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Pharmaceutical Outcomes & Policy

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May 13, 2019

State University System of Florida
Board of Governors

On behalf of the University of Florida, I am submitting our application to become the lead institution for the Consortium for Medical Marijuana Clinical Outcomes Research. For questions or clarification I can be reached at almut@ufl.edu or phone 352.273.6268.

Sincerely,

Almut Winterstein, RPh, PhD, FISPE
Professor and Chair
Dr. Robert and Barbara Crisafi Chair for Medication Safety
Director, Center for Drug Evaluation and Safety (CoDES)

**Board of Governors, State University System of Florida**
**Application to be Lead Institution for the**
**Consortium for Medical Marijuana Clinical Outcomes Research**

University of Florida
SUS Institution Submitting Application

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| Signature of SUS President | Date 5/8/19 |
| Joseph Glover/wtz<br>Vice President for Academic Affairs | Date 5/8/19 |
| Vice President for Research | Date 5/8/19 |
| Chair, Board of Trustees | Date 5/9/19 |

# Lead Institution for the Consortium for Medical Marijuana Clinical Outcomes Research – Application to the Board of Governors, State University System of Florida

The University of Florida (UF) is excited to submit its application to become the lead institution for the Consortium for Medical Marijuana Clinical Outcomes Research to the Florida Board of Governors. UF has been involved in the administration and evaluation of the Florida Medical Marijuana (MMJ) Program since its inception and is well-prepared to leverage its extensive research infrastructure and broad faculty expertise to contribute to the necessary evidence for the safe and effective use of MMJ in the state of Florida. UF's application is supported by the University of Miami, Florida State University and Florida International University, which have pledged their support for the Consortium.

There is an urgent need to conduct research related to the emerging marijuana and cannabis market in Florida. As of May of this year, 215,435 persons were actively registered with the Florida Office for Medical Marijuana Use (OMMU), and over 60,000,000 mgs of MMJ and low-THC cannabis were dispensed in just the first week of May. Persons seeking MMJ are suffering from serious health conditions and symptoms, many of which are not responsive to approved medications. There are also many anecdotal reports of persons using MMJ as a substitute for opioids to address chronic pain in an era of consistently decreasing access to opioids, yet steadily increasing overdose deaths. While MMJ could potentially improve health outcomes, there are also significant safety concerns related to cognitive effects, accidents, interactions with other medications, psychosis, and addiction. Moreover, MMJ varies significantly in terms of its specific components (such as tetrahydrocannabinol (THC), cannabinol (CBD), and the THC/CBD ratio) and mode of administration (including smoking). There is a substantial need to understand how these differences in composition and mode of consumption impact health and safety outcomes. But due to the complex federal and state legal restrictions for both MMJ use and MMJ research, the development of evidence is lagging far behind the rapid uptake of MMJ.

With this application, we will formally establish infrastructure to serve the state of Florida in supporting research and safety monitoring on MMJ. The Consortium will build upon the existing strengths and experience at UF to create partnerships with other state and private universities as well as the Florida Department of Health. We will support research that is unbiased and engages patients, MMJ providers, and business stakeholders. The infrastructure will help researchers across the state to obtain competitive federal research and attract additional research funding partners.

## Program administration and integration of existing resources

*Describe how the institution plans to administer the program and meet the requirements outlined in section 1004.4351, Florida Statutes. Within the plan, please include a description of any existing resources the institution plans to use.*

### 1. Program administration

The Consortium for Medical Marijuana Clinical Outcomes Research has been established by Florida law to conduct rigorous scientific research and to disseminate such research. The Consortium is directed by the Medical Marijuana Research Board, which is composed of representatives from each participating university. The Consortium, open to all public and private universities, is administered by a lead university that organizes a variety of activities on behalf of the Consortium and supports the Board.

The following proposal is grounded in our extensive experience in supporting the FL MMJ program, which included a statutory requirement for UF to build a repository based on MMJ provider treatment plans and to conduct research on the safety and efficacy of MMJ. UF established a secure treatment plan submission platform and collected treatment plans for the first 7900 patients who became licensed to use MMJ. Dr. Winterstein, who oversaw the program, also developed a research plan that was based on integration of MMJ dispensing data and other outcomes data into the repository. Soon after initiation of the program, SB8A was passed, which assigned responsibility for data collection and analysis to OMMU and the Coalition for MMJ Research and Education within the Moffitt Cancer Center and Research Institute. The following is a description of the proposed scope of work to be conducted by the UF program on MMJ Clinical Outcomes Research (**UF MMJ-COR**) if UF is chosen as lead university.

Central to the Consortium is its mission to foster clinical outcomes research on MMJ across the state. Three core pillars of Consortium activities are proposed to support such research: a new and unique data repository to be known as the

**ME**dical **M**arijuana Clinical **O**utcomes **R**epositor**Y** (**MEMORY)**, a **Clinical Research Core**, and a **Grants Program** (Figure 1). Consistent with its charter, the MMJ-COR will engage scientists and researchers with relevant research programs to participate in the Consortium and foster research collaborations to accelerate the development of evidence on MMJ clinical outcomes. Outreach will be realized through a comprehensive **communication plan**, which is enhanced through exhibits and other activities of MMJ-COR at state-wide meetings and a MMJ provider survey. The Consortium will maintain an **Expert Group** of researchers representing the breadths of research methodology and clinical and policy expertise relevant to MMJ research. Finally, the MMJ-COR will assume a variety of administrative functions. Further detail on each core component of MMJ-COR is provided in the paragraphs below.

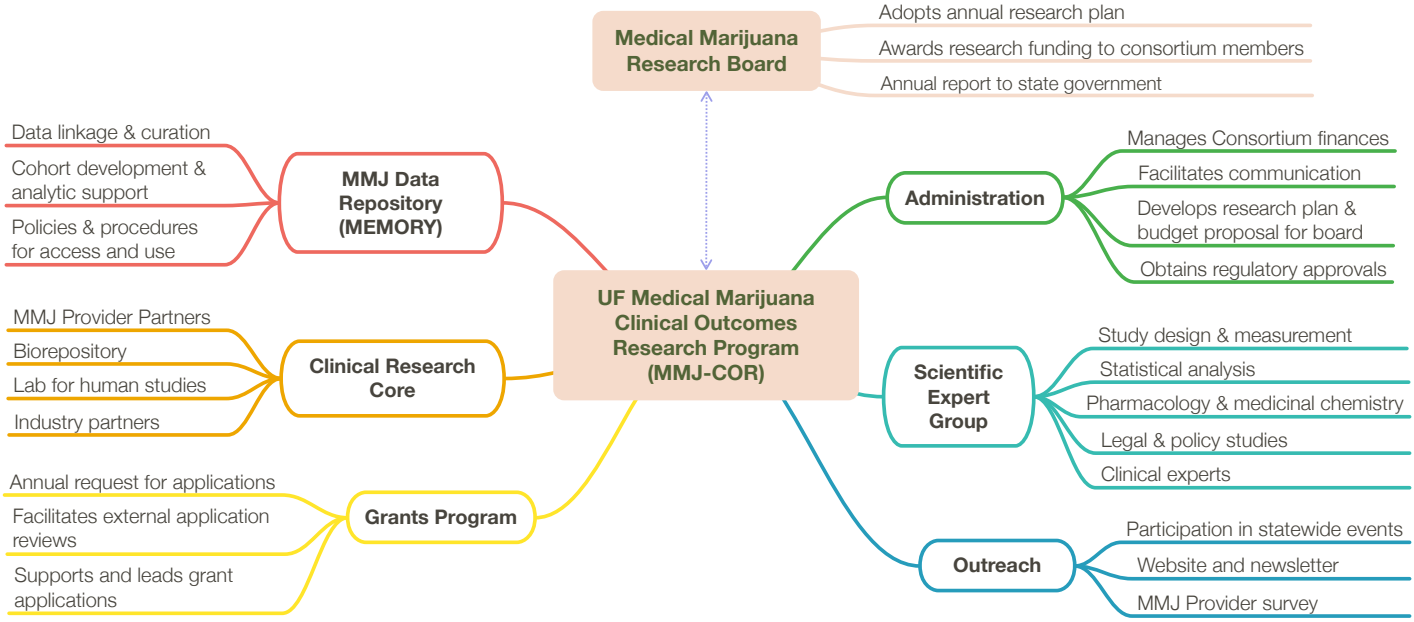


Figure 1. Consortium of Medical Marijuana Clinical Outcomes Research: Organizational Structure
The Medical Marijuana Research Board will consist of one member from each participating university in the Consortium. The Consortium headquarters, based at UF, will house three cores (MEMORY, Clinical Research Core, and Grants Program), supported by an administrative team, a scientific expert group, and communications and outreach support. This infrastructure will support research that is funded directly by the consortium as well as other funding sources, including NIH.

**MMJ Clinical Outcomes Research Data Repository (MEMORY)**. Unlike medications that have undergone rigorous testing, only a small number of controlled studies are available for MMJ. Randomized controlled trials (RCTs) are considered ideal study designs to evaluate drug safety and efficacy because they allow contrast of treatment outcomes rates against similar comparison groups, but controlled substance laws limit conduct of such trials. Moreover, RCTs are typically confined to small samples and not representative of real-world populations or able to evaluate rare events.

To address drug safety concerns, the Food and Drug Administration (FDA) can require the drug manufacturer to conduct additional studies after drug approval, which oftentimes involve controlled *observational* studies, where experiences of real-world populations are evaluated. These studies are realized with registries clinical encounter records collected in routine clinical care. MEMORY will establish the infrastructure for real-world MMJ clinical outcomes evaluations similar to those employed by the FDA. Specifically, we will link the Office of Medical Marijuana Use (OMMU) MMJ dispensing data with other clinical databases commonly used for outcomes research to create a robust research-ready repository. The planned linkages will optimize detail on MMJ use (type, dose, route, originating plant from the OMMU registry) and detail on patient health history, other treatments and outcomes (from linked clinical encounter data), and facilitate *controlled* longitudinal studies on safety and effectiveness outcomes. In close collaboration with OMMU and pending relevant ethics and data security / privacy review, a deidentified version of the repository will be made available to researchers within the Consortium, thus providing state-wide infrastructure for real-world clinical outcomes research. Core functions to develop MEMORY will include (a) data acquisition, curation and linkage, resulting in a well-documented longitudinal database of patients who initiated MMJ and adequate control groups who have not (yet) initiated MMJ; (b) provision of adequate study cohort data for researchers along with analytic support, and (c) the development and implementation of policies and procedures to access and use the data (see also Research #3 below).

**Clinical Research Core**. While MEMORY facilitates *retrospective* studies of routinely collected data, thus maximizing sample size, the clinical research core will provide infrastructure support for *prospective* studies (including RCTSs) involving collection of new data. To facilitate patient recruitment, the Consortium will assemble a group of **MMJ Provider Partners**. These will be physicians throughout the state who are willing to recruit patients for specific research studies or help to inform the Board about the most pressing clinical outcomes research needs. MMJ provider partners will be included in a directory on our web site. Provider-based recruitment could either be specific to a particular research protocol or use a Consent-to-Share (C2S) protocol, which has been implemented successfully at UF. Under C2S, patients could elect to provide consent to be directly contacted by Consortium researchers. Access to patients through their providers will greatly enhance researchers' ability to evaluate patient experiences with MMJ, particularly in respect to outcomes that may not be fully captured on medical records. This could include studies that capture detail on patients' mental of social function or that evaluate blood levels to examine drug-drug interactions. UF MMJ-COR will work with OMMU and relevant IRBs to explore the feasibility for state-wide implementation.

The clinical research core will connect researchers to the **broad range of services and support infrastructure** made available by the **Clinical and Translational Science Institutes** (CTSIs) at UF, the University of Miami and Florida State University, and support offered by Florida International University (see letters of support). CTSIs have the broadest reach and infrastructure to connect and support clinical researchers in universities and are therefore the ideal collaborators for the Consortium (see UF CTSI resources in Research #2). Depending on study needs, such support can include assistance with recruitment, data collection or analysis or storage of specimen (biorepositories). The clinical research core will also help to connect potential industry and business partners to researchers, using the Consortium interactive website (see Outreach #5). MMJ-COR will also provide access to laboratory experts who can analyze MMJ products or study aspects of the human endocannabinoid system.

Additional resources planned for future years include the establishment of a clinical research facility for human medical marijuana research on the UF campus. Such a facility will require regulatory approvals related to MMJ storage and monitoring (e.g., DEA Schedule 1 licenses). Currently, eight UF faculty hold such a license. Finally, the clinical core will seek independent funding to establish a longitudinal cohort of persons using MMJ and who are willing to provide patient-reported information that could be linked to other data, including the MEMORY repository described above.

**Grants Program.** Pending approval by the MMJ Research Board, a portion of the state appropriation will be invested into the Consortium MMJ Clinical Outcomes Research Grants Program, open to all members of the Consortium and teaching nursing homes. Calls for proposals and grant awards will be prioritized at the beginning of the fiscal year to ensure optimal fund utility. The grants program will be administered by the lead institution who will solicit independent scientific reviews from out-of-state researchers to inform board decisions. Final grant awards will be made by the board based on study quality, impact, relevance to the research priorities, and other criteria to be decided by the board. Calls for proposals will be disseminated by each board member within their university systems and through other media (e.g., the Consortium website). The grants program will generate evidence to support clinical, personal and regulatory decision-making and act as catalyst for new research programs that allow pursuit of extramural funding.

In addition to the Consortium grants program, UF will further expand its current portfolio of extramurally-funded studies involving marijuana (see Research #4 below). Both the proposed director and associate director of UF MMJ-COR have an active federally funded research program that is relevant to this application. Both will collaborate with other members of the Consortium and the scientific expert group to apply for extramural funding, utilizing the infrastructure (MEMORY, Clinical Research Core, collaborative network) created by the Consortium. Besides furthering the MMJ research agenda, applications for extramural grant support will also aim to enhance the Consortium research infrastructure through development of additional tools or resources that can be used by Consortium members.

**Outreach**. The Consortium's outreach activities will be directed to patients, providers, researchers and industry to maximize participation in research. In addition to ongoing dialogue with MMJ Provider Partners, the Consortium will survey *all* MMJ providers annually. The **MMJ Provider Survey** will gather providers' need for answers to support treatment decisions such as specific considerations for dose or route in light of certain patient comorbidities or comedications or concerns about safety issues among patients with certain risk factors. In the first year, providers will be asked: (a) to identify clinical conditions and other information needs for prioritization in research, (b) to identify barriers to MMJ research, (c) to provide their medical opinions regarding the pros and cons of smokable MMJ, and (d) to

share questions regarding MMJ use by older persons, the population with the steepest growth in opioid overdoses and deaths in recent years. In subsequent years, the survey may focus on the management of specific medical conditions.

In Florida, although MMJ physicians may make specific recommendations regarding specific products, often the final decisions regarding product choice is made in collaboration with persons working directly within the medical marijuana treatment centers (dispensaries). Therefore, future surveys could be expanded to dispensaries and patients to gain insight into factors that influence how persons use MMJ and identify the most effective and safe products.

To promote the consortium and reach out to providers, patients and researchers, UF MMJ-COR will also staff **exhibit tables or host workshops at statewide meetings** of medical professionals, public health officials, consumers, and other relevant stakeholders. The purpose of participating in these exhibits will be to promote the Consortium to providers and researchers in the field and to strengthen research collaborations within the state of Florida and nationwide. Finally, outreach is realized through a comprehensive **Communication Plan** that includes an active website and quarterly newsletters distributed via email (see also Collaboration #5) The communication plan will aim to enhance the dialogue between relevant stakeholders with interest in MMJ clinical outcomes research and disseminate information about Consortium activities to these stakeholders. For example, an effective communication plan will facilitate new research collaborations, highlight new research findings and ensure that such findings reach local MMJ providers and patients, increase participation in the Consortium research program and provide links to other state MMJ resources.

**Scientific Expert Group**. MMJ research needs span a broad range of clinical indications and require a variety of methodological approaches. To ensure relevant expertise is available to inform the MMJ research agenda, MMJ-COR will maintain a statewide expert group. The expert group is expected to represent the full breadth of rapidly expanding clinical treatment scenarios and the evolving evidence on MMJ outcomes (desirable and undesirable). Building on experience with UF's strong translational program, which has successfully connected bench and clinical sciences, experts in pharmacology and medicinal chemistry are included to inform clinical studies. Our expert group may also include faculty in law and policy to help with interpreting legal issues and suggest changes and evaluations of policy. Expert group members are expected to contribute to the development of the Consortium research agenda, provide scientific advice to the board and collaborate with Consortium members. For example, we envision that an expert group specialized in assessing effects of smoking marijuana might be charged to provide a critical summary of the existing evidence and to identify and prioritize research needs.

**Administration**. To support the functions of the board, the Consortium director will organize bi-annual meetings of the MMJ Research Board, which will adopt an annual research plan and organize a program to implement the research plan. Both a proposal for the research plan and research program implementation will be developed and presented to the board by the director along with a budget for endorsement by the board. Other administrative activities will include administration of the grants program including facilitation of the award process by the board and fiscal management of research grant subcontracts, management of regulatory requirements and general management of Consortium finances.

With the above-described input from the MMJ Research Provider Group, the annual MMJ Provider Survey, the Expert Group and feedback gathered on state-wide conferences and through other outreach activities, the Consortium director and associate director will develop an **Annual MMJ Clinical Outcomes Research Plan** for presentation to and endorsement by the board. Overall, the research plan will consider needs for research pertinent to the MMJ Program in the state and relevant global research progress in the field and focus per statute on clinical outcomes (effectiveness, efficacy and safety), certification standards, dosing standards, administration routes and the effects of smoking marijuana to treat debilitating medical conditions.

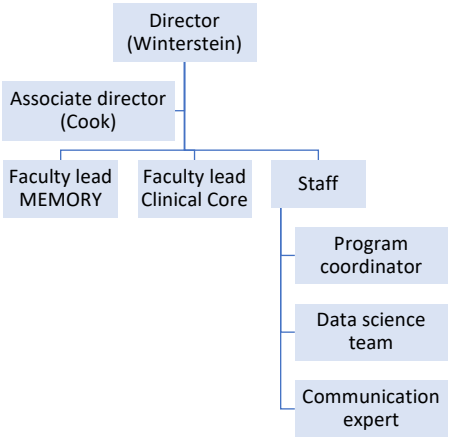


Figure 2. UF MMR-COR program, to lead the Consortium: Organizational Structure

The UF-based program, UF MMJ-COR, to lead and support the Consortium will be directed by Dr. Almut Winterstein, RPh, PhD, FISPE who is chair and professor of Pharmaceutical Outcomes and Policy and director of the Center for Drug Evaluation and Safety (CoDES) at UF (Figure 2). She will be supported by Dr. Robert Cook, MD, MPH, professor of Epidemiology and Internal Medicine and director of the Southern HIV and Alcohol Research Consortium

(SHARC) Center for Translational HIV Research. Pending approval by the Board, Dr. Winterstein will serve as director of the Consortium. Leveraging her 20-year experience in directing research on drug outcomes in real-world populations and her 6-year tenure as chair of the FDA Drug Safety and Risk Management Advisory Committee, Dr. Winterstein will lead the development of MEMORY, administer the grants program and assume primary responsibility for UF MMJ-COR administration and support of the Board. Dr. Cook will assume responsibility for developing the Clinical Research Core, lead the statewide Scientific Expert Group and MMJ Provider Partners Group, and oversee the outreach activities. They will be supported by a faculty lead for the data science team charged with the development of MEMORY and a faculty lead for development of the clinical research core. Program staff include a program coordinator to support day-to-day operations, a communication expert who leads outreach activities and a data science team. The UF CTSI has committed to provide additional personnel (see below).

## 2. Integration of existing resources

The University of Florida offers internal expertise as well as support in the development and implementation of Consortium activities. Together these activities will ensure development of a unique and robust research infrastructure based on real-world data, a deeply-informed research agenda, a comprehensive network allowing novel research collaborations, and an extramural MMJ grants program, which will jointly address key questions regarding the clinical outcomes and use of medical marijuana. This section highlights UF resources directly involved in supporting the Consortium organizational structure proposed above.

**Institutional expertise to support MMJ Research.** UF will provide access to a breadth of research programs that have already or have the capacity to address MMJ Clinical Outcomes Research (see Research #1 & #2 below). Collaboration with these programs will be realized through lead researchers' involvement in the scientific expert group and using the communication platform of the UF CTSI. While the we aim to capitalize on expertise throughout the state, UF faculty represent the full breadth of research methods and clinical expertise pertinent to MMJ clinical outcomes research. Figure 3 provides an overview of major research units within UF, organized by research and clinical expertise, reflecting the major indications for MMJ that are either currently endorsed by Florida statute or discussed in the recent report National Academy of Medicine report on MMJ. Research units also span all relevant research methods expertise in all aspects of study conduct, including medical chemistry, pharmacology, clinical trial and observational study design and law and policy research.

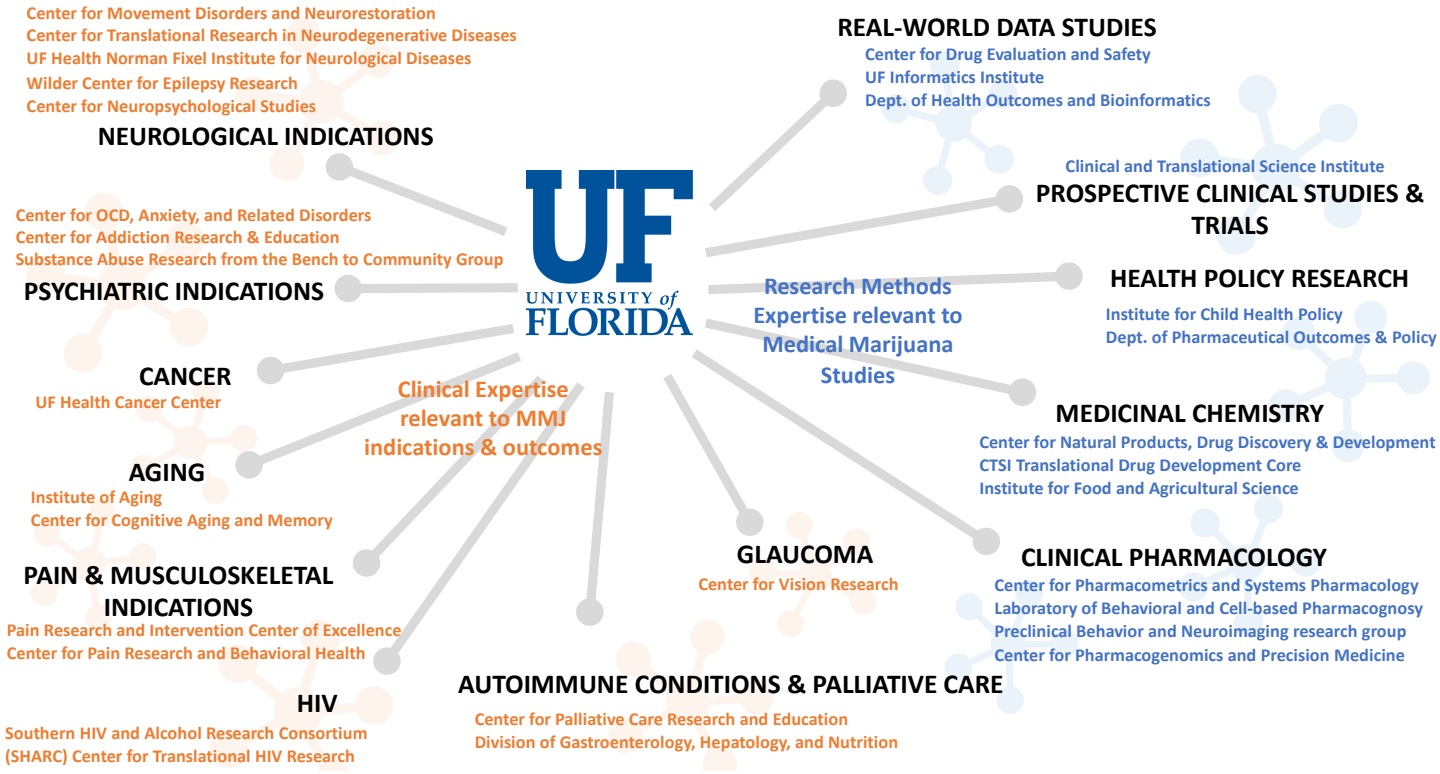


Figure 3. Existing clinical research expertise at the University of Florida to support MMJ research

**Clinical and Translational Science Institute** (UF CTSI)**.** UF MMJ-COR will be housed in the UF Clinical and Translational Science Institute, which serves as a catalytic hub connecting resources, people and ideas across UF's 16 colleges, the state, and the national Clinical and Translational Science Awards (CTSA) consortium. Established in 2008, the CTSI performs three central functions: 1) develops new capabilities for research and translation to practice; 2) delivers high-quality and efficient services and resources for translational research; and 3) cultivates a strong translational workforce**.**

**The UF CTSI will provide space for Consortia staff, contribute up to $50,000 personnel support to build research infrastructure and develop grant applications, and offer its breadths of resources that will facilitate MMJ research.** Examples of CTSI services and resources highly relevant to the Consortium include:

- Data support through the CTSI Research Electronic Data Capture (REDCap) teams. We will use the REDCap database infrastructure to conduct the provider survey and to facilitate data collection from multiple clinical settings.
- Clinical Research Space. UF investigators, including Dr. Cook, are currently using the CTSI Clinical Research Center in their ongoing studies related to marijuana and health outcomes. These include phlebotomy services, blood and urine processing, and clinical nursing assessments.
- The OneFlorida Clinical Research Consortium, which in collaboration with FSU, the University of Miami CTSA hub and other stakeholders offer the OneFlorida Data Trust with collated health care claims and electronic health record (EHR) data of ~10 million people in Florida. We will seek to link data from the MMJ registry to some aspects of the OneFlorida Data Trust to develop the MMJ repository MEMORY.
- HealthStreet, CTSI's community engagement program with more than 10,000 members from underrepresented populations. As of 2019, HealthStreet reports a membership of n=5,659 individuals who use marijuana with 94.9% stating that they would be willing to participate in research. HealthStreet also organizes monthly forums "Our Community, Our Health (OCOH)" that address relevant health topics and disseminate research findings. Our group is participating in an upcoming OCOH event related to MMJ (see announcement). These events are streamed nationwide and are interactive using social media.
- CTSI's Translational Drug Development Core, with expertise in the analysis of raw plant material, commercial cannabis products, and clinical pharmacokinetic studies.
- CTSI's Advanced Communication Program in collaboration with UF Health Communications, a division of 80 communication professionals, and the STEM translational communication center, which helps in the translation of complex scientific messages for various audiences.
- CTSI's training program including career development and pilot grant awards program that can provide support for faculty to build a research program in MMJ clinical outcomes research.


**Center for Drug Evaluation and Safety** (CoDES). The University of Florida Center of Drug Evaluation and Safety (CoDES), directed by Dr. Winterstein, was founded to support research on the safety, effectiveness and value of medication use in real-world populations. CoDES unites a multi-disciplinary group of big data researchers in epidemiology, health economics, health services research and decision-sciences who evaluate drug outcomes to guide regulatory, clinical and personal decision-making. In addition to delivering new actionable evidence, CoDES fosters the development of new methods and analytic tools to enhance drug evaluation and regulatory science. CoDES houses longitudinal data on drug use and clinical outcomes from over 300 million lives. This vast data repository can support assessment of rare side effects or small high-risk populations. CoDES has supported a host of drug safety and drug effectiveness studies, including for example evaluations of the risk for suicide or accidents among patients exposed to certain psychotropic medications, thus demonstrating its capability to develop adequate data sources and methods that can evaluate MMJ outcomes. CoDES, directed by Dr. Winterstein, will facilitate development of MEMORY (see Research #3). CoDES also

hosts a speaker series with focus on drug evaluations that can be expanded to MMJ, and connects to the graduate program in the department of Pharmaceutical Outcomes and Policy with about 30 PhD students and over 100 MS students who specialize in the use of observational methods to evaluate drug outcomes.

**The SHARC Center for Translational HIV Research** (SHARC). Dr. Cook, proposed associate director for UF MMJ-COR, has served as the director for the Southern HIV Alcohol Research Consortium (SHARC) since 2012. The SHARC Center has several components that will facilitate Consortium activities. For its prospective studies, SHARC has established data use agreements and data sharing procedures with investigators at several collaborating universities. SHARC has a training program that encourages the involvement of trainees in research related to substance use and clinical outcomes. The SHARC infrastructure currently supports Dr. Cook's ongoing, prospective NIH study on marijuana and HIV infection, which involves the collection of blood and urine samples at multiple sites, a shared database using the CTSI's RedCap secure data system, and a single IRB plan that involves collaboration with multiple IRBs across the state, including the Florida Department of Health. With SHARC, we have demonstrated an ability to collaborate and share data across multiple institutions, and to create administrative infrastructure to conduct statewide research activities. Experiences collected with SHARC will greatly inform and support development of the Clinical Research Core within the Consortium.

**The combination of the broad UF research community, the UF CTSI, CoDES and SHARC will support all operational aspects of the Consortium and ensure a rich and thriving state-wide research program that encompasses all clinical areas of MMJ use, and that takes advantage of demonstrated excellence in both retrospective big data analysis and prospective study designs to optimize assessments of MMJ effectiveness and safety.**

# Research

## 1. Prior experience in funded medical marijuana research

*(What experience does the institution have in the area of medical marijuana research? Please provide any examples of grants that the institution has received specific to this type of research.)*

UF is a leading institution in Florida for marijuana research, as evidenced by an expansive portfolio of funded projects that encompass research related to clinical outcomes and mechanistic pathways of marijuana. In this section, we provide specific examples of funded marijuana projects awarded to UF researchers since 2015 (Table 1). The knowledge base developed from the research efforts outlined below will dovetail with the Consortium's agenda for further advancing MMJ research and will be efficiently integrated into the larger UF research portfolio, while fostering statewide collaboration with other Florida universities and institutional partners.

Table 1. Overview of extramurally funded research studies initiated in the past 5 years

| Funding Agency | Principal Investigator | Study Title and Collaborations |
|---|---|---|
| **NIH-NIDA** | R. Cook | Health Outcomes and Cognitive Effects of Marijuana Use among Persons Living with HIV/AIDS. **Collaboration: University of South Florida, Florida International University, University of Miami, Florida Department of Health** |
| **NIH-NIDA** | C. Okafor | Impact of Long-Term Marijuana Use on the Neurocognitive Functioning of Individuals Living with HIV/AIDs. |
| **NIH-NIDA** | V. Joseph | Patterns of Marijuana Use for HIV Pain: a Mixed Methods Approach. |
| **FL- DoH** | P. Carney | Effects of cannabidiol use on the developing brain in medically refractory childhood epilepsy. |
| **Gatorade trust** | E. Zimmermann | Safety and efficacy of cannabis in the treatment of Crohn's disease. |
| **UF-CRISP** | Y. Wang | Medical marijuana use in older adults with chronic pain: A pilot project to build a prospective cohort. **Collaboration: Medical Marijuana Clinic Partners** |
| **NIH-NIDA** | M. Heaton | Critical Mechanisms underlying the THC Neurotoxicity in developing CNS. |
| **NIH-NIDA** | L. Knackstedt & L. Cottler | Identifying Patterns of Human Polysubstance Use to Guide Development of Rodent Model. |
| **NIH-NIDA** | B. Setlow & A. Maurer | Development of a Rat Model of Cannabis Smoke Self-Administration. |
| **McKnight Brain Institute** | M. Gold | Passive exposure to second-hand marijuana smoke. |
| **UF-Office of Research** | B. Setlow | Dissecting Interneuron Function in Addiction (to Marijuana and other Substances) using Optogenetics. |

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| **McKnight Brain Institute** | L. Colon-Perez | Perinatal cannabis smoke exposure and development of brain network connectivity. |
| **McKnight Brain Institute** | M. Gold & B. Setlow | Passive Exposure to Second-hand Marijuana Smoke: Long-term Neuropsychiatric Effects. |
| **NIH-NIDA** | L. McMahon | Treatment of cannabinoid withdrawal in Rhesus monkeys. |
| **NIH-NIDA** | M. Febo | Preclinical Imaging of Adolescent Cannabidiol in Brain Structure and Functional Connectivity. |
| **NIH-NIDA** | A. Brujinzeel & B. Setlow | Lasting behavioral and neuroimaging consequences of adolescent exposure to cannabis smoke. |
| **NIH-NIDA** | C. Lopez-Quintero | Drug Use Disparities among Hispanics: Elucidating the Complex Interaction between Socio-cultural, Neurocognitive and Drug Use-related Factors. |
| **NIH-NIDA** | A. Yurasek | A Behavioral Economic Intervention to Reduce Marijuana Use in Truant Youth. |
| **NIH-NIDA** | L. Cottler & S. Nixon | The Adolescent Brain Cognitive Development (ABCD) Study [for Health and Developmental Outcomes related to Marijuana and other Substances].<br>**Collaboration: Florida International University and 21 other Universities nationwide.** |

Below, we highlight a selection of funded projects directly relevant to MMJ *Clinical Outcomes* Research.

**Outcomes research related to HIV infection.** HIV infection is one of the current indications for MMJ in Florida, yet little is known about the effects of marijuana on inflammation, pain, and HIV viral control. Dr. Cook is the PI for a 5-year grant entitled, Health outcomes and cognitive effects of marijuana use among persons living with HIV/AIDS, funded by NIH (R01DA042069). This project will track health outcomes in over 450 persons with HIV in Florida for 4 years. This multi-site study includes collaborations across Florida with university partners USF, FIU, UM and the Florida Department of Health. This study assesses outcomes related to marijuana use from both illicit and licit sources. The study conducts detailed cognitive assessments, blood testing for markers of systemic inflammation, and urine toxicology to evaluate different cannabinoid components.

**Outcomes research in Aging and Pain Indications.** Building on the extensive research programs on pain and aging at UF, PI Yan Wang received recently funding from UF-CRISP to assess MMJ and chronic pain in older adults. This study collects data from adults aged >50 years old who seek MMJ to treat chronic pain from three medical marijuana clinics in Jacksonville and Gainesville. This research involves real-time assessments of symptoms such as pain, stress, and anxiety before and after starting MMJ. Following the conclusion of the pilot, an NIH R01 grant will be submitted to evaluate the efficacy and side effects of medical marijuana for treating chronic pain and reducing opioid use in older adults.

**Outcomes research in Neurological Indications.** The Florida Department of Health funded $1 million in grants to UF investigators to examine outcomes related to cannabidiol treatment for children with drug-resistant epilepsy and other seizure-causing neurological disorders. This study enrolled 50 children and assessed the safety and efficacy of cannabidiol treatment for a 3-year follow-up period. Additionally, the research team led by PI Robert Cook has recently submitted a $250,000 supplement request to the NIH to extend the MAPLE Study (as described above) to a population of patients at greater risk for Alzheimer's disease. Funding decisions for this supplement will be announced in June of 2019. The goal of this proposed study is to better understand the relationship between marijuana use, the human gut microbiome, and mild cognitive impairment, which is a precursor to Alzheimer's disease. If awarded, the UF research team will lead this multi-site study and collaborate with FIU as an additional study site.

**Outcomes research in Inflammatory Bowel Disease Indications.** Funding was received by PI Ellen Zimmermann to study the effect of THC on inflammation and fibrosis on patients with Crohn's Disease, a type of inflammatory bowel disease. The team has performed translational studies using cell culture and animal models as well as clinical studies of marijuana use among young adults with Crohn's Disease diagnoses. The age group most commonly affected with Crohn's Disease, young adults, are also the population most likely to encounter marijuana socially as well as to seek out MMJ information, so the prior research experience of this group demonstrates excellent capacity to further their studies of marijuana efficacy related to inflammatory bowel disease.

**Ongoing MMJ Research Collaborations to Support Future Work.** In addition to the funded projects and collaborations with Florida institutions as described above, the research teams of Dr. Robert Cook and Dr. Wang have worked with UF to establish nondisclosure agreements, memorandums of understanding, and research partnerships with MMJ treatment providers and other industry partners that will benefit MMJ Consortium members via connection to established shared resources and partnerships. Drs. Cook and Wang have emphasized to all potential industry partners that their goal is to be open to any and all partnerships and to not enter any exclusive arrangements, in order to be unbiased. Neither of them has any existing conflicts of interest with the MMJ industry.

**Prior Research Experience with the Florida MMJ Program.** Also noteworthy is UF's direct experience with the state's MMJ program. The original SB1030 'Compassionate Medical Cannabis Act of 2014' included a mandate for ordering physicians to submit treatment plans to UF for research on the safety and efficacy of low-THC cannabis. UF responded to this unfunded legislative mandate with the development of a secure web-based platform for data collection. In collaboration with the Office of Medical Marijuana Use (OMMU, formerly the Office for Compassionate Use), Dr. Winterstein, who led the UF effort, developed a proposal for a comprehensive MMJ safety surveillance system that would have integrated treatment plans and MMJ dispensing information (now referred to as the MMJ registry) with a host of additional clinical data to track both safety and effectiveness outcomes. Soon after patient certification commenced, SB8A was passed, which established the Coalition for Medical Marijuana Research and Education within the H. Lee Moffitt Cancer Center and Research Institute and which released UF from the requirement to collect treatment plans. Instead the OMMU was charged to integrate physician-provided and dispensing information into the MMJ registry. During its existence, Dr. Winterstein supported the mission of the Coalition for Medical Marijuana Research and Education as Vice Chair of the Coalition's Board and has continued to work with OMMU to establish the regulatory infrastructure to develop the originally proposed repository.

## 2. Integration of the consortium into UF's research portfolio

*(How would the Consortium for Medical Marijuana Clinical Outcomes Research fit into the institution's research portfolio?)*

The UF research portfolio is supported by a robust infrastructure, including more than 150 research centers and institutes embedded across sixteen academic colleges. The following programs are featured to illustrate the breadths of research collaborations on campus. Programs directly applicable to the use of *registry data* for research are discussed under Research #3 below.

**Pain Research.** UF is home to the Pain Research and Intervention Center of Excellence (PRICE), which is a multi-college Center of Excellence that serves as the professional home for scientists, clinicians and trainees dedicated to improved understanding and treatment of pain. PRICE is affiliated with and supported by the UF CTSI and receives strong support from the UF Institute on Aging and the UF Health Cancer Center. PRICE provides member investigators with several resources and services in order to facilitate clinical and translational pain research, including the Pain Clinical Research Unit that facilitates quantitative sensory testing of pain. PRICE can assist MMJ consortium members and applicants with the recruitment of research participants, as it maintains a registry of more than 1,000 potential research participants who have provided permission for future contact regarding pain research. PRICE is currently collaborating on a large translational research center grant proposal focused on the intersection of pain and addiction.

**HIV-Related Research.** UF participates in and leads several statewide initiatives related to HIV research involving substance use, mental health, and stigma. For example, the SHARC Center, directed by Dr. Cook, sponsors the Florida Cohort project, funded by the NIH, which has enrolled over 900 persons with HIV infection from 9 clinic locations across Florida. Participants' answers to survey questions are linked to information from medical records and state surveillance data. Researchers and trainees from 7 different public and private universities in Florida are involved in the Florida Cohort project, and the data have supported papers and PhD dissertations from trainees at UF, FIU, USF, UCF, Larkin University, and the University of Miami. To support the collaborative activity, SHARC has established a "concept system" that allows research collaborators from anywhere in Florida (or the US) to request access to SHARC data, and has an authorship review system to ensure that persons who contribute data are invited to participate as co-authors.

**Geriatrics and Aging.** The UF Institute on Aging (IOA) is the home of faculty members from diverse disciplines who pursue careers focused on research and education on aging, including the full spectrum of research from applying discoveries made in the laboratory and developing trials and studies for humans, to enhancing the adoption of best treatment practices into the medical community. IOA research elucidates the biochemical, genetic, and physiological mechanisms of aging that result in age-related functional (both physical and cognitive) decline in humans and animal models. This includes investigations of the gradual or programmed alterations of structure and function that characterize normal aging and investigations of the adverse changes that accompany age-related disease states. The Division of Clinical Research within IOA provides the infrastructure and resources for conducting clinical research in aging, including both controlled trials and epidemiological studies, which could include assessments of MMJ use in older persons. IoA faculty listed approximately 50 ongoing studies and more then 300 scientific publications in the past year.

**Neurological Conditions.** UF's research portfolio for neurological conditions is supported by the infrastructure of several centers with foci on specific neurological conditions with indications for MMJ. For example, the Center for Movement Disorders and Neurorestoration (CMDNR) is of international prominence, as reflected by multiple Centers of Excellence within, including; a National Parkinson Foundation Center of Excellence, Tyler's Hope Center for a Dystonia Cure, a Huntington's Disease Society of America Center, a Bachmann-Strauss Dystonia Parkinson Center of Excellence, and a Tourette Syndrome Association Center of Excellence. Additionally, the UF Center for Translational Research in Neurodegenerative Diseases has a state of the art, multi-disciplinary research center focused on the discovery, development and evaluation of future treatments and diagnostics for degenerative central nervous system conditions including Parkinson's disease, Alzheimer's disease, Amyotrophic Lateral Sclerosis (ALS), Frontotemporal Lobar Degeneration, and Stroke. The UF Health Norman Fixel Institute for Neurological Diseases is home to scientists and clinicians working on neurological disorders that include Parkinson's, dystonia and other movement disorders, Alzheimer's disease and dementias, concussion, traumatic brain injury, and neuromuscular disorders like amyotrophic lateral sclerosis. The Wilder Center for Epilepsy Research supports interdisciplinary research in epilepsy. Lastly, the research performed at the UF Center for Neuropsychological Studies is directed to increase understanding of the anatomy, physiology, and neurochemistry of normal behaviors mediated by the brain.

**Psychiatric Conditions.** Research related to psychiatric conditions crosses multiple colleges, centers, and institutes. Here, we highlight Centers with particular expertise and infrastructure that will support the MMJ Consortium. The UF Center for OCD, Anxiety, and Related Disorders (COARD) is an interdisciplinary group of researchers and clinicians who conduct clinical and translational research in obsessive compulsive disorder, PTSD, and anxiety disorders. The Center for Cognitive Aging and Memory (CAM) conducts cutting-edge interdisciplinary clinical neuroscience and translational research on age-associated cognitive, behavioral and emotional functioning, factors that contribute to impairments and functional decline, and future avenues for intervention. CAM faculty are currently collaborating with the MAPLE study, described above, to assess marijuana's effects on motivation, apathy, and planning.

**Addiction.** The UF Center for Addiction Research & Education (CARE) is one of the oldest continuing University-wide Centers and CARE investigators have active research programs in highly diverse domains; ranging from molecular neuroscience and drug discovery through epidemiology and clinical trials. One of CARE's core missions is to conduct community and inter-institutional outreach and educational programs, which ensures that diverse scientific and community stakeholders are represented and actively engaged. This successful approach for inter-institutional collaborations has resulted in a CARE membership that includes 44 addiction scientists, collaborating institutions, and a community and external advisory committee to support all outreach activities.

**Smoking.** The UF Behavioral Health and Technology (BHaT) Clinic includes the first ever behavior analysis clinic to provide remote, technology-based treatments for health behaviors related to smoking. Laboratory infrastructure built and operated by BHaT includes devices and mechanisms to assess smoking and smoking behaviors as well as the development of remote technologies that allow for testing for smoke in the home and environment of study subjects. Additionally, BHaT's collaborative research program has contributed to methodological and conceptual frameworks for testing and evaluating technology-based interventions, including mechanisms responsible for treatment-induced changes in addictive behavior. The review of mechanisms of change by BHaT and collaborators was the first publication related to the conceptual and empirical underpinnings of technology-based interventions for substance use disorders. The cross adaptability of BHaT technologies and techniques between tobacco and other substances will be of substantial value for MMJ Consortium members who are investigating clinical outcomes related to marijuana smoking.

**Preclinical Behavior and Neuroimaging.** The Preclinical Behavior and Neuroimaging (PBN) research group, composed of psychiatrists, pharmacodynamics experts, and analytical chemists, has the capacity to evaluate effects of smoked cannabis and cannabis constituents on multiple behavioral and neurobiological outcome variables in animal models, such as; pain, reward, dependence, withdrawal, addiction liability, cognition, brain imaging, and biochemistry. To our knowledge, this capacity is unique in the state of Florida. Hence, PBN could serve as a state-wide resource for preclinical research on smoked cannabis. PBN has a smoke exposure apparatus (Teague Enterprises Smoking Machine) used to expose rodents to smoke from burning cannabis. This is useful for assessing effects of acute or chronic cannabis smoke inhalation on physiology and behavior, as well as for conducting PK/PD studies of cannabis smoke. PBN can address research questions concerning medical cannabis use that are highly translational, such as the effects of exposure to smoke from different cannabis strains or MMJ products on behavioral and functional neuroimaging variables, and PBN

members are active affiliates in several of the Centers and Institutes highlighted elsewhere, such as CARE and CTSI. To date, PBN members have received 5 NIH grants to perform research related to safety, physiological outcomes, and behavior following exposure to cannabis smoke.

**The CTSI Translational Drug Development Core (TTDC).** The TDDC, led by Dr. McCurdy, has expertise in the analysis of raw plant material, commercial cannabis products, and clinical pharmacokinetic samples to bridge the gap that exists between raw plant material, commercial cannabis products, and ultimately the clinical/therapeutic outcomes. The core has ability to do pharmacokinetic/pharmacodynamic modeling derived from clinical data and will therefore, be able to develop dosing standards for various cannabis products based on bioavailability, permeability and dose proportionality studies, that can be then tested in clinical outcomes research. The core has developed a method that can simultaneously quantify multiple cannabinoids in *Cannabis sativa L.* This method can be used to quantify plant material, commercial products, and human biological samples using ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) and has already been used to quantify cannabinoids in commercial *C. sativa* products, in oral and edible forms, as well as plant samples. Additionally, the TDDC has three UPLC-MS/MS, and one ultra-performance liquid chromatography-quantum time of flight (UPLC-QTOF) instruments, which are able to perform both structure elucidation and simultaneous quantification of cannabinoids.

**The UF Center for Pharmacogenomics and Precision Medicine.** Research in the Center for Pharmacogenomics and Precision Medicine spans from mechanistic studies to multi-omic approaches to elucidate genetic contributions to drug response. Center investigators collaborate with investigators across the University of Florida and other institutions, both nationally and internationally, to ensure innovation in this cutting-edge science. The center also supports the UF Health Precision Medicine Program through the translation of pharmacogenomic research findings into patient care and examining outcomes with genotype-guided therapies. Sixteen center faculty can expand existing research programs to evaluate person-level differences in MMJ metabolism and potential drug-drug or drug-disease interactions highly relevant to MMJ users with multimorbidity and polypharmacy.

**Institute for Food and Agriculture Science (IFAS).** IFAS is conducting one of the two industrial hemp pilot projects in the state of Florida aimed at providing horticultural advice on ideal growth conditions. The results of this project and ongoing research into hemp derived cannabinoids will directly benefit the Consortium for Medical Marijuana Clinical Outcomes Research. Collaborations could be fostered throughout the state with both industrial hemp and marijuana growers. The consortium can serve as the central testing point for growers, manufactures, and consumers by linking product composition, dosing recommendations and clinical outcomes.

**Integrative Medicine.** As a clinical and not a research program, the UF Health's Integrative Medicine Clinical Program represents a highly-relevant cross-section of patients who might consider MMJ and has indicated strong interest in participating in MMJ research. The program currently provides education on cannabis use for symptom and pain reduction in patients with chronic neuropathic and musculoskeletal pain, inflammatory bowel diseases and cancer. These patients often have several co-morbidities that include anxiety, depression, PTSD, arthritis, and present with complex treatment regimen. For example, patients seen in this practice with chronic pain use high-dose opioids and are interested to reduce doses due to opioid side-effects and reduced opioid access; elderly patients with arthritis and musculoskeletal pain who are not candidates for surgery seek effective pain control; and patients with IBD or cancer are looking to use MMJ in addition to, or in lieu o, standard drug therapy to maintain remission, each requiring different considerations regarding optimal THC:CBD ratios and dosing regimen.

**In summary, clinical outcomes research on dosing, safety and effectiveness of MMJ integrates logically into a number of established and well-funded research programs. We envision collaborative research that integrates the full translational spectrum of sciences to understand mechanisms and clinical effects of MMJ products considering both patient and product characteristics that might effectively alter the risk-benefit of MMJ.**

## 3. Integration of medical marijuana registry data into UF's research portfolio and plans for data use

*(Pursuant to section 1004.4351, the Florida Department of Health is required to provide data to the Consortium that includes, for each patient registered in the medical marijuana use registry, the patient's qualifying medical condition and the daily dose amount, routes of administration, and forms of marijuana certified for the patient. How does this aspect of the Consortium fit into the institution's research portfolio and how would the institution use the data?)*

The following proposal for MMJ registry data use is closely aligned with UF's experiences and efforts in collaboration with OMMU over the past four years to develop a surveillance system that ensures the safety of MMJ and facilitate clinical outcomes studies. It is informed through UF's close relationship with the FDA with specific emphasis on building data repositories that allow post-approval assessments of treatment safety and effectiveness in real-world populations, realized through FDA's National Medical Product Monitoring System, Sentinel. Dr. Winterstein serves as one of the academic partners for Sentinel. The proposal builds on UF's capacity in the use of big data in the evaluation of medications post-approval, which, in terms of comprehensiveness and output, is unique in the state.

Central to this research is the **Center for Drug Evaluation and Safety** (CoDES), which connects UF researchers who specialize in the post-marketing evaluation of drugs and their use in real-world populations; and **the Clinical and Translational Science Institute** (CTSI), a NIH-funded catalytic research hub, with the core mission to accelerate translation of scientific discoveries and the implementation of evidence-based practices. Two additional centers are relevant in understanding the variability of drug effects in patients, the **Center for Pharmacometrics and Systems Pharmacology** (CPSP) and the **Center for Pharmacogenomics and Precision Medicine** (CPGx).

**CoDES** houses vast data repositories of over 300 million lives to support the evaluation of drug effectiveness and safety, including the evaluation of drug-drug and drug-disease interactions. The backbone of those data are clinical encounter billing records ("claims data") from patients in public (Medicaid and Medicare) and private insurance, which provide detail on diagnosis and procedures associated with billed medical encounters and pharmacy dispensing records, thus allowing longitudinal studies of drug exposure and outcomes. CoDES has further enhanced those data with extensive linkages to other data sets that provide more granular access to specific risk factors or health outcomes, including for example (a) birth certificates for research on drug effects on pregnancy and childhood, (b) death certificates for detail on cause of death in the evaluation of drug risks on suicide or sudden cardiac death or overdose, (c) car crash data for the evaluation of drug effects on driving, and (d) the minimal data set (MDS) with detail on cognitive function, pain and other health outcomes among nursing home residents. In collaboration with the UF Institute on Aging, CoDES has linked Medicare claims data to clinical trial data which offer a wealth of validated measurements of mobility, frailty, cognitive performance and other outcomes oftentimes not formally assessed in routine care. CoDeS support offered to researchers also includes a host of methodological tools including a SAS program library that facilitates cohort building, validated algorithms to measure specific health outcomes, conventions for exposure assignment in complex real-world scenarios of frequently changing drug regimen, and advanced pharmacoepidemiologic approaches to address confounding or other biases. CoDES faculty, located in 4 health colleges, have published new evidence of drug effects in top clinical journals, including for example JAMA and BMJ. Examples of ongoing research conducted by CoDES faculty relevant to MMJ research include: an evaluation of the effects of gadolinium-enhanced MRI on birth defects funded by the FDA (Winterstein PI); effects of types, duration and dose of opioid-benzodiazepine combinations on overdose deaths funded by NIDA; and an evaluation of pain management among patients with Alzheimer's disease funded by NIA. CoDES, directed by Dr. Winterstein, will support the development of the MMJ Clinical Outcomes Research Repository MEMORY.

**CTSI** (described previously) is home to the **OneFlorida Data Trust**, which founded by UF in 2011, combines electronic health records from a network of health systems that provide care for approximately 10M or 40% of all Floridians with a catchment area covering all 67 Florida counties. OneFlorida is used by CoDES faculty and other outcomes researchers for a number of observational studies, including for example an evaluation of factors that determine patient response to antihypertensives. In year 1 of the Consortium, we propose to link OMMU registry data to Medicaid claims records, followed by extracts of OneFlorida EHR data in the following years.

**CPSP and CPGx** contribute to the understanding of drug action on the mechanistic level by explaining variability of drug effects based on differences in drug formulations or patient characteristics. For example, differences in patient characteristics such as genetic variation or combinations with other drugs that affect each other's metabolism can result in drug over- or underdoses. Thus, both centers can contribute to our understanding of drug-drug or drug-disease interactions, which can then be evaluated in real-world settings. CoDES and CPSP and CPGx faculty collaborate closely in the evaluation of drugs and are prepared to expand this collaboration toward the evaluation of MMJ as single substance or in combination with other medications.

UF's research infrastructure supporting the use of these extensive data sets (for example, CoDES houses more than 20 Tb of data) also comprises super-computing facilities with the capability to store and analyze highly sensitive data including SSN and relevant bioinformatics support to effectively manage such data.

**Following these descriptions, the extension of this vast clinical outcomes research enterprise is intuitive. Like pharmacy dispensing records allow detailed measurement of exposure to types, doses and routes of medications, the DoH medical marijuana registry can provide the same detailed information about the initiation, frequency, type and route of medical marijuana. Thus, using the same pharmacoepidemiologic methods that UF applies in its vast spectrum of extramurally-funded evaluations of drug products, UF will build the infrastructure and implement research studies that evaluate clinical outcomes of medical marijuana use.**

Specifically, UF will build the **MMJ Clinical Outcomes Research Repository (MEMORY)**, which links registry marijuana dispensing data with a variety of data sets that allow longitudinal ascertainment of health outcomes, considering MMJ dose and routes, and concomitant medication use and concomitant diseases. Development of MEMORY will follow sequential steps that are implemented over several years, resulting in a consistently expanding wealth of clinical outcomes research data made available to Consortium researchers (Figure 4). To begin, in year one, the MMJ-COR data team under direction of Dr. Winterstein will work with OMMU on the extraction specification and secure transmission of MMJ registry data to UF, which is made available to the Board under Section 1004.4351, Florida Statute. Received data will be initially curated manually and eventually with customized automated algorithms. Data will be then transformed into specific research variables that allow detailed descriptions of MMJ exposure such as product types, dose, route, treatment initiation and duration and other information available in the registry. OMMU has shared detail on the data fields in the MMJ registry with Dr. Winterstein previously, allowing an assessment of the scope of studies the registry can support. Dr. Winterstein has obtained UF IRB approval to build MEMORY including all proposed data linkages.

Registry data is uniquely rich in defining MMJ exposure, including detail about the specific product and THC/CBD content, daily dose, the route as well as the originating plant, but its detail on patient health status, health history, concomitant medication use or use of other treatments, and health outcomes is limited for several reasons: (a) statutory requirements for MMJ providers to enter data into the registry are limited; (2) MMJ providers submit information to the registry in a separate system that does not link to their electronic health record system; (3) MMJ providers are oftentimes not the patient's primary healthcare provider and have limited access to both health history and subsequent health outcomes. Linkage to claims data can overcome these shortfalls by providing data on all healthcare services that were reimbursed by a health plan including for example, ED visits or hospitalizations along with associated diagnoses following initiation of MMJ. Claims data allow furthermore establishment of control populations who share similar indications and health history of MMJ users but have not initiated MMJ yet. Controlled studies, including patients with and without MMJ use can then be used to assess the risk for certain MMJ outcomes (harmful or beneficial) in the context of baseline risk or natural disease progression.

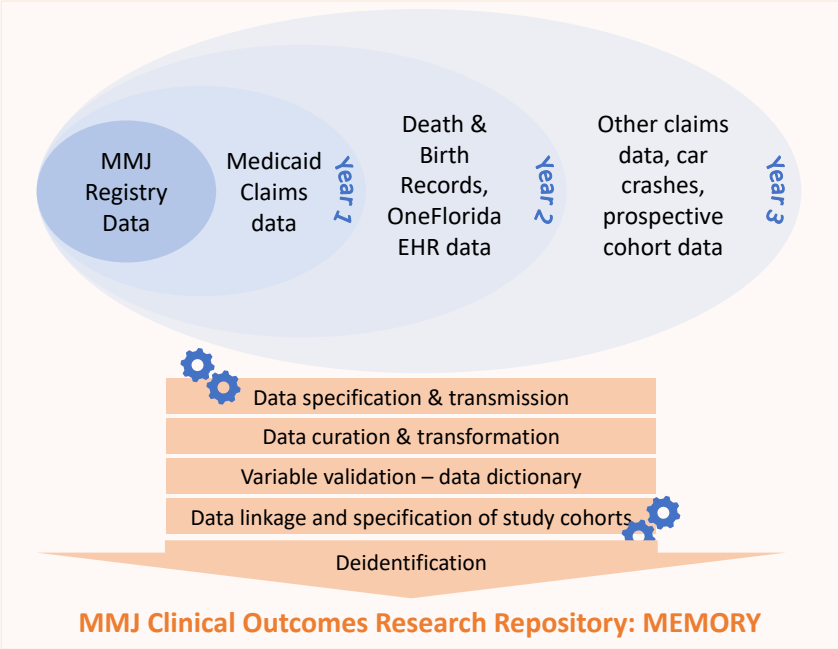


Figure 4. MEMORY Development Process

**MEMORY development**. In year 1, UF will link MMJ registry data to Medicaid claims data, which are already provided by AHCA to UF quarterly within the OneFlorida Data Trust. Due to their comprehensive structure covering all healthcare services, claims data can generate millions of study variables. To support researchers, UF will begin development of variables that are anticipated to play important roles in MMJ clinical outcomes research (e.g., psychoses, seizures, opioid overdose) using previously validated algorithms. All final variables will undergo customary validation procedures and are then listed in a data dictionary along with documentation of their source and validation efforts for future use by Consortium researchers. Data will be stored in a secure computing environment that has been approved for storage of sensitive information including SSN. In year 2 and subsequent years, we envision expansion of

the data linkage to DoH death and birth certificates and OneFlorida EHR data, and additional datasets managed by the state and others that are relevant to health outcomes (e.g. cancer registry, DMV car crashes).

As the lead institution for the Consortium, UF MMJ-COR will be responsible for (a) sharing information about MEMORY including detail about its variable specifications and capabilities, (b) the process to request access to the data for research, (c) ensuring data security, and (d) communicating this information via the Consortium web site and other means. UF will develop policies and procedures that will facilitate sharing of the data for research purposes, with adequate governance via Data Use Agreements for each individual project. This will include safeguards that ensure the data cannot be used to identify individual persons, unless explicitly needed for patient safety purposes.

**Descriptive MEMORY analyses**. Finally, UF MMJ-COR will provide descriptive analyses of the data that characterize socio-demographic and clinical conditions (indications, comorbidities and co-medications) of MMJ users throughout the growth of the Florida Medical Marijuana Program to understand utilization pattern and prioritize research needs. This initial study will provide a status quo assessment of MMJ use in the state that will be shared with OMMU and Consortium researchers. For example, researchers with interest in evaluating patients with seizure disorders or who utilized opioids chronically prior to MMJ initiation will be able to refer to data tables that provide sample size estimates. In year 1 of Consortium work, that stage of data linkage will allow *general* descriptions of all registry enrollees and *detailed* assessments of disease and medication use history of registry enrollees who are also enrolled in Medicaid. Later years will allow expansions of these assessments via linkage to other claims data and OneFlorida EHR records.

**Outlook**. In the future, individual researchers may propose to do research directly with the MEMORY repository (for example, to study emergency room visits before and after starting MMJ), or to link individual participant research data to MEMORY. For example, patients in the MMJ program in Florida might consent to enroll in a statewide longitudinal cohort study to participate in ongoing surveys, to provide clinical samples, or to provide direct data (including real-time data on symptoms and side effects, fit-bit data monitoring for outcomes like sleep), and this information could be linked securely to the data in MEMORY. Also, MEMORY could be linked to provider-collected data to capture additional detail about clinical assessments. Planned extramurally-funded research using MEMORY is provided under Research #4 below.

## 4. Plans for federal / external funding

*(Does the institution have any plans to use the Consortium to apply for federal and/or external grant opportunities to support this research? If so, please provide details of any plans.)*

Our institution has plans to use the Consortium to apply for medical marijuana-related research funding and to support investigators interested in this research area. The long trajectory of biomedical research at the University of Florida is highlighted by a record high of $560.6 million in *federal* research funding in Fiscal Year 2018 – a nearly 23 percent increase over last year - and a total of over $860 million.

In collaborations promoted and initiated by the Consortium for MMJ Clinical Outcomes Research, our institution will prioritize applications to current funding mechanisms from the National Institutes of Health. A list of NIH funding announcements explicit to marijuana is provided below, and many additional announcements incorporate aspects of clinical outcomes research pertinent to MMJ. Of note, the research infrastructure provided for the Consortium will also help investigators at other participating universities to compete for funding from the same funding mechanisms.

- Public Policy Effects on Alcohol-, Marijuana-, and Other Substance-Related Behaviors and Outcomes (PA-17-132; PA-17-134; PA-17-135)
- Marijuana, Prescription Opioid, or Prescription Benzodiazepine Drug Use Among Older Adults (PA-18-079; PA-18-080; PA-18-061)
- Developing the Therapeutic Potential of the Endocannabinoid System for Pain Treatment (PA-18-917)
- Notice of Intent to Publish a Funding Opportunity Announcement for Exploring the Mechanisms Underlying Analgesic Properties of Minor Cannabinoids and Terpenes (NOT-AT-19-009)
- Mechanism for Time-Sensitive Drug Abuse Research (PAR-19-064)
- Limited Competition for Adolescent Brain Cognitive Development (ABCD) Study - Coordinating Center (RFA-DA-20-004)

In the following we will highlight two research programs that will be closely integrated into the UF MMJ-COR: Dr. Winterstein's program in collaboration with CoDES faculty and Dr. Cook's research program within SHARC. Drs. Winterstein and Cook have collaborated on several projects and have co-mentored research trainees and junior faculty.

**Dr. Winterstein's research program** focuses on the evaluation of drug effectiveness and safety and specializes in retrospective analysis of drug effects in large real-world populations. She has published safety studies on the risk of psychotropic medications on suicidal and cardiovascular risk, risk factors for the development of opioid use disorder and the effects of various drugs on pregnancy outcomes, all areas that can be easily expanded to the assessment of MMJ outcomes. In her previous work with OMMU aimed at developing a MMJ clinical outcomes research program using registry data, she proposed a variety of high-priority research studies, which she will pursue with the development of MEMORY. Of note, MEMORY will be to-date the only data repository *nationwide* that allows granular longitudinal detail on MMJ use and similarly granular detail on disease history and clinical outcomes. This uniquely rich data environment with more than 200,000 persons, paired with the increasing pressure to expeditiously enhance evidence on MMJ use outcomes and to find safe and effectively approaches to combat the national opioid crisis will strongly enhance chances for federal funding. *Planned applications for federal funding using MEMORY include*:

**Evaluation of the safety and effectiveness of medical marijuana in subpopulations with specific indications considering comorbidities and concomitant medication use:**

- Prescription opioid use, manifestation of substance use disorder (SUD) and opioid overdoses (OD): this is a high-priority area for clinical care, public health and NIH, because of the unresolved challenges involving uncontrolled chronic pain, related mental comorbidities and detrimental trajectories to SUD and OD. The role of MMJ – whether a viable alternative or supplement to standard pain management strategies or contributor to SUD and ODs – is not understood and likely the highest priority for research.
- Risk for car crashes and driving citations, falls, fracture and other traumatic injury: these questions don't only address regulatory needs but also important safety concerns, especially in high-risk populations. For example, evaluation of the impact of MMJ on falls and fractures is particularly important in elderly patients, the age group with the strongest growth in opioid ODs in recent years. Fractures are strongly linked to mortality in elderly patients and quantification of fracture risk is therefore critical for risk benefit considerations.
- Changes in hospitalizations for seizures (in patients with epilepsy), severe anxiety (in patients with post-traumatic stress disorder) and other potential benefits of medical marijuana in defined subpopulations (especially pediatric populations); evidence on MMJ effectiveness lags behind its rapidly growing uptake, which calls for rigorous evaluations. Using control populations with similar disease history, these studies can evaluate improvements in clinical outcomes attributable to MMJ.
- Pregnancy complications and adverse pregnancy outcomes: one recent cross-sectional study in Colorado, which relied on mothers' self-report of marijuana use has raised concerns about effects on fetal growth. MEMORY can enhance such assessments with more granular exposure data to MMJ and superior capture of disease history of user and non-user groups to isolate effects of MMJ (and MMJ types) on the fetus and related pregnancy outcomes.
- Risk for severe psychosis, cognitive problems and other potential side effects of MMJ overall and among vulnerable populations such as children and elderly: this set of studies will follow up on previous case reports or small controlled studies on side effects, including assessments of patients' predisposition and other risk factors. Regarding smoking, short-term studies can assess risk for persistent cough or deterioration of symptoms among patients with asthma or COPD, while longer-term studies will address associations with cancer. This will allow development of recommendations for conditions where MMJ is contraindicated or used with caution, similar to FDA's drug labelling.

**Evaluation of mechanisms and variation in outcomes related to MMJ product, dose, route, and interactions with other drugs or patient characteristics (e.g., genomics, comorbidities).**

- This set of studies will join clinical outcomes researchers with faculty in pharmacology and chemistry to help characterize the variation in both beneficial and harmful MMJ outcomes. For example, active ingredients can vary tremendously across plant species, horticultural conditions, product manufacturing, dose, and route and their clinical effects can be further modified by patient characteristics and comedications. Established relationships between CoDES and CPSP and CPGx faculty as well as collaboration with the CTSI TDDC will allow targeted comparisons of MMJ effectiveness by a variety of product, use and patient characteristics.

- A set of studies that evaluate the mechanistic and clinical effects of marijuana's role in the interaction between pain and addiction. These studies will take advantage of a new research collaboration that has formed around a large NIDA center grant proposal and is currently jumpstarted by a grant of $600,000 through UF Moonshot Initiative: the Center for Research to Investigate Substance Use and Pain (CRISP). CRISP includes researchers in basic and clinical pharmaceutical sciences with the explicit goal to combine approaches to understand relationships between pain and addiction and to identify optimal treatment approaches that consider both. Dr. Winterstein who co-directs the CRISP Clinical Core co-leads one pilot study that evaluates the interplay between drugs (including marijuana) and patient characteristics among patients who present with opioid overdoses in the ED.

**Dr. Cook's research program** is characterized by prospective approaches to assess drug effects, including multi-site randomized clinical trials and prospective cohort studies. Ongoing projects related to marijuana and health outcomes are described above. Together with Dr. Wang, Dr. Cook is currently working on one new NIH grant application and will welcome involvement from other investigators across the state. Specifically, he proposes a large, 5-year study to understand whether or not MMJ improves outcomes related to chronic pain in older adults in Florida. In addition to both subjective and objective measures of pain, the research will evaluate the impact of MMJ on overall functioning and quality of life, symptoms of anxiety and insomnia, and cognitive functioning. The team plans to use biomarkers such as telomere length to examine how long-term exposure to MMJ changes stress system function, as an objective measure of effects on overall functioning and aging. Finally, the research will seek to understand whether certain types of MMJ (including smoking) will have more benefits or side effects than others. This proposal is focused on the enhancement of efforts to combat the opioid crisis while ensuring adequate management of pain. Despite the generally accepted promise in the use of MMJ to reduce opioid addiction and alleviate withdrawal symptoms, there is little evidence to support this assumption. Our collaborations with industry partners will also evaluate whether mobile technology can improve outcomes related to opioids.

Another important focus for future research funding will be the assessment and potential improvement of clinical care delivery related to MMJ. Currently, MMJ healthcare is occurring separately from other healthcare in most of Florida, exaggerating concerns about fragmented care. Interventions that provide for more frequent assessments or patient feedback on signs and symptoms, or that help to provide additional information to providers could aid providers in tailoring their assessments and treatment plan to patient characteristics that may alter MMJ effects (as investigated within MEMORY). With engagement of our MMJ provider group, we will seek funding for research that seeks to maximize the health benefits, while minimizing side effects, for those using MMJ in Florida.

**Public-private partnerships**. While we are not aware of current active mechanisms for external funding from the private sector, we will also plan to pursue non-federal grant opportunities to support the Consortium research agenda. Through our proposed framework of collaboration, we will explore the involvement of marijuana trade associations and private organizations interested in investing in clinical research. The University of Florida has experience in these endeavors and has been successful in securing continued funding from public-private partnerships. For instance, HCV-TARGET, co-led by Dr. Nelson at UF, is a prospective cohort of over 12,000 patients treated for hepatitis C. The data repository was created as a partnership between academia, seven industry partners, FDA and the community to improve clinical outcomes information about patients underrepresented in pre-approval clinical trials and facilitate real-world evaluations of treatment safety and effectiveness. HCV-TARGET has generated more than $60 million in funding, has generated a number of scientific papers that have shaped clinical treatment guidelines and has been awarded the FDA-CDER Civilian Honor Award for Regulatory Science Excellence, recognizing outstanding public-private partnership leveraging real-world evidence to enhance the safety and effectiveness of HCV treatment. The University of Florida has specific resources to help researchers and companies compete jointly for proposals such as the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) funding programs. The NIH also has a system of supporting academic partnerships with emerging commercial enterprise

## Collaboration

### 1. Examples of lead functions on state- or nation-wide research consortia

*(Provide any examples of consortiums and/or research groups for which the institution serves as a lead institution.)*

As the State's Flagship University and designated as land-grant university, sea-grant university, and space-grant university, the University of Florida is at the forefront of research innovation in the United States. The following provides examples of consortia where UF and UF Faculty serve as leads for state-wide, national, and international research collaborations across *health-related* research areas. These accolades highlight the prime position of UF as lead institution in research collaborations and as coordinating center for biomedical research.

The **OneFlorida Clinical Research Consortium** is a complex and robust research infrastructure to address some of Florida's biggest health challenges. Led by Dr. Shenkman and Dr. Nelson who also direct the UF CTSI, OneFlorida is one of the nation's 13 clinical data research networks supported by the Patient-Centered Outcomes Research Institute (PCORI). Core of OneFlorida is its vast electronic health data repository from 22 hospitals and 1,240 practice/clinic settings throughout the state.

The **Southern HIV & Alcohol Research Consortium (SHARC)** The Southern HIV and Alcohol Research Consortium (SHARC, Director: Robert Cook) is one of the five NIH-funded national Consortia for HIV/AIDS and Alcohol Research Translation (CHAART). SHARC leads several large research projects (including MAPLE) in Florida in collaboration with several universities (e.g., USF, UCF, FSU, FIU, UM) and public health agencies (e.g., DOH). SHARC also holds annual conference to bring together partners across the state to share research findings and important updates in the area of HIV and substance use.

Led jointly by Dr. David Nelson at the University of Florida and Dr. Michael Fried at the University of North Carolina at Chapel Hill, the **Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET)** is an international research consortium created to inform the ongoing transformation of hepatitis C treatment and research. HCV-TARGET includes 104 academic and community sites in 31 states, Puerto Rico, Canada and Europe as well as partnerships with multiple industry sponsors, the FDA and patient advocacy groups.

The **Florida Climate Institute** (FCI) is a multi-disciplinary network of national and international research and public organizations, scientists, and individuals concerned with achieving a better understanding of climate variability and change. The FCI is led by an executive board consisting of two faculty from each of the ten member universities in Florida. The University of Florida currently serves as the FCI host institution and coordinates the central operational duties. The FCI brings together over 400 individual affiliates.

The **1Florida Alzheimer's Disease Research Center** (ADRC) is a National Institutes of Health-funded University of Florida-led consortium of institutions including Mount Sinai Medical Center, the University of Miami, Florida Atlantic University and Florida International University. Over 40 affiliated faculty members work together to conduct research around Alzheimer's disease.

The **Florida Consortium on the Neurobiology of Cognition** (FCNC), led by UF faculty, was established in 2016 by researchers from Florida International University, Florida State University and the University of Florida. Consortium members conduct multidisciplinary and state-of-the-art neuroscience research integrating pharmacology, cellular and molecular neuroscience, in vivo neurophysiology, and anatomical and functional magnetic resonance imaging in a variety of model systems.

The **Southeast Regional Center of Excellence in Vector-Borne Disease**, housed with the Emerging Pathogens Institute (EPI) at UF, was funded in 2016 by the Centers for Disease Control. UF collaborates with the University of Miami, Florida International University and the University of South Florida on research to address the statewide challenge of Zika and other diseases. Another large UF-led consortium, also based in EPI and partnering with Florida DoH and FDACS is the **NIOSH Southeastern Coastal Center for Agricultural Health and Safety**, which has collaboration with USF, FAMU, FSU, Emory, and University of the Virgin Islands, with responsibilities that cover FL, MS, AL, GA, NC, and SC – and the U.S. Virgin Islands and Puerto Rico.

## 2. Plans for engagement of SUS and private institutions

*(How does the institution plan to engage other SUS institutions and private institutions in the Consortium?)*

The UF MMJ-COR has developed a comprehensive communication plan that will establish a Consortium website and quarterly newsletters, which will be disseminated to Consortium members and others interested in MMJ Clinical Outcomes Research throughout the state (see Collaboration #5). Initially, to launch the Consortium, UF will reach out to

the presidents of all public and private universities in the state to invite their participation. The invitation will include a synthesis of UF's proposal to emphasize the resources made available to Consortium members including the proposed grants program, and a copy of Section 1004.4351, Florida Statutes. Per statute, each participating university will select a representative for the MMJ Research Board, who will need to have experience in a medical or scientific field relevant to MMJ clinical outcomes research. Once identified, board members will become an important communication channel between the UF MMJ-COR and Consortium members, which will be defined as all interested researchers within the participating universities.

Consortium members will be engaged through a communication platform that provides relevant and up-to-date information about MMJ research in the state and nationwide and through access to a variety of unique resources:

- MEMORY – the MMJ Clinical Outcomes Research Repository, which will be available to Consortium members
- The MMJ Clinical Research Core, including access to the MMJ Provider Group for patient recruitment, connections to industry partners and research collaborators, and access to research support services provided by the participating CTSIs (UF, UM and FSU).
- The MMJ Expert Group, uniquely assembled to represent recognized experts in a broad area of MMJ research
- The Consortium grant program that awards pilot funding for MMJ clinical outcomes research studies.

We anticipate that especially the grants program, which is proposed to avail $600,000 in research funding annually, will be attractive to many researchers in the state and enhance their engagement in and contribution to the Consortium.

## 3. Plans for engagement of institutions not permitted to possess, test, transport or lawfully dispose of marijuana for research purposes

*(Please include specific examples of how the institution would engage and collaborate with other institutions that are not permitted to possess, test, transport, and lawfully dispose of marijuana for research purposes (section 381.986(14)(h), Florida Statutes) on their campuses.)*

While the Consortium will build infrastructure for experimental studies, the currently proposed focus of Consortium activities to support research is on the conduct of observational studies, i.e., studies of patients who elect to use MMJ outside of a formal research protocol. Such research is feasible regardless of respective licensure and can be conducted by all Consortium members. This includes use of MEMORY for retrospective observational studies and recruitment of prospective cohorts of MMJ users through our MMJ Provider Group and supported by the Clinical Research Core.

Because one core Consortium activity is to connect researchers in the field, we also anticipate that researchers from universities with less developed research infrastructure will be able to form new collaborations that can greatly enhance their scientific reach and ultimately enhance the state's prominence in the field of MMJ clinical outcomes research. The clinical core will also seek to provide guidance and infrastructure for conduct of clinical trials. In future program years, should UF build a MMJ clinical research facility including relevant regulatory approvals, we will ensure that this facility is available to other consortia members.

## 4. Plans to foster collaboration with teaching nursing homes

*(Describe any plans the institution has to foster collaboration between the Consortium and teaching nursing homes as outlined in section 1004.4351?)*

Per the Florida Agency for Health Care Administration (AHCA) and pursuant to section 430.80, there is currently one institution designated as a teaching nursing home in the state (Morse Life in West Palm Beach). Initial conversations with Morse Life suggest great interest in collaboration and engagement in research. The institution, which currently has more than 300 patients whose care is funded by Medicaid or Medicare, recognizes constraints in use of MMJ based on federal law and is seeking opportunities to help enhance our understanding of MMJ effectiveness and safety in this particularly vulnerable population. The CEO states that many of their patients are using MMJ privately.

UF MMJ-COR will continue communication with Morse Life and other nursing homes in the state to understand research needs specific to their patient population and to explore participation in recruitment efforts for geriatric-focused research studies. Through its outreach efforts, the Consortium will also offer to connect teaching nursing homes with geriatric researchers to support applications for research funding to the Consortium.

## 5. Plans to foster medical marijuana research collaborations in the state

*How could the Consortium foster medical marijuana research collaborations in the State of Florida?*

The Consortium will utilize a comprehensive communication plan that aligns with its goals for research, training, and collaboration and that will focus on outreach to researchers, providers, patients and other stakeholders. Our proposed multipronged communication and dissemination strategy will make use of our institution's proven track record of designing, building, and marketing online educational and research programs. We will create a **website** that will comply with best practices of online content design and navigation. Our website will contain up-to-date information on ongoing projects, training opportunities, dynamically generated and automated listings of relevant publications along with relevant information for patients, embedded social media feed, and relevant links for the State of Florida current regulatory information on MMJ and other relevant resources. Seminars and other presentations will be recorded and shared as well. To foster collaboration, the website will also include a searchable database of research expertise among Consortia members, identify providers willing to participate in research throughout the state, and provide updates on research activity within the state and relevant to the state. To ensure that content is updated and accurate, we will develop Communications Policies in consultation with the Board and analyze website traffic with Google Analytics.

As headquarters for the Consortium, we will share relevant content with Consortium members and interested parties with a **quarterly newsletter**. The newsletter will highlight decisions by the Board, research conducted by consortia members, new information available on the web site, and discuss upcoming events that could be opportunities for researchers to network and form collaborations. For example, as described previously, UF MMJ-COR will represent the Consortium at state-wide or national conferences through exhibit tables, round tables or workshops with an initial plan to participate in the Annual Meeting of the American Medical Marijuana Provider Association in Orlando (scheduled for October 2019).

In order to have an adequate response to emerging issues in the field of MMJ and provide accurate and timely information to the media and stakeholders, UF MMJ-COR will include a communications expert that will implement our comprehensive communications plan. As the consortium grows, we imagine that future years could include an Annual Conference of the Consortium for MMJ Clinical Outcomes Research, which would be open to researchers, providers and patients. Researchers funded through the Consortium would be expected to present their work at the conference, but others would be invited to submit proposals for presentation. Additional program elements may include a keynote speaker representing a prominent researcher in the field and disease-specific roundtables that allow researchers, providers and patients to connect. The goal of the conference would be to promote the consortium to researchers to stimulate collaboration and enhance MMJ research output, and to facilitate close interaction between researchers, providers and patients to unveil pressing research needs.

# Budget

## 1. Budget justification

We propose a budget that balances development of research infrastructure, outreach activities and direct monetary research support to optimize impact of the Consortium across the state. The following provides relevant budget detail.

**Salaries and benefits.** The budget includes funds for a total of 0.9 FTE (10.8 calendar months) faculty time to lead the UF MMJ-COR. This includes 0.3 FTE (3.6 calendar months) for Dr. Winterstein who will serve as director and assume primary responsibility for all administrative tasks, development of MEMORY and administration of the grants program; 0.2 FTE (2.4 calendar months) for Dr. Cook who will lead the Clinical Research Core, the Expert Group and the Consortium outreach efforts; and 0.2 FTE (2.4 calendar months) each for two additional faculty members trained in epidemiology and big data methods to support development of MEMORY and the Clinical Research Core. They are supported by 3 FTE (36 calendar months) divided across: a program administrator devoted to supporting all board functions and communication, regulatory agreements, development of meeting materials and reports and coordination of MMJ-COR; a communication specialist devoted to development of website content, the quarterly newsletter, conference exhibit materials and other outreach efforts; and a data analyst for MEMORY data curation and cohort development.

**Other personal services**. Budget allocated for other personnel includes two research fellows; one fellow will have clinical and epidemiologic training and will support development and validation of MEMORY variables, draft documentation for

the data dictionary and conduct descriptive analyses; the other fellow will assist with the development and conduct of research infrastructure and writing papers with data from the consortium and related projects. This budget item also includes $50,000 for the MMJ Expert Group, which may include faculty members from UF and other universities. Expert group members will receive up to $5,000 honorarium to develop written assessments of research priorities for board consideration and provide expert feedback to the board.

**Grants program.** A total of $620,000 are reserved for the Consortium grants program with an anticipated $20,000 for honoraria for out-of-state grants reviewers. Depending on the number of grant applications the allocation for honoraria might require readjustment. Grants will be awarded by the board to Consortium members who have responded to a call for applications.

**Electronic data processing.** Cost for data processing include funds for staff to link registry data to the OneFlorida Data Trust ($50,000) and $5,000 for the CoDES computing infrastructure including cost for relevant software licenses, research server support and data recovery.

**Website design and maintenance**. A total of $15,000 are budgeted for Consortium website development and maintenance.

**Conference travel, exhibits & publications**. A total of $25,000 are budgeted to support travel and costs for exhibits and exhibit materials at state-wide conferences to promote the Consortium; $900 are budgeted for 3 trips to Tallahassee to meet with legislators or OMMU staff; additionally $5,000 are budgeted for open access fees for publications about Consortium work in scientific journals.

**Board meetings.** Cost for 2 annual board meetings in Gainesville include reimbursement of board member travel expenses ($10,000) and event costs ($8,000).

**MMJ Provider Survey**. A total of $20,000 is budgeted for development, administration and data analysis of a survey to MMJ providers. This will involve the creation of an online database, distribution of the survey, data analysis, and writing a manuscript and update for the web site.

**Expenses**. Administrative / operating costs are charged at 12.5% for a total of $110,000. The base for the calculation of these expenses excludes funds allocated for the grants program in anticipation that a large portion of these funds will be passed on to other universities in the Consortium.

## 2. Organizational and physical location of the Consortium UF staff

UF Program on MMJ Clinical Outcomes Research (MMJ-COR) includes a director (Winterstein), an associate director (Cook), staff members and select faculty to support specific functions. Dr. Winterstein will develop and oversee MEMORY, lead the grants program and all administrative functions, while Dr. Cook will take responsibility for development of the Clinical Research Core, organize the expert group and lead the Consortium's outreach effort.

The UF MMJ-COR will be housed organizationally within the Clinical and Translational Science Institute (CTSI), which offers the broadest reach to health scientists and the most comprehensive set of resources to support the Consortium. The Data Repository MEMORY will be developed and maintained in the Center for Drug Evaluation and Safety (CoDES), taking advantage of its existing infrastructure in development and use of big data sets for the evaluation of medical treatments. The MMJ Clinical Research Core will be housed within the CTSI. CTSI will provide an annual contribution of $50,000 to be used for personnel to support UF MMJ-COR functions.

Dr. Winterstein is chair and professor in the department of Pharmaceutical Outcomes and Policy within the College of Pharmacy and affiliate faculty in the department of Epidemiology in the Colleges of Medicine and Public Health and Health Professions. She also serves as director for CoDES and as director for Regulatory Sciences within the CTSI. Dr. Cook holds a joint appointment as professor in the department of Epidemiology and the department of Medicine in the College of Medicine and is director of SHARC. Dr. Winterstein's office is located in the HPNP building, while Dr. Cook is located in the CTSI building, both located on the health science campus. Their offices are in 5-minute walking distance. CTSI will provide office space for center staff in close proximity to ensure effective collaboration. It is anticipated that MMJ-COR staff will transition into the new UF Data Science Building once completed.

**Education and General**
**Position and Fiscal Summary**
**Operating Budget Form II**

**University:** **University of Florida**
**Issue Title:** **Lead Institution for the Consortium for Medical Marijuana Clinical Outcomes Research**

| | RECURRING | NON-RECURRING | TOTAL |
|---|---|---|---|
| Positions | | | |
| Faculty | 0.90 | | 0.90 |
| Other (A&P/USPS) | 3.00 | | 3.00 |
| Total | 3.90 | | 3.90 |
| Salary Rate (for all positions noted above) | | | |
| Faculty | $167,656 | $0 | $167,656 |
| Other (A&P/USPS) | $190,000 | $0 | $190,000 |
| Total | $357,656 | $0 | $357,656 |
| Salaries and Benefits | $467,718 | $0 | $467,718 |
| Other Personal Services | $162,100 | $0 | $162,100 |
| Grant program | $620,000 | $0 | $620,000 |
| Operating Capital Outlay | $0 | $0 | $0 |
| Electronic Data Processing | $55,000 | $0 | $55,000 |
| Website design & maintenance | $15,000 | | $15,000 |
| Conference travel, exhibits, publications | $30,900 | $0 | $30,900 |
| Board meetings | $18,000 | $0 | $18,000 |
| Provider survey | $20,000 | | $20,000 |
| Expenses | $110,000 | $0 | $110,000 |
| Total All Categories | $1,498,718 | 0 | $1,498,718 |

UFHealth
UNIVERSITY OF FLORIDA HEALTH

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May 9, 2019

Almut Winterstein, PhD
Chair of Pharmaceutical Outcomes & Policy
University of Florida

Dear Dr. Winterstein:

UF has been involved in the administration and evaluation of the Florida Medical Marijuana Program since its inception and is well-prepared to leverage its extensive research infrastructure and broad faculty expertise to contribute to the urgently-needed evidence to support the safe and effective use of medical marijuana (MMJ) in the state of Florida. The UF Program on MMJ Clinical Outcomes Research (MMJ-COR) will be organizationally housed in the UF Clinical Translational Science Institute (CTSI), which will provide its full spectrum of services to support researchers in the MMJ Clinical Outcomes Research Consortium. This will include up to $50,000 salary support and office space for MMJ-COR research personnel. UF CTSI will be joined by the CTSIs at the University of Miami and at Florida State University who have likewise pledged to provide their support infrastructure and services to Consortium researchers.

In line with the goals of your proposal, the CTSI undertakes transformational initiatives and provides services and resources to facilitate health research in any disease area and to advance knowledge across the translational spectrum – from laboratories to health-care settings to the public health and policy arenas. As a catalyst and hub connecting resources, people and ideas, the CTSI expands collaboration and advances science across UF's 16 colleges, the state of Florida and the national Clinical and Translational Science Award consortium. Our CTSIs will provide MMJ researchers with access to their extensive research infrastructure, pilot funding mechanism, and connections to our University's talented research extertise, which is aimed at jump starting research studies for future NIH funding. The CTSI will facilitate rapid activation of research for investigators performing translational research across campuses and provides a range of research services and resources that may be valuable to the implementation of the MMJ-COR pilot studies.

There is an urgent need to conduct research related to the emerging marijuana and cannabis market in Florida. Persons seeking MMJ are suffering from serious health conditions and symptoms, many of which are not responsive to traditional medications. While MMJ could potentially improve health outcomes, there are also significant safety concerns and lingering questions about dosing regimen, differences in marketed products and their interaction with other medications and patient comorbidities.

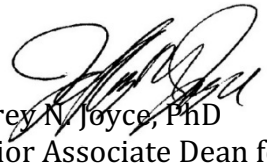
Based on my personal experience in overseeing the development of the OneFLorida Clinical Research Consortium and HCV-Target, both data repositories that facilitate large-scale clinical outcomes research, I am particularly excited about the planned development of MEMORY, the proposed MMJ Clinical Outcomes Research Repository. MEMORY along with the comprehensive research infrastructure and outreach activities put forward by the Consortium will allow answering some of the most pressing questions for personal, clinical and regulatory decision-making surrounding the risk-benefit and appropriate use of MMJ in the state.

This letter reflects the high priority that UF and our statewide CTSI partners place on MMJ clinical research, and the concomitant advantages it will provide to the state of Florida and our respective universities. You have our enthusiastic collective support in pursuit of this important project.

Sincerely,

David Nelson, MD FAASLD FACG
Senior Vice President for Health Affairs
President, UF Heath
Director, Clinical and Translational Science Institute
University of Florida

Ralph L. Sacco MD MS FAHA FAAN
Professor and Olemberg Chair of Neurology
Senior Associate Dean for Clinical & Translational Science
Executive Director McKnight Brain Institute
Director, Miami Clinical and Translational Science Institute
University of Miami Leonard M. Miller School of Medicine
President, American Academy of Neurology 2017-19



Jeffrey N. Joyce, PhD
Senior Associate Dean for Research and Graduate Programs
College of Medicine
Florida State University

FIU | Research & Economic Development

FLORIDA INTERNATIONAL UNIVERSITY

May 9, 2019

Almut Winterstein, PhD
Chair of Pharmaceutical Outcomes & Policy
University of Florida

Dear Dr. Winterstein:

FIU has a long history of research regarding the etiology and consequence of substance abuse, as well as the treatment of addictions. Regarding marijuana, we have various research teams across our Academic Health Center with expertise and a track record of funding from the National Institutes of Health. One such project is the Adolescent Brain Cognitive Development (ABCD) Study, a national study, which seeks to establish how diverse patterns of Substance Abuse impact the structure and function of the developing brain. The ABCDC is a national study with 21 sites, which includes both UF and FIU (Co-Principal Investigators at FIU are Drs. Raul Gonzalez and Angela Laird). Thus, we already have a track record of collaboration in the area of substance abuse.

Two other notable large research programs focusing on marijuana use are an Endowment Grant from the National Institute on Minority Health and Health Disparities (NIMHD), and a Research Center for Minority Institutions (also funded by NIMHD), which focuses on research addressing health disparities associated with substance use.

The research listed above are illustrative of a series of population-based studies that are ongoing and that are engaging and enrolling participants from throughout South Florida. In addition, there are new groups of faculty in our Academic Health Center with research interests in the subject of medical marijuana. These researchers are partnering with potential private sector partners and donors that have interest in disease-specific applications of medical marijuana.

There is an urgent need for the State of Florida to conduct research in the emerging marijuana and cannabis market and its medical applications. We, at FIU, are supportive of your proposal in response to the call from the Florida Board of Governors for the establishment of a Consortium for Medical Marijuana Clinical Outcomes Research. We enthusiastically agree to be a partner in the Consortium, with the expectation of aligning collaboration within the Consortium.

I believe that the establishment of MEMORY, the MMJ Clinical Outcomes Research Repository, will be a catalyst to foster collaborative research in the State of Florida in the area medicinal use of marijuana, and thus benefit the people of the State of Florida.

This letter reflects FIU's enthusiastic support of your proposal to the BOG, and FIU's commitment to be an active partner in the Consortium. I wish you success with the proposal and look forward to the resulting future collaboration.

Sincerely,

Andrés G. Gil, Ph.D.
Vice President for Research & Economic Development,
Dean, University Graduate School