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The *Cannabis Act*: implications for human participant research with cannabis

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In Canada, cannabis was legalized for medical purposes in 2001 and for nonmedical use in 2018, with edibles, concentrates, and topicals following in 2019 under the Canadian *Cannabis Act* (Bill C-45).[1] This legislation regulates the production, distribution, sale, and possession of cannabis, aiming to protect public health and safety, restrict youth access, and undermine the illegal market. Importantly, it also includes provisions for cannabis research. Five years after legalization, we evaluate the impact of this regulatory shift. We first summarize the initial data reflecting the effects of new cannabis regulations on public health (e.g., trends in cannabis use, health outcomes, hospital visits) and discuss the progress in clinical cannabis research; the current regulatory environment; and the challenges faced, including sourcing cannabis and placebo under the current regulatory framework. The *Cannabis Act* itself is an ongoing experiment in public policy, and monitoring these developments is crucial for providing valuable input into its ongoing review, ensuring it remains evidence-based and adaptable. We conclude with pitfalls and hurdles ahead, as well as recommendations for future cannabis research.

Early health indicators of cannabis policy changes

Canada's decision to legalize nonmedical cannabis marked a major shift from existing drug policies and sparked significant debate both domestically and internationally. As the first G7 country to legalize cannabis at the federal level, Canada set a precedent for other nations. Over the past 5 years, policy objectives have been assessed, and initial metrics have been examined.[2–5] Early findings show mixed results. Legalization reduced the criminalization of cannabis-related behaviours without increasing other crimes, indicating progress in social justice goals.[6,7] However, in Ontario, cannabis use, daily use, and related problems increased, especially among people older than 55 years.[8] Emergency department visits for adverse reactions, including cannabis hyperemesis syndrome and pediatric poisoning, have risen.[9–12] An increase in cannabis-induced psychosis in young adults (older than 19 yr) has been reported in some[13] but not all studies,[14] and the number of pregnant women needing hospital care for cannabis-related problems has doubled.[15] Additionally, studies have shown an increase in injured drivers who used cannabis.[16] These findings primarily reflect periods with immature cannabis markets and coincide with the COVID-19 pandemic, complicating the assessment of Bill C-45's impact. As the stigma around cannabis use declines[17] and the market diversifies,[18] continuous monitoring and adaptive regulatory measures are essential to address emerging health risks and optimize policy outcomes.

Trends in emerging clinical research on cannabis in Canada

Since cannabis legalization, Canada has experienced a surge in research interest, with the Canadian Institutes of Health Research (CIHR; the main government funder of medical research) leading funding initiatives. However, progress has been slow, particularly in studying the inhalation of dried cannabis, the most common consumption method. Knowledge gaps on the effects of cannabis have been identified by an expert panel[1]; urgent research is needed in the areas of dosing standards, high-potency effects on mental health, prenatal exposure, driving performance, treatment efficacy, and long-term consequences. Accelerating research on the effects of cannabis is necessary postlegalization.

We searched ClinicalTrials.gov, the National Institute of Health (NIH) database, for trials conducted in Canada between 2013 and 2024 (5 yr before and 5 yr after legalization) to explore the status of interventional cannabis studies. The search terms included "cannabis," "tetrahydrocannabinol,"

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"THC," "cannabidiol," and "CBD." We excluded studies on synthetic cannabinoid products (e.g., nabilone, nabiximols) and those not conducted in Canada, but included studies on phytocannabinoids, THC, and/or CBD, regardless of formulation or administration route. We extracted data on study status, conditions, interventions, primary outcome measures, study duration, and locations. The findings are reported in Figure 1. Note, however, that not all active clinical trials are registered on ClinicalTrials.gov, so this sample may not be fully representative.

Out of 102 registered studies, 45 met our eligibility criteria. There was a notable doubling of studies registered after legalization (n = 31) compared with before (n = 14). Among the postlegalization studies only 19 appear to be successfully active or completed. These studies investigate both behavioural (e.g., driving, stress) and physiologic effects (e.g., cardiovascular) of cannabis on healthy individuals as well as its therapeutic potential for conditions like cancer, multiple sclerosis, Alzheimer disease, major depressive disorder, chronic headaches, and postsurgery pain. Importantly, only 4 of the active studies involve inhaled cannabis. Despite the inherent limitations of platforms like ClinicalTrials.gov, which may contain errors or omissions and does not specify if the listed trials operated under the *Cannabis Act*, our examination clearly highlights the sparse state of cannabis research, notably in the domain of smoked cannabis.

The complex, evolving regulatory framework for clinical research involving cannabis

A cornerstone to successful and ethical human participant research in the area of cannabis is the regulatory oversight provided by federal authorities. These regulations provide guidance to the investigator as to how to ensure the protection of the rights, safety, and well-being of the participants as well as data integrity. Since cannabis legalization, the regulatory framework for clinical research in Canada has undergone considerable changes. In the next section, we review the trajectory of the Canadian regulatory framework for human participant research in Canada. We start with an overview of the framework in the years before legalization and then describe the changes over the past 5 years.

Regulations before legalization

Before legalization, researchers had to go through several regulatory procedures to conduct cannabis-related studies. Studies involving cannabis conducted before legalization followed guidelines similar to those governing pharmaceutical clinical trials. These guidelines were outlined in the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices E6 (R2) (GCP)[19] and were in accordance

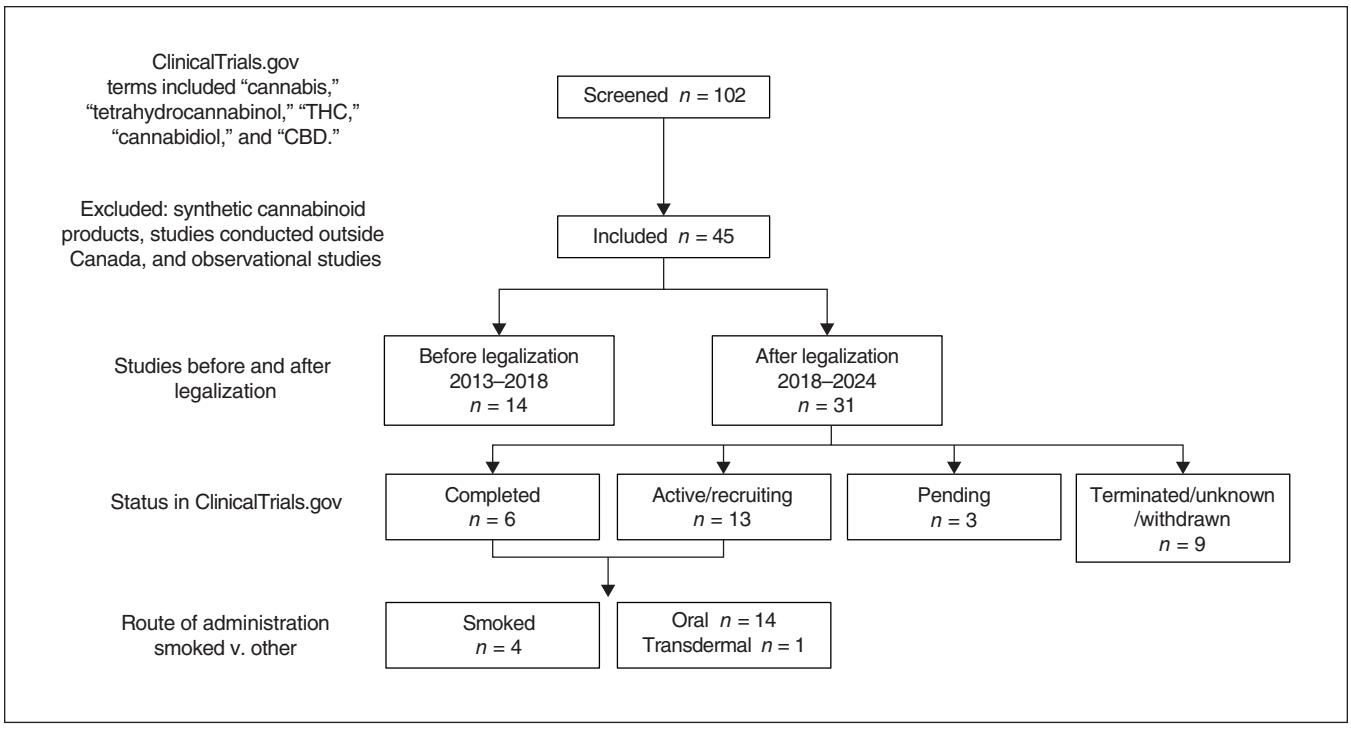

Fig. 1: Flow diagram representing the search on ClinicalTrials.gov for clinical cannabis studies conducted in Canada with terms including "cannabis," "tetrahydrocannabinol," "THC," "cannabidiol," and "CBD," and excluding synthetic cannabinoid products (e.g., nabilone, nabiximols). Out of 102 registered studies, 45 met our eligibility criteria, and 31 studies were conducted after legalization compared with 14 before legalization. Among the postlegalization studies, 6 were completed; 13 are active/recruiting; 3 are pending recruitment; and 9 were terminated, withdrawn, or have unknown status. Of the 19 completed or active/recruiting studies, 4 involved inhaled cannabis, 14 used oral administration (e.g., oil), and 1 used transdermal administration.

with Division 5 of the Food and Drug Regulations.[20] Of note, clinical trial application (CTA) regulations were applied uniformly, regardless of whether the study focused on therapeutic applications or not (Figure 2).

Conducting interventional studies with cannabis presented a key challenge: cannabis, a plant, had to meet the same standards as manufactured investigational products. The GCP and Division 5 regulations outlined the crucial details necessary to describe the investigational product in the investigator brochure. The requirements for an investigator brochure meant that the cannabis product needs preclinical studies, including detailed pharmacokinetic, carcinogenicity, and other data. However, cannabis lacks a clear preclinical development pathway typical of laboratory-synthesized drugs. Additionally, investigational products used in clinical trials had to adhere to Good Manufacturing Practice (GMP) standards to ensure consistent production and quality, covering all involved entities from fabrication to distribution, a requirement that is costly to producers.

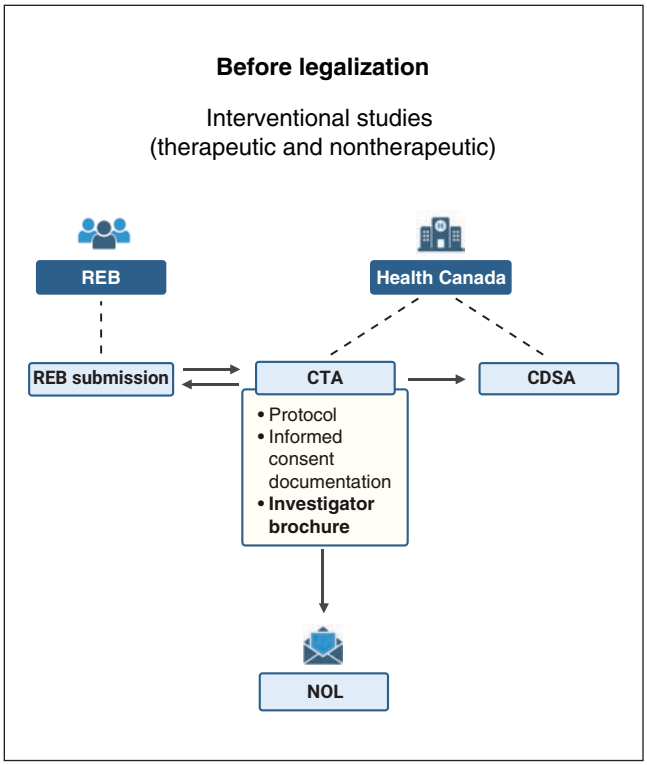

Fig. 2: Process of approval for therapeutic and nontherapeutic interventional studies involving cannabis before legalization. Researchers had to submit an application to their research ethics board (REB) as well as a Clinical Trial Application (CTA) to Health Canada. Key documents required with the CTA submission were the study protocol, informed consent documentation, and the investigator brochure for cannabis. Institutions also had to apply for a *Controlled Drugs and Substances Act* (CDSA) exemption, which could take up to 30 days. A no objection letter (NOL), which also could take up to 30 days, had to have been granted by Health Canada before study initiation. Created with BioRender.com.

Before cannabis legalization in Canada, the sole legal source of Canadian cannabis available for scientific and medical research was through Health Canada's Research and Development branch. Prairie Plant Systems operated a facility under a government contract, where it produced medical cannabis. However, the variety of strains were limited. With the emergence of a legal nonmedical and medical cannabis market, the "Canadian government strain" produced by Prairie Plant Systems was largely discontinued. Under a CTA, cannabis had to be produced by a licensed producer because of the requirement for manufacture under GMP and the requirement of an investigator brochure. This posed challenges in testing the utility of retail cannabis as a medicine.

Changes with legalization

Following legalization, and depending on the jurisdiction, cannabis is now accessible in person and through government-run online stores, marking a significant shift. This change holds considerable importance for scientific inquiry, as researchers can now investigate the substances individuals are consuming, and Bill C-45 allows a new regulatory framework to facilitate this research. Another significant change was the introduction of the institutional cannabis licence (granted by Health Canada), which replaced the *Controlled Drugs and Substances Act* (CDSA) exemption previously required for cannabis research.

Currently, there are 2 main streams for cannabis research in Canada: the CTA route (for therapeutic use of cannabis) and the newly developed Non-Therapeutic Research with Cannabis (NTRC) framework https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/industry-licensees-applicants/types-research.html. For noninterventional studies, there is also an observational route (Figure 3).

As was the case before legalization, the CTA route requires adherence to the GCP and Division 5 guidelines and, as such, necessitates sourcing cannabis from a vendor capable of providing an investigator brochure and producing cannabis under GMP. While established producers expressed interest in meeting GMP standards and creating investigator brochures for research or clinical trials, the volatile market and high entry costs deterred these companies from entering the field. This is problematic partly because cannabis is available on the legal market for medical purposes, but research into the safety and efficacy of cannabis for medical purposes is hampered. Canadian scientists voiced concerns about the challenges of obtaining cannabis for research studies.[21] Consequently, some researchers advocated for reforms to simplify the research approval process and enhance access to a broader range of cannabis strains, thereby facilitating more extensive scientific investigations. This led to the initiation of discussions with relevant parties, providing Canadian scientists with the opportunity to share their perspectives with Health Canada. Health Canada was receptive to the scientific community's input and collaborated with a diverse array of interested parties to revise regulatory requirements.

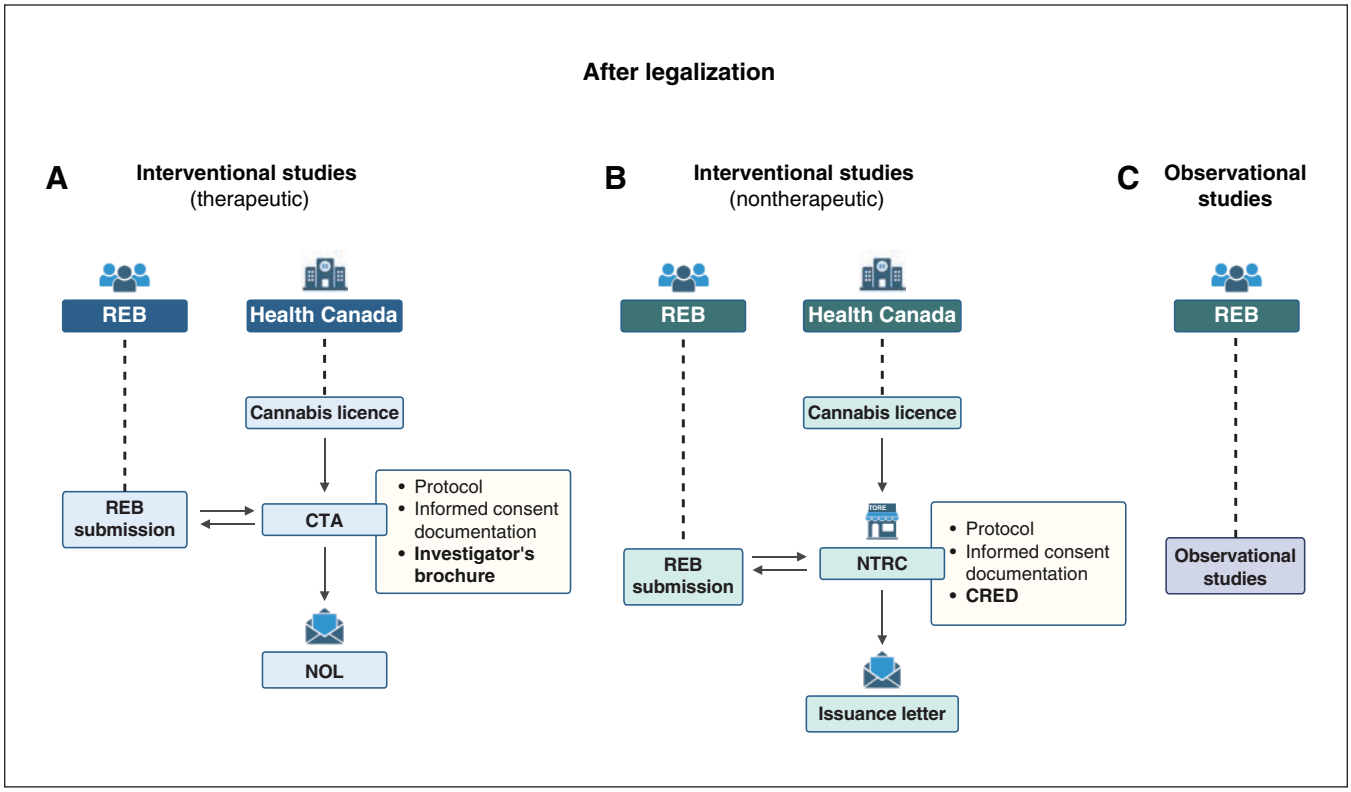

Fig. 3: Process of approval for interventional and observational studies involving cannabis after legalization. (A) Clinical Trial Application (CTA) route: For therapeutic interventional studies, researchers must submit an application to their corresponding research ethics board (REB) and a CTA to Health Canada. Key documents that must be submitted include the study protocol, informed consent documentation, and the investigator brochure for cannabis. To obtain cannabis for an interventional study, the researcher or institution must have or apply for a cannabis licence from Health Canada. A no objection letter (NOL) must be granted by Health Canada before study initiation. (B) Non-Therapeutic Research on Cannabis (NTRC) route: Since December 2022, researchers can submit an application to their REB and an NTRC application to Health Canada for the nontherapeutic use of retail cannabis in interventional studies. Key documents to be submitted include the application form; study protocol; cannabis information form; informed consent documentation (in some cases); and, for some types of studies, the Cannabis Research and Evidence Dossier (CRED), which replaced the investigator brochure. For NTRC studies, the investigator or institution must have a cannabis licence from Health Canada. An issuance letter must be granted by Health Canada before study initiation. (C) Observational route: A noninterventional route can be taken that allows participants to bring in their own cannabis and have their normal behaviour observed. This type of study still requires REB approval; however, it is not regulated by Health Canada. Created with BioRender.com.

In December 2022, Health Canada introduced the NTRC framework, tailored for nontherapeutic studies that fall outside Division 5 regulations. This framework allows for the examination of legal source cannabis as long as the study lacks therapeutic intent. Although this change was encouraging, it came 4 years after cannabis was available on the legal market. Compared with the CTA process, this framework offers a more streamlined approach, facilitating cannabis research. It is particularly suitable for foundational investigations into the effects of cannabis on cognition, driving, and pharmacodynamics, offering substantial ecological validity and enabling the evaluation of consumer products. Canada's federal legalization of cannabis places it in a distinctive position globally, leveraging this framework for research.

Despite the significant progress shown by the NTRC framework over the CTA route for nontherapeutic research, several challenges persist. A major challenge relates to the timelines, with the current review period for NTRC applications set at 42–72 business days. Although Health Canada can make information requests during this period, the clock stops, potentially extending the review period beyond the initial timeframe. Additionally, both NTRC and CTA studies require a cannabis licence, which can be project-specific or institution-wide. Submissions for approval under the NTRC framework must be made through the cannabis licence, leading to potential bottlenecks as Health Canada currently allows only 1 submission, amendment, or application at a time per institutional licence. Another challenge involves ensuring compliance with Good Production Practices (GPP), which are unique to Canada and necessary to maintain cannabis quality. Collaborations with foreign partners can be challenging because of GPP requirements if cannabis is sourced from outside Canada. This is exemplified in the challenges faced by researchers in obtaining placebo cannabis. Currently, there is no dried flower placebo cannabis available in Canada, necessitating a request for an exemption from the *Cannabis Act* to use

dried flower placebo cannabis imported from elsewhere in NTRC studies. Although straightforward, this process places an extra administrative burden on scientists and institutions. Finally, the NTRC framework mandates specifying the brand name of cannabis in the application form, which may pose challenges as the supply of retail cannabis is subject to market demands and products can vary over time. Any changes to the cannabis used in a study require approval by Health Canada, potentially leading to significant bottlenecks given the approval timelines.

A final avenue of studies with cannabis is the observational route. This framework allows for the study of retail cannabis legally obtained by the participant in simple designs. It does not allow for the storage or distribution of cannabis on the part of the investigator, so does not require a cannabis licence or approval by Health Canada in the form of either an issuance letter or a no objection letter. It does still require approval by a research ethics board. One unclear aspect of conducting observational studies in the context of cannabis research is the determination of whether the study actually meets the criteria for being classified as observational. The study protocol is evaluated by Health Canada to determine whether it meets the criteria of an observational study based on aspects such as inclusion criteria, data collection methods, the role of the researcher in influencing the choice of cannabis, and the risk level of outcome measures. These criteria have been evolving over time, which means that different interpretations of these criteria can lead to disagreements or uncertainties about the classification of a study, which may affect the regulatory requirements. The clear advantages of the streamlined approval process under the observational route must be weighed against the disadvantages of not having control over the dose or a placebo control.

Looking to the future

Following the 5-year milestone since legalization, it is important to assess the research landscape, particularly as Canada stands at the forefront of cannabis research. As scientists, we bear the responsibility to deliver an impartial evaluation of the risks and benefits of legally available cannabis to consumers. With the significant public interest and evolving usage patterns postlegalization, it is our duty to comprehensively study and understand this widely accessible product.

Canadian consumers are increasingly using cannabis for self-medication and are advocating for tax relief on its use. Despite beliefs in its efficacy for treating conditions like anxiety and depression, there is a lack of clinical trials to support the use of cannabis for these indications. As scientists, we have a duty to test the safety and efficacy of cannabis products to inform the public accurately. However, there are several factors that make researching the safety and efficacy of medical cannabis — especially retail products — challenging. As described in this editorial, compliance with regulatory standards can be burdensome, deterring potential investigators. Another concern is that there may be limited profit potential for licensed growers to develop strains tested medically, as cannabis cannot be patented naturally. Furthermore, the easy accessibility of cannabis without a prescription, compounded by abundant Internet information trusted by users, might, at many levels, discourage scientific evaluation (over commercialization). Advocating for evidence-based research and incentivizing stakeholders to prioritize clinical trials is essential for ensuring safe and effective use of medicinal cannabis.

The regulatory tapestry around cannabis research in human participants is evolving in Canada. Over the 5 years since legalization, we have seen the introduction of the project/institutional cannabis licence and the new NTRC framework. The next few years will hopefully bring a more streamlined process for the review of NTRC applications, clearing some of the bottlenecks. It would be beneficial if more than 1 application per institution could be reviewed at a time. Similarly, under the NTRC framework, the timelines (turnaround of 42–72 business days) can pose challenges. These delays to obtaining regulatory approval should be lifted. Under the *Cannabis Act*, researchers are held to the same standards as licensed producers when they "distribute" cannabis to their participants. Although these strict regulatory standards can be justified when selling cannabis to the public, researchers distribute retail source cannabis under controlled conditions, with medical supervision. Perhaps more exemptions to the *Cannabis Act* could be allowed for research.

With respect to clinical trials under Division 5 that require a CTA, the challenges around obtaining an investigator brochure and meeting GMP compliance remain. As a plant with a long and varied history of use, cannabis does not fit easily into the terminology of clinical trials. Consumers are turning to provincially run retail cannabis to self-medicate. These sources eliminate some of the obstacles of obtaining medical cannabis, including the requirement of authorization from a physician and learning how to navigate websites. Thus, Canadian researchers should be able to study the therapeutic applications of retail source cannabis. We have a duty to inform the public about the safety of the cannabis they are using for all purposes.

We can turn to an example from the United States: in the US, there is available federally regulated and controlled cannabis for research purposes. Through centralization, the cannabis supply can be produced to the strictest standards and in compliance with all regulations. By being government-run, the availability of cannabis would not depend on the financial viability of marketing cannabis as a treatment for a specific indication. Rather, it could supply the variety of research interests deemed important by the scientific community, often led by public interest.

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