VALIDATION OF THE DRUG IMPAIRED DRIVING SCENARIO (DIDS) ON THE CRCDS-MINISIM: EVALUATING SENSITIVITY TO THE EFFECTS OF CANNABIS AND ALPRAZOLAM

NCT04970342

14 July 2021

Informed Consent Document

INFORMED CONSENT FORM

Sponsor / Study Title:	**National Highway Transportation Safety Administration (NHTSA) / "Validation of the Drug Impaired Driving Scenario (DIDS) On the CRCDS-miniSim: Evaluating Sensitivity To The Effects of Cannabis and Alprazolam "**
Protocol Number:	**202105389**
Principal Investigator:	**Timothy Brown, Ph.D.**
Telephone:	[redacted]
Address:	**National Advanced Driving Simulator** **2401 Oakdale Blvd** **Iowa City, IA 52242**

KEY INFORMATION

You are invited to take part in an investigational research study. The primary purpose of this study is to establish and validate a standardized protocol for assessing drug impaired driving by using cannabis, alprazolam (Xanax), a placebo (inactive substance), and a driving simulator. Additional objectives of this study are to learn about the effects of cannabis on cognitive and psychomotor functioning, as well as the relationship between blood cannabis concentration and driving performance.

You will first complete a screening visit to ensure eligibility for the study. This visit will last approximately 4 hours. During your screening visit you will be asked to complete a variety of questionnaires and assessments. You will also be asked to drive the driving simulator.

If you are eligible to participate in the study and decide to continue, you will be asked to participate in 3 study treatment visits. The first study treatment visit will be scheduled between 3 and 14 days after the screening visit. Each study treatment visit will last approximately 23 hours and involves an overnight stay. There will be 7 days between each study treatment visit. During the study treatment visits you will be dosed with the study drug and be asked to complete a number of questionnaires and assessments, as well as provide blood samples and complete a series of drives on the driving simulator. Seven days after your final study treatment visit, there will be a follow-up phone call to close out your participation. This call will last approximately 10 minutes.

Your participation in this study will assist us in developing tools to improve drugged driving research, specifically validation of driving scenarios that allow for detection of impairment from cannabis and other drugs (for example, Xanax). The number and length of visits may require you to take time off from work or school or find childcare. We are requesting you not drive

yourself on the day of your study visits, which you may find inconvenient. You may also be using cannabis less frequently in this study than you would normally (for example, you use once a day, but we are asking you to use once a week). You will be getting "high" as part of this study, which you may or may not find enjoyable. You are being asked to take alprazolam, a benzodiazepine, which you may not be used to consuming.

Main risks of participation: Cannabis and alprazolam (alone, not in combination) can cause several side effects. However, the amount you are receiving should not cause effects you do not usually experience. Simulator disorientation is also a risk. Symptoms include uneasiness, warmth, and eyestrain. If you experience anything during the study that makes you uncomfortable, please let study staff know.

Possible benefits: There are no direct personal benefits. However, the findings of this study about the effects of cannabis and alprazolam on drivers and their driving performance may benefit society in the future.

Your participation is entirely voluntary, meaning that you are free to say yes or no. Please read this form carefully. Take your time to ask the study staff as many questions about the study as you would like. Study staff can explain words or information that you do not understand. Reading this form and talking to the study staff may help you decide whether to take part or not. If you decide to take part in this study, you must sign your name at the end of this form and date it.

BACKGROUND AND PURPOSE

You are being asked to participate in this research study because you are a healthy driver between 19 and 45 years old (inclusive) who has used cannabis recently. Up to 30 subjects will participate in this study.

The purpose of this research study is to

- Establish and validate a standardized protocol for assessing drug impaired driving,
- Learn about the effects of cannabis on cognitive and psychomotor functioning, and
- Learn about the relationship between blood cannabis concentration and driving performance.

The following drugs will be used in this study:

- Cannabis (6.18% delta-9-tetrahydrocannabinol [THC]/less than 0.025% cannabidiol [CBD]), approximately 30.9 mg of THC (the psychoactive component of cannabis)
- Alprazolam (Xanax) 0.75 mg
- Placebo (0% THC / 0% CBD cannabis, 0% Alprazolam)

In this study, you will receive a 500 mg dose of bulk cannabis (30.9 mg of THC) taken by breathing in a vapor through your mouth. You will also receive Alprazolam, a United States Food and Drug Administration (FDA) approved drug commonly prescribed as a swallowable tablet to treat panic and anxiety disorders. The use of Alprazolam in this study is investigational. Investigational means that the drug is not approved by the FDA for the indication it is being studied for. Placebos in the form of an inhaled vapor and a swallowable tablet will both be used.

WHAT WILL HAPPEN DURING THE STUDY?

Your participation in this study will last approximately 42 days and will include

- Up to 14 days for Screening (screening occurs on a single day, but the time between screening and study treatment is up to 14 days),
- Three 2-day visits ("Study Treatment Periods") to the National Advanced Driving Simulator (NADS), with at least 7 days between visits, and
- One final safety follow-up phone call about 7 days after the final visit.

Screening Visit

Before any study-related tests and procedures are performed, you will be asked to read, sign, and date this consent document. The following screening tests and procedures will then be performed to determine if you qualify to take part in this study:

- Examine your driver's license to confirm it is valid.
- Demographic information about you (age, race, sex, and ethnicity) will be collected, as well as measurements of your height and weight.
- Review of your medical history and current medications.
- A full physical examination will be performed on you which will include assessment of your general appearance, head, eyes, ears, nose, throat, and skin, as well as of your neck/thyroid/lymphatic, cardiovascular, respiratory, gastrointestinal, neurological, and musculoskeletal/extremities systems.
- Your vital signs (blood pressure, heart rate, breathing rate, oxygen saturation [the level of oxygen in your blood] and temperature) will be measured.
- Your heart function will be assessed with an electrocardiogram (ECG, a test that measures and records the electrical activity of your heart) using the KardiaMobile 6L (https://store.alivecor.com/products/kardiamobile6l).
- You will be screened for alcohol with a breathalyzer.
- You will provide a urine sample to test for
    - Drugs of abuse (***Note:*** The result of the test must meet study entry criteria evaluated by the study staff for you to participate in this study).
    - Pregnancy, if you are a woman (***Note:*** The result of the pregnancy test must show that you are not pregnant for you to qualify to participate in this study).
- You will be asked several questions to determine if you are at an increased risk of suicidal actions (based on the Columbia-Suicide Severity Rating Scale). Some of the questions may be upsetting and you can refuse to answer. If you refuse to respond or complete this assessment, you will not be allowed to participate in this study. If you are

having suicidal thoughts call the study investigator at the telephone number listed on the first page of this form. If you feel in crisis, you can call 911 and/or a Nationwide Suicide Hotline that is answered 24 hours a day with a skilled, trained counselor. One example is the National Suicide Prevention Lifeline at 1-800-273-TALK (8255).

- You will be screened for excessive daytime sleepiness and sleep disorders (using the Epworth Sleepiness Scale).
- You will screen and familiarize yourself with the driving simulator through training and practice opportunities.
- You will complete a Simulator Sickness Questionnaire.
- You will familiarize yourself with the cognitive performance (CogScreen and TOVA) tests that will be administered to you during the study through training and practice opportunities.

Study Treatment Periods Overview

Within 3 to 14 days of your screening and training visit, you will return to NADS to start the first of your three 2-day Study Treatment Periods.

You will spend the first day of each Study Treatment Period on various study admission and intake activities, as well as practice sessions on the driving simulator and cognitive performance (CogScreen) tests used in this study. Between the end of procedures on Day 1 and start of procedures on Day 2, you will spend the night at an off- site residential facility under study staff supervision.

On the second day of each Study Treatment Period, you will be given one of the following study treatments:

- 1 dose of alprazolam taken by mouth in the form of a swallowable tablet.
- 1 dose of cannabis taken by inhaling (breathing in) a vapor through your mouth.

You will also be given a placebo that is either inhaled via vaporizer or taken by mouth as a tablet. The order in which you receive each of these study treatments across the three visits will be determined by random assignment (that is, by chance – like flipping a coin), which will take place on the first day of your first Study Treatment Period (Day 1 of Treatment Period 1). Neither you nor the study staff will know which study treatment you will be receiving at each visit. In case of an emergency, however, the study investigator can get this information. In order to maintain this "blinding" across the 3 visits, you may be given additional placebo vaporizers or tablets during your visits.

Study Treatment Period Day 1 Procedures and Activities

- You will be asked if there have been any changes in your health and medications since your last visit.
- A brief physical examination will be performed on you which will include assessment of your general appearance and your cardiovascular, respiratory, gastrointestinal, and

neurological systems (***Note:*** You may receive additional physical examinations at the study staff's discretion based on your symptoms during the study).

- Your vital signs (blood pressure, heart rate, breathing rate, oxygen saturation [the level of oxygen in your blood] and temperature) will be measured.
- You will be screened for alcohol with a breathalyzer.
- You will provide a urine sample to test for
    - Drugs of abuse
    - Pregnancy (if you are a woman who may be able to become pregnant)
- You will complete a practice drive on the simulator as well as practice sessions of the cognitive performance (CogScreen) tests that will be administered to you during the study.

<u>Study Treatment Period Day 2 Procedures and Activities</u>

- You will be given a tablet (containing either alprazolam or placebo) to swallow 40 minutes before being administered a vapor (containing either cannabis or placebo) to inhale.
- Blood samples will be collected from you (1 before and 2 after you receive your assigned study treatment).
- You will complete a number of questionnaires to assess your self-reported sleepiness level and safety perceptions.
- You will complete a number of cognitive performance (CogScreen and TOVA) tests.
- Your driving performance will be assessed through a 1-hour activity on a driving simulator comprised of suburban, urban, and highway driving tasks.
- You will complete visual analog scales to assess your motivation and self-appraisal of your performance on the driving simulator.
- You will be discharged from NADS at the end of Day 2 if you are sufficiently medically stable for discharge in the opinion of the study staff.
- You agree to not drive yourself home from NADS and to either make prior arrangements for a designated sober driver to take you home or to be transported home via a taxi or rideshare.
- You will be required to sign a release agreement prior to leaving NADS that states your mode of transport home and that you agree to not drive for at least 8 hours after leaving NADS.

<u>Safety Follow-up Visit/Phone Call</u>

One week after the last study treatment is received (Study Treatment Period 3), study staff will call you to ask you if

- There have been any changes in your health or medication use/medical procedure information since your last visit, or
- You have experienced any adverse effects from the study treatments since your last visit.

EXPECTATIONS

If you participate in this study, you will be expected to

- Follow all the instructions and the schedule you are given,
- Visit with the study staff and complete required procedures for the study,
- Tell the study staff about any changes in your health or the way you feel, and
- Report any newly started medications or changes to ongoing medication that may be used during the study and 30 days prior to study start.

RISKS, SIDE EFFECTS, AND/OR DISCOMFORTS

For Cannabis

The risks for taking a single dose of cannabis are variable and will depend upon the dose, method of administration, prior experience, any concurrent drug use, personal expectations, mood state, and the social environment in which the drug is used.

- Euphoric mood
- Throat irritation
- Dysphonia (hoarse voice)
- Throat pain
- Feeling of relaxation
- Dry eye
- Dry mouth
- Confusion
- Stress
- Bronchial (throat) irritation
- Tracheal (throat) pain
- Fatigue (tiredness)
- Feeling abnormal
- Hunger
- Upper abdominal pain
- Protein in urine present
- Headache
- Cold sweats

For Alprazolam (Xanax)

The risks for taking a single dose of alprazolam are minimal compared to therapeutic use over time, but the following side effects are still possible.

- Drowsiness
- Fatigue (tiredness)
- Coordination impairment (loss of coordination)
- Irritability
- Decreased salivation
- Increased appetite

- Memory impairment
- Dizziness/light-headedness, difficulty concentrating
- Difficulty sleeping
- Headache
- Cognitive disorder (mental status changes, including memory loss and impaired thinking
- Decreased appetite
- Weight gain
- Constipation
- Difficulty speaking
- Weight loss
- Nausea/vomiting
- Blurred vision
- Diarrhea
- Abdominal pain
- Nasal congestion
- Anxiety
- Increased heart rate
- Sweating
- Abnormal involuntary movement
- Dry mouth
- Decreased sexual desire
- Depression
- Urination difficulties
- Skin rash
- Chest pain
- State of confusion (delirium)
- Menstruation disorders (changes to the menstrual cycle)
- Low energy
- Altered Interest in Having Sexual Intercourse

RISKS OF STUDY PROCEDURES

- Simulator Drive(s): One risk involves the possibility of discomfort associated with simulator disorientation. This can occur as a consequence of driving the simulator. Previous studies with similar driving intensities and simulator setups produced few disorientation effects. When effects were reported, they were usually mild to moderate and consisted of slight uneasiness, warmth, or eyestrain for a small number of subjects. These effects typically last for only a short time, usually 10-15 minutes, after leaving the simulator. You may quit driving at any time if you experience any discomfort. If you ask to quit driving as a result of discomfort, you will be allowed to quit at once. You will then

be escorted to a comfortable chair where you can sit and rest. Water will be offered. A trained study staff member will determine when you will be allowed to leave. If you show few or no signs of discomfort, you will be allowed to return home.

- Allergic Reactions: As with any drugs, there is a risk of allergic reaction. Some symptoms are shortness of breath, itchy rash or swelling, flushing (feeling warm), low blood pressure and slow heart rate. If you have a very serious allergic reaction, you may be at risk of death. Please seek treatment immediately and tell the study staff if you have any of these symptoms.
- Blood samples: Possible side effects from blood drawing include faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight possibility of infection.
- Questionnaires: The questionnaires used in this study may be upsetting. You do not need to answer any questions that you are not comfortable with.
- Confidentiality: There is a risk of loss of confidentiality of your data. Measures in place to protect your confidentiality are indicated in the ***Confidentiality*** section later in this document.
- Lost or Stolen Personal Items: You will be spending the night at an off- site residential facility and bringing items necessary for overnight comfort (for example, change of clothes, items to bathe/shower, electronic device chargers). The University of Iowa is not responsible for lost or stolen personal items while you are staying at this University-provided lodging.

UNFORESEEN RISKS

There may be other risks to using cannabis that are currently unknown. Additionally, there may be unknown risks to a pregnancy, embryo, or fetus if you or your female partner become pregnant.

CANNABIS USE RESTRICTIONS

As a subject in this study, you are agreeing to abstain from cannabis use (other than the study drug) beginning 7 days prior to admission for your first study treatment period (Day 1 of Study Treatment Period 1) until discharge from NADS on the last day of your last study treatment period (Day 2 of Study Treatment Period 3).

BIRTH CONTROL RESTRICTIONS

Taking the drugs used in this study may involve risks to a pregnant woman, embryo, fetus (unborn baby) or nursing infant. Therefore, if you are pregnant, planning to become pregnant, planning to father a child, or breastfeeding a child, you cannot participate in this study.
If you are a woman of non-childbearing potential, you should be surgically sterile or in a menopausal state in order to participate in this study.

Females

If you are of childbearing potential (that is, you may be able to become pregnant), you should use two effective methods of birth control **while you are participating in this**. Acceptable methods of birth control for use in this study are

- Abstinence from heterosexual intercourse,
- Systemic contraceptives (birth control pills, injectable/implant/insertable hormonal birth control products, transdermal patch,
- Intrauterine device (IUD, with or without hormones), or
- Condom with spermicide or condom with intravaginally applied spermicide.

Study staff will discuss these options with you.

If you become pregnant while you are participating in this study, tell the study staff immediately. You will receive no further study drug doses and your participation will end.

NEW FINDINGS

Any new important information that is discovered during the study and that may influence your willingness to continue participation in the study will be provided to you.

BENEFITS

You will not benefit directly from being in this study.

However, the findings of this study about the effects of cannabis and alprazolam on drivers and their driving performance may benefit society in the future. This knowledge may allow for the development and refinement of new technologies or interventions that can minimize drugged driving-related traffic crashes and the resulting injuries, deaths, and property damage in the future.

COMPENSATION FOR PARTICIPATION

You will be paid up to a total of **$1100.00** if you complete this study. You will be paid for the visits you complete according to the following schedule:

- **$50.00** for the Screening Period visit.
- **$275.00** for the first Study Treatment Period visit.
- **$300.00** for the second Study Treatment Period visit.
- **$400.00** for the third Study Treatment Period visit.

At each Study Treatment Period visit, you will have the opportunity to be awarded an additional **$25.00** for completing one of the drives on the driving simulator within a specified time period without collisions or speed violations. The drive is designed such that efficient and safe vehicle operation will allow you to complete the drive within the specified timeframe to receive the incentive reward.

You will be paid at the end of your participation in the study. If you do not complete the study for any reason, you will be paid for each study visit you do complete.

If you have any questions regarding your compensation for participation, please contact the study staff.

We will provide $35 per trip to reimburse you for your transportation costs to and from NADS. Your trip reimbursement will be provided at the same time as your study payment.

DATA STORAGE FOR FUTURE USE

As part of this study, we are obtaining blood data, ECG data, cognitive performance data, driving performance data, and questionnaire data from you. We would like to study this data in the future, after this study is over. Your information and/or data may be placed in a central repository or other national repositories sponsored by the National Highway Traffic Safety Administration or other Federal agencies. If this happens, it may be stripped of identifiers (such as name, date of birth, address, etc.). Other qualified researchers who obtain proper permission may gain access to your data for use in approved research studies that may or may not be related to in the purpose of this study.

We are asking for your permission to store your blood data, ECG data, cognitive performance data, driving performance data, and questionnaire data so that we can study them in the future. These future studies may provide additional information that will be helpful in understanding how cannabis and alprazolam impairs driving performance, but it is unlikely that what we learn from these studies will have a direct benefit to you. It is possible that your blood data, ECG data, cognitive performance data, driving performance data, and questionnaire data might be used to develop products tests, or discoveries that could be patented and licensed. In some instances, these may have potential commercial value and may be developed by the study investigator, University of Iowa, commercial companies, organizations funding this research, or others that may not be working directly with this research team. There are no plans to provide financial compensation to you should this occur.

Your blood data, ECG data, cognitive performance data, driving performance data, and questionnaire data will be stored ***without*** your name or any other kind of link that would enable us to identify which are yours. Therefore, if you give permission to store your blood data, ECG data, cognitive performance data, driving performance data, and questionnaire data, it will be available for use in future research studies indefinitely and cannot be removed.

Each blood sample collected is just enough for analysis for the current study. Therefore, there is no long-term storage of your blood sample for future, currently unplanned, analyses. When we use the term “blood data”, we are referring to the results of the current blood sample analysis. Specifically, this data will include information about cannabis and alprazolam metabolites found in your blood sample.

CONFIDENTIALITY

Records of your participation in this study will be held confidential except when sharing the information is required by law or as described in this informed consent. In addition to the study staff, representatives from the following entities may be able to inspect and copy confidential study-related records which identify you by name, which means that absolute confidentiality cannot be guaranteed.

- Federal government regulatory agencies
- Representatives of Cognitive Research Corporation and Acclaro Research Solutions, Inc. (companies that are collaborating with the University of Iowa and involved in this research)
- Research institutional review boards such as the Advarra Institutional Review Board (an independent ethics committee that reviewed the ethical aspects of this study to help protect the rights and welfare of study subjects) and the University of Iowa Institutional Review Board
- Auditing departments of the University of Iowa

To help protect your confidentiality, we will assign a study number to you which will be used instead of your name to identify all data collected for the study. The list linking your study number and your name will be stored in a secure location and will be accessible only to the researchers at the University of Iowa. All records and data containing confidential information will be maintained in locked offices or on secure password protected computer systems that are accessible to the researchers, the study sponsor, and its agents.

The **simulator data** are captured and stored on hard drives located within a limited access area of the study center. Access to simulator data is controlled through permissions established on a per-study basis.

If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

While every effort will be made to protect the privacy of your information, absolute confidentiality cannot be guaranteed. This does not limit the duty of the researchers and others to protect your privacy.

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?

If you become ill or are injured while you are in the study, get the medical care that you need right away.

- If you are injured or become ill from taking part in this study, medical treatment is available at the University of Iowa Hospitals and Clinics.

- The University of Iowa does not plan to provide free medical care or payment for treatment of any illness or injury resulting from this study unless it is the direct result of proven negligence by a University employee.
- If you experience a research-related illness or injury, you and/or your medical or hospital insurance carrier will be responsible for the cost of treatment.

COSTS

There will be no charge to you for your participation in this study. The study drug, study-related procedures, and study visits will be provided at no charge to you or your insurance company.

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a study-related injury, or have questions, concerns or complaints about the study, please contact the study investigator at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, contact:

- By mail:
  Study Subject Adviser
  Advarra IRB
  6100 Merriweather Dr., Suite 600
  Columbia, MD 21044
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00055311.

VOLUNTARY PARTICIPATION / WITHDRAWAL

Your decision to participate in this study is completely up to you. You may choose to not participate or you may stop participating in this study at any time for any reason without penalty or loss of benefits to which you are otherwise entitled and without any effect on your future medical care. However, **please note that information related to your participation in the study that is collected up to the point of your withdrawal from the study cannot be removed from the study records.**

The study staff or sponsors can stop your participation in this study at any time without your consent for the following reasons:

- If it appears to be medically harmful to you,
- If you fail to follow directions for participating in the study (including adhering to protocols related to the overnight stay in the off-site residential facility),
- If it is discovered that you do not meet the study requirements,
- If the study is canceled,
- If there are technical difficulties with the driving simulator, or
- If other unforeseen or administrative issues arise that require we end your participation.

If you leave the study for any reason, study staff will ask you to participate in a safety follow-up visit and/or phone call.

CONSENT

I have read and understand the information in this informed consent document. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. I voluntarily agree to participate in this study until I decide otherwise. I do not give up any of my legal rights by signing and dating this consent document. I will receive a copy of this signed and dated consent document.

_____

Subject's Printed Name

_____ _____

Subject's Signature Date

_____

Printed Name of the Person Conducting the Consent Discussion

_____ _____

Signature of the Person Conducting the Consent Discussion Date