Effects of Cannabis Use in Cancer Patients: A Feasibility Study

Protocol Number: 18-0836

Principal Investigator: Angela Bryan, PhD

Co-Investigators: Ross Camidge, MD, PhD; Daniel Bowles, MD; Cinnamon Bidwell, PhD; Jost Klawitter, PhD

Coordinating Center: University of Colorado Boulder

Version Date: May 31st, 2022

ClinicalTrials.gov ID: NCT03617692

STATEMENT OF COMPLIANCE

This is an investigator-initiated study. The principal investigator Angela Bryan, PhD, is conducting the study and acting as the sponsor. As the sponsor-investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed.

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by applicable United States (US) laws and applications, including but not limited to United States (US) Code of Federal Regulations (CFR) as applicable (45 CFR Part 46, 21 CFR).

The PI will assure that no changes to the protocol will take place without documented approval from the Institutional Review Board (IRB). All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator
Print/Type Name:

Signed: _____ **Date:** _____

LIST OF ABBREVIATIONS

ACRONYM	DESCRIPTION
11-OH-THC	11-Hydroxy-Δ^9-tetrahydrocannabinol
AUDIT	Alcohol Use Disorder Identification Test
BAI	Beck Anxiety Inventory
CAT	Computerized Adaptive Test
CBC	Cannabichromene
CBD	Cannabidiol
CBD-A	Cannabidiolic Acid
CBG	Cannabigerol
CBG-V	Cannabigevarin
CBN-COOH	Carboxy- cannabinol
CI	Confidence Interval
Co-I	Co-Investigator
EMR	Electronic Medical Record
FACT-Cog	Functional Assessment of Cancer Therapy - Cognitive
FACT-G	Functional Assessment of Cancer Therapy - General
FDA	Food and Drug Administration
IIT	Investigator-Initiated Trial
HPLC-MS	Multianalyte high-performance liquid chromatography + tandem mass spectrometry
M	mean
MCQ	Marijuana Craving Questionnaire
Mg	milligram
N	Number of participants
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
OCRST	Oncology Clinical Research Support Team
OR	Odds Ratio
PI	Principle Investigator
PSQI	Pittsburgh Sleep Quality Index
REDCap	Research Electronic Data Capture
STAI	State-Trait Anxiety Inventory
THC	Δ^9-tetrahydrocannabinol
THC-COOH	Carboxy- Δ^9-tetrahydrocannabinol
THC-V-COOH	Carboxy- Δ^9-tetrahydrocannabivarin
TLFB	Timeline Followback Substance Use Assessment
UCH	University of Colorado Hospital
VA	Veterans Affairs Medical Center

PROTOCOL SUMMARY / SYNOPSIS

Protocol Title: *Effects of Cannabis Use in Cancer Patients: A Feasibility Study*

Objectives:

- ***Primary Objective:***

The goal of this study is to determine the feasibility of a human observational study of orally administered *Cannabis* use among cancer patients, towards developing feasibility/pilot data in support of an R01 grant application to the National Cancer Institute. The primary objective will be to enroll 30 patients and demonstrate reasonable compliance with study procedures within fifty-four months of active recruiting.

Endpoint:

- ***Recruitment Outcomes:***

Number of interested patients who contact the research team
Number of eligible potential participants
Number of enrolled eligible participants
Number of study assessments completed by enrolled participants
Number of participants who complete the study

Population:

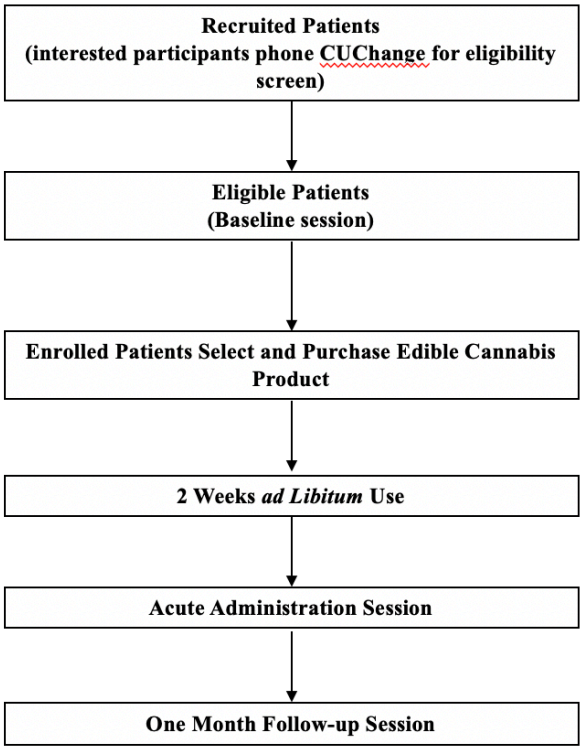
- ***Sample size***
  - Maximum number of participants that can be enrolled is 150 (allow for screen failures)
  - Minimum number of participants to be enrolled: **30** (number of participants needed to answer scientific question/aims)
- ***Gender***
  - Male and Female
- ***Age Range***
  - 21-100
- ***Demographic group***
  - Have a diagnosis of any solid tumor type who has or is undergoing either curative or palliative treatment
- ***General health status***
  - Oncology Patients
- ***Geographic location***
  - Denver/Boulder Area

Phase: Pilot

Number of Participating Sites enrolling participants: UC Central; UC Boulder

Description of Study Agent:	Self-Administered *Cannabis*
Study Duration:	Fifty-Four Months

SCHEMATIC OF STUDY DESIGN



1 PARTICIPATING SITES

A complete and current listing of investigators, research personnel, research facilities and other study centers (if applicable) participating in this study will be maintained throughout the duration of this study on a **Protocol Contact List** form, incorporated herein by reference.

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

2.1.1. Cannabis Use and Cancer. The American Cancer Society (*www.cancer.org*) quotes a lifetime risk of invasive cancer of 42% in men and 38% in women in the USA. Consequently, with the emergence of medical *Cannabis* as a therapeutic option in many states, particularly for cancer treatment-related symptomatology, this population represents one of the largest opportunities for real world medical *Cannabis* use research. As of early 2017, twenty-nine states

and the District of Columbia have legalized medical *Cannabis* programs. Importantly, recreational use is now legal in several states, making *Cannabis* even more accessible to potential medical users *even without a doctor's explicit recommendation or prescription*. Recent polls indicate that 77% of Americans believe that *Cannabis* has legitimate medical purposes[2]. Likewise, a recent poll of physicians in North America found that 76% would recommend the use of *Cannabis* to alleviate symptoms, specifically in the case of a patient suffering from advanced cancer and severe cancer treatment-related side effects[3]. In addition, because of its potential to target multiple symptoms, it has been suggested that *Cannabis* might reduce polypharmacy among cancer patients[4]. While there is a great deal of cultural support for medical *Cannabis* programs, cancer patients and doctors alike have very little scientific information on which to base decisions regarding whether or not to use *Cannabis* or which product, cannabinoid composition, or route of administration to use[5]. This information is critical as some products may be more or less beneficial, or more or less harmful in this population. **Given the fact that acceptance of and access to *Cannabis* is rapidly increasing across the nation, research on the risks and benefits of legal market cannabis use in this vulnerable population should clearly be a high priority.** The bulk of research on the use of medical *Cannabis* in cancer focuses on physical symptom reduction, while in contrast almost no studies have examined the *psychological and cognitive* impacts of medical *Cannabis* on cancer patients. This lack of research is surprising, given that the importance of examining new strategies with the potential to improve quality of life in cancer care is well-recognized among clinicians[6].

As noted, research examining medical *Cannabis* use in cancer patients has focused primarily on the effects of *Cannabis* on the reduction of physical symptoms related to cancer and anti-cancer treatment (e.g., chemotherapy). Recent reviews of this literature suggest that there is some evidence that medical *Cannabis* and/or synthetic cannabinoids can alleviate nausea and vomiting, stimulate appetite, reduce pain, alleviate anxiety, and mitigate neuropathy in this population[7,8]. Importantly, some studies have illustrated that *Cannabis* may be more effective and/or desirable than standard treatments for these symptoms. For example, a review of 30 randomized studies investigating antiemetic properties of *Cannabis* compared to either placebo or standard antiemetics found that oral cannabinoids were more effective at reducing nausea and vomiting, and in these studies, between 38 and 90% of patients reported that they preferred the cannabinoids[9]. While its antiemetic properties are clear, much less is known about other potential beneficial effects.

The current state of the research on *Cannabis* is fraught with important limitations. Most relevant to the current proposal is the fact that much of the research on cannabinoids in cancer treatment examines the effects of synthetic cannabinoids administered in capsule form (e.g., nabilone, dronabinol[10]). However, given the changing legal status and availability of *Cannabis* both recreationally and medicinally, it is increasingly the case that cancer patients who use *Cannabis* are using it in plant derived form. While there are a vast number of products available in state-regulated medical and recreational markets, there is very limited research on how these new products might influence the consumer. *Cannabis* in its plant form contains more than 60 different cannabinoids, and the potencies of each vary significantly across strains[10,11]. One of these cannabinoids, cannabidiol (CBD) may actually mitigate detrimental psychological effects of the more well-known and psychoactive cannabinoid, Δ9-tetrahydrocannabinol (THC)[12]. Yet most published research on *Cannabis* in cancer care equates effects of isolated synthetic THC to the far more complex plant form. The current proposal seeks to assess the feasibility of conducting a fully-powered study of the effects of plant-derived legal market *Cannabis* as used

by current cancer patients. Specifically, we wish to determine whether it is feasible to appraise the effects of orally administered *Cannabis* products among a cancer patient group by determining whether this group is willing to participate in all necessary components of a study examining how differing ratios of cannabinoids in cannabis products (based on type of product strain used) relate to symptom relief, quality of life, and cognitive measures.

2.1.2. Psychological effects of *Cannabis* use in cancer patients. There is some research that suggests the potential for positive psychological effects of *Cannabis* use that may improve quality of life. For example, some of the effects that are commonly described as adverse or harmful (e.g., feeling "high", euphoria, sleepiness), may be reframed as positive effects for those suffering from cancer and the side effects of treatment (i.e., mood elevation, reduced anxiety, improved sleep quality)[7]. One study examined the effects of medical *Cannabis* on psychological symptom management by interviewing Israeli cancer patients before and 6-8 weeks after they received a medical *Cannabis* license, and found reductions in self-reported mood disorders, sleep disorders, and pain, as well as reduced use of pain medication and depression/anxiety medication after initiation of medical *Cannabis* use. Given these findings, the study authors concluded that medical *Cannabis* may be an important contribution to palliative cancer care[13].

At the same time, it is important to acknowledge the potential negative effects. Specifically, the literature is fairly clear that acute use of *Cannabis* temporarily compromises cognitive function. For example, one study observed impaired performance on an executive function task and two motor control tasks after a 13% THC dose of *Cannabis*[13]. On the other hand, the evidence is mixed regarding the long-term effects[14,15]. Notably, this evidence base is somewhat limited in that relatively few researchers have examined these effects, and results of such studies have in some cases been inconclusive or have important limitations (including studying only the effects of very low doses of THC that are rarely used in the real world)[15]. Regardless, it is nearly inevitable that cancer patients are faced with both self-regulatory challenges (i.e., adhering to complicated drug regimens, healthy eating, exercising to reduce fatigue) as well as cognitively taxing decisions (e.g., weighing pros and cons of treatment options) that rely on high-level working memory and executive function processes that may be influenced acutely by *Cannabis* use. Further, one of the greatest concerns of cancer patients and survivors are changes to their cognitive abilities[16–18]. Research using traditional neuropsychological assessment has documented deficits in processing speed, attention/working memory and episodic memory[19–21]. Moreover, cancer patients' subjective reports of cognitive difficulties are often greater than the deficits when compared to performance on objective tests[22]. Finally, there is a large body of research demonstrating that cancer patients may experience reduced cognitive functioning due to the effects of chemotherapy[23]. Thus, it is essential to examine the impact of *Cannabis* use on both objective and subjective cognitive function in this already-vulnerable population.

2.1.3. Synergistic effects of multiple cannabinoids on pain, anxiety, and insomnia. It is worth noting that pain, anxiety, and insomnia are three of the most common complaints among cancer patients and are also the three most common conditions cited for use of medical *Cannabis*[24]. Importantly, an expert panel convened by the National Academies of Sciences, Engineering, and Medicine concluded in their 2017 report that there was conclusive evidence that *Cannabis* is effective for treatment of chronic pain, moderate evidence for its effect on sleep outcomes, and limited evidence for effects on anxiety[25]. They also concluded that there is conclusive evidence for *Cannabis* effectiveness at treating chemotherapy-induced nausea and vomiting, however this was the only symptom domain where research has been conducted primarily or exclusively with

cancer patients. Further, much of the existing research has been conducted with synthetic individual cannabinoids. Thus, research on pain, insomnia, and anxiety among cancer patients and using products widely available in the legal market is critically needed. Currently, relief from chronic pain is by far the most common condition cited by patients for use of medical *Cannabis* in U.S. states with legal markets; 87%-94% of self-reported medical *Cannabis* users report using *Cannabis* for relief of a pain condition[26,27]. Treatment of anxiety and insomnia are the next most common medical uses[24]. In addition, there is some evidence that individuals are replacing the use of traditional pain, mood, and sleep medications with *Cannabis*. For example, one recent study reported survey data suggesting that medical *Cannabis* use in pain patients was associated with a 64% decrease in opiate use[28]. A second study recently observed significantly lower opiate overdose deaths in states with medical access to *Cannabis*[29]. Similarly, recent analyses of prescription data in states with medical access to *Cannabis* suggest a significant reduction in the prescription of medications for pain, anxiety, and sleep dysfunction[30].

Pain. Across five high quality reviews conducted in the past four years, results were consistent in suggesting that cannabinoids demonstrate an effect on pain[31–35]. For example a rigorous, systematic review by Whiting et al[35] covered 28 chronic pain studies (2454 participants) primarily conducted in Canada or Europe. Twenty-two of these studies evaluated plant-derived cannabinoids (cannabis extract mouth spray or nabiximols n=13, plant flower that was smoked or vaporized n=5, oramucosal spray n=3, oral THC n=1) while 5 studies evaluated synthetic THC (i.e., nabilone). All of the selected studies included either an active comparator or placebo control. Analyses across studies that evaluated the effects of inhaled plant-derived *Cannabis* suggested a statistically significant effect on the odds of a 30% or greater improvement in pain (OR = 1.41). The largest single effect size presented across the reviews was observed with inhaled *Cannabis* on pain [e.g. OR, 3.43; 38]. Consistent with this, an average OR of 3.22 (CI: 1.59 to 7.24) was found across 9 doses of inhaled THC tested across five studies[31]. While the analgesic properties of THC are the most widely studied, pharmacological and clinical data suggest that cannabidiol (CBD) is another primary cannabinoid that may work synergistically with THC in a multi-target analgesic approach to pain relief. For example, nabiximols which are an administration of a plant-based mixture of THC and cannabidiol (CBD) via mouth or nasal spray were associated with significant reductions in numerical pain ratings across the available studies.

Anxiety/affect. There is evidence demonstrating that *Cannabis* use is associated with increased anxiety and anxiety disorders[36]. However, other data, including our own prospective work, suggests that *Cannabis* use may be protective for anxiety and may decrease the chances of developing an anxiety disorder[37]. A number of studies have found that *Cannabis* acutely increases positive mood and measures of reward[38,39] even when using a "balanced placebo" design to control for expectancy effects[40]. This finding is consistent with a growing body of evidence from animal models suggesting that *Cannabis* has anxiolytic effects[41]. Overall, however, research studies have largely ignored the fact that *Cannabis* exists in different forms with differing ratios of THC to CBD and have not characterized the effects of *Cannabis* as the compound action of different cannabinoids that vary in terms of their pharmacological effects. Two primary cannabinoids, THC and CBD, may have opposing effects with regard to anxiety. Importantly, THC is thought to be acutely anxiogenic[42], while treatment with CBD has anxiolytic effects without the experience of a "high"[43]. Clarifying the anxiolytic effects of specific strains that differ in their cannabinoid composition may explain these discrepant findings.

Sleep. THC has been shown to dose dependently reduce wake time and increase Stage 4 sleep across human and animal studies[44,45]. Whereas it has been well established that THC promotes sleep, contradictory results on the effect of CBD on sleep have been reported. For instance, an early study found a diminution in sleep after systemic administration of CBD[46], whereas other work showed an improvement in sleep in insomniacs after using CBD[47]. Much of this work has been done, again, with synthetic oral forms of THC and CBD in isolation, leaving a limited knowledge base on the effects of the synergistic effects of plant-derived cannabinoids in common forms of administration.

A 2017 survey study of cannabis use among cancer patients showed that pain, stress, and sleep were all identified as reasons for *Cannabis* use[5]. Though the study did not ask specifically about quality of life, over half (51%) of patients felt that *Cannabis* was a "major benefit" while another 39% agreed it was a "moderate benefit." It is logical to assume, therefore, that to the extent that *Cannabis* alleviates negative symptoms from cancer and cancer-treatment, it should also increase overall quality of life. Also, while there is evidence to suggest that *Cannabis* may be effective for pain, anxiety, and sleep—and consequently quality of life—it is not clear whether these effects are driven by one of the primary cannabinoids (THC or CBD) or the synergistic combination of the two. Overall, very little is known about the efficacy, dose, routes of administration, or side effects of commonly used *Cannabis* products in the U.S that come in a variety of potencies and cannabinoid contents, nor critically how these products may work differently in cancer patients.

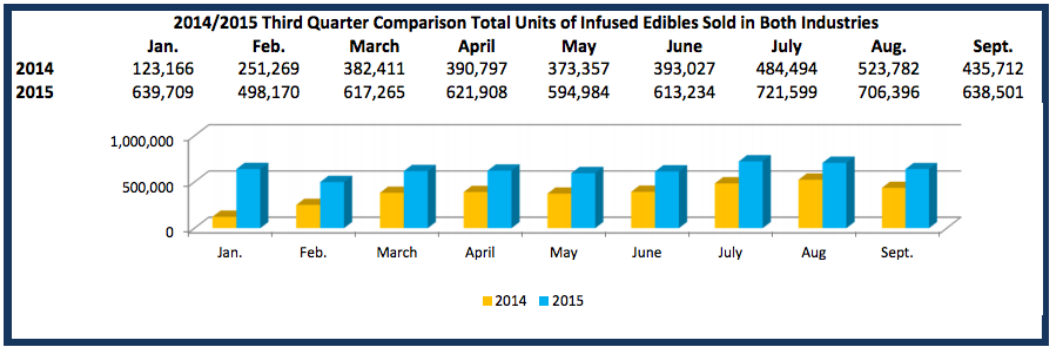
2.1.4. THC and cognitive impairment. A number of studies indicate that *Cannabis* produces acute cognitive impairment, especially relating to memory and attention during intoxication and possibly for hours to days after use[48,49]. For example, studies that were published as early as the 1970's suggest that *Cannabis* disrupts immediate and delayed free recall of information [e.g., 50,51]. Recall of words from a list is one of the most common approaches to demonstrating the effect of THC on recall performance [e.g., 52]. Studies have also suggested working memory may be the most sensitive to the acute effects of *Cannabis* [*see* 53]. Among the studies that included two THC concentrations, higher doses mostly yielded greater cognitive impairment[15,54–56]. In neuroimaging work, *Cannabis* users showed differential brain response to an associative memory task while under the influence of THC compared with a placebo. Specifically, THC attenuated brain activity in the insula, right inferior frontal gyrus (IFG) and left middle occipitals gyrus during encoding, and increased network-wide activity during recall. Taken together, these results suggest that THC has a negative effect on the neurocognitive processes involved with encoding, and neural activation changes during recall likely reflect a compensatory mechanism for the affected encoding. That is, the memory system as a whole must work harder in order to account for the cognitive deficits induced by THC. In sum, the literature suggests that acute administration of *Cannabis* impairs the encoding and retrieval of information, albeit to a modest degree, and these effects may be dose-dependent on THC level. Further, this *Cannabis*-induced cognitive impairment can last from hours to days after use[48] and potentially longer in heavy chronic users. Thus, the potential cognitive side effects of regular use of current *Cannabis* products are highly relevant to cancer patients, who may use *Cannabis* on a regular basis to treat their symptoms but who also want to maintain as much cognitive function as possible.

2.1.5. Does CBD mitigate the harmful cognitive effects of THC? Clearly, the evidence suggests that acute *Cannabis* use is associated with at least modest cognitive impairment. However, almost all of this research was conducted with low potency cannabis provided by the

government and almost all of this research was focused on the effect of one particular cannabinoid, namely THC. The effects of other primary cannabinoids, such as CBD, are important to consider when interpreting the harmful effects of *Cannabis* use, especially given that *Cannabis* includes more than 80 additional phytocannabinoids[57,58]. Products commonly available in states like Colorado differ dramatically on the potency of these cannabinoids. As noted previously, studies suggest that THC is associated with memory and other cognitive impairment [48]. Conversely, analyses suggest that CBD may attenuate the negative effects of THC on cognition and other measures[59–68]. Most of the work on CBD has involved the administration of THC and CBD in synthetic pill form. Much less is known about the combined effects of THC and CBD when using cannabis in the forms commonly available in dispensaries across the U.S. This is a high priority area of research in terms of understanding how to reduce the potentially harmful effects of cannabis use in cancer patients.

2.1.6. Limitations of existing literature. Most of the *Cannabis* products that are sold in state regulated markets bear little resemblance to the products that are available for research from NIDA at the federal level in the U.S. For example, per Figure 1[69], the most recently available data in Colorado alone show that >600,000 edible units of *Cannabis* were sold across medical and recreational dispensaries each month of 2015, nearly a 50% increase from the monthly data reported for 2014, the first year of legal *Cannabis* sales in our state[69]. Data also suggest that medical *Cannabis* patients are more likely to use edible products than recreational users[69]. Importantly, using *Cannabis* in orally administered form represents a very different way to use cannabis, in part because in contrast to *smoked* forms of *Cannabis* which produce acute effects that begin to diminish rapidly after consumption (blood levels dramatically decrease within 15 minutes of smoking), *orally administered Cannabis* produces prolonged effects that last at least 4 hours post-consumption[70,71]. This in part explains their increased use in patients who seek sustained relief from symptoms. However, no data are available to understand the mechanisms or effects of orally administered *Cannabis* of various potencies and cannabinoid ratios. Thus, while the use of particular forms of *Cannabis* in cancer patients is supported by well-controlled clinical trials as reviewed above, very little is known about the efficacy, dose, routes of administration, or side effects of *commonly available and increasingly used orally administered Cannabis products*. In the case of cancer patients, our clinician co-investigators instruct their patients not to inhale *Cannabis*, but instead to use orally administered forms. More research is desperately needed given the increased availability of *Cannabis* across the nation and the lack of any research in the U.S. on the beneficial or harmful effects of orally administered *Cannabis* for cancer patients.

Figure 1. State of Colorado Official Reporting on Edible Cannabis Sales



2.2 RATIONALE

2.2.1. Overview. We submitted a grant to NIH/NCI using an observational design that is well established by the CUChange Lab to do a fully powered trial with cancer patients. While the reviewers noted that "the proposed research will provide much needed scientific data to the public, physicians, patients, and to the larger research community on the varying effects of different forms of *Cannabis* on cancer treatment-related symptoms and patient quality of life" they were concerned that "while the group is experienced with the methodology proposed, the lung cancer population is a new endeavor. The team is bolstered by inclusion of coinvestigator effort with experience in this population, but there are no pilot data to indicate proof-of concept and feasibility of yielding a sufficient sample with reasonable compliance with procedures." Thus, we seek to demonstrate proof-of-concept and feasibility.

Our lab has been conducting neurobehavioral research on *Cannabis*[39,72] as well as observational research on the relationship of *Cannabis* use to broader health behavior[72–74] for many years. Recently, we have focused on the development of cutting edge observational designs to examine the effects of *legal market* cannabis in recreational and medical users. The goal of a fully powered version of this study would be to examine the effects of orally administered *Cannabis* on measures of symptom relief, quality of life, and cognitive function in the context of a human observational study of cancer patients. **Our central hypothesis for a future, fully powered trial would be that the analgesic, anxiolytic, and somnolent effects of Cannabis will be strongly related to the potency ratio of the cannabinoids THC and CBD in the products participants select for use (i.e., products with a combination of THC and CBD as opposed to those with THC only will attenuate cognitive impairment, and also will be correlated positively with quality of life outcomes).**" Thus, an observational study will provide concrete data to inform medical decision making and reduce the harm of *Cannabis* use in cancer patients. Note that in the *current* legal environment, and despite the fact that *Cannabis* use is legal in our state and nearly 30 other states, we are not permitted to handle *Cannabis*, have *Cannabis* in our research lab, nor provide *Cannabis* itself nor instructions for its use to research participants. Tightly controlled experimental laboratory studies (e.g., clinical trials with randomization) using products available in state-regulated markets are simply, at this point, not possible owing largely to federal law and the University requirements related to the Controlled Substances Act and Drug Free Schools and Communities Act. Because a traditional clinical trial design is not possible given the current federal status of *Cannabis* products, we would employ our established prospective observational design. Specifically, individuals who have already decided to try *Cannabis* for their cancer treatment-related symptoms will initiate use of an orally administered product they have selected. A research assistant will provide information on the range of edible *Cannabis* products and basic information about their various cannabinoid profiles, approximate prices, and nearby locations where participants may choose to purchase their product. The participants will then purchase the product and decide how often and how much to use. This approach is consistent with federal law, supported by our preliminary and ongoing studies, and timely given that *Cannabis* is widely used by cancer patients in state legalized markets and yet almost no scientific data are available to aid cancer patients or their physicians in optimally prescribing medical *Cannabis* in this setting. An observational design that balances adequate internal validity with high external validity is critical for beginning to build the knowledge base about why so many cancer patients are turning to *Cannabis*. To that

end, we have developed and deployed innovative procedures that allow us to study legal market *Cannabis* in the compositions and forms that are widely available, while staying within the current regulatory framework and maintaining a high level of internal validity (see preliminary studies). Our purpose in future studies is to explore the pharmacological properties of THC, CBD, and their combination in orally administered cannabis with regard to differential impacts on symptom relief and cognition in order to understand and maximize any potential positive impact of *Cannabis* and minimize potential harm. Moving from our prior studies in recreational users to a cancer patient population has required an evolution in our research approaches, including addressing rapidity of accrual in a symptomatic population, together with capturing co-medications, anti-cancer therapies and outcomes from these therapies as potential confounders of symptomatic and cognitive effects. Our studies will provide much needed scientific data to the public, physicians, patients, and to the larger research community on the varying effects of different forms of cannabis on cancer treatment-related symptoms and patient quality of life. Our proposed research is innovative and significant for the following reasons:

2.2.2. Opportunity to examine orally administered *Cannabis* products in a state with legalized medical and recreational use. We capitalize on a novel opportunity to examine effects of orally administered *Cannabis* products currently legally available to, and used in growing amounts by, individuals with cancer. As reviewed, prior human clinical and laboratory work on the effects of *Cannabis* on pain and anxiety has focused on short acting nabiximols in studies outside the U.S or on U.S. government grown *Cannabis* of very low THC potency and with no CBD, which is smoked or vaporized. It is important to note that there is no federal source of orally administered *Cannabis* products for research, despite the fact that >600,000 edible units are sold in Colorado alone every month. Given federal laws, the only way to conduct research on this widely consumed product is a naturalistic design, employing legal market orally administered products. Thus, although this study does NOT meet the definition of an interventional clinical trial per FDA guidelines, our observational design balances adequate internal validity with high external validity to result in a unique capacity to directly inform individual and policy decisions. This design is the only path forward in terms of understanding the effect of *Cannabis* in cancer patients because an actual clinical trial with edible *Cannabis* would never be allowed given the current legal environment at the federal level.

2.2.3. Despite clinical data suggesting that certain forms of *Cannabis* are associated with reduced pain and other symptoms, there is a dearth of data on the mechanisms and effects of widely available forms of medical *Cannabis* with varying *Cannabis* potencies and cannabinoid ratios. Specific to pain, clinical data support nabiximols, which is a short acting *Cannabis*-based oral mucosal spray that combines THC and CBD, for pain relief. However, *Cannabis* users have a range of options that may vary in their benefits and harmful side effects, and importantly many cancer patients use *Cannabis* without obtaining a medical card nor receiving advice from a physician because *Cannabis* is easily purchased in recreational dispensaries. To our knowledge, there are no human studies in the literature that report the effects of legally available orally administered *Cannabis* in cancer patients, nor are there any reports in the literature of how various types of *Cannabis* may differentially impact pain, other symptom areas, and cognitive side effects in cancer patients. Using legal market orally administered *Cannabis* products will provide new, externally valid, and more reliable assessments of the relationship of THC and CBD to both the potential beneficial and harmful effects of *Cannabis*. This research thus fills an important gap in the knowledge base on the effects of primary cannabinoids on symptom relief in cancer patients.

2.2.4. Addresses the need for timely empirical data on the harms and benefits of *Cannabis* use in cancer patients in order to impact public health. Given the extremely high rates of use of *Cannabis* in cancer patients, data on potential benefits and harms related to *Cannabis* use in this patient group are critical. An evidence-based message clearly describing the potentially beneficial effects on pain, anxiety, and sleep, as well as any harms related to cognitive effects of specific forms or compositions of *Cannabis* is needed, given the growing perception that *Cannabis* use is beneficial and is relatively safe. It is likely that not all *Cannabis* is equal in terms of harms or benefits. The proposed research will help begin to generate the evidence-base as to which forms, if any, produce the most direct effects on symptom domains as well as which forms produce the most harmful effects on cognition. Successful dissemination of this information to the public can directly inform patient decisions about whether to use *Cannabis* at all and which type to use.

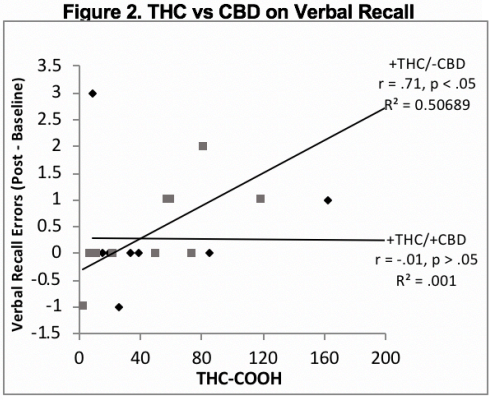
2.2.5. Preliminary studies relevant to this proposal.

Prior experience and expertise of the team. The research team has taken a transdisciplinary approach to the study of the risks and benefits of *Cannabis* use across a number of populations. The PI (Bryan) and major Co-I (Bidwell) are co-directors of the CUChange Lab at the University of Colorado Boulder and have extensive experience in the integration of neurocognitive assessments into longitudinal behavioral research on substance use (e.g., R01 AA017390: PI Bryan; 2R01AA013844: PI Bryan; R01 DA025074: site PI Bidwell, Co-I Bryan; R01AA024632: Co-I's Bidwell and Bryan; R01DA039707: Co-I's Bidwell and Bryan). The PI also brings a wealth of statistical expertise. Co-I Camidge, who is a renowned clinical scientist and thoracic oncologist with medical expertise in the detection, treatment, and palliative care aspects of lung and other thoracic cancers, will serve as the medical director on the project. His medical oversight will be supported by Co-I Bowles, who has considerable expertise in the role of medical *Cannabis* in cancer patients. Drs. Camidge and Bowles are faculty at the University of Colorado Anschutz School of Medicine. Together, they authored a paper on the use of *Cannabis* in cancer care[10]..

*Previous and Current Cannabis Studies in the CUChange Lab***.** Our neurobehavioral research on *Cannabis*[75,76] as well as observational research on the relationship of *Cannabis* use to broader health behavior is well documented[12,72–74]. One pilot study utilized a design similar to the one proposed in this application. In the pilot study, regular *Cannabis* users (n=22) were asked to switch strains for three days after a washout period. Participants used either a +THC/-CBD (~14% CBD, <1% CBD) or a +THC/+CBD (7% THC, 14% CBD) smoked strain that was acquired from a local dispensary. Both the researchers and participants were blind to condition, and the blind was maintained by the dispensary and one senior investigator. After the washout period of no *Cannabis* use, participants used the assigned *Cannabis* strain daily for three days, including a final use on the third day. Immediately after this final use, participants came to the lab, by taxi, for assessment of its effects on cognitive responses. Our data (Figure 2) suggest that CBD may mitigate the negative effects of THC on verbal recall[12].

University of Colorado Thoracic Oncology Program. The program cares for close to 1000 patients in total at the University of Colorado Hospital (UCH) and sees approximately 400 new thoracic oncology patients a year. In 2017, an informal survey in the clinic suggested approximately 40-50% of patients have tried medical *Cannabis* and 2 new medical *Cannabis* cards are being issued a month to this population. Although recall, nearly identical *Cannabis* products are available at recreational dispensaries to any adult 21 or over; thus, a medical card is not necessary. All aspects of clinical and translational research are well established in the program, with consistent rates of 30-40% of new patients engaged in classical interventional clinical trials. The main University of Colorado Hospital (UCH) is also associated with the largest VA in the Western region (set to move on site in 2018) and is part of a clinical network of hospitals across the Rockies front range run by UCHealth giving additional opportunities to explore to increase participant numbers as needed (see section 5.3.4). The study of *Cannabis* as an adjunct to palliative care approaches is thus critical and highly relevant to this patient group.

Figure 2. THC vs CBD on Verbal Recall



2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

- Human Subjects Involvement and Characteristics: Participants for the proposed research will be individuals who have been diagnosed with cancer of any solid tumor type and are interested in using *Cannabis* in the context of their cancer care. Participants' medical charts will be reviewed by our study physician, with the documented consent of the patient participant, to ensure their safety to engage in study participation. To account for expected attrition (20-25% based on our similar *Cannabis* studies) 150 participants will be recruited in total, though we anticipate that only 30 of these will complete the study.
- Sources of Materials: The source of the majority of research data will be the participants' responses to questionnaires or questions on interviews. Other research data will involve cognitive tests. Finally, we will obtain information on health status and current medications from HIPAA compliant review of electronic medical records accessed by the study team and our oncology co-investigators.
- Potential Risks: Potential risks are minimal. They include: **a)** Breach of confidentiality; **b)** Adverse effects of *Cannabis* such as intoxication, acute mood shifts, odd perceptual experiences, etc.; and **c)** The need for medical oversight in a cancer patient population.

2.3.2 KNOWN POTENTIAL BENEFITS

The risks to participants are reasonable in relation to the anticipated benefits to participants and/or society, and in relation to the importance of the knowledge that may reasonably be expected to result, thereby falling in favor of performing the study:

- To Participant: This study is expected to add to the knowledge base of information on the effects of different types of *Cannabis* and cannabinoids on cancer-related symptoms, quality of life, and cognition and are expected to inform patient choices and future harm reduction efforts. Given only a slight risk to participants and the greater possibility of long-term benefits to the scientific and public knowledge bases and providing highly externally valid data to inform harm reduction efforts, the risks/benefits ratio seems reasonable. The risks associated with participating have been minimized via procedures described above.
- To Society: From a larger perspective, the findings of this investigation will increase the body of knowledge about the potential benefits and risks of orally administered legal market *Cannabis* use in cancer patients with any solid tumor type. Existing research on the connection between *Cannabis* and cancer related processes has used either animal models with extracted constituents of *Cannabis* (which is not how it is used by humans) or has focused on low potency forms and/or forms of *Cannabis* not typically used or available to U.S. residents, but are silent in several important ways. First, such studies are completely silent on the effects of orally administered *Cannabis* in forms widely available to cancer patients across the U.S. In addition, limited information is available on the impact of various potencies and the different components of the *Cannabis* used. We also have limited data on the impact of these legal market *Cannabis* products on cognitive functioning in cancer patients with any solid tumor type.
- Justify the importance of the knowledge: Ultimately, the proposed study will add critical information to the knowledge base and provide an evidence-base that will inform personal decisions and reduce harm in patients who are considering using *Cannabis* in the context of their cancer treatment. In addition, these studies will allow for the development of public policy approaches to harm reduction, which is much needed in states that are legalizing *Cannabis* use for either medicinal or recreational purposes.

3 OBJECTIVES AND PURPOSE

The goal of this study is to determine the feasibility of a human observational study of orally administered *Cannabis* use among cancer patients with any solid tumor type, towards developing feasibility/pilot data in support of an R01 grant application to the National Cancer Institute. The primary objective will be to demonstrate the number of contacts necessary to enroll 30 eligible patients and demonstrate reasonable compliance with study procedures (see section 10.5.4) within fifty-four months of active recruiting.

4 STUDY DESIGN AND ENDPOINTS

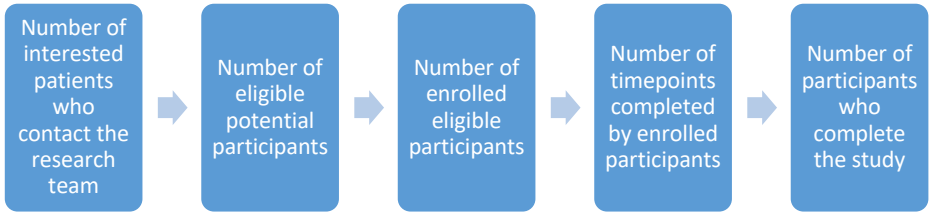
4.1 DESCRIPTION OF THE STUDY DESIGN

Tightly controlled experimental laboratory studies (e.g., clinical trials with randomization) using *Cannabis* products available in state-regulated markets are simply, at this point, not possible owing largely to federal law and the University requirements related to the Controlled Substances Act and Drug Free Schools and Communities Act. Because a traditional clinical trial design is not possible given the current federal status of *Cannabis* products, we will use a patient-oriented, prospective observational design. Specifically, individuals who have already decided to try *Cannabis* for their cancer treatment-related symptoms will initiate use of an orally administered product they have selected. A research assistant will provide information on the range of edible cannabis products and basic information about their various cannabinoid profiles, approximate prices, and nearby locations where participants may choose to purchase their product. The participants will then purchase the product and decide how often and how much to use. This approach is consistent with federal law and supported by our preliminary and ongoing studies[77] (1R01AT009541-01, 1R01DA044131-01, CDPHE2902, R01DA039707). Participants will take the product as they see fit, without any frequency or dosing instructions from study staff, for two weeks, at which time they will be scheduled for their Pre- and Post- Administration Assessment (Ta1-Tc1) so that we may examine the acute effects of the product. The final follow-up will be one month later via an online survey sent directly to the participant via email. Details about the various study sessions are provided in Section 7.

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINT

Our study endpoints are recruitment based. Please refer to the figure below.



5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision to sign and date the consent form.
2. Stated willingness to comply with all study procedures and be available for the duration of the study.
3. Be a female or male aged at least 21 years.
4. Have a diagnosis of any solid tumor type who has or is undergoing either curative or palliative treatment.
5. Have intent to use *Cannabis* to treat their symptoms.

5.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Report of other non-prescription drug use, such as cocaine, heroin, methamphetamine in the past 60 days
2. Actively seeking or in treatment for any substance use disorder
3. Acute illness other than cancer that could affect cognition or compliance per the decision of the study M.D.
4. Premenopausal females who are pregnant or trying to become pregnant. Participants who become pregnant while participating in the study will also no longer be eligible for participation.
5. A Telephone Interview for Cognitive Status (TICS) score indicating moderate or severe cognitive impairment at screening

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

5.3.1. Recruitment. With assistance from our Medical Director and co-investigator Dr. Camidge and co-investigator Dr. Bowles, we will advertise our study with flyers in local oncology clinics affiliated with the University of Colorado Health (UCHealth) system. Our partner oncologists will not actively recruit or consent study participants, but rather contribute by making patients aware of the opportunity to participate in this research. Flyers will also be posted in local oncology clinics not affiliated with UCHealth. Paid advertisements through Facebook and other social media sites that allow for targeting based on age, geographic location, and interests will be used. We will also utilize targeted mailings. A list of names and addresses of individuals who fit our age demographic and geographical area will be obtained from publicly available records purchased from a marketing firm (http://www.alescodata.com/reseller-programs.html). The recruitment flier will be mailed to each address on the list. In addition, print advertisements in local newspapers and magazines will be used. In terms of minority inclusion, the percentage of ethnic groups in the study will reflect the demography of the UCHealth Cancer clinics. Specifically, approximately 74% of participants will be non-Hispanic white, 12% will be Hispanic/Latino, 5% will be African American, and the remaining participants will be Asian, Native American/American Indian, or of mixed or other race. With respect to the recruitment of women, approximately 50% of cancer patients at UCHealth are female (51.4%). In terms of the inclusion of children, this is a study of the influence of *Cannabis* use on cancer care-related symptoms and cognitive function among cancer patients. Because the legal age for *Cannabis* use in Colorado is 21, we will not include any children in this project.

5.3.2. Participant Selection. A trained research assistant will screen prospective participants who call in for the study according to the inclusion/exclusion criteria. If any subject is questionable for inclusion, Dr. Bidwell (a licensed clinical psychologist) and Dr. Camidge (a licensed M.D.), will make the final determination of eligibility. Finally, all female potential study participants of child-bearing age will undergo a pregancy test to confirm eligibility. For the pregnancy screening, a trained research assistant will deliver a urine receptacle to the participant's home. The participant will then use the restroom in their home and return the receptacle to the research assistant to complete the urine test in the mobile laboratory.We expect that the proposed studies will reflect the ethnic diversity of the cancer population at the Cancer Center at Anschutz School of Medicine, such that approximately 20-30% of the final sample will represent Latino and non-Caucasian individuals.

5.3.3. Informed Consent. Potential participants who meet inclusion criteria will be scheduled for a remote baseline session. Participants will be emailed the eConsent in advance of this session. The eConsent may be viewed in its entirety and may be accessed at a later date if they want to think about participation. Each participant will go through the informed consent process with a trained research assistant over the phone or via Zoom, which will include reviewing all sections of the form, and answering any questions patients may have about study procedures or processes. Should participants choose to participate, they will verbally confirm that they agree to be in the study and will document informed consent electronically on the eConsent. Participants will be given the option of printing, downloading, or having the research team mail them a copy of the signed consent form for their own records. The REDCap e-consent framework will be used to document informed consent. The research assistant obtaining informed consent will electronically sign a separate instrument in REDCap associated with that participant's record to document the informed consent process.

5.3.4. Incentives and Retention. Our recruitment plan is to include patients with a diagnosis of any solid tumor type who has or is undergoing either curative or palliative treatment. However, because patients are not currently asked about their desire to use cannabis by their clinicians, and clinicians currently only know about patients' cannabis use desires if they are asked to sign an authorization for medical use, we are not certain that our recruitment goals are obtainable. A second potential pitfall is that a cancer patient population is cognitively and medically vulnerable, so it is possible that our assessments may be too taxing in terms of length or duration for patients to comfortably complete. We have ordered and scheduled assessments in this feasibility study prioritizing measures that would be representative of primary outcomes in a fully powered study to be collected first should patients fatigue and wish to quit. If it becomes clear that the number or order of assessments is not feasible, we will assure that procedures are adjusted to minimize burden on our patient participants. Incentives are offered at three different time points in the study (see Table 7.1 for compensation rates at Baseline, Two-week Acute Use, and One-Month Online Follow-Up appointments).

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if any clinical adverse event (AE), laboratory abnormality, new pregnancy, or other medical condition or situation occurs such that continued

participation in the study would not be in the best interest of the participant. Though highly unlikely, other circumstances under which a participant would be withdrawn without her consent include: (1) obviously not following study instructions (note: we will carefully track the number of participants who do not or cannot follow instructions as this is critical for feasibility and the design of the fully powered trial) or (2) behaving in a way that is verbally or physically abusive towards research staff. Those who experience early withdrawal will receive prorated payment based on the number of sessions they completed.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

All procedures in this study are completely voluntary, and participants may withdraw their consent to participate at any point. Attempts will be made to understand why participants withdraw, as this is important for a feasibility trial, but even in that case giving investigators information concerning withdrawal is voluntary. Termination of participant by investigators, as described above, will also be tracked in case there are procedures that are not feasible for cancer patients to follow. Again, this is critical for a feasibility trial. Once participants withdraw or are terminated, there will be no attempt to follow up with or further engage with the participant.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY (STUDY STOPPING RULES)

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the funding agency and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Insufficient compliance to protocol requirements.
- Data that are not sufficiently complete and/ or evaluable.
- Determination of futility.

6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

Study staff will not acquire orally administered *Cannabis*. The proposed work will utilize a design that is observational and does not involve assignment by the research team. More specifically, participants who are already planning to try *Cannabis* will choose their own product at baseline and purchase the product at a dispensary. Colorado law requires all edibles to be

tested by a state lab, which allows us to have a precise measure of potency after the participants purchase their products. Importantly, the researchers who conduct the assessments as well as all the senior investigators including the statistician (PI Bryan) will be blind to the participant's product choice.

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

According to Colorado state law, we cannot relabel the packaging of any *Cannabis* product.

6.1.3 DOSING AND ADMINISTRATION

The patient will use their orally administered *Cannabis ad libitum* at home. This aspect of the design is again consistent with an observational design and differentiates it from a classical interventional clinical trial, which is critically important because it is the only path forward for research on orally administered, legal market *Cannabis* given current federal law. Study staff will not advise participants on or participate in dosing and administration practices.

The disadvantage of our observational design is that we do not have direct control over the choice of product or the dosing and administration of the *Cannabis* product. To address this limitation, we will have participants take and send a picture of their purchased oral cannabis product to our lab via the REDCap system. Colorado requires all strains to be tested by a state licensed lab, and the dispensary that we work with performs cannabinoid and terpene potency testing on each batch produced and sets aside a specific lot of strains corresponding to the ratios utilized in this project (a CBD-dominant strain, a THC-dominant strain, and a THC+CBD strain). Thus, having a picture of the participant's purchased product will allow us to verify the strain and thus, the ratio of cannabinoids contained in the product for a measure of potency to operationalize our user groups.

6.1.4 ROUTE OF ADMINISTRATION

Oral administration *ad libitum*

6.1.5 STARTING DOSE AND DOSE ESCALATION SCHEDULE

Starting dose and escalation *ad libitum*

6.1.6 DURATION OF THERAPY

Two weeks use *ad libitum*

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

The complete schedule of measures taken at each assessment are outlined in Table 7.1.

Table 7.1: Schedule of Locations and Assessments

Timepoint	Measures	Location	Compensation
Baseline (T00)	Pain interference, pain intensity, anxiety symptoms, state and trait anxiety, sleep, quality of life, objective cognition, subjective cognition, demographics, alcohol and substance use history, cancer staging/treatment regimen (EMR)	At home (online)	$60, 1.5 hours
Two weeks *ad libitum* use		At home	
Pre-acute *Cannabis* use (Ta1)	Pain interference, pain intensity, anxiety symptoms, state and trait anxiety, sleep, quality of life, objective cognition, subjective cognition, alcohol and substance use history(timeline follow-back).	At home (online)	
1 hour post-acute *Cannabis* use (Tb1)	Pain intensity, state anxiety, objective cognition	At home (online)	
2 hour post-acute *Cannabis* use (Tc1)	Pain intensity, state anxiety, objective cognition	At home (online)	$100, 2.5 hours
One month follow-up (M1)	Pain interference, pain intensity, anxiety symptoms, state and trait anxiety, sleep, quality of life, subjective cognition, other substance use, Disease status/treatment regimen (EMR)	At home (online)	$10, 20 minutes

NOTES: EMR=electronic medical record, total compensation possible for 4 hours, 20 minutes of assessment=$170

7.2 LABORATORY PROCEDURES/EVALUATIONS

The complete list of measures and procedures is detailed in Table 7.2 below.

Table 7.2: Study Measures

Domain	Measure
Pain interference	REDCap: Promis Pain Interference CAT
Pain intensity	REDCap: Pain Intensity
Anxiety symptoms	Beck Anxiety Inventory (BAI)

State and trait anxiety	State-Trait Anxiety Inventory (STAI)
Sleep	Pittsburgh Sleep Quality Index (PSQI)
Quality of life	Functional Assessment of Cancer Therapy - General (FACT-G)
Objective cognition	Telephone Interview for Cognitive Status (TICS) Neurocognitive battery targeting executive function*
Subjective cognition	Functional Assessment of Cancer Therapy – Cognitive Function (FACT-Cog)
Substance Use History	Marijuana Consumption Questionnaire (MCQ) Alcohol Use Disorder Identification Test (AUDIT) Timeline Follow-Back (TLFB)
*Tests for which deficits have been observed previously among cancer patients [78–80] and include measures that are recommended by the International Cancer and Cognition Task Force	

7.2.1 CLINICAL LABORATORY EVALUATIONS (RESEARCH PROCEDURES)

Pregnancy screening. A urine pregnancy screening test will be administered to all female potential study participants of child-bearing age after informed consent has been obtained at the Baseline visit to verify eligibility for the study. For the pregnancy screening, a trained research assistant will deliver a urine receptacle to the participant's home. The participant will then use the restroom in their home and return the receptacle to the research assistant to complete the urine test in the mobile laboratory.

7.2.2 OTHER ASSAYS OR PROCEDURES (RESEARCH)

Pain Intensity and Pain interference. We employ two self-report measures of pain intensity and interference. Pain Intensity consists of one item asking about the participant's level of pain in the past seven days. Participants are asked to rate their pain on a scale from 0 (no pain) to 10 (worst imaginable pain). The Promis Pain Interference CAT asks participants about how their experience of pain interfered with or affected their enjoyment of various daily activities in the past seven days. The scale is computer-adapted and has a minimum of four questions and a maximum of 12 questions.

Anxiety and Mood Disturbance. The primary measure of lasting effects of *Cannabis* anxiety, the Beck Anxiety Inventory (BAI)[82] consists of 21 items, each describing a symptom of anxiety. Secondary assessments of anxiety and mood disturbance include the Positive and Negative Affect Schedule (PANAS), a brief, reliable and valid measure of positive and negative affect[83] and the Beck Depression Inventory-II (BDI-II) consisting of 21 scaled statements designed to assess symptoms of depression[84]. As its name suggests, the State-Trait Anxiety Inventory (STAI)[85] assesses both trait and state anxiety.

Sleep. Perceived sleep quality will be assessed by the commonly-used and well-validated Pittsburgh Sleep Quality Index[86].

Quality of Life. A commonly-used quality of life measure specific to cancer patients will be used to assess perceived quality of life: the Functional Assessment of Cancer Therapy - General

(FACT-G)[87] assesses aspects of quality of life specific to cancer patients, including physical (e.g., nausea, lack of energy), social, emotional, and cognitive well-being[88].

Objective and Subjective Cognitive Functioning. The Telephone Interview for Cognitive Status (TICS) will be used at screening to assess for moderate to severe cognitive impairment that would preclude enrollment as a study participant. The TICS is a widely used and validated measure of cognitive impairment that is highly correlated to the Mini Mental State Exam (MMSE) [89]. To assess objective cognitive functioning, we will conduct a neurocognitive battery on all participants that targets executive function. We will conduct this battery using Tatool, an open-source software developed to run psychological experimental studies[90]. This battery includes tests for which deficits have been observed among cancer patients[78–80] and include measures that are recommended by the International Cancer and Cognition Task Force[91]. The battery covers the domains found to be sensitive to the effects of *Cannabis* [55]. Specifically, the cognitive battery will include the Stroop Task[92] to assess inhibition and the Shape/Color Shifting Task[93] to assess shifting. We will assess subjective cognitive functioning with the Functional Assessment of Cancer Therapy – Cognitive Function (FACT-Cog), a reliable and valid assessment of perceived cognitive functioning specifically designed for cancer patients[94].

Health/Disease Status and Treatment Regimen. With the assistance of our oncology collaborators and OCRS staff, and with explicit informed consent from our patient participants, we will access Electronic Medical Records (EMRs) via the Health Data Compass[95] coinciding with the Baseline encounter and the One Month Follow-up. We will obtain data regarding cancer staging, tumor characteristics, treatment regimen (observation versus chemotherapy, targeted therapy, immunotherapy, combination of therapies, or other), current medications and doses (including treatment-supporting medications only), and any co-existing conditions.

Substance Use History. The Marijuana Consumption Questionnaire (MCQ)[96] is used to collect information on the frequency and quantity of cannabis use, age of first use, peer use, perceived risk from *Cannabi*s, and perceived availability of *Cannabis*. The Alcohol Use Disorder Identification Test (AUDIT)[97] will be used to examine the extent of alcohol use and problems related to alcohol use. A Timeline Follow-Back (TLFB) will be used to assess daily substance use for the 30 days prior to the baseline session and for the 14 days prior to the 2-week pre-acute use session[98]. The TLFB is a calendar assisted structured interview that provides a study participant with temporal cues to increase the accuracy of recall. This instrument has demonstrated test-retest reliability and validity[99]

Demographics. Personal information including gender, age, detailed race/ethnicity, and SES will be collected by self-report in addition to extraction from the EMR obtained via Health Data Compass.

Pregnancy Screening. A urine pregnancy screening test will be administered to all female potential study participants of child-bearing age after informed consent has been obtained at the Baseline visit to verify eligibility for the study. For the pregnancy screening, a trained research assistant will deliver a urine receptacle to the participant's home. The participant will then use the restroom in their home and return the receptacle to the research assistant to complete the urine test in the mobile laboratory.

7.3 STUDY SCHEDULE

7.3.1 SCREENING

A trained research assistant will screen prospective participants who call in for the study according to the inclusion/exclusion criteria. Research assistants will also provide an explanation of the study timeline and schedule of assessments, and compensation during this call, and answer any questions that participants may have about participation. If any subject is questionable for inclusion, Dr. Bidwell (a licensed clinical psychologist) and Dr. Camidge (a licensed M.D.), will make the final determination of eligibility. If a patient is deemed eligible for participation and wishes to proceed, an appointment will be made for a Baseline remote session. All female potential study participants of child-bearing age will then be asked to participate in pregancy testing to verify eligibility. A trained research assistant will deliver a urine receptacle to the participant's home. The participant will then use the restroom in their home and return the receptacle to the research assistant to complete the urine test in the mobile laboratory.

7.3.2 ENROLLMENT/BASELINE

Potential participants who meet inclusion criteria will be scheduled for a baseline session. A trained research assistant will meet remotely with the participant via phone or Zoom. Each participant will go through the informed consent process. Once consented, participants will complete current and historical health and substance use assessments and cognitive testing (see Table 7.1). Participants will complete assessments via emailed, individually tailored links hosted by and integrated into the study's REDCap databases (*https://redcap.ucdenver.edu/*). Participants will then receive a consultation from research staff on the range of edible *Cannabis* products and basic information about their various cannabinoid profiles, approximate prices, and nearby locations where participants may choose to purchase their product. Again, research staff will not advise study participants to purchase any specific product. Participants will be compensated with a $60 grocery store gift card for their time and effort at the end of the visit, which will be mailed to their home.

7.3.3 FOLLOW-UP

Figure 3. Example of an edible *Cannabis* product

***Ad Libitum Cannabis* Administration at Home.** The participant will use their orally administered *Cannabis ad libitum* at home. This aspect of the design differentiates the proposed research from a classical interventional clinical trial, which is critically important because it is the only path forward for research on orally administered, legal market *Cannabis* given current federal law. It is well known in the pain and broader medication literatures that expectancies regarding the effects of a medication have profound influences on the patient experience of symptom reduction [100,101]. Colorado requires all orally administered *Cannabis* products to be tested by a state lab, which allows us to have a precise measure of potency despite the inability to assign products to users. While participants are not blind to the type of product they are ingesting, it is important to note that the subjective effects of THC and CBD are quite different[59–62,64–68,102], and thus participants who are not naïve to *Cannabis* use would likely not be blind even if assigned to a product. Importantly, the researchers who conduct the assessments as well as most of the senior investigators *will* be blind to condition. The observational aspect of the design involves the instruction to use their selected product at home consistent with the packaging directions and/or as they see fit. Consistent with federal law, study staff will not provide any directions regarding dosing and administration. For verification purposes, participants will take and send a picture of their purchased product to the CUChange Lab via the REDCap system as mentioned in section 6.1.3.

Pre- and Post- Administration Assessment (Ta1-Tc1). The Pre- and Post- Administration Assessment will take place two weeks (+/- 4 days) following the baseline session. A trained research assistant will meet remotely with the participant via phone or Zoom. Links to assessments will be emailed to the participannt at the start of the session. Prior to taking their *Cannabis*, participants will complete self-report assessments, including those assessing quantity/frequency of *Cannabis* use and symptom severity over the prior two weeks (Ta1). They will then consume their orally administered *Cannabis*. Because 60 minutes is the average time that CBD and THC levels begin to peak in the blood after oral administration of *Cannabis* extract[70,71], assessments of the acute effects of *Cannabis* (see Table 7.2) will begin one hour (+/- 5 minutes) post-edible consumption (Tb1). After peak, levels steadily decrease over the next 2-3 hours and by 4 hours post-ingestion begin to rapidly drop off in blood[70,71]. To account for individual differences in metabolism and sensitivity, participants will be assessed again at 2 hours (+/- 5 minutes) post-consumption (Tc1). After completing the 1- and 2- hour post-consumption assessments,, participants will receive a $100 grocery store gift card as compensation for their time and effort, which will be mailed to their home.

7.3.4 FINAL STUDY VISIT

At the end of the Pre- and Post- Administration Assessment, participants may elect to continue use of the same product, switch to another product, or discontinue their *Cannabis* use. While the main observational portion of the study will be complete at that point, we will follow-up with participants in regard to their symptoms levels, *Cannabis* use, and cognition, using an online survey one month (+/- 7 days) later (M1), in keeping with the observational nature of the design. This aspect will provide important data on feasibility of longer-term follow-up with this population, and further valuable data in regard to patient choice, patient behavior, patterns of use of *Cannabis* products, and associated experience of symptoms related to cancer treatment in a fully-powered iteration of the study. The survey will assess their *Cannabis* use, other substance use, symptom levels (pain, anxiety, and sleep), quality of life, and subjective and objective cognitive functioning over the past month. We also will conduct the final health status and treatment regimen review of the participant's EMR separately at this time point via Health Data Compass. Participants will receive a $10 grocery store card as compensation for their time and effort, which will be mailed to their home.

7.3.5 Schedule of Events Table

Table 7.3 Schedule of Events

	Demographics	AEs	MCQ	AUDIT	TLFB	EMR Review	Obj. Cognition	Sub. Cognition	FACT-G	PSQI	Anx-Mood (State)	Anx-Mood (Trait)	Pain (7 days)	Pain (Right now)
T00: Baseline	X	X*	X	X	X	X	X	X	X	X	X	X	X	
Ta1: 2-Week Pre-Acute Use		X	X		X		X	X	X	X	X	X	X	X
Tb1: 2-Week 1-Hour Post-Acute Use		X	X				X				X			X
Tc1: 2-Week 2-Hour Post-Acute Use		X	X				X				X			X
M1: 1-Month Follow-Up		X	X	X	X	X	X	X	X	X	X	X	X	

MCQ = Marijuana Craving Questionnaire
AUDIT = Alcohol Use Disorder Identification Test
TLFB = Timeline Followback Substance Use Assessment
Objective Cognition = Stroop task, Shape/Color Shifting Task.
Subjective Cognition = Functional Assessment of Cancer Therapy – Cognitive Function (FACT-Cog)
FACT-G = Functional Assessment of Cancer Therapy - General
PSQI = Pittsburgh Sleep Quality Index
Anx-Mood (Trait)= Beck Anxiety Inventory (BAI), Beck Depression Inventory-II (BDI-II),
Anx-Mood (State) = Positive and Negative Affect Schedule (PANAS), State-Trait Anxiety Inventory (STAI)
Pain (7 days) = Pain Intensity (7 days), the Promis Pain Interference CAT
Pain (Right now) = Pain Intensity (Right now)

* The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after Tc1.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

We define **adverse event** as "Any untoward or unfavorable medical occurrence in a participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research" (http://www.colorado.edu/vcr/sites/default/files/IRB%20Policy%20Procedures-%20Final%2010-01-11_website.pdf).

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

We define **serious adverse event** as an event that "Results in death, is life threatening, or places the participant at immediate risk of death from the event as it occurred, requires hospitalization, causes persistent or significant disability or incapacity, or is another condition which investigators judge to represent significant hazards." (http://www.colorado.edu/vcr/sites/default/files/IRB%20Policy%20Procedures-%20Final%2010-01-11_website.pdf).

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UAP)

This study will use the Office of Human Research Protection (OHRP) definition of an **unanticipated problem**: "involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized."

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 EXPECTED ADVERSE EVENTS

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. Given the observational nature of our study and the disease state of our target participants, common events in our study population such as feeling intoxicated from marijuana, mild or consistent with baseline levels of pain, anxiety, drowsiness, or nausea are to be expected and will be documented on case report forms but not be reported as adverse events.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study sessions. All AEs including local and systemic reactions 1) not meeting the criteria for SAEs, 2) not included in the list of expected events in Section 8.2.3, or 3) beyond a threshold for an expected event listed in Section 8.2.3 (such as greater than mild symptoms or significant change from baseline in pain, anxiety, drowsiness, or nausea) will be captured on the appropriate case report form by a CUChange Lab professional research assistant. Information to be collected includes event description, time of onset, assessment of severity, and time of resolution/ stabilization of the event.

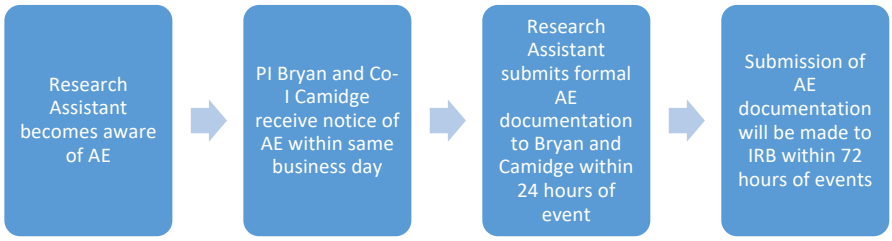
Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

At each study visit, the professional research assistant will inquire about the occurrence of AE/ SAEs since the last visit.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

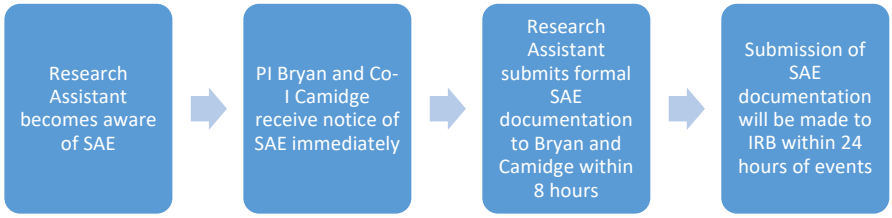
The study team will adhere to the protocol detailed in the figure below for reporting adverse events.



The study team will record all reportable events with start dates occurring any time after informed consent is obtained until seven days after the last day of study participation. All AEs will otherwise be followed to adequate resolution or stabilization.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

Since the study procedures are not greater than minimal risk, SAEs are not expected. Should an SAE occur, the study team will adhere to the protocol detailed in the figure below for reporting serious adverse events.



The study team will record all reportable events with start dates occurring any time after informed consent is obtained until 30 days after the last day of study participation. All SAEs will otherwise be followed to adequate resolution or stabilization.

8.4.3 UNANTICIPATED PROBLEM REPORTING

Since the study procedures are not greater than minimal risk, UAPs are not anticipated. Incidents or events that meet the OHRP criteria for UAPs require the creation and completion of a UAP report form and including the following information:

- Protocol-identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents a UAP;

- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UAP.

To satisfy the requirement for prompt reporting, UAPs will be reported using the following timeline:

- UAPs that are SAEs will be reported to the IRB within 24 hours of the investigator becoming aware of the event.
- Any other UAP will be reported to the IRB within 72 hours of the investigator becoming aware of the problem.

8.4.4 REPORTING OF PREGNANCY

Patients who are pregnant or trying to become pregnant are ineligible for participation. If a participant becomes pregnant after enrolling in the study, the participant will be withdrawn.

9 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by CU Cancer Center Clinical Monitor in accordance with the clinical monitoring plan (CMP), incorporated herein by reference. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of the monitoring reports.

The principal investigator will be responsible for the conduct of this study, overseeing participant safety, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study participant safety for all trials at the CU Cancer Center. A summary of the DSMC's relevant activities is as follows:

- Conduct of internal audits
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Study audits conducted by the DSMC will consist of a review of the regulatory documents, consent forms, and source data verification. Documentation of the audit conducted by the DSMC will then need to be submitted to the IRB of record at the time of the IRB's continuing review of this trial (if applicable).

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

This is a feasibility study and thus underpowered for meaningful analysis; the endpoints are strictly recruitment based. We will however examine the data for completeness (i.e., were any measures or items consistently left blank). In addition, we will examine the summary statistics including mean and standard deviation for continuous items as well as skew and kurtosis to evaluate whether the measures approximate a normal distribution. For categorical outcomes, we will examine proportions in each category to get some idea of variability on the measure.

10.2 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):
  This section is not applicable.

- Secondary Efficacy Endpoint(s):
  This section is not applicable.

10.3 DESCRIPTION OF STATISTICAL METHODS

10.3.1 ADHERENCE AND RETENTION ANALYSES

This feasibility study has an 80% retention goal for reasonable compliance with study procedures by enrolled study participants. Reasonable compliance is defined as 75% completion of study assessments. Adherence is not applicable to this observational study design.

10.3.2 BASELINE DESCRIPTIVE STATISTICS

We will characterize the cohort based on demographics, disease stage, and other relevant descriptives.

10.4 SAMPLE SIZE

We plan to recruit 30 participants into this feasibility study, as we believe this will be adequate to determine whether the larger trial is possible and whether there are changes in study procedures that would be required before initiating a fully powered study.

10.5 MEASURES TO MINIMIZE BIAS

The investigators and research assistants will be blind to *Cannabis* edible product condition. A member of the study team not responsible for data collection will maintain the experimenter blind.

10.5.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

Participants will be free to select the edible Cannabis product of their choice and use their product *ad libitum*. They will report on their selection via an individualized, emailed REDCap survey blinded to the study team with the exception of a member of the study team not responsible for data collection.

10.5.2 EVALUATION OF SUCCESS OF BLINDING

Because we do not anticipate the blinding to be maintained by participants, we will not assess the success of the blind.

10.5.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

Since participants are aware of which product they are taking, there are no conditions under which the blind needs to be broken.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

We have taken a number of measures to ensure the confidentiality of the data and the safety of the participants. All data from the proposed study will be identified by a numerical ID code only. The information linking the numerical ID code to identifying information will be maintained separate and secure from the data themselves. At the conclusion of the final data collection session, the list linking the ID code to identifying information will be destroyed.

12 QUALITY ASSURANCE AND QUALITY CONTROL

The CUChange Lab has established standard operating procedures (SOPs) to ensure **quality assurance (QA)** in the design of databases for observational studies such as the proposed project. The data entry system has been well established with previous studies and relies on a strategy of centralized data capture through REDCap. Raw data is uploaded daily to REDCap either manually or through automated application programming interface (API) call. Professional research assistants review all case report forms and raw data at the conclusion of every study session or upon receipt of data from collaborators (such as cannabinoid lab results) as applicable.

Quality control (QC) SOPs at the CUChange Lab include quarterly data review of 10 randomly selected participant records. This will be logged (who checked the data, what parts of the data were checked if not all assessments, when the data was checked, and if there are any outlying

issues or discrepancies to follow-up on, and who will follow-up with any discrepancies and when).

The investigational team will provide direct access to all study-related sites, source data/ documents, and reports for the purpose of monitoring and auditing by the DSMC audit team, and inspection by local and regulatory authorities.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

The PI will ensure that this study is conducted in full conformity with regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Colorado Multiple Institutional Review Board (COMIRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by COMIRB before the changes are implemented to the study. All changes to the consent form will COMIRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 INFORMED CONSENT PROCESS

Participants are informed of all procedures beforehand, and they must read and sign the eConsent stating that they understand and agree to the procedures before beginning the study. As part of this process, they are informed that they may withdraw from the study at any time. Acceptance into the study will be contingent on a review of current health status and health history by our study physicians (Co-Is Dr. Camidge and Dr. Bowles) to ensure that illness is not present at a level severe enough as to impede informed consent and/or participation in a research study. In addition, Dr. Bidwell (Co-I) will review the patient's screening assessment of cognitive and psychological functioning, including the TICS score to ensure that there are no psychological comorbidities or cognitive deficits that impede decisional capacity, informed consent, and/or study participation.

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

eConsent forms describing in detail the study procedures, timeline, and risks are given to the participant and written online documentation of informed consent is required prior to starting participation in this observational study.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

The informed consent process will be initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families.

The eConsent will be IRB-approved and the participant will be asked to read and review the document. The professional research assistant will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the eConsent and ask questions prior to signing. The participants will have the opportunity to think about the study prior to agreeing to participate. The participant will sign the eConsent document prior to any procedures being done specifically for the study.

The participants may withdraw consent at any time throughout the course of the trial. A copy of the eConsent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The study excludes non-English speakers.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating PIs, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor-investigator.

Authorized representatives of the sponsor-investigator and representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to medical records (office, clinic, or hospital) and case report forms for the participants in this study. The CUChange Lab will permit access to such records.

The study participant's contact information will be securely stored at the CUChange Lab for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Colorado Cancer Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the CUChange Lab and by the

University of Colorado Cancer Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the University of Colorado Cancer Center.

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

Intended Use: Samples and data collected under this protocol may be used to study the effect of *Cannabis* use among cancer patients. No genetic testing will be performed. **Storage:** Data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
Tracking: Data will be tracked using REDCap.
Disposition at completion of the study: Not applicable—no stored samples will be collected.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Assessment data collection is the responsibility of the CUChange Lab study personnel under the supervision of the site PI. Data collected by EMR review will be the responsibility of the study team with the help of Drs. Camidge and Bowles and collaboration from the PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source, paper documents will be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, study personnel will cross out the original entry with a single line, and initial and date the change. Study personnel will NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Data reported in the REDCap electronic case report forms (eCRFs) derived from source documents should be consistent with the source documents/raw data, otherwise the discrepancies will be explained and captured in a progress note and maintained in the participant's official electronic study record. Copies of the blank eCRF forms will be maintained for documentation purposes.

Clinical data (including AEs and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by the University of Colorado Denver. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered manually directly from the source documents or through automated API call.

14.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of two years after the final participant has completed the study. These documents should be retained for a longer period, however, if required by local regulations, or institution policies. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the PI when these documents no longer need to be retained.

14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or SOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6, sections:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3.
- 5.1 Quality Assurance and Quality Control, section 5.1.1.
- 5.20 Noncompliance, sections 5.20.1 and 5.20.2.

It is the responsibility of the study team to use continuous vigilance to identify and report deviations within 2 working days of identification of the protocol deviation, or within 2 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to PI Bryan and Co-I Camidge. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/ study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the -SOP and/or study procedures manual.

14.4 PUBLICATION AND DATA SHARING POLICY

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH-funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human participants to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007 requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional

clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated PI) register and report results of certain "applicable clinical trials".

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

The pilot study will be under the leadership of PI Bryan with assistance from Co-Is Camidge, Bowles, Bidwell, and Klawitter.

16 CONFLICT OF INTEREST POLICY

Independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed.by the University of Colorado Denver's (UCD) Office of Regulatory Compliance Conflict of Interest and Commitment Management (COIC) program. Persons with a perceived conflict of interest will have such conflicts managed in a way that is appropriate to their participation in the trial. Conflict of Interest management plans are project-specific and are reviewed at least annually. UCD has integrated the institutional conflict of interest management program with its existing program.

17 LITERATURE REFERENCES

1. Temel JS, Greer JA, Muzikansky A, et al. Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer. *N Engl J Med*. 2010;363(8):733-742. doi:10.1056/NEJMoa1000678.
2. Pew Research Center. Majority now supports legalizing marijuana. *US Polit Policy*. 2013;(202):1-13. http://www.people-press.org/2013/04/04/majority-now-supports-legalizing-marijuana/.
3. Adler JN, Colbert JA. Medicinal Use of Marijuana — Polling Results. *N Engl J Med*.

2013;368(22):e30. doi:10.1056/NEJMclde1305159.
4. Maida V, Daeninck PJ. A user's guide to cannabinoid therapies in oncology. *Curr Oncol*. 2016;23(6):398-406. doi:10.3747/co.23.3487.
5. Pergam SA, Woodfield MC, Lee CM, et al. Cannabis use among patients at a comprehensive cancer center in a state with legalized medicinal and recreational use. *Cancer*. 2017;123(22):4488-4497. doi:10.1002/cncr.30879.
6. Baldwin K. Studies Reveal New Strategies to Improve Quality of Life for Patients, Survivors and Caregivers | ASCO. *Am Soc Clin Oncol Press Cent*. 2014. https://www.asco.org/about-asco/press-center/news-releases/studies-reveal-new-strategies-improve-quality-life-patients. Accessed March 9, 2018.
7. Abrams D, Guzman M. Cannabis in cancer care. *Clin Pharmacol Ther*. 2015;97(6):575-586. doi:10.1002/cpt.108.
8. Ostadhadi S, Rahmatollahi M, Dehpour AR, Rahimian R. Therapeutic potential of cannabinoids in counteracting chemotherapy-induced adverse effects: An exploratory review. *Phyther Res*. 2015;29(3):332-338. doi:10.1002/ptr.5265.
9. Tramèr MR, Carroll D, Campbell FA, Reynolds DJ, Moore RA, McQuay HJ. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ*. 2001;323(7303):16-21. doi:10.1136/bmj.323.7303.16.
10. Bowles DW, O'Bryant CL, Camidge DR, Jimeno A. The intersection between cannabis and cancer in the United States. *Crit Rev Oncol Hematol*. 2012;83(1):1-10. doi:10.1016/j.critrevonc.2011.09.008.
11. Hagerty SL, York Williams SL, Mittal VA, Hutchison KE. The cannabis conundrum: Thinking outside the THC box. *J Clin Pharmacol*. 2015;55(8):839-841. doi:10.1002/jcph.511.
12. Bidwelll LC, Mueller R, Yorkwilliams SL, Hagerty S, Bryan AD, Hutchison KE. A Novel Observational Method for Assessing Acute Responses to Cannabis : Preliminary Validation Using Legal Market Strains. *Cannabis Cannabinoid Res*. 2018;3(1):35-44. doi:10.1089/can.2017.0038.
13. Bar-Sela G, Vorobeichik M, Drawsheh S, Omer A, Goldberg V, Muller E. The medical necessity for medicinal cannabis: Prospective, observational study evaluating the treatment in cancer patients on supportive or palliative care. *Evidence-based Complement Altern Med*. 2013;2013. doi:10.1155/2013/510392.
14. Jager G, Kahn RS, Van Den Brink W, Van Ree JM, Ramsey NF. Long-term effects of frequent cannabis use on working memory and attention: An fMRI study. *Psychopharmacology (Berl)*. 2006;185(3):358-368. doi:10.1007/s00213-005-0298-7.
15. Crean RD, Crane NA, Mason BJ. An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. *J Addict Med*. 2011;5(1):1-8. doi:10.1097/ADM.0b013e31820c23fa.An.
16. Vardy J, Rourke S, Tannock IF. Evaluation of cognitive function associated with chemotherapy: A review of published studies and recommendations for future research. *J Clin Oncol*. 2007;25(17):2455-2463. doi:10.1200/JCO.2006.08.1604.
17. Boykoff N, Moieni M, Subramanian SK. Confronting chemobrain: an in-depth look at survivors' reports of impact on work, social networks, and health care response. *J Cancer Surviv*. 2009;3(4):223-232. doi:10.1007/s11764-009-0098-x.
18. Livestrong Foundation. How Cancer Has Affected Post-Treatment Survivors : A Livestrong Report. 2010:1-29. https://www.livestrong.org/what-we-do/our-research.

19. Jim HSL, Phillips KM, Chait S, et al. Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. *J Clin Oncol*. 2012;30(29):3578-3587. doi:10.1200/JCO.2011.39.5640.
20. Ahles TA, Saykin AJ, Furstenberg CT, et al. Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. *J Clin Oncol*. 2002;20(2):485-493. doi:10.1007/s10499-012-9533-5.
21. Janelsins MC, Kohli S, Mohile SG, Usuki K, Ahles TA, Morrow GR. An update on cancer- and chemotherapy-related cognitive dysfunction: current status. *Semin Oncol*. 2011;38(3):431-438. doi:10.1053/j.seminoncol.2011.03.014.
22. Ganz PA, Kwan L, Castellon SA, et al. Cognitive complaints after breast cancer treatments: Examining the relationship with neuropsychological test performance. *J Natl Cancer Inst*. 2013;105(11):791-801. doi:10.1093/jnci/djt073.
23. Arndt J, Das E, Schagen SB, Reid-Arndt SA, Cameron LD, Ahles TA. Broadening the cancer and cognition landscape: The role of self-regulatory challenges. *Psychooncology*. 2014;23(1):1-8. doi:10.1002/pon.3351.
24. Reinarman C, Nunberg H, Lanthier F, Heddleston T. Who are medical marijuana patients? population characteristics from nine California assessment clinics. *J Psychoactive Drugs*. 2011;43(2):128-135. doi:10.1080/02791072.2011.587700.
25. The Health Effects of Cannabis and Cannabinoids: The Current State of ... - National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Population Health and Public Health Practice, Committee on the Health Effects of. https://books.google.com/books?hl=en&lr=&id=Ov2dDgAAQBAJ&oi=fnd&pg=PR17&dq=The+Health+Effects+of+Cannabis+and+Cannabinoids:+The+Current+State+of+Evidence+and+Recommendations+for+Research.+2017:+Washington+(DC).&ots=oBej9bUavh&sig=okrYiZO8nPruzqyUX1Pfqwew_. Accessed February 15, 2018.
26. Light MK, Orens A, Lewandowski B, Pickton T. Market size and demand. Report prepared for the Colorado Department of Revenue. 2014:1-32. https://www.google.es/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=0CCAQFjAA&url=http://www.colorado.gov/cs/Satellite?blobcol=urldata&blobheadername1=Content-Disposition&blobheadername2=Content-Type&blobheadervalue1=inline;+filename=%22.
27. Ilgen MA, Bohnert K, Kleinberg F, et al. Characteristics of adults seeking medical marijuana certification. *Drug Alcohol Depend*. 2013;132(3):654-659. doi:10.1016/j.drugalcdep.2013.04.019.
28. Boehnke KF, Litinas E, Clauw DJ. Medical Cannabis Use Is Associated with Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients with Chronic Pain. *J Pain*. 2016;17(6):739-744. doi:10.1016/j.jpain.2016.03.002.
29. Bachhuber MA, Saloner B, Cunningham CO, Feingold J, Barry CL. Could Delaware's medical marijuana law reduce harms from opioid analgesics? *Del Med J*. 2014;86(11):341-343. http://www.ncbi.nlm.nih.gov/pubmed/25647864. Accessed February 15, 2018.
30. Bradford AC, Bradford WD. Medical marijuana laws reduce prescription medication use in medicare part d. *Health Aff*. 2016;35(7):1230-1236. doi:10.1377/hlthaff.2015.1661.
31. Andreae MH, Carter GM, Shaparin N, et al. Inhaled Cannabis for Chronic Neuropathic Pain: A Meta-analysis of Individual Patient Data. *J Pain*. 2015;16(12):1121-1232. doi:10.1016/j.jpain.2015.07.009.

32. Fitzcharles M-A, Ste-Marie PA, Häuser W, et al. Efficacy, Tolerability, and Safety of Cannabinoid Treatments in the Rheumatic Diseases: A Systematic Review of Randomized Controlled Trials. *Arthritis Care Res (Hoboken)*. 2016;68(5):681-688. doi:10.1002/acr.22727.
33. L RB, L WS, Rachelle B. Neuromodulators for pain management in rheumatoid arthritis. *Cochrane Database Syst Rev*. 2012;(1). doi:10.1002/14651858.CD008921.pub2.
34. Snedecor SJ, Sudharshan L, Cappelleri JC, et al. Systematic review and comparison of pharmacologic therapies for neuropathic pain associated with spinal cord injury. *J Pain Res*. 2013;6:539-547. doi:10.2147/JPR.S45966.
35. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA - J Am Med Assoc*. 2015;313(24):2456-2473. doi:10.1001/jama.2015.6358.
36. Hayatbakhsh MR, Najman JM, Jamrozik K, Mamun AA, Alati R, Bor W. Cannabis and anxiety and depression in young adults: a large prospective study. *J Am Acad Child Adolesc Psychiatry*. 2007;46(3):408-417. doi:10.1097/chi.0b013e31802dc54d.
37. Grunberg VA, Cordova KA, Bidwell LC, Ito TA. Can Marijuana Make It Better? Prospective Effects of Marijuana and Temperament on Risk for Anxiety and Depression. *Psychol Addict Behav*. 2015;29(3):590-602. doi:10.1037/adb0000109.
38. Cooper ZD, Haney M. Cannabis reinforcement and dependence: Role of the cannabinoid CB1 receptor. *Addict Biol*. 2008;13(2):188-195. doi:10.1111/j.1369-1600.2007.00095.x.
39. Schacht JP, Selling RE, Hutchison KE. Intermediate cannabis dependence phenotypes and the FAAH C385A variant: An exploratory analysis. *Psychopharmacology (Berl)*. 2009;203(3):511-517. doi:10.1007/s00213-008-1397-z.
40. Metrik J, Kahler CW, Reynolds B, et al. Balanced placebo design with marijuana: Pharmacological and expectancy effects on impulsivity and risk taking. *Psychopharmacology (Berl)*. 2012;223(4):489-499. doi:10.1007/s00213-012-2740-y.
41. Sethi BB, Trivedi JK, Kumar P, Gulati A, Agarwal AK, Sethi N. Antianxiety effect of cannabis: Involvement of central benzodiazepine receptors. *Biol Psychiatry*. 1986;21(1):3-10. doi:10.1016/0006-3223(86)90003-X.
42. Schramm-Sapyta NL, Cha YM, Chaudhry S, Wilson WA, Swartzwelder HS, Kuhn CM. Differential anxiogenic, aversive, and locomotor effects of THC in adolescent and adult rats. *Psychopharmacology (Berl)*. 2007;191(4):867-877. doi:10.1007/s00213-006-0676-9.
43. Campos AC, Moreira FA, Gomes F V., Del Bel EA, Guimaraes FS. Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders. *Philos Trans R Soc B Biol Sci*. 2012;367(1607):3364-3378. doi:10.1098/rstb.2011.0389.
44. Pivik RT, Zarcone V, Dement WC, Hollister LE. Delta-9-tetrahydrocannabinol and synhexl: Effects on human sleep patterns. *Clin Pharmacol Ther*. 1972;13(1):426-435.
45. Feinberg I, Jones R, Walker JM, Cavness C, March J. Effects of high dosage deita-9-tetrahydrocannabinoi on sleep patterns in man. *Clin Pharmacol Ther*. 1975;17(4):458-466. https://s3.amazonaws.com/academia.edu.documents/41034658/Feinberg-1975-Effects_of_high_dosa.pdf?AWSAccessKeyId=AKIAIWOWYYGZ2Y53UL3A&Expires=1520626765&Signature=jywJBlQgbxvB3CpjGWEJKa5w8uE%3D&response-content-disposition=inline%3B filename%3DEffects_of_. Accessed March 9, 2018.
46. Monti JM. Hypnoticlike effects of cannabidiol in the rat. *Psychopharmacology (Berl)*. 1977;55(3):263-265. doi:10.1007/BF00497858.

47. CARLINI EA, CUNHA JM. Hypnotic and Antiepileptic Effects of Cannabidiol. *J Clin Pharmacol*. 1981;21(S1):417S-427S. doi:10.1002/j.1552-4604.1981.tb02622.x.
48. Ranganathan M, D'Souza DC. The acute effects of cannabinoids on memory in humans: A review. *Psychopharmacology (Berl)*. 2006;188(4):425-444. doi:10.1007/s00213-006-0508-y.
49. Lundqvist T. Cognitive consequences of cannabis use: Comparison with abuse of stimulants and heroin with regard to attention, memory and executive functions. *Pharmacol Biochem Behav*. 2005;81(2 SPEC. ISS.):319-330. doi:10.1016/j.pbb.2005.02.017.
50. Abel EL. Marihuana and memory: acquisition or retrieval? *Science*. 1971;173(4001):1038-1040. doi:10.1126/science.173.4001.1038.
51. Darley CF, Tinklenberg JR, Roth WT, Atkinson RC. The nature of storage deficits and state-dependent retrieval under marihuana. *Psychopharmacologia*. 1974;37(2):139-149. doi:10.1007/BF00437420.
52. Heishman SJ, Stitzer ML, Yingling JE. Effects of tetrahydrocannabinol content on marijuana smoking behavior, subjective reports, and performance. *Pharmacol Biochem Behav*. 1989;34(1):173-179. doi:10.1016/0091-3057(89)90369-9.
53. Wilson WH, Ellinwood EH, Mathew RJ, Johnson K. Effects of marijuana on performance of a computerized cognitive-neuromotor test battery. *Psychiatry Res*. 1994;51(2):115-125. doi:10.1016/0165-1781(94)90031-0.
54. Ramaekers JG, Kauert G, Van Ruitenbeek P, Theunissen EL, Schneider E, Moeller MR. High-potency marijuana impairs executive function and inhibitory motor control. *Neuropsychopharmacology*. 2006;31(10):2296-2303. doi:10.1038/sj.npp.1301068.
55. Ranganathan M, D'Souza DC. The acute effects of cannabinoids on memory in humans: a review. *Psychopharmacology (Berl)*. 2006;188(4):425-444. doi:10.1007/s00213-006-0508-y.
56. McDonald J, Schleifer L, Richards JB, De Wit H. Effects of THC on behavioral measures of impulsivity in humans. *Neuropsychopharmacology*. 2003;28(7):1356-1365. doi:10.1038/sj.npp.1300176.
57. Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. *Trends Pharmacol Sci*. 2009;30(10):515-527. doi:10.1016/j.tips.2009.07.006.
58. Huestis MA. Human cannabinoid pharmacokinetics. *Chem Biodivers*. 2007;4(8):1770-1804. doi:10.1002/cbdv.200790152.
59. Bhattacharyya S, Atakan Z, Martin-Santos R, A. Crippa J, K. McGuire P. Neural Mechanisms for the Cannabinoid Modulation of Cognition and Affect in Man: A Critical Review of Neuroimaging Studies. *Curr Pharm Des*. 2012;18(32):5045-5054. doi:10.2174/138161212802884636.
60. Englund A, Morrison PD, Nottage J, et al. Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. *J Psychopharmacol*. 2013;27(1):19-27. doi:10.1177/0269881112460109.
61. Hermann D, Schneider M. Potential Protective Effects of Cannabidiol on Neuroanatomical Alterations in Cannabis Users and Psychosis: A Critical Review. *Curr Pharm Des*. 2012;18(32):4897-4905. doi:10.2174/138161212802884825.
62. Zuardi AW. Cannabidiol : from an inactive cannabinoid to a drug with wide spectrum of action Canabidiol : de um canabinóide inativo a uma droga com amplo espectro de ação.

Rev Bras Psiquiatr. 2008;30(3):271-280. doi:10.1590/S1516-44462008000300015.
63. Morgan CJA, Schafer G, Freeman TP, Curran HV. Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study: naturalistic study [corrected]. *Br J Psychiatry*. 2010;197(4):285-290. doi:10.1192/bjp.bp.110.077503.
64. Demirakca T, Sartorius A, Ende G, et al. Diminished gray matter in the hippocampus of cannabis users: Possible protective effects of cannabidiol. *Drug Alcohol Depend*. 2011;114(2-3):242-245. doi:10.1016/j.drugalcdep.2010.09.020.
65. Schubart CD, Sommer IEC, van Gastel WA, Goetgebuer RL, Kahn RS, Boks MPM. Cannabis with high cannabidiol content is associated with fewer psychotic experiences. *Schizophr Res*. 2011;130(1-3):216-221. doi:10.1016/j.schres.2011.04.017.
66. Vann RE, Gamage TF, Warner JA, et al. Divergent effects of cannabidiol on the discriminative stimulus and place conditioning effects of Δ9-tetrahydrocannabinol. *Drug Alcohol Depend*. 2008;94(1-3):191-198. doi:10.1016/j.drugalcdep.2007.11.017.
67. Ren Y, Whittard J, Higuera-Matas A, Morris C V., Hurd YL. Cannabidiol, a Nonpsychotropic Component of Cannabis, Inhibits Cue-Induced Heroin Seeking and Normalizes Discrete Mesolimbic Neuronal Disturbances. *J Neurosci*. 2009;29(47):14764-14769. doi:10.1523/JNEUROSCI.4291-09.2009.
68. Griffith-Lendering MFH, Huijbregts SCJ, Vollebergh WAM, Swaab H. Motivational and cognitive inhibitory control in recreational cannabis users. *J Clin Exp Neuropsychol*. 2012;34(7):688-697. doi:10.1080/13803395.2012.668874.
69. Marijuana Enforcement. *Color Dep Revenue, Enforc Div*. https://www.colorado.gov/pacific/enforcement/marijuanaenforcement. Accessed March 9, 2018.
70. Nadulski T, Sporkert F, Schnelle M, et al. Simultaneous and sensitive analysis of THC, 11-OH-THC, THC-COOH, CBD, and CBN by GC-MS in plasma after oral application of small doses of THC and cannabis extract. *J Anal Toxicol*. 2005;29(8):782-789. doi:10.1093/jat/29.8.782.
71. Ohlsson A, Lindgren J -E, Andersson S, Agurell S, Gillespie H, Hollister LE. Single-dose kinetics of deuterium-labelled cannabidiol in man after smoking and intravenous administration. *Biol Mass Spectrom*. 1986;13(2):77-83. doi:10.1002/bms.1200130206.
72. Schmiege SJ, Bryan AD. Heterogeneity in the Relationship of Substance Use to Risky Sexual Behavior Among Justice-Involved Youth: A Regression Mixture Modeling Approach. *AIDS Behav*. 2016;20(4):821-832. doi:10.1007/s10461-015-1219-3.
73. Callahan TJ, Caldwell Hooper AE, Thayer RE, Magnan RE, Bryan AD. Relationships between marijuana dependence and condom use intentions and behavior among justice-involved adolescents. *AIDS Behav*. 2013;17(8):2715-2724. doi:10.1007/s10461-013-0417-0.
74. Bryan AD, Schmiege SJ, Magnan RE. Marijuana use and risky sexual behavior among high-risk adolescents: Trajectories, risk factors, and event-level relationships. *Dev Psychol*. 2012;48(5):1429-1442. doi:10.1037/a0027547.
75. Schacht JP, Selling RE, Hutchison KE. Intermediate cannabis dependence phenotypes and the FAAH C385A variant: An exploratory analysis. *Psychopharmacology (Berl)*. 2009;203(3):511-517. doi:10.1007/s00213-008-1397-z.
76. Haughey HM, Marshall E, Schacht JP, Louis A, Hutchison KE. Marijuana withdrawal and craving: Influence of the cannabinoid receptor 1 (CNR1) and fatty acid amide hydrolase (FAAH) genes. *Addiction*. 2008;103(10):1678-1686. doi:10.1111/j.1360-

0443.2008.02292.x.
77. Bryan AD, Hutchison KE, Bidwelll LC, Mueller R, Yorkwilliams SL, Hagerty S. A Novel Observational Method for Assessing Acute Responses to Cannabis : Preliminary Validation Using Legal Market Strains. *Cannabis Cannabinoid Res*. 2018;3(1):1-11. doi:10.1089/can.2017.0038.
78. Phillips KM, Jim HS, Small BJ, Laronga C, Andrykowski MA, Jacobsen PB. Cognitive functioning after cancer treatment: A 3-year longitudinal comparison of breast cancer survivors treated with chemotherapy or radiation and noncancer controls. *Cancer*. 2012;118(7):1925-1932. doi:10.1002/cncr.26432.
79. Small BJ, Rawson KS, Walsh E, et al. Catechol-O-methyltransferase genotype modulates cancer treatment-related cognitive deficits in breast cancer survivors. *Cancer*. 2011;117(7):1369-1376. doi:10.1002/cncr.25685.
80. Jim HSL, Donovan KA, Small BJ, Andrykowski MA, Munster PN, Jacobsen PB. Cognitive functioning in breast cancer survivors: A controlled comparison. *Cancer*. 2009;115(8):1776-1783. doi:10.1002/cncr.24192.
81. Klawitter J, Sempio C, Mörlein S, et al. An Atmospheric Pressure Chemical Ionization MS/MS Assay Using Online Extraction for the Analysis of 11 Cannabinoids and Metabolites in Human Plasma and Urine. *Ther Drug Monit*. 2017;39(5):556-564. doi:10.1097/FTD.0000000000000427.
82. Beck AT. *Beck Anxiety Inventory®*. Vol 2nd ed. San Antonio: Pearson (Psychological Corporation); 1993. https://www.pearsonclinical.com/psychology/products/100000251/beck-anxiety-inventory-bai.html. Accessed March 20, 2018.
83. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: The PANAS scales. *J Pers Soc Psychol*. 1988;54(6):1063-1070. doi:10.1037/0022-3514.54.6.1063.
84. Beck AT, Steer RA, Brown GK. *Beck Depression Inventory®-II*. San Antonio: Pearson (Psychological Corporation); 1996. https://www.pearsonclinical.com/psychology/products/100000159/beck-depression-inventoryii-bdi-ii.html. Accessed March 20, 2018.
85. Spielberger CD, Vagg PR. Psychometric Properties of the STAI: A Reply to Ramanaiah, Franzen, and Schill. *J Pers Assess*. 1984;48(1):95-97. doi:10.1207/s15327752jpa4801_16.
86. Buysse DJ, Reynolds CF, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193-213. doi:10.1016/0165-1781(89)90047-4.
87. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy Scale : Development and Validation of the General Measure. *J Clin Oncol*. 1993;11(3):570-579. https://www.researchgate.net/profile/David_Cella/publication/14754744_Cella_DF_Tulsky_DS_Gray_G_Sarafian_B_Linn_E_Bonomi_A_Silberman_M_Yellen_SB_Winicour_P_Brannon_JThe_Functional_Assessment_of_Cancer_Therapy_scale_development_and_validation_of_the_genera. Accessed March 20, 2018.
88. Luckett T, King MT, Butow PN, et al. Choosing between the EORTC QLQ-C30 and FACT-G for measuring health-related quality of life in cancer clinical research: Issues, evidence and recommendations. *Ann Oncol*. 2011;22(10):2179-2190. doi:10.1093/annonc/mdq721.
89. Brandt J, Spencer M, Folstein M. The Telephone Interview for Cognitive Status.

Neuropsychiatry Neuropsychol Behav Neurol. 1988;1(2):111-117. https://www.researchgate.net/publication/232211604. Accessed May 23, 2018.
90. Von Bastian CC, Locher A, Ruflin M. Tatool: A Java-based open-source programming framework for psychological studies. *Behav Res Methods*. 2013;45:108-115. doi:10.3758/s13428-012-0224-y.
91. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncol*. 2011;12(7):703-708. doi:10.1016/S1470-2045(10)70294-1.
92. Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol*. 1935;18(6):643-662. doi:10.1037/h0054651.
93. von Bastian CC, Souza AS, Gade M. No evidence for bilingual cognitive advantages: A test of four hypotheses. *J Exp Psychol Gen*. 2016;145(2):246-258. doi:10.1037/xge0000120.
94. Wagner LI, Sweet J, Butt Z, Lai JS, Cella D. Measuring patient self-reported cognitive function: Development of the Functional Assessment of Cancer Therapy - Cognitive Function instrument. *J Support Oncol*. 2009;7(6):W32-W39.
95. University of Colorado Denver. Health Data Compass. 2017. http://www.ucdenver.edu/about/departments/healthdatacompass/Pages/default.aspx. Accessed May 23, 2018.
96. Heishman SJ, Singleton EG, Liguori A. Mari j uana Craving Questionnaire : development and initial validation of a self-report instrument. *Shock*. 2001;(September 2000):1023-1034. doi:10.1080/09652140120053084.
97. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The Alcohol Use Disorders Identification Test Guidelines for Use in Primary Care. *World Heal Organ*. 2001:pp1-40. doi:10.1177/0269881110393051.
98. Sobell LC, Sobell MB. Timeline Follow-Back: A technique for assessing self-reported alcohol consumption. In: *Measuring Alcohol Consumption*. Vol Totowa, NJ: Humana Press; 1992:41-72. doi:10.1007/978-1-4612-0357-5_3.
99. Sobell MB, Sobell LC, VanderSpek R. Relationship between clinical judgment, self-report, and breath-analysis measures of intoxication in alcoholics. *J Consult Clin Psychol*. 1979;47(1):204-206. doi:10.1037/0022-006X.47.1.204.
100. Benedetti F, Pollo A, Lopiano L, Lanotte M, Vighetti S, Rainero I. Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. *J Neurosci*. 2003;23(10):4315-4323. doi:23/10/4315 [pii].
101. Price DD, Milling LS, Kirsch I, Duff A, Montgomery GH, Nicholls SS. An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. *Pain*. 1999;83(2):147-156. doi:10.1016/S0304-3959(99)00081-0.
102. Morgan CJA, Freeman TP, Schafer GL, Curran HV. Cannabidiol attenuates the appetitive effects of Δ9- tetrahydrocannabinol in humans smoking their chosen cannabis. *Neuropsychopharmacology*. 2010;35(9):1879-1885. doi:10.1038/npp.2010.58.

18 APPENDICES

This section is not applicable.

Version	Date	Significant Revisions
1	4/20/2018	
2	5/22/2018	Updates per PRMS review comments
3	6/8/2018	Updated Statistical and Analytical Plan
4	8/27/2018	COMRIB Requested Revisions
5	6/12/2019	Eligibility edits for enrollment
6	6/30/2020	Edits for remote visit descriptions and eliminating research blood draws due to COVID