**PROTOCOL TITLE:**
Medical Marijuana Use and Driving Performance: A Test of Psychomotor Function in Adults 50 and Older**.**

# INVESTIGATORS:

## Florida State University:

Principal Investigator
Nicole Ennis, PhD
Florida State University
Department of Behavioral Science and Social Medicine
850-644-7955
nicole.ennis@med.fsu.edu

Study Coordinator/Participant Data Collection
Caitlyn Kloss, BA
Florida State University
Department of Behavioral Science and Social Medicine
caitlyn.kloss@med.fsu.edu

Research Assistant
Colleen Beichner
Florida State University
Department of Behavioral Science and Social Medicine
colleen.beichner@med.fsu.edu

Research Assistant
Marielise Torres
Florida State University
Department of Behavioral Science and Social Medicine
marieliese.torres@med.fsu.edu

## University of Florida:

Co-Investigator/Driving Simulator Development
Sherrilene Classen, PhD, MPH, OTR/L, FAOTA, FGSA
University of Florida

Co-Investigator/Pharmacist/Drug-Drug Interaction Expert
John Markowitz, Pharm D, BCPP
University of Florida

Co-Investigator/UF Research Coordinator
Nichole Stetten, PhD, MPH, CPH
University of Florida

Driving Simulator Manager
Jason Rogers
University of Florida

PROTOCOL TITLE: Medical Marijuana Use and Driving Performance: A Test of Psychomotor Function in Adults 50 and Older.

## VERSION NUMBER/DATE:

version 3/6.27.2022

## REVISION HISTORY

| Revision # | Version Date | Summary of Changes | Consent Change? |
|---|---|---|---|
| 2 | 2.8.22 | Added Colleen Beichner and Mariliese Torres; removed Abbey Folsom | No |
| 3 | 6.27.22 | Added i2b2 | No |
| 4 | 7.20.22 | Remove i2b2; added Consent2Share | No |

## Table of Contents

# 1.0 Study Summary

| | |
|---|---|
| **Study Title** | Medical Marijuana Use and Driving Performance: A Test of Psychomotor Function in Adults 50 and Older |
| **Study Design** | We will use a naturalistic observational trial design to compare psychomotor function at baseline (in the week prior to starting medical marijuana) as well as 1 month and 3 months post-medical marijuana initiation. |
| **Primary Objective** | Simulated driving performance (i.e., errors in response time, attention, and executive functioning tasks that predict on-road performance) |
| **Secondary Objective(s)** | Adverse effects |
| **Research Intervention(s)** | Medical marijuana |
| **Study Population** | Adults 50 and Older |
| **Sample Size** | 60 |
| **Study Duration for individual participants** | 3 months and 1 week |
| **Study Specific Abbreviations/ Definitions** | MMTC = Medical Marijuana Treatment Clinics of Gainesville |

## 1.1 Abstract

1.1.1 Background: Approximately 6.9 million people in the State of Florida are aged 50 and older. Further estimates of chronic pain in this population ranges from 35-52%. Of the 33 states (including Florida) with laws that legalize marijuana for medical use, chronic pain, a condition with greater prevalence in mid to late life, is recognized as a common ailment for which physicians prescribe medical marijuana. However, little is known about marijuana use during late-middle age (ages 50–64) and older adulthood (ages 65 and older). While medical marijuana may benefit older adults by reducing pain, factors such as how use may affect everyday functioning during real world tasks such as driving is underexamined. To date, a study that examines older adults' pre-exposure to medical marijuana and systematically tracks medical marijuana initiation, dosage, and psychomotor functioning has not been done.

1.1.2 Method/Design: This protocol describes an assessment of Medical Marijuana Use and Driving Performance: A Test of Psychomotor Function in Adults 50 and Older. Sixty participants will be recruited from Medical Marijuana Treatment Clinics (MMTC) of Gainesville. The intervention group will be comprised of adults 50 and older who report severe or chronic pain, are newly registered for the Medical Marijuana Registry in the State

of Florida, have no prior history of medical marijuana use, can communicate in English, and are willing and able to complete study procedures. The control group will be age, gender, and race matched. The primary study outcome is simulated driving performance (i.e. errors in response time, attention, and executive functioning tasks that predict on-road performance). Secondary outcomes include adverse effects.

1.1.3 Expected Value: Currently, there is limited scientific data on how medical marijuana affects psychomotor functioning in real world situations among those 50 and older. Further, extant literature suggests that certain factors (i.e. dosage, frequency, CBD/THC content, and route of administration) may be associated with greater risk of adverse effects for older adults. While some evidence suggests that marijuana is beneficial for pain, other evidence suggests that marijuana use may be associated with slowed response time, poor attention, and poor executive functioning. Physicians, patients, and policy makers need data-driven guidelines for medical marijuana use in older adults, a prevalent population in the State of Florida. To that end, the National Institute on Drug Abuse has called for data on medical marijuana in adults 50 and older specifically. The long range goal of this work is to improve our understanding of the consequences of medical marijuana use in later life and to facilitate the development of best practice guidelines for adults 50 and older.

## 2.0 Objectives*

2.1 The specific aims for the current project are:

**Aim1:** Test the association between medical marijuana use and driving errors that predict on-road performance on a high-fidelity driving simulator in adults 50 and older with chronic or severe pain.

**H1a:** We hypothesize that medical marijuana use will be associated with slower response time in a driving performance task.
**H1b:** We hypothesize that medical marijuana use will be associated with poorer divided attention in a driving performance task.
**H1c:** We hypothesize that medical marijuana use will be associated with poorer executive functioning in a driving performance task.

**Aim2:** Examine the association between medical marijuana use factors (dosage, frequency, CBD vs. THC products, and route of administration) and adverse effects in adults age 50 and older.

**H2a:** We hypothesize that higher dosage and frequency of administration will be associated with greater adverse effects.
**H2b:** We hypothesize that THC-based products will be associated with greater adverse effects.
**H2c:** We hypothesize that products administered by vaporizer will be associated with greater adverse effects.

## 3.0 Background*

3.1 Prevalence of marijuana use has increased 300% in the last 10 years among those 50 and older, and this upward trend is expected to continue[22]. Marijuana initiation at age 50 and older has also increased exponentially due to changing cultural norms [23, 24]. In addition, prevalence estimates of chronic or severe pain in this population ranges from 35-52%, with some estimates as high as 74% [2-4, 25, 26]. In the United States, chronic pain is the most frequently endorsed reason for medical marijuana use [5, 10, 27].

Current research indicates that marijuana users may experience cognitive impairment in areas such as attention, executive functioning, and psychomotor speed [7, 19, 20, 28, 29]. Specifically, research has explored the effect of marijuana use on psychomotor skills, which are skills that combine thinking and movement. Researchers assessed psychomotor function on measures of critical tracking, attention, and reaction time, and findings indicated that cannabis usage created deficits in psychomotor function up to 3.5 hours after use, which is congruent with prior work [30, 31]. Impairments to psychomotor abilities have practical implications, as these impair an individual's ability to drive [30]. In a study that evaluated psychomotor function using the same critical tracking and divided attention tasks, Bosker et al. (2013) examined whether psychomotor functioning would improve, following abstinence among chronic, daily cannabis users[32]. Extending previous research[33], results of this study indicated that psychomotor function was impaired, but sustained abstinence (3 weeks) did improve psychomotor performance, which is consistent with other findings[19]. However, psychomotor performance did not completely recover to a normal performance as based on the control group. Solowij & Pesa (2010) extended this conclusion by suggesting that long-term marijuana use is also associated with impaired attention, inhibition, working memory, and verbal memory[20]. Furthermore, Nestoros & colleagues (2017) found that chronic, heavy cannabis use was related to general cognitive dysfunction[34]. Some researchers suggest that the aforementioned cognitive impairments may be due to the extent of changes in CB1 stimulation[35], while other studies indicate that cannabis composition may influence the type/severity of the marijuana-related cognitive impairment[16, 17]. Together, this lack of consensus indicates that further work is needed to understand if medical marijuana use creates a long-term impact on psychomotor functioning that impact real world tasks such as response time, attention, and executive functions—all critical for the task of driving. Further, clarity is needed regarding whether specific factors of marijuana use are associated with greater adverse effects in this population.

Research on psychomotor functioning in older adults generally uses cognitive assessment tools such as the Trails Making test which have limited real world application[36-41]. However, studies of driving performance using driving simulators have been shown to be a valid predictor of on-road driving performance[42-44]. Driving simulators allow for the systematic presentation of events and the manipulation of variables, which offers experimental control that is impossible on the road[43, 44]. Driving simulators also offer optimal stimulus presentation which

allows for analysis of both healthy and impaired drivers under similar conditions[42]. Therefore, using a driving simulator we can examine response time, attention, and executive functions using valid real world tasks[42]. Research shows that crash patterns for older adults are different [45, 46]. Older adults are more likely to be involved in crashes at intersections or during merges, and these crashes are inherently more fatal [47, 48]. The challenging, fast-paced environment presented by intersections and merges puts extra demand on cognitive, sensory, and motor domains applicable to driving; therefore, slower response time, inattention, and difficulty with executive functions may lead to more fatal crashes [48]. Therefore, how marijuana use influences driving performance needs to be examined, and the driving simulator is the safest option to do so.

## 4.0 Study Endpoints*

4.1 Simulated Driving Performance

Data will be collected via the kinematic functionality of the high-fidelity driving simulator (i.e., speed in mph, lateral lane positioning, braking, etc.) and also through observing the performance of the driver.

4.1.1 Response Time

Type: Primary
Time Frame: Baseline (T1), 1 Month (T2) and 3 Months (T3)
Brief Description: After the first 5-minute acclimation scenario, the driver will drive the main drive for another 15 minutes. The first 7 minutes of the drive will include daytime driving, start in a rural area with some ambient traffic, rolling hills, curves in the road, and include the occasional lead vehicle, oncoming traffic, and some vehicles behind the driver. Data will be collected via the kinematic functionality of the high-fidelity driving simulator (e.g. speed in mph, braking, swerving, lateral lane positioning, etc.) and also through observing the performance of the driver -- for yes/no responses – via a trained evaluator who will use the playback function of the simulator to scrutinize the errors. To assess response time, a vehicle is pulling out in front of the driver and the driver's behavior is measured via braking milliseconds (ms) and swerving (SD of lateral deviation from center lane).

4.1.2 Divided Attention

Type: Primary
Time Frame: Baseline (T1), 1 Month (T2) and 3 Months (T3)
Brief Description: Data will be collected via the kinematic functionality of the high-fidelity driving simulator and observation. During the course of the main drive consisting of straight residential roadways connecting 8 left turns and 2 right turns with minimal ambient traffic using an established protocol, during the course of the drive divided attention (being aware of the traffic and surrounding while focusing on critical stimulus) is assessed

via a diamond on the screen turning to a triangle and the participant needs to honk (i.e. respond) as soon as (s)he sees it (measured in ms and number of omissions and commissions).

4.1.3 Executive Functions

Type: Primary
Time Frame: Baseline (T1), 1 Month (T2) and 3 Months (T3)
Brief Description: The last 8 minutes of the drive starts in a residential area with low speeds (15-30 mph) and then progresses to city with speeds 30-45 mph. This part of the drive will occur in a suburban environment, daytime driving with minimal lead, following and oncoming traffic, and some pedestrians and cyclists. Streets will be surrounded by buildings and strip malls. Executive functions are measured by providing the driver with an instruction before the drive (e.g. to turn into a McDonald's, pull into a parking bay, park the car (vehicle positioning), and when it is safe to do so, back up out of the parking bay (visual scanning) exit the lot and merge into the flow of traffic. Executive functions are measured via visual scanning (yes/no), speed regulation (mph over or under the speed limit), adjustment to stimuli (notice the McDonald's (yes/no), slow down (mph), signaling (yes/no), vehicle positioning (buffer around the vehicle yes/no), and gap acceptance (narrow or tight via ms).

4.2 Adverse Effects

In this study, adverse effects are defined as undesired effect that occurs medication is administered. We will use Scripted Prompting, a proactive form of adverse effect capture recognized in the field[18]. This method is designed to elicit adverse effects without biasing the patient; it is a standardized question that allows participant to report important symptoms without being influenced by suggestion. For this study we will ask: *"Since initiating medical marijuana are you having any problems related to use?"*

To describe factors associated with adverse effects we will report the number of adverse effects reported by participants at time points 2 and 3. Adverse Effects will be defined as both a count variable and a binary variable such that absence or presence of adverse effects will be coded as 0/1 respectively. We will then use Poisson and Logistic regression methods to examine analyze the bivariate association between dosage, frequency of use, route of administration (pills, vape, etc.), and type of product (THC v. CBD). Limitations may be related to the frequency and distribution of events leading to complete or quasi-separation of data points. Possible mitigations would be re-categorization of explanatory variables, exact or firth regression, or a different functional form of the model.

**5.0 Study Intervention**

5.1 Type: Drug

Name: Medical Marijuana

Description: Medical marijuana is defined by Florida state statue 381.986 as all parts of any plant of the genus Cannabis, whether growing or not; the seeds thereof; the resin extracted from any part of the plant; and every compound, manufacture, salt, derivative, mixture, or preparation of the plant or its seeds or resin, including low-THC cannabis, which are dispensed from a medical marijuana treatment center for medical use by a qualified patient.

This protocol describes an assessment of Medical Marijuana Use and Driving Performance: A Test of Psychomotor Function in Adults 50 and Older. Sixty participants will be recruited from Medical Marijuana Treatment Clinics (MMTC) of Gainesville. The intervention group will be comprised of adults 50 and older who report severe or chronic pain, are newly registered for the Medical Marijuana Registry in the State of Florida, have no prior history of medical marijuana use, can communicate in English, and are willing and able to complete study procedures. The control group will be age, gender, and race matched. The primary study outcome is simulated driving performance (i.e. errors in response time, attention, and executive functioning tasks that predict on-road performance). Secondary outcomes include adverse effects.

## 6.0 Procedures Involved*

* NOTE: To minimize risk of exposure to COVID-19, we will initially only recruit participants age 50 and older. Any portions of the study that can be conducted via videoconference, such as the informed consent process, will be conducted via videoconference. HIPAA protected Zoom software provided by FSU will be used for videoconferences. FSU Qualtrics will be used for virtual informed consent. Participants who are consented virtually will be mailed a copy of the informed consent. Participants who are consented virtually will also be offered a copy of the informed consent when they arrive for baseline assessments. Appointments will be scheduled so that no overlapping appointments occur among participants in order to minimize exposure. No person who has been exposed to Coronavirus or who is at higher risk for severe illness may take part in our study. Severe illness means certain health conditions related to your heart, liver, or lungs, or if you have diabetes. Also, persons who live in nursing homes, have severe obesity, or who have immune disorders may not take part in this study. There may be other conditions, and this list may change.

We will ask some questions to see who may be at risk of severe illness. We will also ask people to see if they have been exposed to Coronavirus. If you think that you may been exposed to Coronavirus or have a severe illness, let us know. Study staff may or may not include licensed medical doctors, and may not be able to give you any medical advice on your Coronavirus risk. Please talk to your doctor if you have questions about your own risk. Information about persons who may be at risk can be found at the following website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html.

We will make sure that at all times everyone stays a safe distance from one another. This is called "social distancing." We follow the rules about use of equipment to protect you. This includes masks, gloves and other equipment. If needed we will supply these to you. You must wear these in order to take part in this part of the study. If study staff need to be close to you, we will take all the steps needed to protect you. We follow the rules about use of equipment to protect you. This includes masks, gloves and other equipment. If needed we will supply these to you. You must wear these in order to take part in this part of the study. If study staff need to be close to you, we will take all the steps needed to protect you. We will limit the number of people in any face-to-face activity. We will also limit the amount of time that anyone has a face-to-face activity. Only the least amount of people and time will be used in this study.

If at any time you don't feel safe with the steps that we will take to protect you, please let us know and we will stop. We want to be sure to answer your questions and to take any other steps that you feel we should take to protect you.

6.1 Recruitment/Sampling. We will recruit patients using from Medical Marijuana Treatment Clinics (MMTC) of Gainesville. Patients who complete the process of being entered into the medical marijuana registry and meet study inclusion criteria will be informed about the study during their initial visit to their prescribing physician. Recruitment for this study begins pre-medical marijuana exposure. Once a patient has obtained their official card from the state of Florida, the baseline assessment will be scheduled and completed prior to the patient's first dispensation of marijuana. After patients have filled their first prescription, we will track patients through MMTC and follow patients for 3 months post medical marijuana initiation, using both in person visits and EMR abstraction.

We will recruit N=60 participants total. Participants will be eligible for the current study if they: a) report severe or chronic pain; b) are age 50 or older; c) are newly registered for the Medical Marijuana Registry in the State of Florida; d) have no prior history of medical marijuana use; e) can communicate in English; and f) are willing and able to complete study procedures or if they meet control group criteria: (n=30) Medical Marijuana Users **or** (n=30) Age, Gender, Race Matched Controls. Persons will be ineligible if they: a) meet

criteria for current or past alcohol and/or illicit drug dependence; b) have vertigo or any vestibular systems dysfunction (due to the to develop simulator adaptation syndrome)[66]; c) screen high on the simulator sickness prescreen; d) use contraindicated medication (benzodiazepines, beta blockers, antihistamines, or sedatives) from which they cannot abstain due to medical reasons; and/or e) are planning to move out of the area within 6 months.

We will recruit patients in the control group within the local community. This will happen by placing recruitment flyers in public places (i.e. grocery stores, libraries, senior living communities, etc.). Additionally, we will utilize Consent2Share, an initiative of the UF Integrated Data Repository (IDR) and supported by UF CTSI (Clinical and Translational Science Institute) that allows for a large group of potential research participants who have consented to be re-contacted for future research studies. The control group will be matched by age, gender and race. Control subjects will be ineligible if they: a) meet criteria for current or past alcohol and/or illicit drug dependence; b) have vertigo or any vestibular systems dysfunction (due to the to develop simulator adaptation syndrome)[66]; c) screen high on the simulator sickness prescreen; d) use contraindicated medication (benzodiazepines, beta blockers, antihistamines, or sedatives) from which they cannot abstain due to medical reasons; and/or e) are planning to move out of the area within 6 months, f.) have a history of marijuana use. Control subjects will be used to ensure results are not attributed to a simple change in time. Results will provide evidence for the effects of medical marijuana use on the real work task among adults 50 and older.

6.2 Baseline Assessment Procedures. Once eligibility has been met, participants will be scheduled for their baseline assessment in the week prior to starting medical marijuana. At the baseline appointment, participants will be greeted by a study research assistant who will introduce the study and provide the patient with informed consent. We have standardized the informed consent procedure to ensure that participants not only understand the informed consent process but also fully understand what is being asked of them during the study period. Following informed consent, participants will complete the baseline assessment. The baseline assessment will consist of a battery of psychosocial measures, a cognitive test, a 5 minute simulator adaptation drive, and a 15 minute main drive. Adherence to simulator sickness protocol will be ensured before, during, and after the drives[66]. In an effort to maintain engagement, participants will be contacted via telephone 60 days post-baseline to complete a 3-item questionnaire regarding significant life changes as well as a pain scale. We will also request permission to extract needed data on an ongoing basis from patients' electronic medical records.

6.3 Training of Research Assistants. All study research assistants will be trained in Good Research Practices, Safety Concerns in Dealing with Patients, and Data Collection Procedures. The training will also cover 1) familiarization with study aims, instruments, and assessment procedures specific to the study; 2) confidentiality and informed consent, data integrity, and data security; 3) observation of mock assessment conducted by the project director; and 5) a

practice assessment with the project director. Research assistants will also receive "red flag" training on how to recognize and respond to danger to self and others, child abuse, elder/dependent adult abuse, and domestic violence.

Several procedures will help standardize data collection and encourage accuracy and honesty in reporting, as follows: 1) trained research assistants will conduct the assessments; 2) a private interview setting will minimize distractions and ensure confidentiality; and 3) research assistants will remind participants of the confidentiality of the information that they provide.

6.4 Methods and Procedures: We will use a naturalistic observational trial design to compare psychomotor function at baseline (in the week prior to starting medical marijuana) as well as 1 month and 3 months post-medical marijuana initiation.

Principal Investigator Dr. Nicole Ennis, a licensed clinical psychologist (Florida license PY7458), will serve as the clinical supervisor for this study. The clinical supervisor will oversee all data collection and intervene clinically if necessary. As a licensed clinical psychologist, Dr. Ennis is trained in all procedures of the current project's brief intervention and referral to treatment protocol.

6.5 Screening Measure. Self-report questionnaires will be use to discern eligibility. Eligibility will be confirmed using medical records at enrollment. Simulator sickness questionnaire will be administered before, during, and after the drive[67]. The Optec 2500 is a comprehensive vision screener designed to quickly and accurately test patients in a controlled environment. Screening conditions include monocular, binocular, near, far, distance, and intermediate. Tests performed include visual acuity, color and depth perception, contrast sensitivity to ensure results observed in the simulator are not due to visual limitations.

6.6 Medical Marijuana Exposure. We will track dosage, frequency, type of product used (CBD vs THC), and route of administration. We will not be instructing participants on the dosage, frequency, type of product used, and route of administration, we will be observing these variables through the self-report dispensary info provided by the state of Florida's Medical Marijuana Use Registry (MMUR). All medical marijuana participants will be recruited prior to medical marijuana exposure with the assistance of a qualified prescribing physician who is authorized by the State of Florida to determine eligibility and prescribe medical marijuana.

6.7 Driving Simulator. The simulator uses a high-fidelity RTI (Realtime Technologies, MI) configuration with a full car cab (4-door sedan) with seven visual channels. The three forward channels create a 180 degree field-of-view (FOV). This wide FOV is accomplished by connecting three flat screens with scenes provided by three high-resolution LCoS projectors. The rear scene is also projected on a flat screen and viewed through the in-cab rear-view mirror. The side-view mirrors and a virtual dash are simulated with LCD panels. Altogether the

visual channels form an immersive and realistic driving experience. A 5.1 channel audio system external to the car cab provides the environmental sounds such as traffic, passing vehicles, and road noise. An internal audio system to the car cab provides the engine sounds and vibrations, as well as pre-programmed voice commands and any other scripted sounds. A 4-door sedan allows the driver to operate normal accelerator, brake, steering, transmission selection, and signaling controls with the simulator responding accordingly. All driver inputs are controlled by software that interfaces with the electronics in the car cab. The adaptation scenario is standardized for older adults and has been used in our prior driving studies[68, 69]. The main drive consists of straight residential roadways connecting 8 left turns and 2 right turns with minimal ambient traffic. Three scripted events will be randomly presented to the drivers. To assess response time, a vehicle is pulling out in front of the driver and the driver's behavior is measured via braking (ms) and swerving (SD of lateral deviation from center lane). Next, divided attention is assessed via a diamond on the screen turning to a triangle and the participant needs to honk as soon as (s)he sees it (measured in ms and number of omissions and commissions). Lastly, executive functions are measured by providing the driver with an instruction before the drive (i.e. to turn into a McDonald's, pull into a parking bay, and when it is safe to do so, exit the lot and merge into the flow of traffic (measured via visual scanning (yes/no) speed regulation (mph over or under the speed limit), adjustment to stimuli (notice the McDonald's (yes/no), and slow down (mph), signaling (yes/no), vehicle positioning (buffer around the vehicle yes/no), and gap acceptance (narrow or tight via m/sec)[59, 60].

6.8 Adverse Effects: In this study, adverse effects are defined as undesired effect that occurs when the medical marijuana is administered. We will use Scripted Prompting, a proactive form of adverse effect capture recognized in the field[70, 71]. This method is designed to elicit adverse effects without biasing the patient; it is a standardized question that allows participant to report important symptoms without being influenced by suggestion. For this study we will ask: *"Since initiating medical marijuana, are you having any problems related to use?"*

6.9 Control Procedures: Control participants will be community-dwelling age, race, and gender matched.

6.10 Participant Retention: We will develop a strong collaborative relationship between participants and members of the research team through empathy, encouragement and skill building.

6.11 Three- and Six-Month Follow-Up Assessment: The second assessment (T2) will occur one month after the participant has been dispensed medical marijuana for the first time. T3 will occur 3 months after the participant has been dispensed medical marijuana for the first time. The follow-up assessments will consist of a minimally reduced psychosocial assessment battery, and the same simulator adaptation and main drive (described above). All participants will be paid $50 per assessment visit ($150 total across all visits over the 3 month period). Participants

will not be paid for screening assessments or chart abstracted data. Data will be collected using both self-directed methods such as ACASI with headphones or self-administered on paper and Research Assistant administered tasks. The Baseline Assessment is expected to take approximately 90 minutes, and follow-ups will take approximately 60 minutes. Though it is time-consuming, we do not anticipate participant barrier as a burden based on prior work.

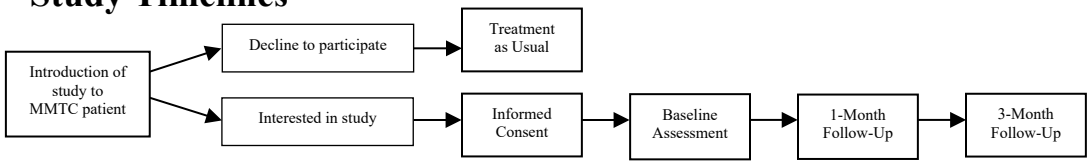
## 7.0 Data and Specimen Banking*

N/A.

## 8.0 Sharing of Results with Subjects*

N/A.

## 9.0 Study Timelines*




9.1 Each subject will be enrolled for a total of 3 months and 1 week. The duration anticipated to enroll all study subjects is 12 months.

## 10.0 Subject Population*

10.1 We will recruit 60 patients from Medical Marijuana Treatment Clinics (MMTC) of Gainesville. The intervention group will be comprised of adults 50 and older who report severe or chronic pain, are newly registered for the Medical Marijuana Registry in the State of Florida, have no prior history of medical marijuana use, can communicate in English, and are willing and able to complete study procedures. The control group will be age, gender, and race matched.

10.2 Inclusions and Exclusions of Special Populations

10.2.1 Adults unable to consent will be excluded from the study.
10.2.2 Individuals who are not yet adults (infants, children, teenagers) will be excluded from the study.
10.2.3 Pregnant women will be excluded from the study.
10.2.4 Prisoners will be excluded from the study.

## 11.0 Vulnerable Populations*

N/A

## 12.0 Local Number of Subjects

12.1 N = 60

## 13.0 Recruitment Methods

13.1 We will recruit patients using convenience sampling technique from Medical Marijuana Treatment Clinics (MMTC) of Gainesville.

## 14.0 Withdrawal of Subjects*

14.1 The Principal Investigator can withdraw participants from this study for unanticipated reasons.

## 15.0 Risks to Subjects*

15.1 Questions may be unpleasant or difficult for participants to answer. Additionally, despite taking appropriate steps to safeguard collected information, there is a slight risk that participant information could be revealed accidentally or inappropriately. This release of information may upset a participant or even affect their insurability or employability. A Certificate of Confidentiality issued from the National Institute of Drug Abuse will assist us in protecting participant information.

## 16.0 Potential Benefits to Subjects*

16.1 Participants will not directly benefit from this study.

## 17.0 Data Management* and Confidentiality

17.1 **Test of Aim 1 (Driving Simulator):** Between group (medical marijuana users vs controls) comparisons will first be examined using independent samples t-test (controlling for unequal variances using Levene's test) or Mann-Whitney U tests if the data are nonparametric. Repeated measures ANOVA will be used to examine within participants differences on measures at all 3 time points in order to answer the question of whether medical marijuana impacts response time, divided attention, and executive functions. Limitations may be related to the distribution of the dependent and independent variables. Possible mitigation approaches include creating a dichotomous variable of high versus low for outcomes and using logistic regression or other functional form as dictated by the distribution of the dependent and independent variables.

17.2 **Test of Aim 2 (Adverse Effects):** To describe factors associated with adverse effects we will report the number of adverse effects reported by participants at time points 2 and 3. Adverse Effects will be defined as both a count variable and a binary variable such that absence or presence of adverse effects will be coded as 0/1 respectively. We will then use Poisson and Logistic regression methods to examine analyze the bivariate association between dosage, frequency of use, route of administration (pills, vape, etc.), and type of product (THC v. CBD). Limitations may be related to the frequency and distribution of events leading to complete or quasi-separation of data points. Possible mitigations would be re-categorization of explanatory variables, exact or firth regression, or a different functional form of the model. The goal of aim 2 is to examine the strength of the association between factors of medical marijuana use and adverse effects. As there may be insufficient power for statistical

significance, effect size estimates (Cohen's d) will be used to examine the strength of the association between variables.

17.3 Power Analysis

17.4 We compute the power to detect a medium effect size of 0.5 standard deviations across groups. Assuming a correlation of 0.2 across the repeated measures at three time points, the standard deviation of the average of three measures is 0.683 times the standard deviation of one measure. Therefore, with 31 per group we can detect a difference in this average of 0.5 times the standard deviation of one measure, using a two-sided test with 80% power. We calculated Cohen's d using Dr. Classen's prior work that examined total driving errors and specific errors (Lane maintenance) in healthy controls (M= 24.08 SD=12.38) and (M= 5.78 SD=4.26) versus Parkinson patients (M=31.99 SD=22.01) and (M=10.23 SD= 9.26) which yielded a Cohen's d of .46-.65 (medium effect size)[59]; therefore we will be powered to detect this medium effect size.

17.5 Missing Data

17.5.1 We will handle missing data values with a 3-step process. First, the dropout rates will be compared across the groups with chi-square analyses to assess systematic differences due to condition. Second, demographic and dependent variables will be examined for their relationship to dropout. Those variables related to dropout status will be used to impute missing values for use in the analyses described (via SPSS Missing Items Analysis). Finally, comparison of the completers vs. imputation analyses will yield an additional estimate of the effect of dropouts on hypothesis tests.

17.6 Procedures to Safeguard Against Adverse Events

17.6.1 All data collection protocols include a form on which research staff members record any problems with the data collection, concerns about the participant, or unusual occurrences during the collection. These forms allow our research staff an opportunity to quickly review and respond to any possible concerns or adverse effects.

17.7 Data and Safety Monitoring Activities

17.7.1 The data collected by the current project presents low to minimal risk to participants. Participants will be asked to answer a set of questionnaires, provide a urine specimen which will be used to detect the presence or absence of THC and other drugs, and participate in an approximately 20 minute simulated drive. Participants who meet criteria for current or past alcohol and/or illicit drug dependence, have vertigo or any vestibular systems dysfunction (due to the risk to develop simulator adaptation syndrome), screen high on the simulator sickness prescreen (a score of 13 or greater), use medications as identified by the

referring physicians that would negatively impact mental or physical functioning due to side effects, or have a diagnosis of severe psychiatric (e.g., psychoses) or physical conditions (e.g., missing limbs) that would preclude full participation will be excluded from the study. Further, vulnerable populations will not be enrolled in the current trial.

17.8 Confidentiality Safeguards

17.8.1 To ensure confidentiality, all information will be coded so that it cannot be associated with any individual. A master sheet with individual names and their respective code numbers will be kept in a locked file that can be accessed only under supervision of the PI. All data entered into the computerized database will be identifiable by subject code number only. No one outside of the lead research team will have access to records identifying participants' names at any time. The information gathered will be used only for scientific, educational, or instructional purposes.

17.9 Data Safeguards

17.9.1 All data collection protocols include a form on which research staff members record any problems with the data collection, concerns about the subject, or unusual occurrences during the collection. These forms allow our research staff an opportunity to quickly review and respond to any possible concerns or adverse effects.

17.10 Oversight

17.10.1 The PI is responsible for the general oversight of all grant activities and will inform the IRB about any changes to the DSMP. The proposed study will have a yearly review of its DSMP by the Florida State University IRB during the regular continuing review process, outlining the following points:

- Reassessment of the risks and benefits to study participants
- Participant recruitment, accrual, and retention
- Data quality and confidentiality
- Consideration of external scientific or therapeutic developments with impact on the safety of participants or the ethics of the study
- Review any adverse events

## 18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

18.1 Protection to Reduce or Eliminate Simulator Sickness

18.1.1 In the proposed study, we will implement a simulator sickness prevention protocol to reduce the occurrence of simulator sickness. The protocol for safeguarding against simulator sickness is detailed in the Protection of Human Subjects document and is briefly outlined here. The protocol includes a seven minute acclimation

period during which participants will begin with simple and slow straight-line driving without much texture in the road image. Then, speed, texture, curves and turns will be progressively added. During the acclimation period and simulation, participants will be carefully observed and asked for verbal feedback regarding the presence of motion sickness. If at any point throughout the experiment the participant reports, or is observed to have motion sickness, the trial will be terminated. If participants experience symptoms after driving, we will measure simulator sickness with the SSQ. We will allow a recovery period for the participants and monitor them for 10-minute intervals (up to 30 minutes) to determine if their symptoms lessen with time. Participants will be released once their SSQ scores are at or near baseline.

## 19.0 Provisions to Protect the Privacy Interests of Subjects

19.1 Discomfort with Procedures or Disclosure Safeguards

19.1.1 During the course of participation in the research, a participant may have questions about the assessment procedure. A project staff member or interventionist will be available to answer questions. To prevent discomfort or embarrassment, staff are trained in building rapport and skillful interviewing. Participants are informed prior to the assessment that they may choose to skip any questions or procedures they find uncomfortable. If any individual becomes overly distressed or distraught, the assessment will be stopped immediately and a staff clinician will talk privately with the affected individual(s) and appropriate referrals will be made, as needed.

19.2 Mandatory Reporting Safeguards

19.2.1 **As a Licensed Clinical Psychologist in the State of Florida I am a mandatory reporter and must inform all patients I work (research and clinical) with of my duty to report.** Therefore, participants are informed in the consent document that staff must report to authorities any report by any respondent of child abuse, or any report of suicidal or homicidal behavior or specific ideations. Research and clinical staff are trained to identify events that would fall under mandatory reporting guidelines. These include physical injury to any child caused by anything other than accidental means or information from a study participant that leads staff to believe a person is in imminent danger of physically harming oneself or others.

19.3 Response Procedures for Adverse Events

19.3.1 *Discomfort with disclosure:* During the course of participation in the research, a participant may have questions about the assessment procedure. A project staff member or interventionist will be available to answer questions. To prevent discomfort or embarrassment, staff are trained in building rapport and skillful interviewing. Participants are informed prior to the assessment that they may choose to skip any questions or procedures they find uncomfortable. If any individual becomes overly distressed or distraught, the assessment will be stopped immediately and a staff clinician will talk privately with the affected individual(s) and appropriate referrals will be made, as needed.

19.3.2 *Mandatory reporting*: One serious adversity a subject may encounter is the possibility that staff must report to authorities the instances of physical abuse, neglect, or threat of physical harm among participants to themselves or others. To anticipate these concerns, the project has established procedures and guidelines to respond to risk disclosures and crisis situations. Staff will be trained to recognize risks or crises that require immediate reporting response. Certain situations require special procedures (see sections 19.3.3 – 19.3.5).

19.3.3 *Suicide thoughts or attempts*: Two types of risks will be addressed in the project: (a) ideation or the presentation of thoughts or interest in suicide, and (b) action, which includes both thoughts of suicide as well as the presence of a plan and means to accomplish a suicide act. If the disclosure occurs during an on-site session, the staff member will follow through with an in-person interview to clarify the presence of suicidal risk or develop a plan of action. In the most extreme cases of risk, the PI then assumes follow-up responsibility for the plan of action.

19.3.4 *Abuse:* Child abuse concerns may arise from any or a combination of the following sources: (a) a subject indicates that abuse has occurred or is occurring, and/or (b) a subject answers one or more assessment questionnaire items suggesting the possibility of abuse. At any time, if any of the above indicators of abuse lead staff to suspect abuse or neglect of children, the PI will be notified to review the information and determine next steps.

19.3.5 *Threat of danger to others:* The threat of danger to others includes disclosure of potential physical harm by a participant to others, including members of the participant's family or other individuals in the community. At any time, if any information derived through assessment or intervention lead staff to suspect a participant poses a threat of harm to others, steps are outlined for staff to obtain

additional information and contact the PI. In all situations that are referred to the PI, the written report is kept in a participant's confidential file for future reference.

19.4 *Reporting Procedures for Adverse Events*

19.4.1 The anticipated potential adversity inherent in assessment involves situations detailed above and is addressed by the timely intervention of the PI skilled in risk assessment and mandatory reporting requirements.

## 20.0 Compensation for Research-Related Injury

20.1 N/A

## 21.0 Economic Burden to Subjects

21.1 N/A

## 22.0 Consent Process

22.1 Informed Consent. All participants will be required to read detailed consent forms prior to participation. Before signing, participants will be given the opportunity to ask any questions they may have about the study. Participants are advised of the voluntary nature of participation and of their right to withdraw from the project at any time and their right to require that information about themselves be removed from data analysis. Each study participant receives a verbal and written description of the study.

22.2 **Special Considerations**

22.2.1 **Non-English Speaking Subjects**

N/A

22.2.2 **Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)**

N/A

22.2.3 **Subjects who are not yet adults (infants, children, teenagers)**

N/A

22.2.4 **Cognitively Impaired Adults**

N/A

22.2.5 **Adults Unable to Consent**

N/A

## 23.0 Process to Document Consent in Writing

23.1 All participants will sign an Informed Consent and they will receive a signed copy of the form and a signed copy will be kept for the

study. These forms will then be digitized and stored in a secure password protected file on the FSU server.

## 24.0 Setting

24.1 Patients will be recruited using convenience sampling technique from Medical Marijuana Treatment Clinics (MMTC) of Gainesville.

24.2 Patients will be assessed at the Smart House which is the current location of the Driving Simulator. The Smart House, property of the College of Public Health and Health Professions, is a single-family home located in Oak Hammock at the University of Florida, a vibrant and energetic retirement community in Gainesville, Florida. Built in 2005, the 2,350 square foot home was designed to allow researchers to explore how novel applications of technology can facilitate independent living and elder care. The Smart House, located 3.5 miles from the UF campus, provides convenient access for UF's designated employees and researchers, as well as participants who enjoy dedicated parking and lessened traffic as compared to the university site.

## 25.0 Resources Available

25.1 It will be feasible to recruit the patients needed due to the fact that MMTC issues between 800 and 1000 medical marijuana cards per month on average.

25.2 This project will have the resources needed to complete it in the next two years.

25.3 The Center for Translational Behavioral Science (CTBScience) is a university center, affiliated with the FSU College of Medicine. This facility provides 6 faculty offices, 4 research core offices, a program manager office, two shared postdoc offices, offices for a research coordinator and research assistants, and a shared space for students and staff working with faculty. The center also houses 4 multifunctional participant spaces, 2 of which have the ability to function as working sleep laboratories equipped with state-of-the-art sleep diagnostic equipment, video monitoring / recording capability and 2 of which have the ability to be used as both assessment rooms and therapy rooms. Further, the center houses a conference room with video conferencing capabilities and a community space that functions as a group meeting room and/or classroom. Within its three cores (Management Core, Methods Core, and Tech Core), the Center has a dedicated clinical trials coordinator, administrative coordinator, grants contracts administrator, data manager, biostatisticians, and a communications expert as well as access to FSU's IT, library,

and other administrative resources. The Center also has a dedicated phlebotomy lab space, equipped with the necessary sample collection and sample storage equipment for human biological specimens. This facility hosts multiple research initiatives related to translational behavioral science.

25.4 Investigators will utilize the UF Integrated Data Repository, supported by CTSI (Clinical and Translational Science Institute), which is a large-scale database that securely collects and organizes data from across UF Health's clinical and research enterprises, particularly Consent2Share, an initiative of the UF Integrated Data Repository (IDR) and supported by UF CTSI (Clinical and Translational Science Institute) that allows for a large group of potential research participants who have consented to be re-contacted for future research studies

25.5 Principal Investigator Dr. Nicole Ennis, a licensed clinical psychologist (Florida license PY7458), will serve as the clinical supervisor for this study. The clinical supervisor will oversee all data collection and intervene clinically if necessary. As a licensed clinical psychologist, Dr. Ennis is trained in the motivational interviewing skills, referral strategies, and all procedures of the current project's brief intervention and referral to treatment protocol.

25.6 During the course of participation in the research, a participant may have questions about the assessment procedure. A project staff member or interventionist will be available to answer questions. To prevent discomfort or embarrassment, staff are trained in building rapport and skillful interviewing. Participants are informed prior to the assessment that they may choose to skip any questions or procedures they find uncomfortable. If any individual becomes overly distressed or distraught, the assessment will be stopped immediately and a staff clinician will talk privately with the affected individual(s) and appropriate referrals will be made, as needed.

## 26.0 *Multi-Site Research**

As defined by the NIH, this study is a single-site clinical trial. The PI of the study, Dr. Ennis (FSU) proposed the study examining how medical marijuana effects driving in individuals 50 years and older. Dr. Ennis and her research team are recruiting for the study in Gainesville, FL through the Medical Marijuana Treatment Clinics (MMTC) of Florida.

Study participants will be assessed at the UF Smarthouse in order to use the driving simulator. Although the study is a collaboration between FSU and UF, the NIH defines this study as a single-site clinical trial because participants are only being assessed at one location. If participants were beings assessed at both locations, then the study would be considered a multi-site trial.

## References Cited

1. 1. Administration, S.A.a.M.H.S., *Florida Population*, 2012: Police Academy State Profile.

2. Cimas, M., et al., *Chronic musculoskeletal pain in European older adults: Cross-national and gender differences.* Eur J Pain, 2018. **22**(2): p. 333-345.

3. Langley, P.C., *The prevalence, correlates and treatment of pain in the European Union.* Curr Med Res Opin, 2011. **27**(2): p. 463-80.

4. Reid, M.C., C. Eccleston, and K. Pillemer, *Management of chronic pain in older adults.* BMJ, 2015. **350**: p. h532.

5. Park, J.Y. and L.T. Wu, *Prevalence, reasons, perceived effects, and correlates of medical marijuana use: A review.* Drug Alcohol Depend, 2017. **177**: p. 1-13.

6. Choi, N.G., et al., *Older adults' marijuana use, injuries, and emergency department visits.* Am J Drug Alcohol Abuse, 2018. **44**(2): p. 215-223.

7. National Academies of Sciences, E., and Medicine, *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*
2017: Washington (DC).

8. Choi, N.G., D.M. DiNitto, and C.N. Marti, *Older marijuana users: Life stressors and perceived social support.* Drug Alcohol Depend, 2016. **169**: p. 56-63.

9. Salas-Wright, C.P., et al., *Trends and correlates of marijuana use among late middle-aged and older adults in the United States, 2002-2014.* Drug Alcohol Depend, 2017. **171**: p. 97-106.

10. Hill, K.P., et al., *Cannabis and Pain: A Clinical Review.* Cannabis and Cannabinoid Research, 2017. **2**(1): p. 96-104.

11. Hill, K.P., *Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: a clinical review.* JAMA, 2015. **313**(24): p. 2474-2483.

12. Jensen, B., et al., *Medical marijuana and chronic pain: a review of basic science and clinical evidence.* Current pain and headache reports, 2015. **19**(10): p. 50.

13. Lynch, M.E. and F. Campbell, *Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials.* British Journal of Clinical Pharmacology, 2011. **72**(5): p. 735-744.

14. Choi, N.G., D.M. DiNitto, and C.N. Marti, *Risk Factors for Self-reported Driving Under the Influence of Alcohol and/or Illicit Drugs Among Older Adults.* The Gerontologist, 2016. **56**(2): p. 282-291.

15. Choi, N.G., D.M. DiNitto, and C.N. Marti, *Older adults driving under the influence: associations with marijuana use, marijuana use disorder, and risk perceptions.* Journal of Applied Gerontology, 2017: p. 0733464817745379.

16. Thomsen, K.R., M.B. Callesen, and S.W.F. Ewing, *Recommendation to reconsider examining cannabis subtypes together due to opposing effects on brain, cognition and behavior.* Neuroscience and Biobehavioral Reviews, 2017. **80**: p. 156-158.

17. Colizzi, M. and S. Bhattacharyya, *Does Cannabis Composition Matter? Differential Effects of Delta-9-tetrahydrocannabinol and Cannabidiol on Human Cognition.* Curr Addict Rep, 2017. **4**(2): p. 62-74.

18. Mahvan, T.D., et al., *Marijuana Use in the Elderly: Implications and Considerations.* Consult Pharm, 2017. **32**(6): p. 341-351.

19. Umut, G., et al., *The Changes of the Cognitive and Psychomotor Functions in the Chronic Cannabis Users after a Month of Remission.* Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology, 2016. **26**(2): p. 109-118.

20. Solowij, N. and N. Pesa, *Cognitive abnormalities and cannabis use.* Revista Brasileira de Psiquiatria, 2010. **32**: p. 531-540.

21. Abuse, N.I.o.D. *Is marijuana safe and effective as medicine?* 2018 [cited 2018; Available from: https://www.drugabuse.gov/publications/marijuana/marijuana-safe-effective-medicine.

22. Azofeifa, A., et al., *National Estimates of Marijuana Use and Related Indicators - National Survey on Drug Use and Health, United States, 2002-2014.* Mmwr Surveillance Summaries, 2016. **65**(11): p. 1-Cover3.

23. Szaflarski, M. and J.I. Sirven, *Social factors in marijuana use for medical and recreational purposes.* Epilepsy Behav, 2017. **70**(Pt B): p. 280-287.

24. Nielsen, A.L., *Americans' Attitudes toward Drug-Related Issues from 1975-2006: The Roles of Period and Cohort Effects.* Journal of Drug Issues, 2010. **40**(2): p. 461-493.

25. Sawyer, P., et al., *Pain and pain medication use in community-dwelling older adults.* The American Journal of Geriatric Pharmacotherapy, 2006. **4**(4): p. 316-324.

26. Rustoen, T., et al., *Age and the experience of chronic pain - Differences in health and quality of life among younger, middle-aged, and older adults.* Clinical Journal of Pain, 2005. **21**(6): p. 513-523.

27. Ilgen, M.A., et al., *Characteristics of adults seeking medical marijuana certification.* Drug & Alcohol Dependence. **132**(3): p. 654-659.

28. Volkow, N.D., et al., *Adverse health effects of marijuana use.* N Engl J Med, 2014. **370**(23): p. 2219-27.

29. Meier, M.H., et al., *Persistent cannabis users show neuropsychological decline from childhood to midlife.* Proc Natl Acad Sci U S A, 2012. **109**(40): p. E2657-64.

30. Battistella, G., et al., *Weed or wheel! FMRI, behavioural, and toxicological investigations of how cannabis smoking affects skills necessary for driving.* PLoS One, 2013. **8**(1): p. e52545.

31. Prashad, S. and F.M. Filbey, *Cognitive motor deficits in cannabis users.* Curr Opin Behav Sci, 2017. **13**: p. 1-7.

32. Bosker, W.M., et al., *Psychomotor function in chronic daily Cannabis smokers during sustained abstinence.* PLoS One, 2013. **8**(1): p. e53127.

33. Desrosiers, N.A., et al., *Smoked cannabis' psychomotor and neurocognitive effects in occasional and frequent smokers.* J Anal Toxicol, 2015. **39**(4): p. 251-61.

34. Nestoros, J.N., et al., *Long lasting effects of chronic heavy cannabis abuse.* The American journal on addictions, 2017. **26**(4): p. 335-342.

35. Mizrahi, R., J.J. Watts, and K.Y. Tseng, *Mechanisms contributing to cognitive deficits in cannabis users.* Neuropharmacology, 2017. **124**: p. 84-88.

36. Dobbs, B.M. and S.S. Shergill, *How effective is the Trail Making Test (Parts A and B) in identifying cognitively impaired drivers?* Age Ageing, 2013. **42**(5): p. 577-81.

37. Roy, M. and F. Molnar, *Systematic review of the evidence for Trails B cut-off scores in assessing fitness-to-drive.* Canadian Geriatrics Journal, 2013. **16**(3): p. 120-142.

38. Vaucher, P., et al., *The trail making test as a screening instrument for driving performance in older drivers; a translational research.* BMC Geriatrics, 2014. **14**(1): p. 123.

39. Papandonatos, G.D., et al., *The Clinical Utility of the Trail Making Tests As Predictors of Driving Performance in Older Adults.* Journal of the American Geriatrics Society, 2015. **63**(11): p. 2358-2364.

40. Karthaus, M. and M. Falkenstein, *Functional Changes and Driving Performance in Older Drivers: Assessment and Interventions.* Geriatrics, 2016. **1**(2): p. 12.

41. Chaytor, N. and M. Schmitter-Edgecombe, *The ecological validity of neuropsychological tests: a review of the literature on everyday cognitive skills.* Neuropsychol Rev, 2003. **13**(4): p. 181-97.

42. Casutt, G., et al., *The drive-wise project: driving simulator training increases real driving performance in healthy older drivers.* Front Aging Neurosci, 2014. **6**: p. 85.

43. Campos, J.L., et al., *Guiding Framework for Driver Assessment Using Driving Simulators.* Front Psychol, 2017. **8**: p. 1428.

44. Lee, H.C., et al., *Using a driving simulator to identify older drivers at inflated risk of motor vehicle crashes.* Journal of Safety Research, 2003. **34**(4): p. 453-459.

45. Belanger, A., S. Gagnon, and A. Stinchcombe, *Crash avoidance in response to challenging driving events: The roles of age, serialization, and driving simulator platform.* Accid Anal Prev, 2015. **82**: p. 199-212.

46. Cicchino, J.B. and A.T. McCartt, *Critical older driver errors in a national sample of serious U.S. crashes.* Accid Anal Prev, 2015. **80**: p. 211-9.

47. Lombardi, D.A., W.J. Horrey, and T.K. Courtney, *Age-related differences in fatal intersection crashes in the United States.* Accid Anal Prev, 2017. **99**(Pt A): p. 20-29.

48. Yamani, Y., et al., *Age-Related Differences in Vehicle Control and Eye Movement Patterns at Intersections: Older and Middle-Aged Drivers.* PLoS One, 2016. **11**(10): p. e0164124.

49. Elm, E.v., et al., *Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies.* BMJ, 2007. **335**(7624): p. 806-808.

50. Ennis, W.N., H.L. E., and B. Larry, *The Association Between Depressive Symptoms, Anger, and Perceived Support Resources Among Underserved Older HIV Positive Black/African American Adults.* AIDS Patient Care and STDs, 2014. **28**(9): p. 507-512.

51. Hearn, L., et al. *AGE AND CHRONIC DRUG USE MAY INCREASE SUSCEPTIBILITY TO TRICHOMONAS VAGINALIS AMONG MIDDLE AGE AND OLDER ADULTS*. in *ANNALS OF BEHAVIORAL MEDICINE*. 2014. SPRINGER 233 SPRING ST, NEW YORK, NY 10013 USA.

52. Mannes, Z.L., et al., *Loneliness and substance use: the influence of gender among HIV+ Black/African American adults 50+.* Aids Care-Psychological and Socio-Medical Aspects of Aids/Hiv, 2016. **28**(5): p. 598-602.

53. Mannes, Z.L., et al., *Contextualizing Psychosocial Determinants of Alcohol Use by Age Cohorts of Adults Living With HIV, Ages 50 and Older.* Janac-Journal of the Association of Nurses in Aids Care, 2017. **28**(2): p. 279-288.

54. Whitehead, N.E., et al. *UNDERSTANDING FACTORS INFLUENCING ILLICIT DRUG USE AMONG UNDESERVED HIV+ ADULTS 50 AND OLDER*. in *ANNALS OF BEHAVIORAL MEDICINE*. 2015. SPRINGER 233 SPRING ST, NEW YORK, NY 10013 USA.

55. Whitehead, N.E., et al., *Age Cohort Differences in Illicit Drug Use and Hepatitis C Among African American Substance Users.* Journal of Addictive Diseases, 2014. **33**(4): p. 314-321.

56. Whitehead, N.E., et al., *Younger Versus Older African Americans: Patterns and Prevalence of Recent Illicit Drug Use.* Journal of Ethnicity in Substance Abuse, 2014. **13**(2): p. 126-138.

57. Mannes, Z.L., et al., *The prevalence and patterns of substance use by birth cohort among HIV-positive adults in Florida.* Aging & Mental Health, 2018: p. 1-9.

58. Campos, J.L., et al., *Guiding Framework for Driver Assessment Using Driving Simulators.* Front Psychol, 2017. **8**(1428).

59. Classen, S., et al., *Driving errors in Parkinson's disease: moving closer to predicting on-road outcomes.* American journal of occupational therapy, 2014. **68**(1): p. 77-85.

60. Classen, S., et al., *Visual Correlates of Fitness to Drive in Adults With Multiple Sclerosis.* OTJR: Occupation, Participation and Health, 2018. **38**(1): p. 15-27.

61. Dickerson, A.E., et al., *Transportation and Aging: An Updated Research Agenda for Advancing Safe Mobility.* Journal of Applied Gerontology. **0**(0): p. 0733464817739154.

62. Krasniuk, S., S. Classen, and S.A. Morrow, *Relationships Among Vision, Visual Attention, and Fitness to Drive in Adults With Multiple Sclerosis.* American journal of occupational therapy, 2017. **71**(4_Supplement_1): p. 7111500009p1-7111500009p1.

63. Medhizadah, S., S. Classen, and A.M. Johnson, *Constructing the 32-item Fitness-to-Drive Screening Measure.* OTJR: Occupation, Participation and Health, 2018. **38**(2): p. 89-95.

64. Morrow, S.A., et al., *On-road assessment of fitness-to-drive in persons with MS with cognitive impairment: A prospective study.* Multiple Sclerosis Journal. **0**(0): p. 1352458517723991.

65. Rapoport, M.J., et al., *An International Approach to Enhancing a National Guideline on Driving and Dementia.* Current Psychiatry Reports, 2018. **20**(3): p. 16.

66. Stern, E.B., Akinwuntan, A., & Hirsch, P., *Simulator sickness: Strategies for mitiation and prevention*, in *Driving simulation for assessment, intervention, and training: A guide for occupational therapy and health care professionals*, S. Classen, Editor. 2017, AOTA Press: Bethesda, MD. p. 107-120.

67. Brooks, J.O., et al., *Simulator sickness during driving simulation studies.* Accident Analysis and Prevention, 2010. **42**(3): p. 788-796.

68. Shechtman, O., *Validation of driving simulators.* Advances in Transportation Studies: an International Journal, 2010: p. 53-62.

69. Shechtman, O., et al., *Comparison of driving errors between on-the-road and simulated driving assessment: a validation study.* Traffic injury prevention, 2009. **10**(4): p. 379-385.

70. Thomas, E.J. and L.A. Petersen, *Measuring errors and adverse events in health care.* Journal of general internal medicine, 2003. **18**(1): p. 61-67.

71. Katz, N.P., *The measurement of symptoms and side effects in clinical trials of chronic pain.* Contemporary clinical trials, 2012. **33**(5): p. 903-911.

72. Radloff, L.S., *The CES-D scale: A self-report depression scale for research in the general population.* Applied psychological measurement, 1977. **1**(3): p. 385-401.

73. Vance, D.E., et al., *Predictors of driving exposure and avoidance in a field study of older drivers from the state of Maryland.* Accid Anal Prev, 2006. **38**(4): p. 823-31.

74. Health, U.o.F. *Intervention Research Advancing Care Equity (i-RACE)*. 2018 [cited 2018 April]; Available from: http://irace.phhp.ufl.edu/.

75. Health, U.o.F. *Institute for Mobility, Activity, & Participation*. 2018 [cited 2018 April]; Available from: http://mobility.phhp.ufl.edu/.