Northwestern | OFFICE FOR RESEARCH

Cannabis Research & IRB Review

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Cannabis industry and research implications

$12.4 Billion

Legal cannabis sales in 2019

$23 Billion

Estimated legal cannabis sales in the US in 2025

$266 Million

NIH funded research in cannabis in 2019

- Use of Marijuana is increasing
- Legal status of the plant impedes research at NIH & FDA
- Botanical medicine research with plant extracts
- Rigorous research studies are needed to better characterize risks and benefits of Marijuana

Sources: https://www.statista.com/statistics/933384/legal-cannabis-sales-forecast-us/ and https://report.nih.gov/categorical_spending.aspx

Objectives

- Describe essential elements of the study design needed to generate reliable, reproducible and generalizable data
- Identify elements of safety monitoring needed to protect research subjects and cannabis users in general, including assessment of addiction/abuse potential
- Apply regulatory criteria to determine review pathways (expedited or full convened board) and criteria for approval

History of Cannabis Use

- Cannabis is a plant that is grown and used by humans for thousands of years
- Currently there are 3 cultivated species of Cannabis-The more common are Cannabis Sativa, Cannabis Indica, and the less commonly used is the Cannabis Rudaralis
- Hundreds if not thousands of different hybrid strains of the plant, that have varying ratios of THC (which is the more psychoactive component of Cannabis) or CBD

History and Legal status of Cannabis in the US

- At the beginning of the last century in the US it was legal and an accepted medicine
- Regulated by 1906 Pure Food & Drug Act
- In 1920's and 1930's it was stigmatized
- 1970 – Comprehensive Drug Abuse Prevention and Control Act
- 2012- recreational use legalized in Washington & Colorado. Currently 33 states have legalized medical marijuana & 11 have legalized recreational uses.
- FDA schedule I

FDA supports sound scientific research

- FDA fact sheet – “deceptive marketing of unproven treatment raises significant public health concerns because patients may be influenced to try unapproved therapies for serious & even fatal diseases”
- FDA process of drug approval evaluates efficacy, dosage, drug-drug interactions, side-effects, and other safety concerns
- Conduct research with requires an IND

Cannabis as a Botanical Medicine

- Chemical constituents
- *THC, CBD* (most commonly referred to molecular constituents)
  -600 constituents: 100 different cannabinoids, terpenoids, flavonoids…
- Chemical complexity creates research challenges

What do we know?

- FDA has approved 4 cannabis derived products for marketing in the US–Marinol, Syndros, Cesamet (Which use synthetic THC) and Epidiolex (purified CBD)
- All three FDA approved for use in cachexia and nausea in people with Aids or Cancer
- Epidolex is used in Children with seizures associated with Dravet syndrome and LGS syndrome (Lennox-Gastaut)
- Reasonable evidence for efficacy in neuromuscular disorders, sleep disorders, Tourette's syndrome
- Lack of evidence of efficacy in depression, anxiety, psychosis, and glaucoma

Cannabis Research Protocols: Essential Design elements

Chemical constituents

- Plant characteristics (extract whole plant or synthetic)

  -Species, strain or variety

- Growth and harvesting parameters
- Parts of the plant used

  -whole, seed, flower

- Extraction methods
- Concentrations of the chemical moieties including batch to batch variability.

Cannabis Research Protocols: Essential Design elements

Interventional agent development

- Dosing parameters
- Route, frequency, and dose of identified compounds
- PK and PD analyses per dosing regimen
- Characterization of metabolites
- Correlation between physiological levels and outcomes of interest will inform future dosing paradigms

Outcome measures:

- Support therapeutic application
- Quantitative better than Qualitative
- Power studies adequately
- Placebo-controlled design. Pros & cons should be evaluated

Cannabis Research Protocols: Essential Design elements

Inclusion/Exclusion Criteria

- Maximize safety of participants
- Consider co-morbidities
- Minimize overall variability of population
- Minimize confounding variables

Cannabis Research Protocols: Essential Design elements and Safety monitoring

Duration:

- Design studies of sufficient duration to evaluate long-term safety and efficacy

Behavioral sequelae:

- Driving under influence
- Drug testing
- Potential for abuse
- Addiction

What can sponsors and IRBs do?

- **Evaluate pre-clinical drug abuse models**
  - Self-administration studies
  - Micro-dialysis studies changes in brain
- **Evaluate human models**
  - Epidemiological studies
  - Non-treatment seeking users (relapse and cravings)
- **Ensure proper storage of drugs to avoid abuse**
  - Limited access
  - Double locked doors
- **Dosing schemas**
  - Blister packs when possible
  - Limit 7-10 day supply.

FDA Regulatory Status

- Schedule 1 drug (for now)
- 4 products approved: Marinol, Syndros, Cesamet (synthetic THC); Epidiolex (purified CBD)
- No approved marketing application for the Cannabis plant as a whole or extract of the whole plant
- Does not allow THC or CBD to be sold as a dietary supplement or a food additive
- Parts of the plant that contain <0.3% THC by dry weight (e.g hemp seeds) may be marketed as hemp and are not considered to be a controlled substance

Informed Consent

- Source of evidence
- Therapeutic misconception
- Safety “misconception”
- Discussion of abuse/addiction potential

Privacy & Confidentiality:

- State law of site
- Anonymous data collection.
- Certificate of confidentiality
- Waiver of documentation

When is an IND required?

- The IND regulations in 21 CFR 312 require that human research studies be conducted under an IND if all of the following conditions exist:
  - The research involves a drug as defined by the FDA
  - The research is a clinical investigation as defined in the IND regulations
  - The clinical investigation is not otherwise exempt from the IND requirements
- **If in doubt, ask the FDA!**

Expedited pathways

- Research is no more than minimal risk
- Research involves only procedures listed in one or more of the Expedited categories
- Will identification of subjects and/or their responses reasonably place them at risk?
- Are there reasonable and appropriate protections implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal?

Example

- Survey study with adult and pediatric participants
- Participants are currently being treated at clinics and given SOC medical cannabis recommendations in accordance with state law (OH, FL, PA, IL and expanded to other states where permitted)
- Cannabis use is NOT being determined/influenced by participation in the study (dose not prescribed by study)
- An anonymized online questionnaire to determine participants' qualifying condition(s) for medical cannabis use, cannabis ingestion method, frequency of use, prescription drug use, demographic information, evaluation of pain control, quality of life, adverse side effects from cannabis use, and changes in adjunctive treatments
- May include data collection from clinic records
- Survey data is not stored with any identifying information

Expedited review

Expedited under categories 5 and 7

- Medical use of cannabis is SOC and research procedures involve data collection and survey procedures
- Research involves collection of sensitive information and includes reasonable and appropriate protections so that risks are no greater than minimal, survey data is anonymized.
- Survey research with minors can not be exempt

Example

Randomized study of effect of cannabis on neuropathic pain in adult HIV participants

- Objective: assess 120 adult participants with HIV who have neuropathic pain and currently use cannabis

The study includes two phases:

- **Phase 1:** Crossover study involving three different doses of vaporized cannabis that contain THC and varying concentrations of CBD

This phase will examine the acute effects of cannabis on pain intensity, blood endocannabinoid levels, and the relationship of pain with heart rate variability (HRV)

- **Phase 2:** Evaluation of the association between dispensary obtained cannabis and changes in pain reported via a health text messaging app that will serve as a tool to monitor the relationship between pain and cannabis use

Full board review

Randomized study of effect of cannabis on neuropathic pain in adult HIV participants

- This is a clinical investigation assessing the effects of cannabis and endocannabinoid use for treating neuropathic pain in people living with HIV
- Study is subject to IND regulations

Duties of the IRB

- Further the development of therapeutic options
- Duty to protect human subjects
- Opportunity to further the conduct of rigorous and probative clinical trials

Resources

- FDA Regulation of Cannabis and Cannabis Derived Products, Including Cannabidiol (CBD) https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd
- The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research.
- Reefer Sanity: IRB Review that won't vaporize Cannabis protocols. Advarra webinar 2/4/2020 https://www.advarra.com/resource-library/reefer-sanity-irb-review-that-wont-vaporize-cannabis-protocols/
- FDA and Cannabis: Research and Drug Approval Process https://www.fda.gov/news-events/public-health-focus/fda-and-cannabis-research-and-drug-approval-process
- J. Corroon, R. Kight. "Regulatory Status of Cannabidiol in the United States: A Perspective." Cannabis and Cannabinoid Research. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6154432/
- FDA Guidance "Investigational New Drug Applications (INDs)Determining Whether Human Research Studies Can Be Conducted Without an IND" https://www.fda.gov/media/79386/download

Questions