, and provide content area expertise regarding cannabis effects. Dr. Kruger is a salaried-exempt-exempt Research Investigator with a Y1 salary of $84,872.

Avinash Hosanagar, MD, Co-Investigator (20% FTE – VA Effort)
Dr. Hosanagar is Clinical Assistant Professor of Psychiatry at the University of Michigan and a psychiatrist for the Ann Arbor VA Healthcare Center Mental Health Clinic. The VA Ann Arbor Healthcare System Psychiatry program is an integral part of the University of Michigan Department of Psychiatry. Dr. Hosanagar is addiction medicine-boarded and provides addiction-related services to Veterans, as well as leading the ketamine clinic for severe depression at the Ann Arbor VAMC. Important goals of his clinical program include providing the highest quality psychiatric care to eligible veterans, conducting state-of-the-art basic and clinical psychiatric research relevant to veterans, and providing excellent training to the next generation of mental health clinicians and researchers. As a VA researcher and psychiatrist, He will lead

efforts to monitor and conduct risk assessments and treatment referrals in this project. Dr. Hosanagar is a salaried-exempt-exempt Psychiatrist with a Y1 salary of $141,235.

Dr. Hosanagar's primary appointment is with the VA Ann Arbor Healthcare System and will be paid through a service agreement with the VA. ***His salary and fringe benefits are budgeted under VMR Contractual Services.***

Maria J. Silveira, MD, MPH, Co-Investigator, (25% FTE – VA Effort)
Maria Silveira MD MA MPH is a palliative care physician and symptom scientist at the University of Michigan and Ann Arbor VAMC. She has led or co-led clinical trials of symptom management interventions, including one VA-sponsored study which recruited Veterans with cancer from the Ann Arbor VA and their caregivers into a trial of electronic symptom assessment and advice. She has over twenty years of experience at the Ann Arbor VA where she has cared for Veterans with PTSD and complex chronic pain in primary care and palliative care settings. She is a member of the Geriatric Research Education Clinical Center, Institutional Review Board, and Pain Committee at the Ann Arbor VA, providing her with robust relationships throughout the organization to draw from in the conduct of the research proposed. Dr. Silveira will provide risk management for enrollees in the study, insight on the web-based intervention, and aid with Veteran outreach and engagement efforts. Dr. Silveira is a salaried-exempt-exempt Investigator with a Y1 salary of $95,710.

Dr. Silveira's primary appointment is with the VA Ann Arbor Healthcare System and will be paid through a service agreement with the VA. ***Her salary and fringe benefits are budgeted under VMR Contractual Services.***

<u>VMR Personnel Program Staff</u> ($4,410,374 Salary + $1,498,433 FB = $5,908,807)

Laura Thomas, VA Program Manager (40% effort)
Ms. Thomas is a project manager with a background in social work and public health. Ms. Thomas has worked with Dr. Bohnert leading human subjects research for over eight years, including working with Veterans, and starting and closing projects. Ms. Thomas will assist in the day-to-day operations of the project and oversee IRB applications and other regulatory applications and amendments. Ms. Thomas is a salaried-exempt-exempt Project Manager with a Y1 salary of $93,000.

TBN, Study Coordinator (100% effort)
We will hire an experienced study coordinator in the VA with a background in social work. This study coordinator will have experience working with Veterans, and ideally working with individuals with chronic pain. This coordinator will lead community outreach staff in engaging and enrolling participants into both clinical trials and the registry. This salaried-exempt-exempt Study Coordinator is budgeted for a Y1 salary of $75,000.

Primary appointments for Ms. Thomas and the TBN study coordinator are with the VA Ann Arbor Healthcare System and will be paid through a service agreement with the VA. ***Their salary and fringe benefits are budgeted under VMR Contractual Services.***

TBN, UM Program Manager (100% effort)
A senior level project manager will be hired with a background in social work and public health. The project manager will assist in the day-to-day operations of the project and oversee IRB applications and other regulatory applications and amendments for both projects. Ms. Thomas will help train this program manager. This salaried-exempt-exempt Program Manager is budgeted for a Y1 salary of $95,000.

TBN, Postdoctoral Research Fellow (75% effort)
We will hire a post-doctoral research fellow with expertise in qualitative research and mixed methods, including semi-structured interviewing and qualitative data analysis. This person's primary role will be assisting with qualitative analysis to advance community-engaged, veteran-centered approaches for clinical application of cannabis and CBD. Under Dr. Bergmans' supervision, this person will collect and analyze data from those who are eligible for the proposed studies (both participants and those who declined study participation) to understand barriers to participation. This person will

also assist with evaluating the processes and activities for the Community Advisory Board. This salaried-exempt Postdoctoral Research Fellow is budgeted for a Y1 salary of $55,373.

TBN, Communications Specialist (20% effort)
Our experienced graphic designer and communication specialist will assist with developing materials for dissemination and will be in charge of marketing the program and disseminating key findings to the communities of interest as well as more broadly to the state and other stakeholders. They will also work to create, produce, and deliver a range of promotional, educational, and informational presentations, and/or resource materials related to the study activities and successes and support the community engagement activities, including website, social media, community data reports, media and press releases, and assist the communities with developing relevant and engaging materials for community outreach. This salaried-exempt Administrative Specialist is budgeted for a Y1 salary of $52,000.

TBN, Recruitment Ambassador (100% effort Y1-Y3, 50% Y4, 25% Y5)
We will hire a community health worker, community organizer, or individual with similar experience, with deep knowledge of local resources who can serve as a bridge between research and diverse communities as a recruitment ambassador. The recruitment ambassador will lead outreach efforts in Veteran communities, including in the Detroit and Flint areas, to support study recruitment efforts. This individual will also facilitate bidirectional communication and knowledge transmission between the CPFRC and community stakeholders by assisting enrolled participants navigate the challenges of participating in clinical trials, thereby enhancing retention. The recruitment ambassador will take part in biweekly meetings with the investigator team and will be actively engaged in community dissemination efforts. This hourly Project Coordinator is budgeted for a Y1 salary of $50,000.

TBN, Research Specialist Associate (100% effort)
We will hire a research specialist to help with enrolling participants in the qualitative interviews, qualitative coding, data analysis, interviews, literature reviews, and oversight/assistance with advisory board management. This salaried-exempt Research Specialist is budgeted for a Y1 salary of $50,000.

TBN, Behavioral Health Consultants (2) (100% effort)
We will hire 1.5 FTE of behavioral health consultants to help deliver the educational intervention. These behavioral health consultants will have a background in research and social work, and will be trained by Dr. Litinas, Dr. McAfee, and Dr. Williams in faithfully adhering to the educational intervention. Dr. Bohnert's lab has run multiple telemedicine intervention studies, and both Dr. Bohnert and Ms. Thomas have extensive experience overseeing and successfully completing such studies. Behavioral health consultants will also aid with retention and study coordination efforts related to the participants with whom they are directly working in this study. These salaried-exempt Research Specialists are budgeted for Y1 salaries of $62,500.

TBN, Clinical Subjects Coordinators (1.5 FTE @ 100% effort Y1-Y4, 1 FTE @ 100% effort Y5)
We will hire two (2) clinical subjects coordinators who will be charged with study coordination throughout all Aims of this program. In addition, these individuals will work closely with the investigator team regarding recruitment of participants for the registry (Aim 1) and Aim 2 & 3 clinical trials. These hourly Clinical Subjects Coordinators are budgeted for Y1 salaries of $57,500.

TBN, Applications Programmer (100% effort)
The Applications programmer will be responsible for development and maintenance of the database and data collection forms/applications. They will refine any data transfer processes, develop reports as needed, and specific SAE narrative management functions within the application platform. This salaried-exempt Applications Programmer is budgeted for a Y1 salary of $103,000.

TBD, Help Desk Staff (Y1, Y4-Y5 – 2 FTE @ 100.0% effort; Y2-Y3 – 3 FTE @ 100.0% effort)
Informatics staff will be available to answer any questions or trouble shoot issues with the wearable activity device or MyDataHelps data collection program. These hourly Call Center Representatives are budgeted for a Y1 salary of $40,000.

TBN, Data Analyst (100% effort)
The Data Analyst will be responsible for developing report table shells, confirm data quality limitation and work with the Digital Coordinating Center Co-Directors and PIs on refining the project timeline, review query results, establish plausibility and collate query results into a report package for the PIs and project team to review. This salaried-exempt Research Analyst is budgeted for a Y1 salary of $95,000.

TBN, Data Manager (100% effort)
The Data Manager will be responsible for data cleaning and transferring processes, query and resolution processes. This salaried-exempt Data Manager is budgeted for a Y1 salary of $75,000.

TBN, SPH Biostatistics GSRA (100% effort)
The biostatistics graduate student research assistant (GSRA) will execute the statistical analysis under the supervision of Dr. Kidwell. Please note that a 0.5 FTE is considered a full-time GSRA appointment. The salaried-exempt Graduate Student Research Assistant is budgeted in Y1 salary of $71,676.

TBN, Research Assistant (Y4-Y5: 50% effort): A part-time research assistant will be hired to assist Dr. Bergmans with anonymizing the qualitative interviews, conducting qualitative data analysis, developing data figures and tables, conducting literature reviews, and writing manuscripts and reports. This hourly Research Assistant is budgeted for a Y4 starting salary of $32,000.

The procurement of goods and services is the responsibility of the Regents. Per Board of Regents Bylaws 3.07 (2)(d), the Regents have delegated procurement responsibility to the Executive Vice President and Chief Financial Officer, who in turn has delegated this function to Procurement Services. Purchases using sponsored funds often have unique requirements beyond that of the university's normal procurement process. This page describes these unique requirements for federal sponsored funds from the Uniform Guidance 2 CFR 200. Non-federal sponsors may have other unique requirements when making purchases with their funds that may be found in the agreement with the sponsor.

Beginning July 1, 2018, purchases using federal sponsored funds must be made in accordance with Uniform Guidance (2 CFR 200): The Uniform Administrative Requirements, Cost Principles, and Audit Requirements for Federal Awards. The Uniform Guidance requires Sponsored Programs to review transactions meeting certain criteria to determine if they are allowable. The purpose of these federal guidelines is to verify that all expenses charged to a research project have a "direct benefit" and should be charged as "direct costs" to the project. To ensure compliance, all activity affecting a sponsored project/grant should meet the terms and conditions of the grant or contract. It is the expectation that all purchases over $10,000 be either competitively bid or a sole source justification form endorsed by an authorized signer in the school/college justifying and providing information as to why the vendor selected is the optimal choice.

<u>VMR Supplies, Material & Equipment</u> ($228,750)

Wearable Devices (Y1-Y3: $75,000/year = $225,000) All participants will be selected to receive a wearable device (Fitbit or Actigraph) to enable passive activity, sleep data collection and tracking cannabis use. These wearables data will be collected using the MyDataHelps app described below. We anticipate purchasing 1,500 devices at $150/device.

MAXQDA license (2) ($750/year = $3,750) Two standard MAXQDA statistical analysis software licenses will be purchased each year for Dr. Bergmans, her research specialist and research assistant. This software will support data retrieval, qualitative analysis, data visualization, and collaboration across research team members.

<u>VMR Contractual Services</u> ($191,000)

CareEvolution, Inc. App Development / Licensing Fee (Y1 - $80,000) CareEvolution is a national leading provider of Participant-facing Patient Reported Outcomes data collection tools. Built upon the foundation of HIEBus™, their health information exchange (HIE) technology platform, MyDataHelps is a robust Service Oriented Architecture (SOA) to enable participants to enroll in studies, complete outcome instruments, and share wearable data. CareEvolution has received

federal "Authorization to Operate" as the AllOfUs Direct-to-Participant app vendor and SAFER-COVID vendor for all NIH staff. Distinct components of MyDataHelps and RKStudio (the authoring tool for MyDataHelps) include Identity Management, Record Location, Electronic Health Record Integration, Audit & Log, Visualization, Terminology, Data Mining, Data Driven Customizable Research Study Workflow and Content. MyDataHelps is available via the Google Play and Apple App Store and has been used for more than 100,000 patients already, including for eFramingham, MIPACT, and COVID-DETECT. Secure electronic data capture via CareEvolution technology will be used for feasibility and full-scale studies. All participants will be asked to download the app and receive patient reported outcome notifications. Those unable or unwilling to download the app will use the web-based desktop/tablet/phone patient reported outcome completion form.

CareEvolution, Inc. App Usage Fee (Y1-Y4: $36,000) The vendor charges a monthly app usage fee of $2 per participant. Each participant **(N=1,500)** will be on the study for up to 12 months.

1,500 participants X 12 months/participant X $2 = **$36,000**

Litinas, LLC ($15,000/year = $75,000) Evangelos Litinas, MD, MBA, is a medical cannabis expert, researcher and consultant with close to two decades of experience in various healthcare settings, including inpatient and outpatient clinical work, management and strategic planning, research and development for academic and private drug industry with a focus in the Medical Cannabis industry.

Within the field of medical cannabis Dr. Litinas has extensive experience including research, patient outreach and support, with a focus on patient education and individualized medical cannabis usage protocols. His in-depth knowledge on the subject of Medical Cannabis includes but not limited to scientific and medical research, patient and healthcare professional education, debilitating medical conditions and symptom treatments, pharmacokinetics and pharmacodynamics of cannabinoid-based medicines, drug interactions, and methods of administration and dosing.

Within the emerging Medical Cannabis industry, he has executed projects including but not limited to the development of patient educational materials, employee training manuals, management methods specifically tailored to the Cannabis healthcare industry and experience in state-based application processes.

Dr. Litinas has training and experience in management with a healthcare focus; hospital operations, healthcare capital management, strategic planning, hospital finances, short-term and long-term financial health and resources management for the design, development, and operation of medical cannabis-based organizations.

For this project, we will contract with Dr. Litinias to provide his expertise on refining and deploying the educational intervention for use and safety of medical cannabis, training cannabis coaches, and outreach to Veterans groups and individual veterans and their families.

<u>VMR Travel (VMR Staff)</u> ($7,020/year = $35,100)

We anticipate that the Recruitment Ambassadors will travel throughout the state of Michigan in order to meet with Veteran's Organizations to promote and recruit for the study. We anticipate that each Recruitment Ambassador will drive approximately 750 miles/year. UM uses federal government GSA CONUS rates to reimburse faculty and staff for travel expenses in the continental U.S. The current mileage reimbursement rate is $0.585.

1,200 miles/year X $0.585/mile X 2 travelers = **$7,020/year**

We understand that if the State of Michigan Standardized Travel Regulations for mileage reimbursement are lower than the federal rate, we will charge that rate to the grant.

<u>VMR Other</u> ($2,215,192)

Community Partners - Veteran Non-profit Groups (Y1 - $20,000, Y2 - $15,000 = $35,000) Funds are requested to compensate community organizations that partner with us (e.g., American Legion, Disabled American Veterans, Veterans Action Council) for their contribution of time and expertise to (1) developing and refining recruitment materials, (2) refining the recruitment strategy, (3) referring study participants and promoting the study statewide, (4)

pre-screening participants for initial study eligibility, (3) interpreting study findings, and (5) translating study findings to inform policy recommendations.

Honorariums ($20,000/year = $100,000) In acknowledgement of their time and commitment, we will pay annual honorariums to the Data Safety Monitoring Board (DSMB) and Community Advisory Board Members.

Data Safety Monitoring Board: 5 Members X $2,000/member/year X 5 years = **$50,000**

Community Advisory Board: 10 members X $1,000/member/year X 5 years = **$50,000**

Purchased Services via VA Service Agreement ($1,268,788 – detailed below) Veterans Administration personnel will be paid via a service agreement with the VA Ann Arbor Healthcare System. The VA will invoice the University of Michigan quarterly. Fringe benefit rates of 30% have been used for faculty and 47% for staff.

- **A. Hosanagar ($149,967 salary + $44,990 FB = $194,957)**

Co-Investigator Avinash Hosanagar MD, whose role is described above under VMR program staff, is a VA employee.

- **M. Silveira ($152,441 salary + $45,732 FB = $198,174)**

Co-Investigator Maria Silveira, MD, whose role is described above under VMR program staff, is a VA employee.

- **L. Thomas ($197,500 salary + $92,825 FB = $290,324)** Program Manager Laura Thomas whose role is described above under VMR personnel staff is a VA employee.

- **TBN Study coordinator ($398,185 salary + $187,147 FB = $585,332)** Study Coordinator TBN, whose role is described above under personnel staff, will be a VA employee.

Participant Reimbursement ($557,560) We anticipate enrolling 2,000 subjects into the registry, who will each receive $150 for their participation. 455 of those enrolled will be randomized into the CBD intervention arm. These individuals will receive an additional $260 for their participation. 422 of those enrolled will be randomized into the educational intervention arm. These individuals will receive an additional $330 for their participation.

Aim 1: Registry	2,000 subjects X $150/subject	=	$300,000
Aim 2: CBD Clinical Trial	450 subjects X $260/subject	=	$118,300
Aim 3: Educational Clinical Trial	422 subjects X $330/subject	=	$139,260
			$557,560

Michigan Institute for Clinical & Health Research (MICHR) IND/IDE Investigator Assistance Program (MIAP) (Y1-$8,000; Y2-Y5 - $4,000/year = $24,000) The MICHR IND/IDE Investigator Assistance Program (MIAP) provides comprehensive regulatory support, guidance, and education services to investigators involved in Food and Drug Administration (FDA) regulated clinical research. MIAP's primary focus is providing regulatory assistance to sponsor-investigators of drugs, biologics, and medical devices. This includes Investigational New Drug (IND) services such as: regulatory needs assessments; exemption rationale development; assistance with FDA meeting preparation; assistance with IND application submissions, including protocol and informed consent development; assistance with regulatory compliance, document preparation, and FDA contact and correspondence; sponsor investigator training; and ongoing study assistance, including safety reporting, FDA annual report preparation, protocol amendments, and IND closeout.

The fee for MIAP regulatory support for the initial IND application submission is **$8,000**. **$4,000** is charged for each year the IND is open for preparation and submission of protocol amendments, safety reports, and annual reports. The MIAP fee also includes Clinical Trial Monitoring from the MICHR monitoring group which is required for studies under an IND.

Advertising and Recruitment (Y1-Y3 - $3,300/year = $9,900) In order to advertise and promote the study statewide, funds are requested to create and print flyers, postcards and brochures for distribution to Veterans groups and VA hospitals and healthcare centers.

Shipping/Postage for Aim 1 ($12,383) The activity devices to be used for data capture for Aim 1 will be shipped to all study participants using USPS Prepaid Forever Priority Mail flat rate boxes at $7.90 each.

Year 1: 300 participants X 1 shipment/participant X $7.90/package = **$2,370**
Year 2: 450 participants X 1 shipment/participant X $10.30/package = **$3,662**
Year 3: 450 participants X 1 shipment/participant X $10.61/package = **$3,768**
Year 4: 300 participants X 1 shipment/participant X $10.93/package = **$2,583**

CBD Purchase (Y1-Y4 $25,000/year = $100,000) CBD will be purchased from Ananda Professional, a national CBD brand that has experience obtaining Investigational New Drug licenses for their products from the FDA for use in clinical trials. Per their letter of commitment, Ananda Professional will provide placebo, broad-spectrum, and full-spectrum capsules for this project. We will purchase approximately 320,000 softgels over the course of this project at a cost of $0.30 per soft gel. We estimate shipping costs for these products to University of Michigan to be ~$4,000 over the course of the study.

Research Pharmacy Costs for Aim 2 Clinical Trial ($90,032) The University of Michigan Research Pharmacy is a health-system service within the Department of Pharmacy Services that ensures human subject research involving investigational drugs is conducted safely, efficiently and correctly. This unit will be responsible for the acquisition, storage, blinding, packaging and dispensing the investigational drugs and placebo compounding throughout the study. Inflationary increases of 3% are added in out years.

Study Initiation (Y1: $3,000) and Amendments (Y3-Y4: $1,000/year = $2,000)
Study Maintenance. Pharmacy charges $131-143/month for inventory maintenance
~$137/month X 48 months = ~**$1,643/year**

Drug Dispensing

Participants will receive study medication three times throughout the study at a cost of $45/dispensing.

Year 1: 68 participants X 3 dispensing/participant X $45.00/dispensing = **$9,180**
Year 2: 160 participants X 3 dispensing/participant X $46.35/dispensing = **$22,248**
Year 3: 159 participants X 3 dispensing/participant X $47.74/dispensing = **$22,753**
Year 4: 68 participants X 3 dispensing/participant X $49.17/dispensing = **$10,006**

Shipping/Postage

Shipping by Research Pharmacy to participants will occur on the same schedule of dispensing with three shipments to each participant at a cost of $10/package.

Year 1: 68 participants X 3 shipments/participant X $10.00/package = **$2,040**
Year 2: 160 participants X 3 shipments/participant X $10.30/package = **$4,944**
Year 3: 159 participants X 3 shipments/participant X $10.61/package = **$5,060**
Year 4: 68 participants X 3 shipments/participant X $10.93/package = **$2,229**

Transcription Services (Y1-Y3: $5,843/year = $17,528): We will hire a local transcription service at $2.05/minute to transcribe interviews with participants from Aims 1-3:

80 participants X 60 min interview X $2.05/minute = **$9,840**
50 participants X 75 min interview X $2.05/minute = **$7,688**

<u>Indirect Cost</u> (Y1-$212,788; Y2-$226,318; Y3-$228,777; Y4-$212,114; Y5-$195,014 = $1,075,001)

The University of Michigan has a DHHS negotiated rate (dated 5/14/2020). Any tuition, equipment, and the subaward less $25,000 would be excluded from the indirect cost calculations.

Indirect costs plus administrative costs total **9.999978%** of the total budget, which is below the sponsor's request that

these not exceed 10% of the overall budget.

$1,075,001 indirect costs + $123,763 administrative expenses = **$1,199,764 / $11,987,667** = **9.999978%**

-

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.

Additional Information and Comments

- Letters of Support from the following parties
    - VA Center for Clinical Management Research, Ann Arbor, MI
    - No Veteran Left Behind, Inc., Lincoln Park, MI
    - Ananda Hemp, Georgetown, KY
- References

VA CENTER FOR CLINICAL MANAGEMENT RESEARCH
Ann Arbor HSR&D Center of Innovation
Wyndy Wiitala
Associate Director

May 13, 2022

Kevin Boehnke, PhD
Research Investigator of Anesthesiology
Michigan Medicine
24 Frank Lloyd Wright Lobby M-3100
Ann Arbor MI 48105-5737

Dear Dr. Boehnke:

We are writing as members of the VA Ann Arbor Healthcare System Center for Clinical Management Research (CCMR) Veteran Research Engagement Council (VREC) to express our support for your proposed application to the Veteran's Marijuana Research Grant Program, entitled "Pragmatic Trials of CBD Products and Tailored Cannabis Coaching to Improve Pain Symptoms among Veterans".

The mission of the VREC is to engage Veteran stakeholders in the multi-faceted aspects of research to improve Veteran-centric health care. Specifically, the VREC can help in the design of interventions, provide feedback on research materials, and disseminate findings. In this vein, we believe that understanding appropriate ways to use cannabis to address chronic pain among military Veterans is crucial to reduce suffering, improve quality of life, and prevent symptoms known to be linked to Veteran suicide.

The VREC members attending the presentations in February and April 2022 all agreed that the proposed studies are very meaningful to Veterans, especially those who are deciding whether or how to use cannabis or CBD products. We feel that your study to investigate the therapeutic potential of cannabidiol (CBD) products will be foundational for understanding whether CBD has a role in pain management, and your study proposing a science-based educational intervention to help Veterans more effectively use cannabis products is very needed in the current cannabis market.

We wholeheartedly support your proposal and look forward to participating in ways such as through having one of our members on the community advisory board, sharing our perspectives on how to involve Veterans appropriately and ethically in this research, and helping with recruitment efforts.

Thank you for including us in the planning of this worthwhile proposal.

Sincerely,

CCMR Veteran Research Engagement Council (VREC)
(see next page for signatures)

Wyndy Wiitala
Associate Director

Steven Bassett, Member

Gary Bourdeau, Member

On behalf of John Hannon, Member (consent on 05/13/2022)

Stuart Jacobson, Member

Douglas Smith, Member

Kevin Vaughn, Member

Cassaundra Peterson, VREC Liaison

Deborah Manderachia, VREC Liaison

Wyndy Wiitala, Associate Director of CCMR

No Veteran Left Behind, Inc.

We Rescue Those Who've Rescued Us

May 04, 2022

Kevin Boehnke, PhD
Research Investigator of Anesthesiology
Michigan Medicine
24 Frank Lloyd Wright Lobby M-3100
Ann Arbor MI 48105-5737

Dear Dr., Boehnke:

We enthusiastically submit this letter of support for your proposed application to the Military Veteran's Marijuana Research Grant Program, entitled "Pragmatic Trials of CBD Products and Tailored Cannabis Coaching to Improve Pain Symptoms among Military Veterans." Understanding appropriate ways to use cannabis to address chronic pain among Military Veterans is crucial to reduce suffering, improve quality of life, and prevent symptoms known to be linked to Military Veteran suicide. Your study to investigate the therapeutic potential of cannabidiol (CBD) products will be foundational for understanding whether CBD has a role in pain management, and your study proposing a science-based educational intervention to help Military Veterans more effectively use cannabis products is desperately needed in the current cannabis market.

We are delighted that you are planning to employ a community advisory board to help with collaborative decision-making and project governance, including helping with recruitment, oversight, and sharing the results from your proposed studies. We believe that this model will enhance collaboration between the Military Veteran community and your academic health center efforts and result in more impactful studies that have the potential to immediately improve the lives of Military Veterans. The scientific validity of your program will be strengthened by incorporating lived experience and voices of Military Veterans in your studies.

We wholeheartedly support your proposal for the Military Veteran's Marijuana Research Grant Program entitled. In this role, we look forward to participating in this proposal, such as through having one of our members on the community advisory board, sharing our perspectives on how to involve Military Veterans appropriately and ethically in this research, and helping with recruitment efforts. Our team feels this effort exemplifies a model community-academic partnership that will impact optimal treatment, access to care, and clinical health treatment associated with use of medical cannabis products. We look forward to contributing to this project.

Sincerely,

Geoffrey Devereaux

Executive Director
NO VETERAN LEFT BEHIND, Inc.

313-595-1262
@noveteranleftbehind on Facebook
www.veteranrescue.org

1515 W Fort St P.O. Box 1429
Lincoln Park, MI 48146

anandahemp

May 5, 2022

Kevin Boehnke, PhD
Research Investigator of Anesthesiology
Michigan Medicine
24 Frank Lloyd Wright Lobby M-3100
Ann Arbor, MI 48105-5**737**

Dear Dr. Boehnke,

The purpose of this letter is to provide the commitment of Ananda Hemp, LLC to the GMP manufacturing of the following products for your clinical study involving veterans who suffer from pain:

15mg placebo softgels
15mg broad-spectrum hemp extract softgels
15mg full-spectrum hemp extract softgels (if required)

Ananda Hemp is a GMP facility, registered with the FDA as a dietary supplement manufacturer as well as a food manufacturer. Our facility site registration is 13877349566.

Additionally, Ananda Hemp's hemp extract has been authorized for IND use in four Phase II clinical studies listed by their ClinicalTrials.gov Identifiers below.

NCT04873453

NCT04436081

NCT04398446

Please let me know if you need any additional information.

With best regards,

Alex Nance
President

190 Corporate Boulevard, Georgetown, KY 40324

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END APPLICANT RESPONSE

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 **understands** ~~is in compliance and agreement with~~ all sections of the Request for Proposal. Failure to comply with grant terms may result in termination.

The Regents of the University of Michigan reserve the right to negotiate any terms and conditions of the agreement that are not acceptable to institutions of higher education. We can accept some terms to the extent allowable by law. However, as a state entity operating in the State of Michigan we can not accept some of the terms related to the following: Indemnification (as a state entity we can not lend the credit of the state), Confidentiality, Non-Disclosure of Confidential Information, Data Privacy & Security, Background Checks, and Survival for an indefinite period after termination of the agreement.

Certified by: 

5/31/2022

Authorized Signatory and Title Date
Name of Organization

Karen Alameddine
Managing Project Representative, ORSP

ATTACHMENT A: VMR BUDGET

Submission Date: 06/01/2022

Selected Applicant's Grant Number: 22-PAF07069

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 & Fees (see attached justification	$74,652
5		
6	**Total Salary**	$74,652
7	*Fringe Benefits*	
8	Administrative Personnel Fringe	$26,131
9		
10	**Total Fringe Benefits**	$26,131
11	***Total Administrative Personnel***	$100,784
12	**Administrative Supplies, Materials, and Equipment**	
13	UM ISR Service Personnel Fee	$22,980
14	***Total Administrative Supplies, Materials, & Equipment***	$22,980
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**	**$123,763**
24	**VMR Program Expenses**	
25	**VMR Program Staff**	
26	*Salary*	
27	Key Personnel	$1,674,281
28		$ -
29	**Total Salary**	$1,674,281
30	*Fringe Benefits*	
31	Key Personnel	$535,772
32		$ -
33	**Total Fringe Benefits**	$535,772
34	***Total VMR Program Staff***	$2,210,053

35	**VMR Personnel Program Staff**	
36	*Salary*	
37	Other Personnel	$4,410,374
38		$ -
39		$4,410,374
40	*Fringe Benefits*	
41	Other Personnel	$1,498,433
42		$ -
43	**Total Fringe Benefits**	$1,498,433
44	***Total VMR Personnel Program Staff***	$5,908,807
45	**VMR Supplies, Materials, & Equipment**	
46	Activity devices (Fitbits) and software licenses	$228,750
47	***Total VMR Supplies, Materials, & Equipment***	$228,750
48	**VMR Contractual Services**	
49	CareEvolution, Inc.	$116,000
50	Lininas, LLC	$75,000
51	Independent Contractor 1	$ -
52	Independent Contractor 2	$ -
53	TBD 4 (Job Title)	$ -
54	TBD 5 (Job Title)	$ -
55	***Total VMR Contractual Services***	$191,000
56	**VMR Travel (VMR Staff)**	
57	Mileage	$35,100
58	Meals	$ -
59	Lodging	$ -
60	***Total EAP Travel***	$35,100
61	**VMR Other**	
62	See Attached Justification	$2,215,192
63	***Total EAP Other***	$2,215,192
68	**Total VMR Program Expenses**	**$10,788,901**
69	**Total Direct Cost**	**$10,912,666**
70	*Indirect Cost (0.0999978)*	$1,075,001
71	**TOTAL PROJECT COST**	**$11,987,667**