Clinical studies with Cannabis in India – A need for guidelines for the investigators and ethics committees

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Abstract

Cannabis is one of the world's oldest cultivated plants and the most commonly used recreational drug worldwide. The plant relevant for medicinal use is *Cannabis sativa* that has two pharmacologically active ingredients – delta-9-tetrahydrocannabinol that is psychoactive and cannabidiol that does not have psychotropic activity. The policy tapestry of Cannabis has undergone a significant change in the past few decades worldwide. Different countries have diverse policies, ranging from classifying use of Cannabis as illicit, to legalization of its use, both for medicinal and recreational purposes. Cannabis products are approved for use, for instance, in multiple sclerosis and Dravet syndrome (US Food Drug and Administration). Against this backdrop, we find that the knowledge foundations for use of Cannabis in clinical trials in India are still evolving. Conducting ethical research within a clinical trials framework is essential to understand dosing, formulation, shelf life, drug–drug interaction, tolerability, and safety before establishing its utility for various indications. In the absence of guidelines or a regulatory framework for conduct of these studies, the various Institutional Ethics Committees (IECs), which are responsible for reviewing projects related to Cannabis, face unique challenges with respect to the basic requirements. The principal investigators (PIs) are equally strained to find local guidance, recommendations, and literature in support of their application to the respective IEC, thus leading to an impasse and delay in initiating the proposed clinical studies with Cannabis. The present article addresses considerations, questions, and issues that affect the conduct of these clinical studies and recommends mandatory documents and some suggested guidelines for use by both PIs and IECs to take studies with Cannabis forward until such time that an interdisciplinary regulatory framework is firmed up by regulatory authority.

Keywords: Cannabis, ethics, research

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CANNABIS AND ITS USES

Cannabis, an important herbaceous species, is one of the world's oldest cultivated plants and used since ancient times for its medicinal properties.[1] It is also the most commonly used illicit drug worldwide. The term Cannabis itself is a generic term that is used to denote several psychoactive substances contained in the plant. While *Cannabis sativa* is the plant of significance, plants of minor importance are *Cannabis indica* and *Cannabis ruderalis*. Of the

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approximately 750 constituents in *C. sativa*, more than 100 are cannabinoids. The two main pharmacologically active compounds of *C. sativa* that are most studied and of clinical importance are (1) delta-9-tetrahydrocannabinol (THC) that is psychoactive and (2) cannabidiol (CBD) that is not.[2] Cannabis in India is commonly known in 3 forms Bhang, Ganja and Charas. Bhang which is a preparation made from leaves and seeds, it is a common ingredient used in a form of used in Thandai, and other preparations during the local festival of Holi. Ganja is flowering tops/fruits, which is commonly smoked. Charas is the extracted resin, which is more potent and available as tar-like ball also used for smoking.[1]

A meta-analysis (2006) showed a wide range of applications of Cannabis ranging from use as an anti-emetic, analgesic, anti-epileptic, application in Tourette's syndrome and glaucoma.[3] In June 2018, Epidiolex® became the first CBD-based drug to be approved for use in Dravet syndrome in children, a rare and severe form of epilepsy.[4] The drug Sativex® (whole plant Cannabis extract) is approved in several countries for the management of spasticity due to multiple sclerosis,[5] while cannabinoid receptor agonists such as nabilone, a synthetic cannabinoid, are used for the management of chemotherapy-induced nausea.[6] Its potential applications in oncology are manifold considering its properties of reducing chronic neuropathic pain, stimulating appetite, alleviating nausea and vomiting, and improving overall well-being that are worth exploring in the palliative as well as an adjuvant setting. A recent placebo-controlled phase 1b study in recurrent brain tumors even showed efficacy in improving progression-free survival when Sativex was combined with temozolomide.[7] The US Food Drug and Administration (FDA) approved the use of synthetic cannabinoids for reducing chemotherapy-induced nausea vomiting.[8] However, there is greater interest in herbal preparations of Cannabis because of the known "entourage effect" of its multiple constituents increasing efficacy rather than exploring synthetic cannabinoids in isolation.[9] In the textile industry, the outer layer of the *C. sativa* stalk is processed to make yarn/fibers with a texture similar to that of cotton, while the inner layer finds application in the fuel industry (oil), and for making animal bedding and building materials such as sails, nets, and ropes.[10]

THE INTEREST IN CANNABIS USE AND RESEARCH IN INDIA AND WORLDWIDE

The World Health Organization through its expert committee on drug dependence met in late 2018 for a critical review of the evidence on Cannabis for medical applications. The current schedule of Cannabis in international law is as strict as for Heroin (Schedule 4, Narcotics Drugs Treaty of 1961). In an important move, the committee called for rescheduling Cannabis, easing control, and reversing a position held for 60 years disallowing even its legitimate use for medical applications. In December 2020, 27/53 members (including India, the US, and most of the EU) of the UN Commission on Narcotic Drugs in a historic vote, removed Cannabis from Schedule 4 paving the way for its use in medicinal and therapeutic research.[11] Currently, 50 countries worldwide allow the use of medicinal Cannabis. Its recreational use has been legalized in several countries, including Canada, Uruguay, and 15 states in the United States.[12]

In India, an nongovernmental organization called the Great Legalization Movement filed a writ petition in the Delhi high court in May 2020 asking for decriminalization of Cannabis so that its medicinal properties could be harnessed.[13] In the Cannabis space in India, there are several start-ups such as The Bombay Hemp Company, Hempster, BE Hemp, and Hempstreet, some of whom offer treatment with Cannabis guided by principles laid down in Ayurveda.[14] The Indian Institute of Integrative Medicine (IIIM) has obtained a license from the Government of India for the development of products for epilepsy and cancer in collaboration with an Indian Cannabis manufacturer.[15] A tripartite agreement has also been signed between the Indian Council of Medical Research (ICMR), the Council for Scientific and Industrial Research (CSIR), and the Department of Biotechnology (DBT) for the active clinical development of phytopharmaceuticals from Cannabis for several therapeutic areas such as chronic pain, pediatric epilepsy, and neurodegenerative disorders.[16] This movement is in line with the interest in medical applications of Cannabis worldwide. In late September 2019, the revenue wing of the Union Finance Ministry sanctioned research and development on CBD and THC. Central Institute of Medicinal and Aromatic Plants and CSIR have announced a joint venture to collect Cannabis germ plasm for preservation and farming. The Narcotic Drugs and Psychotropic Substances Act (NDPS), 1985, emphasizes research focus on Cannabis for horticultural and industrial use as a source of biomass, fiber, and Cannabis seed oil.

CLINICAL TRIALS WITH CANNABIS: CHALLENGES WITH RESPECT TO CANNABIS, CLINICAL INVESTIGATORS, AND THE ETHICS COMMITTEES

The "endocannabinoid system" in the human body has a role in homeostasis which is important due to its neuromodulatory function.[17] This system mediates

its effect through at least two G-protein coupled cannabinoid receptors – CB_1 (regulates neurotransmission) and CB_2 (regulates immune and inflammatory pathways). CB_1 is activated by two known metabolites, anandamide (from Sanskrit word meaning "bliss") and 2-arachidonoylglycerol (2-AG).[18,19] The major problem with Cannabis lies in the several risks associated with its indiscriminate use, some of which include increased risk of stroke, affection of learning and memory, and mental illnesses including psychosis. Groups that are associated with the highest risks are teenagers, pregnant women, and people who may already be at risk of mental illness.[20] The THC: CBD ratio (and their doses) in Cannabis is what is crucial to understanding the harm associated with its use. THC can elicit anxiety, induce psychosis, and produce cognitive impairment while CBD can mitigate this. Products containing Cannabis can have varying doses that give varying ratios of the two compounds and therefore differ in their therapeutic and addictive potential.[21]

The policy debate of Cannabis for clinical and recreational use has undergone a significant change in the past few decades worldwide. Countries have diverse Cannabis policies ranging from classifying its use as illicit to legalization of its use both for medicinal or recreational purposes. In India, its use is governed by the NDPS Act (see below) or NDPS Act. Against this backdrop, it would be relevant for Indian investigators to understand the regulatory status of Cannabis in India, and steps that they need to adhere to while undertaking clinical trials with Cannabis regardless of the indication. For ethics committees, we hope that this article will provide a near-comprehensive list of checks that need to be in place prior to according approval for any clinical trial with Cannabis and evaluate the benefit–risk assessment of the protocol. The article is intended to serve only as a guidance for researchers, clinicians, and IEC members in India for projects/studies related to Cannabis and is not intended to be a discussion or debate on the larger applications (or lack thereof) of Cannabis in the practice of medicine. Our guidance also does not apply to synthetic cannabinoids and phytopharmaceuticals [Table 1 for definitions] which need to follow the regulatory pathway as laid down in the New Drugs and Clinical Trials Rules (NDCT rules 2019).

THE NARCOTIC DRUGS AND PSYCHOTROPIC SUBSTANCES ACT

The NDPS Act, 1985, is the law that governs the production/manufacturing/cultivation, possession, sale, purchasing, transport, storage, and/or consumption of any narcotic drug or psychotropic substance. It came into force on November 14, 1985, and has been subsequently amended at least four times in the years 1988, 2001, 2014, and 2018.[24] Section 2 (3) of this act prohibits the use of the resin of the *C. sativa* plant (also called liquid hash, hash oil) and prohibits the use of flowering tops and fruits called *Ganja*. What is permitted is the use of seeds and leaves, used to make *Bhang* which is permitted in some states for use during certain festivals. In Maharashtra, section 66 (1) (b) of the Bombay Prohibition Act (1949) permits the use of *Bhang* with a license.[24] This act does empower individual states to accord licenses for growing this plant.

Table 1: Key definitions of drugs and new drugs in India

Definition of new drug as per NDCT rules (2019)[22]
i. A drug, including active pharmaceutical ingredient or phytopharmaceutical drug, which has not been used in the country to any significant extent, except in accordance with the provisions of the act and the rules made thereunder, as per conditions specified in the labeling thereof and has not been approved as safe and efficacious by the Central Licensing Authority with respect to its claims; or
ii. A drug approved by the Central Licensing Authority for certain claims and proposed to be marketed with modified or new claims including indication, route of administration, dosage, and dosage form; or
iii. A fixed-dose combination of two or more drugs, approved separately for certain claims and proposed to be combined for the first time in a fixed ratio, or where the ratio of ingredients in an approved combination is proposed to be changed with certain claims including indication, route of administration, dosage, and dosage form; or
iv. A modified or sustained release form of a drug or novel drug delivery system of any drug approved by the Central Licensing Authority; or
v. A vaccine, rDNA-derived product, living modified organism, monoclonal antibody, stem cell-derived product, gene therapeutic product, or xenografts, intended to be used as a drug
While iv. and v. will always remain new drugs, i. to iv. remain new drugs for a period of 4 years after approval by the Central Licensing Authority
Definition of a drug as per Ministry of AYUSH[16]
An "Ayurvedic, Siddha, or Unani drug" includes all medicines intended for internal or external use for in the diagnosis, treatment, mitigation, or prevention of disease or disorder in human beings or animals, and manufactured exclusively in accordance with the formulae described in the authoritative books of Ayurveda, Siddha, and Unani Tibb systems of medicine, specified in the first schedule. These are classified into three categories – classical drugs (e.g., crude drugs and extracts), dosage forms (e.g., bhasmas), proprietary drugs (e.g., syrups, tablets, and ointments)
Definition of a phytopharmaceutical[23]
Phytopharmaceutical drug is defined as purified and standardized fraction with defined minimum four bio-active or phytochemical compounds (qualitatively and quantitatively assessed) of an extract of a medicinal plant or its part for internal or external use of human beings or animals for diagnosis, treatment, mitigation, or prevention of any disease or disorder but does not include administration by parenteral route

r-DNA=Recombinant deoxyribonucleic acid, NDCT=New Drugs and Clinical Trials, AYUSH=Ayurveda, Unani, Siddha, and Homeopathy

ROLE OF THE MINISTRY OF AYURVEDA, UNANI, SIDDHA, AND HOMEOPATHY

The Ministry of Ayurveda, Unani, Siddha, and Homeopathy (AYUSH), in 2010, introduced Rule 158 (B)

which mandated proof of effectiveness for licensing of a patent or proprietary Ayurveda, Siddha, or Unani (ASU) product.[22] The definition of these products is given in Table 1. Good Clinical Practice guidelines also exist for voluntary use by researchers interested in undertaking clinical trials with ASU products. Cannabis products that fit the AYUSH definition are available in the Indian market.

REGULATORY AND ETHICAL ISSUES AROUND CANNABIS FORMULATIONS

Despite the resurgent interest in the potential role and use of Cannabis for therapeutic applications, the epistemic foundations are weak. Conducting ethical research within a clinical trials framework is essential to understand dosing, formulations, shelf life, drug interactions, and efficacy for different indications to ensure reproducible quality and patient safety. In addition, a stable supply and appropriate storage is necessary.

There is poor awareness of guidelines, lack of understanding of the oversight of different governmental agencies and ministries and a lack of clear-cut framework for the regulatory conduct of these studies. Due to these issues, Institutional Ethics Committees who review projects related to Cannabis face unique challenges.[25] This has led to delays in approvals and trial commencement and consequently Cannabis development.[26] India has myriad agencies and acts, sometimes specific to a province or a state which creates multiple steps, each of which has to be navigated. In addition, both the state and central bureaucracies add further steps to get the necessary permissions which strain the principal investigators (PIs) and the Ethics Committee.[27] The sensitive nature of these studies, the stigma associated with the drug, and the lack of clarity lead to "who will bell the cat" situations.[28]

Cannabis studies usually involve oral drugs, in outpatient settings that involve self-medication. This raises several ethical concerns – those of adequate and safe storage, dosing, toxicity measurement, potential use with other illicit drugs (commonly tobacco and alcohol), interaction with other drugs, especially in the setting of cytotoxic chemotherapy when used in cancer patients, drug abuse, drug loss, and use as contraband among others.

Inhalational forms of Cannabis typically involve smoking it as a joint, in a pipe, or using a vaporizer. The inhalation with Cannabis is longer and deeper, and more likely to be deposited in the lower airway. Unlike the short half-life of nicotine (2 h), cannabinoids are deposited for a week or more. Studies evaluating the smoked form of marijuana have not conclusively demonstrated an objective decline in lung function but have shown smoking Cannabis to be associated with chronic respiratory symptoms.[29]

Cannabis formulations can be synthetic, phytopharmaceutical (cannabinoids), or natural plant based (Sativex-like drugs).[17] The regulations differ based on the origin of the molecule used in the formulation. The Central Licensing Authority approves synthetic and phytopharmaceuticals agents, while the Ministry of AYUSH approves plant-based products. The rules, conduct of regulatory framework, and capabilities differ for both these central authorities. The culture of Phase 1/2/3 clinical trials is relatively new for the fields of Ayurveda, Siddha, and Unani, reflecting in the conduct and rigor of data safety monitoring requirements as compared to allopathy drug counterparts.

The production and distribution of these drugs is under tight control and oversight of federal and state authorities based on the origin of the raw material (imported vs. locally grown), transport of the drug between states (needs the nod of individual state authorities), and storage of the drug before dispensation (controlled and overseen by local state FDA and police authorities). This bureaucratic maze lays a huge burden on the PI and the IECs for discovery of and compliance to the nuanced interpretation of these evolving laws.

We enumerate some of these considerations, questions, and issues that affect the PI and the IECs. A clear answer with compatible citation in the regulatory and legal framework and attached documentation eases the project approval and conduct.[22,26,30,31]

1. What is the drug formulation? (oral vs. vaporizer, synthetic, phytopharmaceutical, or plant-based-mention differences between plant-based and phytopharmaceutical agents)
2. Where is the raw material for the drug formulation sourced from? (if imported, may need NCB clearance)
3. Is the manufacturer GMP certified? (to procure and verify license)
4. Which Ministry approves the manufacturer's license? (Ministry of Health or AYUSH)
5. Is there interstate transfer of drugs? (State FDA approval required)
6. Where shall it be stored? (State FDA vs. local police verification)
7. Batch-wise formulation and labeling (audit report to be submitted to state FDA)
8. Contingency for lost or expired/damaged drug product
9. Is the supply chain robust for the completion of the clinical trial? What are the best alternatives available if the supply of drug product is disrupted?

10. Possibility of posttrial access to patients
11. Are the mechanisms for ensuring dose uniformity solved? (particularly for phase 1 and 2 studies as ensuring dose uniformity in plant-based products is challenging)
12. How are the side effects going to be reported? (CTCAE vs. other applicable reporting measures)
13. Are the relevant drug interactions known/measurable/reportable? (IB and clinician understanding become important here).

Suggested guidance for Indian investigators and ethics committees for reviewing proposals with Cannabis

Based on our experience as Investigators and Ethics Committee members dealing with Cannabis projects, we suggest that the following additional documents may be obtained after which ethics committees can review and may accord approval for these projects. We encourage investigators to apprise themselves of state rules/city rules that may differ from the guidance provided. This list is by no means exhaustive.

Requisite documents

1. Application to the Institutional Ethics Committee – When such clinical studies are conducted in institutions, applications are to be made to the IEC per their policy with a statement that guidance from AYUSH will be followed for the conduct of the study where the drug satisfies the definition laid down by the Ministry of AYUSH [Table 1]
2. Approval letter from AYUSH, Government of India – This approval is provided by the Ministry of AYUSH (Drug Policy Division) for the whole leaves of Cannabis for a specific indication (as applied for by the PI) with a statement that it fits the definition of Ayurveda, Unani, Siddha, and Homeopathy under section 3(a) and 3(h) of the Drugs and Cosmetics Act (1940). The drug should be procured from AYUSH-approved, GMP-grade Cannabis manufacturers
3. Permission for storage of Cannabis from the State FDA – This letter from the State FDA gives permission for the storage of Ayurvedic Cannabis at a specific location, for example, at an institute or a hospital
4. Copy of Memorandum of Understanding between the PI, Institute, and the manufacturer of Cannabis product – this should be a standard document per the institute's policy and vetted by the legal expert on the IEC and the institute's legal expert if available and where applicable per institutional guidelines
5. Valid license from the manufacturer that they have permission to manufacture Cannabis from the State FDA under GMP conditions – This license is issued by the AYUSH Drug Controller of the State
6. State/city collector letter granting a license – The state or city collector issues a license for a period of 1 year for the use of Cannabis (as Ganja for example) with strict adherence to an inventory and adherence to the NDPS act
7. State Government Excise Department – Drug inspector appointment letter
9. Storage location map – This gives a map of the storage area for Cannabis including a list of personnel who are authorized to enter the storage area
10. Undertaking from the PI - This undertaking should state that the PI will abide by the protocol and all the relevant AYUSH guidelines for the conduct of the study and submitted to the IEC
11. A detailed clinical study protocol and informed consent form detailing the procedural aspects of the study, and issues pertaining to posttrial access, if any benefit is observed as an outcome of the study.

Regulatory approval from the Drugs Controller of India (DCGI) is needed in case the drug product is a phytopharmaceutical and synthetic cannabinoid. All other pure plant-based products fall under the purview of the Ministry of AYUSH.

SUMMARY AND CONCLUSIONS

As the clamor for use of Cannabis for medicinal purposes grows worldwide and as cannabinoid drugs (synthetic or otherwise) find their way into the therapeutic armamentarium, Indian physicians and members of ethics committees should appraise themselves of guidelines that exist in the country for their use and understand their classification into traditional or modern systems of medicine based on which the appropriate regulatory pathway can be followed. In addition, it would be useful if the Central Drugs Standard Control Organization, State FDAs, the Ministry of AYUSH, and organizations such as the IIIM can come together with agencies such as the ICMR, DBT, and CSIR along with investigators to lay down a clear cut framework and regulatory pathways for the use of Cannabis in clinical studies in India.

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Conflicts of interest

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