Canadian Childhood Cannabinoid Clinical Trials (C4T)

Workshop Report

Toronto, Ontario

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Report prepared by

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Introduction

CONTEXT

Increasingly, Canadian pediatricians are encountering patients that have used cannabis products for medical purposes – whether these products are authorized or not. The motivation behind these decisions stems from both a frustration with the ineffectiveness of current treatment options and the promise of anecdotal evidence in case reports and online forums. The need for high-quality, evidence-backed, licensed products has become paramount to ensure the safe and efficacious use of the cannabis products. It is time to shift our focus to developing the trials needed to inform selection and dosing of cannabinoids in children.

Hear from researchers, parents and doctors why our research is important by following this link:

https://www.youtube.com/watch?v=feAumxMlbJE

This workshop was hosted by the Maternal Infant Child Youth Research Network (MICYRN) who received sponsorship in the form of donations from Aurora, Avicanna, BlissCo, Canopy Growth, TerrAscend and Tilray. The sponsorship donations covered the costs of participant travel, accommodation and meals. Sponsors played no role in the design of the workshop.

OVERVIEW

The Canadian Childhood Cannabinoid Clinical Trials (C4T) was formed in 2018 to better understand the **risks and potential benefits of therapeutic cannabis use in children**. Our mission is to inform, design and conduct clinical trials on cannabinoids in children. The first C4T workshop was hosted at the Hospital for Sick Children Research Institute in Toronto, Canada on February 27-28, 2019. This was the first workshop of its kind to bring together a diverse group of stakeholders focused on pediatric cannabinoid research (see Figure 1). Co-led by Maternal Infant Child and Youth Research Network (MICYRN) and Dr. Lauren Kelly of the University of Manitoba and the George and Fay Yee Centre for Healthcare Innovation, the workshop featured discussion on the lack of evidence for the safe and effective use of cannabis products in pediatrics, potential strategies for future trial designs, and barriers to overcome. Over fifty individuals participated in the workshop, including parents, researchers, clinicians and industry, with representatives present from Health Canada, the Goodman Pediatric Formulations Centre of the CHU Sainte-Justine (GPFC) and the Canadian Institutes of Health Research (CIHR) (Figure 1). With most major child health research institutes at the table, C4T is a passionate national research group spanning from British Columbia to Halifax.

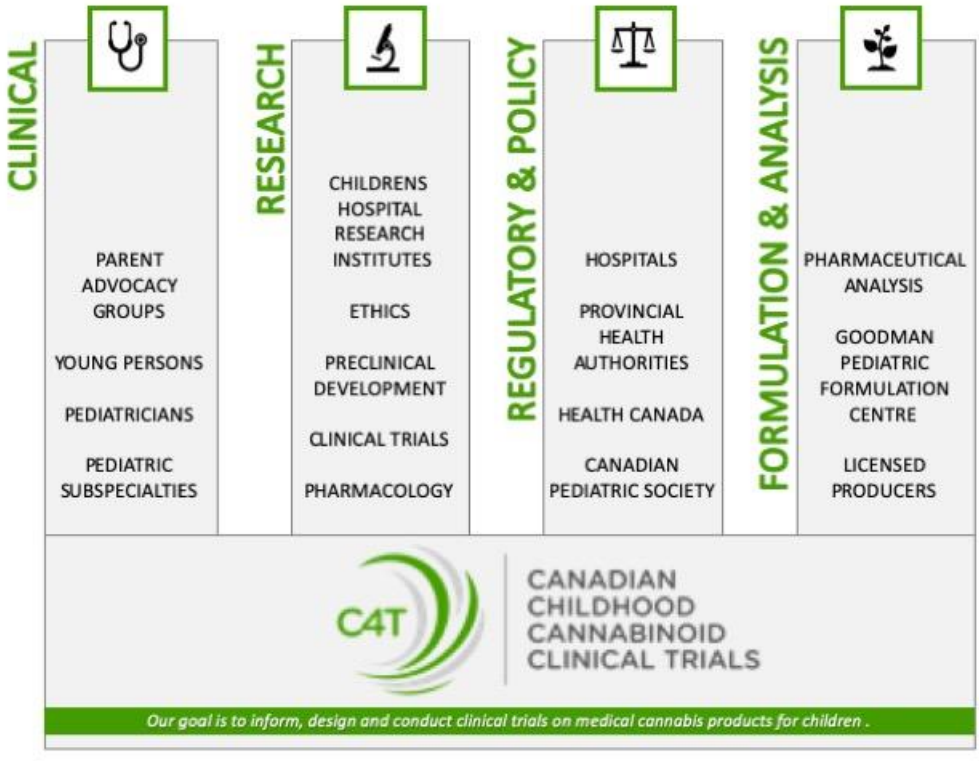

Figure 1. C4T pillars and partners.

ATTENDEE LIST

Hanan Abramovici, Health Canada
Jane Alcorn, University of Saskatchewan
Aras Azadian, Avicanna
Stephen Barbazuk, Maternal Infant Child and Youth Research Network (MICYRN)
Richard Belanger, Centre Hospitalier Universitaire de Quebec
Valerie Bourada, Children's Hospital of Eastern Ontario
Kathy Brodeur-Robb, C-17 Council
Emily Czaplinski, University of Manitoba
Sarah De La Rue, Canadian Institutes of Health Research
David Dyment, Children's Hospital of Eastern Ontario
James Evans, University of Toronto
Allan Finley, Dalhousie University
Andrea Gilpin, Goodman Pediatric Formulation Centre (GPFC)
Justin Grant, Avicanna
Jaspreet Grewal
Richard Huntsman, University of Saskatchewan
Catherine Jacobson, Tilray
Mohammad Jiwan, Solace Health
Lauren Kelly, University of Manitoba
Melanie Kelly, Dalhousie
Charlene Kettlewell, BlissCo
Damian Kettlewell, BlissCo
Carolina Koutras, Aurora
Thierry Lacaze, University of Calgary, MICYRN
Bruno Lafontaine, Health Canada
Catherine Litalien, GPFC
Evan Lewis, Neurology Centre of Toronto
Mandy McKnight
Laura McNair, Canopy Growth
Charlotte Moore-Hepburn, Canadian Pediatric Society
Daniel Morgernstern, SickKids
Kelly Narine, Aurora
Michael Nashat, TerrAscend
Tim Oberlander, University of British Columbia
Shannon O'Hearn, MedReleaf
Antonia Palmer
William Panenka, University of British Columbia
Eleanor Pullenayegum, SickKids
Tanya Ramsamy, Health Canada
Sabrina Ramkellawan, TerrAscend
Alexander Repetski
Adam Rapoport, SickKids
Rod Rassekh, University of British Columbia
Michael Rieder, Western University
Treacey Sheehan, SickKids
Raffaele Spadafora, Tilray
Breanne Stewart, MICYRN
Maria Sultan-Khan, Health Canada
Lilian Sung, SickKids
Geert Jong, University of Manitoba
Regis Vaillancourt, Children's Hospital of Eastern Ontario
Alice Virani, University of British Columbia
Mark Ware, Canopy Growth
Kevin Weingarten, SickKids
Jim Whitlock, C-17, SickKids

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Day 1: Diverse Perspectives

INTRODUCTION to the C4T Initiative

Lauren Kelly

The lead for C4T is Dr. Kelly, a Pharmacologist and Certified Clinical Research Professional. She started the session by thanking the participants for their interest, passion, expertise and support. She highlighted the importance of bringing together the diverse group of stakeholders with specialized knowledge and experience in their respective fields and thanked the workshop sponsors for their contributions. She introduced and outlined the role of MICYRN in the initiative: as clinical trials in children often require involvement from multiple national sites due to small sample sizes limiting the quality and timeliness of research, a network committed to harmonizing research processes across these health centers is of utmost importance.

PANEL 1: Parent, Patient and Prescriber Perspectives

Antonia Palmer

Antonia Palmer, mother of Nate Palmer – a two-time childhood cancer survivor – shared her unique parent perspective on the need for better research in children. Speaking from a systems theory background, Antonia described the importance of involving patients and advocates early on in the clinical trial process to give feedback, identify blind-spots, and optimize retention. She believes the benefits of patient advocates is their ability to connect people together through personal stories that bridge the person to science. Asking the simple questions can break down the barriers and offer a different perspective that may be new to clinicians and researchers. Her systems engineering V-model for engaging families in clinical trials is shown below (Figure 2).

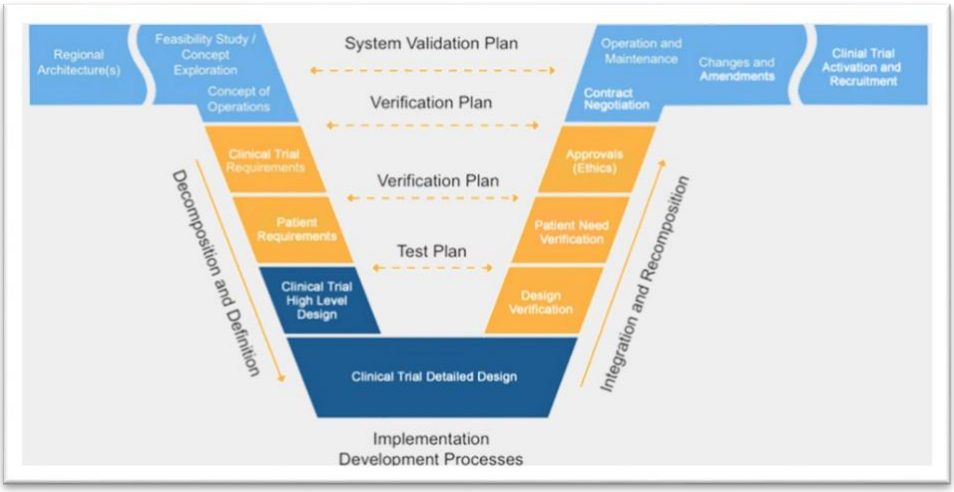

Figure 2. Systems engineering V-model for engaging families in clinical trials.

Alexander Repetski

Alexander Repetski, father and director of communications at Flowr shared his experiences in caring for his daughter diagnosed with intractable epilepsy. With first line therapies failing, and 30 seizures per day causing damage to her brain, Repetski took matters into his own hands. He began researching and developing his own oil-based cannabinoid products at home and seeking outside laboratory testing for quality. After countless hours developing and testing his product, he saw shocking improvements in his daughter's condition, getting her to 22 months seizure-free. His goal is to continue inspiring scientists and practitioners to push for better

research so that future parents don't have to spend the same time and effort in experimenting with cannabis product dosing.

Mandy McKnight

Mandy McKnight became an 'accidental' advocate for safe access to medical cannabis when her son Liam had reached the end of his medical journey with Dravet Syndrome. With a touching video portraying the positive effects of Liam's cannabis use overtime, Mandy was able to portray the challenges her family has faced regarding access to cannabinoid health products. Barriers included cost-prohibiting factors, difficulty in finding doctors who were willing to prescribe cannabinoids, and the dangers of going outside of the legal stream, such as using untested products of unknown origins. Mandy hopes that with clinical trials, more children and families can experience the life transformation Liam did.

Survey on reported use of therapeutic cannabis use by Canadian pediatricians.

Richard Belanger

Dr. Richard Belanger is a pediatrician specializing in adolescent medicine at Centre mère-enfant Soleil, and an assistant professor in the Department of Pediatrics at Université Laval. Canadian pediatricians are receiving increasing amounts of questions regarding medical use of cannabis and practitioners are seeing several pediatric cases with positive reported impact of its use. Dr. Belanger reported on his 2017 survey, conducted using the Canadian Paediatric Surveillance Program (CPSP) platform which includes 2,800 pediatricians: 50% of pediatricians have seen patients actively using cannabis for medical purposes (be it authorized or unauthorized); and 46% of practitioner respondents "believe that there are appropriate indications to support the authorization of cannabis for medical purposes for children and adolescents," with a majority citing palliative care, epilepsy and chronic pain. Respondents largely stated evidence of efficacy, dosing/toxicity and concern for long-term impacts as their main concerns preventing them from authorizing cannabis use for medical purposes among youth. Other barriers included concern for abuse and dependence, availability of relevant continuing medical education and lack of personal knowledge. In closing, Belanger remarked that pediatricians are generally supportive of certain medical indications for cannabinoid authorization, despite having minimal knowledge on its use and reporting general concerns about efficacy and safety.

Canadian Pediatric Society perspectives and policy initiatives.

Charlotte Moore Hepburn

Dr. Moore Hepburn is a pediatrician at the Hospital for Sick Children and Director of Medical Affairs at the Canadian Pediatric Society (CPS). The CPS represents pediatricians across the country, mandating the development of guidelines, professional education, and advocacy at both the federal and provincial levels. One of the top five strategic objectives for the organization in 2019 is to expand access to safe and effective pediatric medications and therapeutics. Four aims under this sub-priority are to advocate for a regulatory framework that meets or exceeds international best practices, advocate for increased access to life-saving and life sustaining medications, guide and support appropriate off-label drug use for children and youth, and promote child health research with a focus on pediatric medications, therapeutics and clinical trials. Dr. Moore Hepburn noted that currently, our Canadian regulatory framework is far below best practice, which informs the nation's high incidence of off-label drug use–an issue she attributes to be largely due to regulatory system failings. Health Canada is currently undertaking an overhaul and modernization of the regulatory system, which Moore Hepburn says is an opportunity for pediatricians to inform regulatory renewal with an eye to pediatrics. Key messages from the CPS perspective include how children deserve the same protections of on-label prescribing as adults, and that we cannot use the fact that pediatrics is a small market as an excuse for further regulatory and reimbursement failings.

PANEL 2: Industry Perspectives

Avicana – Aras Azadian

Aras Azadian, Chief Executive Officer of Avicana, spoke of his company's focus on cannabinoids from a biopharmaceutical perspective. The company's research and development is being done in Toronto in collaboration with the University of Toronto's Faculty of Pharmacy. Today, the licensed producer cultivates in Colombia under good agricultural collection practices. Proprietary extraction and purification processes are done under good manufacturing practices within a GMP-approved plant. Currently, pre-clinical work is being done for a topical application CBD cream for epidermolysis bullosa indication. They are in the process of developing transdermal patches, capsules, tablets, and oil tinctures as non-indication-specific products, and conducting pharmacokinetic data on these

products in animals. Their main three therapeutic areas of focus are on pain, dermatology, and neurology.

Aurora – Kelly Narine

Vice President of Biomedical Research and Medical Affairs, Dr. Kelly Narine outlined her company's unique approach to science: bridging the gap between licensed producer, to academics and researchers, and further, to patients. She cited an integration of clinical knowledge with plant-based research as a great strength of their work. Currently, the company serves 73,000 patients in Canada, keeping an extensive database for real-world outcome studies that is linked to administrative health data. Areas of interest for the company include neurology, pain, and oncology. Dr. Narine highlighted what she called the "cannabis challenge" wherein there is a pressing need to further understand critical points, such as how cannabis affects brain development, and the regulatory barriers, access issues, and difficulty of dosing of these products. The company's goal is to understand and quantify therapeutic doses of cannabinoids through partnering with experts in the field and conducting patient-oriented research.

Blissco – Damian Kettlewell

Founder, CEO, and Chair of Blissco, Damian Kettlewell shared his daughter's experience with acute lymphocytic leukemia. Years of routine medical treatments resulted in neurocognitive impairments, possible sterility, and high risks of secondary cancers. His company's goal is to allow increased access to cannabinoid medical products, provide education for patient families, and ensure formulations are efficacious, compliant, and suitable for children. The company strongly supports non-invasive studies, an example of which was shared by Lilit Antonyan of McGill Psychiatric Genetic Group. Her work is on the non-invasive assessment of cannabis-related compounds on human brain development.

Canopy Growth – Mark Ware

Canopy Growth Chief Medical Officer, Dr. Mark Ware described his company's mandate: to develop medicines based on cannabis for a wide range of conditions, with a predominate focus on therapeutic drugs. The primary pillars focus around pain, mood, and sleep. Ware believes if research teams can produce medicines that are robust, safe, reliable, and effective, they can radically disrupt the existing pharmaceutical markets for particular conditions. Evidence has been greatest for chemotherapy-induced nausea and vomiting and increasing evidence of benefit for

epilepsy is emerging. Ware brought to light dominant discussion points around legalization, including the effects of cannabis on developing brain. He noted that while most safety data in adults is drawn from recreational data, it has been shown that the effects of cannabis in adolescents on cognitive function are small and of questionable clinical importance. Future research will need to look further into the association of cannabis use and risk of depression in young adulthood, as well as how to properly measure exposure.

TerrAscend – Sabrina Ramkellawan

Vice President of Clinical Affairs, Sabrina Ramkellawan spoke about TerrAscend as a biopharmaceutical wellness company. One pillar of the company's foundation is advancing research through enhancing plant genetics, working with partners, and supporting the medical use market. The company's goal is to focus cannabinoid research on debilitating diseases in the pediatric population, including epilepsy, cancer pain, irritability related to autism, chronic pain, and acquired brain injury. Ramkellawan stated that licensed producers have a responsibility to conduct and be a part of clinical research trials, so parents don't have to do the work themselves. She outlined the main focus to be on infrastructure and partnerships, which will allow for the progression of clinical trials. Highlighted issues included limited access to health care providers, lack of education of physicians, cost and coverage, and difficulty of product development in regards to delivery systems and pediatric formulations. The company is working to engage with physicians in both the US and Canada to pool information to provide further medical education to prescribers. The company has an interest in establishing and supporting fellowship programs for physicians or pharmacists specifically regarding cannabis education. TerrAscend is currently working with MDM insurance to provide a pilot insurance coverage program for pediatric coverage support. Lastly, Ramkellawan touched on the creation of Solace Rx, a TerrAscend drug preparation premises where compounding pharmacists work with prescribers to provide non-medical and medical cannabis drug preparations to health care institutions.

Tilray – Catherine Jacobson

Dr. Catherine Jacobson, Vice President of Regulatory and Medical Affairs spoke of her personal push for the "T2:C100" cannabis product, which has been shown to be helpful for pediatric indications, including epilepsy, due to its low THC content. Dr. Jacobson's main message was to urge researchers

to stay on track and provide help to patients “in a time frame that matters.” She reminded the audience that patients do currently have access to these products, and don’t have time to wait, so we must gather data in ways that are meaningful to those patients. She stressed for the need for stable seed varieties to keep the chemical profile of plant products consistent from batch to batch in order to reduce variation of minor cannabinoids. She strongly believes standards for THC containing drugs must be the same as those for other medications–pointing out that only one of fourteen of her son’s anti-convulsant medications which he takes for epilepsy actually has long-term safety data. Her take home message was that while the ideal outcome might be seizure control, in many cases we must find out through interaction with families what the most meaningful end point is in their specific circumstance.

PANEL 3: Decision Maker Perspectives

The Canadian Institutes of Health Research Integrated Cannabis Research Strategy.

Sarah De La Rue, Eric Marcotte

Dr. Sarah De La Rue of the Canadian Institute of Health Research (CIHR) discussed the Government of Canada’s Integrated Cannabis Research Strategy. The overarching vision of the initiative is to position Canada as a world leader in developing research capacity to generate the data needed, create policy and build regulatory models for medical and non-medical cannabis use. The CIHR is actively putting out a call for evidence to fill gaps in specific target areas which underlie the three main streams of research: understanding harms, data standards, and medical benefit. The initiative’s specific objectives include increasing the cannabis health research capacity, building the evidence base on the balance of benefits versus harms of cannabis use, getting evidence into the hands of health care providers and policy makers, and establishing rigorous clinical evidence for therapeutic use of cannabis. Large scale grants are available to catalyze future research in specific areas that can inform the development of future larger scale research projects.

Regulatory requirements for pediatric cannabis clinical trials in Canada.

Tanya Ramsamy, Bruno Lafontaine

Bruno Lafontaine and Dr. Tanya Ramsamy of Health Canada described the newly released Cannabis Regulations which maintain regulatory pathways for health products with cannabis. Health products containing cannabis that seek a drug identification number will require pre-market review for safety, efficacy and quality under the Food and Drug Act, and health claims can be made for these products. Regarding clinical trials with cannabis-containing products, appropriate authorizations for research are required, namely a research licence under the Cannabis Act and authorization under the Food and Drugs Act. The organization is currently exploring three models for licensing:

- 1 license linked to 1 protocol per site
- Multi-center trials, 1 trial requiring only 1 license
- Institution-wide license, covering all trials at an institution

Licenses will be valid for five years. Detailed requirements for these licenses are set out in the Cannabis Licensing Application Guide which can be found on their website, here.

Health Canada is striving to process applications for research licenses in a timely manner of 2 months, subject to completeness of the application. Health Canada reviews the evidence in the context of the proposed clinical trial protocol and determines whether risks can be adequately mitigated. Health Canada's goal is to minimize health risk participants may be exposed to in a clinical trial setting while having regulations in place that are robust enough to frame commercial drug development, but flexible enough to avoid discouraging research.

Day 2: What We Know, What We Don't

MESSAGE FROM MICYRN

Dr. Thierry Lacaze of the Maternal Infant Youth Child Health Research Network (MICYRN) opened the session and communicated this year's priorities for the research network. MICYRN links 20 maternal-child research organizations across Canada and is committed to harmonizing research processes, implementing best practices and supporting national as well as international collaborations. Their 2019 priorities include a thorough assessment of Pediatric Clinical Trial Units across Canada, the creation of a multi-center trial guidance document, the creation of a single point of contact for industry and academic research, provide pediatric expertise to the modernization of our regulatory system, create cross-jurisdictional ethics harmonization, and increase international collaborations.

Cannabinoid pharmacology.

Michael Rieder

Dr. Michael Rieder, a Clinical Pharmacologist, Pediatrician and Professor from the Department of Pediatrics at the University of Western Ontario described the clinical pharmacology of cannabinoids and how this information can inform therapeutic potential. He described cannabinoids as being classic receptor-driven drugs that work within a large volume of distribution within the body as they are fat soluble. Good absorption is achieved by smoking as a method of administration, but low bioavailability is seen when administered through the gastrointestinal system due to first pass metabolism by liver. He highlighted that the drug passes to the brain quickly and in fairly high amounts while later accumulating in adipose tissue. Cannabinoids tend to have a very long elimination half-life and little is known about the activity of the metabolites. Shifting to what is not known about the pharmacology of cannabinoids is how the drugs interact with the body in children and infants. Specifically, the ontogeny of cannabinoid receptor expression and the impact of ontogeny on the pharmacokinetics of cannabinoids is an understudied area. Most pharmacokinetic studies to date have been conducted in healthy adult volunteers based on recreational use not therapeutic use, thus creating gaps in knowledge. Dr. Reider pointed out that the main issue with interpreting recreational use data is the large fluctuations in exposure, as there is a need for constancy in dosing for therapeutic cannabis use.

Ongoing and recently completed cannabis clinical trials in Canada.

Richard Huntsman

Dr. Richard Huntsman, Pediatric Neurologist at the University of Saskatchewan shared the preliminary data from his Cannabidiol in Children with Refractory Epileptic Encephalopathy (CARE-E) clinical trial and described some of the challenges faced. Spurred by Sanjay Gupta special in 2013 highlighting benefits of cannabis especially in Dravet syndrome, a surge of parents came to Dr. Huntsman wanting access to cannabis products. There has been a general reluctance among practitioners to authorize products due to knowledge gaps. This puts parents in the compromised situation of engaging in potentially illegal activity and possibly putting their child in harm's way. Dr. Huntsman was inspired to design a study to answer questions about optimal dosage of a cannabis product in pediatric refractory epilepsy. A multi-site study was initiated with 20 pediatric patients, from 1 to 10 years of age. Researchers collected baseline seizure frequency, then started cannabis herbal extract therapy, increasing doses from 1 to 12 mg 1:20 THC:CBD oil. Assessments were made using EEGs, quality of life assessments, bloodwork for THC/CBD levels, and a seizure log review. Product was purchased from a licensed producer in a single batch to prevent variability in cannabinoid concentrations. Preliminary data (for the 7 patients that completed the study) showed that 3 of 7 participants became seizure free, and all showed benefit once doses hit 8-9 mg/kg/day. Notably, the decrease in seizure frequency was persistent as the patients were weaned off the drug. The best results were seen in the quality of life assessment, especially in cognitive, emotional and social functioning. No evidence of intoxication was found for the 1:20 product investigated. Dr. Huntsman emphasized the surprising amount of polarizing views and pushback about potential benefits of cannabis and stressed the need for unbiased high-quality evidence-based information that can only be achieved by an interdisciplinary approach.

Formulation and delivery challenges and solutions.

Andrea Gilpin

Dr. Andrea Gilpin, the General Manager of the Goodman Pediatric Formulations Centre (GPFC) of the CHU Sainte-Justine, a non-profit organization, shared why there was a need to have a facility of this kind in Canada. A lack of access to appropriate pediatric formulations can result in therapeutic ineffectiveness, adverse events or even treatment failure. Medications specifically adapted for children are important, due to the hazards that tablets or pills can pose to young

children. In addition, taste is an important attribute in pediatric medications and may ensure better adherence. Furthermore, the composition of the excipients should be considered in pediatrics as the proportion of a certain excipient, such as oil, alcohol or sugar, may be acceptable in adults but may not be appropriate in a small child or infant (for example, the large volume of oil needed for certain therapeutic cannabinoid options). When there is a lack of access, parents or pharmacists may be forced to alter adult formulations. GPFC's mandate is to improve access to child-friendly medicines, specifically those on the priority drug list, and to bring commercialized formulations to Canada that are already used in the US, Australia, and Europe. Considerations for the development of pediatric formulations in cannabis were presented, including 'minitabs', oral dispersible films that avoid the first pass effect, and transdermal patches.

Preclinical models for cannabinoid drug development.

James Evans

Dr. James Evans is a Post-doctoral Researcher at the University of Toronto and an academic collaborator with Avicanna Inc. He discussed the current state of cannabinoids as medicines, issues in the approval of Epidiolex and ramifications for preclinical development. Evans' research team conducts pre-clinical cannabinoid research. The preclinical process is comprised of receiving resins from the licensed producer, extracting and isolating cannabinoids in-house, creating appropriate formulations, and finally conducting in vitro assays, stability studies, and in vivo studies in rodents. Evans emphasized a few key points that were found through the preclinical work done by his research team. CBD and THC are compounds that are prone to rapid degradation in the presence of light and oxygen, thus requiring formulations to have a delivery vector. He noted that preclinical studies must be hypothesis-driven; just as they would be for any other pharmaceutical development program. In toxicological analyses of the Epidiolex oral solution used to treat epilepsy, Evans highlighted evidence showing transaminase elevations that are associated with liver damage, as well as reproductive and developmental effects on rats at medium to high doses. He strongly suggested further study on the metabolites of CBD. Unfortunately, major metabolites are not produced to the same extent in the majority of preclinical species routinely used, which exposes the limitations of the model. Evans' considerations for future preclinical development are to include enzyme analysis as part of bloodwork and include metabolites in pharmacokinetic studies. In conclusion, Dr. Evans urges the researchers to consider CBD as any other form of potentially toxic API, and to accept the responsibility to identify safe doses of administration.

Considering the impact of cannabis on the developing brain.

Tim Oberlander

Dr. Tim Oberlander is a Developmental Pediatrician at BC Children's Hospital and is a researcher studying early brain development. Dr. Oberlander's talk centred around cannabinoid exposure during critical periods of development through fetal periods to adolescence. Discussion around developmental impacts on adolescents is typically dominated by a clear association between daily cannabis use and depression. Dr. Oberlander stressed the concept of confounding by indication, wherein the very thing that brings a patient to self-medicate using cannabis could be itself a factor in enhancing vulnerability by presence of cannabinoid exposure. He noted the need to understand interactions with the physical, social and environmental contexts. In regards to fetal and early childhood cannabinoid exposure, Oberlander noted increasing numbers of women using cannabis during pregnancy. It is currently well-understood that cannabinoids actively cross the placenta and enter into breast milk due to their high lipid solubility. In pregnancy, exposure of the developing fetal brain to cannabinoids at one critical time period can have downstream effects. The CB1 receptor has been shown to be highly expressed in critical areas of brain, wherein changes in function are central to success of humans as social learning organisms. The pre-frontal cortex in particular is critical for executive function and is central to early child success in school and playground, especially in social and emotional well-being. Dr. Oberlander shared animal model data that show decreased birth weight, hyperactivity, anxiety in adolescence, and decreased socialization in adulthood with early cannabinoid exposure and stressed the importance of having longitudinal, repeated measure designs to look at the capacity of cannabinoids to shift developmental periods.

Ethical considerations for pediatric cannabis studies.

Alice Virani

Clinical Ethicist, Dr. Alice Virani of BC Children's Hospital acknowledged that, from an ethics point of view, it is ideal to have all stakeholders present at the table, which was a driving motive for developing the C4T workshop. Dr. Virani's presentation outlined the main foundational principles of biomedical ethics of autonomy, beneficence, non-maleficence, and justice. She noted that vulnerable populations, such as children, require substitute decision makers to act on their behalf in their best interest. One must be cautious, however, as ulterior influences factor in on parents' decision-making, and desperate parents may lose focus of the child's best interest. Despite this, in the pediatric setting, clinicians typically should

not intervene in parent decision making unless the line of harm has been crossed. In some instances of disagreement between parent and clinician, the best approach is to aid parents in making decisions that reduce the most harm. In regards to clinical trials, there is a need to ensure minimization of risk and guarantee that there is potential benefit, insofar as intervention is justified. Study design must take into consideration conflicts of interest, and particularly in cannabinoid trials, the potential of licensed producers as a source of conflict of interest must be addressed to ensure there are no compromises in research integrity. Dr. Virani stressed the importance of managing, minimizing, and mitigating the effect of conflict of interest through study design and taking care to fully disclose relevant information. Lastly, she laid out a main consideration for practice: the duty to disseminate results broadly as researchers owe results to participants in a way that is meaningful to them.

A harmonized approach to clinical trials and design considerations for cannabis studies.

Lauren Kelly

Dr. Lauren Kelly summarized study design considerations in the context of cannabinoid therapeutics in a heterogenous population. She recommended the platform trial as an ideal harmonized approach to such a scenario and outlined the benefits and challenges of platform trial design. Study design considerations were shared from her recent CMAJ commentary for cannabinoid use in children including designing for a population with unique conditions and variability in perceived risks and benefits. While the pediatric population may typically be thought to be cannabis-naïve, increased access resulting from legalization has the potential to contaminate control groups. Risks related to cannabis withdrawal syndrome and chronic controlled cannabis use in children are currently understudied. Dr. Kelly highlighted that cannabinoid response variability makes it difficult to fit into the typical medical model for drug prescribing. Researchers must consider inter-individual variability in receptor activity and metabolism, prior exposure and tolerance, variability in plant potency, variability in THC to CBD ratios, and routes of administration. KidsCAN Trials is a network recently funded with PERC (Pediatric Emergency Research Canada) put in place to harmonize pediatric research and conduct clinical trials with children. As a coordinating centre for four trials, the network can leverage existing clinical trial design and centralize monitoring and eCRFs. Dr. Kelly then outlined the reasoning behind her recommendations of the use of the platform trials design, citing the presence of multiple agents, shared controls, a heterogeneous patient population, new

treatments, adaptive responses and multiple sponsors. With a shared control group, cost-effective use of patients and resources and outcome-adaptive randomization ensure more participants receive the most-probable-to-benefit treatment arm. The design allows for flexibility to both alter the standard of care if evidence changes and add additional treatment arms if new products are developed, replacing poorly performing therapies. The challenges with platform designs centre around coordination and complexity. Increased planning is required in setting up trial infrastructure, and the statistics become more difficult with an increased number of interim analyses. Furthermore, the development of master protocols require agreement between many stakeholders including researchers, clinicians, industry and regulators and discussions on data use, publication rights, timing of regulatory submissions must be resolved before the start of the trial.

Approaches to trial design and analysis with rare diseases.

Eleanor Pullenayegum

Dr. Eleanor Pullenayegum, a biostatistician out of the Hospital for Sick Children Research Institute, suggested the Bayesian methods as being best suited for trial design and analysis in rare diseases. The main obstacles in rare disease studies are having a small sample size and low power, resulting in a p-value greater than 0.05. She summarized how p-values are inherently flawed, not giving us any information regarding existence of a treatment effect, clinical importance, nor an adequate summary of the evidence. The overarching goal in these trials is to provide patients and their families with evidence-based guidance on treatment effectiveness and side effects. Although there is uncertainty in both respects, evidence-based medicine is still possible, and Bayesian methods may be best suited to answer these questions. Some outlined benefits of the Bayesian methods are that they are able to answer express uncertainty in a way that is easier to understand than the frequentist paradigm, remove p-value focus, and can incorporate prior information. In short, they use probability theory to describe how prior beliefs should be revised in light of new evidence. Another consideration is for trialists to consider designs that maximize information per patient through longitudinal follow-ups using multiple measures and looking at changes within patients in a multiple baseline design. In a multiple baseline design, all patients start on a control, and the time at which intervention is initiated is randomized. Outcomes are then measured very frequently. The benefits of this design are that it works despite carryover effects or curative treatment and is useful when a trialist does not want to withdraw patients in which the treatment does not work.

Summary of Key Points

- Pediatricians in Canada are increasingly being asked to authorize cannabis and manage patients using cannabis for medical purposes
- “Children must be protected *through* research, not *from* research”
- Many variables create complexity for cannabinoid dosing
- Must consider the delivery, feasibility and palatability of cannabinoid formulations for children
- There is no one size fits all solution to such a heterogeneous population
- The ontogeny of cannabinoid receptors is not well understood
- Other components found within cannabis, including delta-8 THC, terpenes, THC-A, CBD-A and metabolites must be studied
- Requires development of clinical trials, but we also need short-term solutions to improve clinician and parent access to evidence guided use of cannabis products
    - Exposure has proven hard to measure, given challenges of self-report and lack of harmonized data collection
    - Need to collaborate on prospective real-world evidence data gathering (surveillance projects)
    - Share information is encouraged; e.g. link data sets between provinces or producers
- Cost-effectiveness/Health Technology Assessment should be integrated
    - For example, study reduction of cost by fewer follow up appointments, fewer EEGs etc.
- It is important to involve patients, parents and advocates early on in the clinical trial design process
- Streamlining and harmonization efforts for clinical trials enrolling children in Canada are ongoing
- Canada can be a leader in cannabis research, but in order to achieve this goal, we must be innovative, transparent and work together.

Next Steps

There is an urgent need for education, resources and training for health care personnel, along with an access point for people in the community to learn more about the potential risks and benefits of cannabinoids used for medical purposes in children. Disease-specific expert teams must be assembled to work with parents and providers to prioritize research questions. Moving forward, administrative health data should be used to determine how many children are accessing medically-authorized cannabis, to record adverse drug reactions and acceptable dosages. Integration among cannabis research groups and international collaborations will propel this movement forward. A website and social media platform will be put in place to share information and encourage public interaction.

This is an open call to researchers, parents, and clinicians with interest and expertise in cannabinoid use in children, clinical trials, formulations and ethics. If you would like to join C4T please email **C4T.Canada@gmail.com** or for updates, follow us on twitter **@C4T_Canada** or visit **https://www.pharmalauren.com/c4t.html**