CLINICAL TRIALS AT THE SPEED OF COVID-19

Steps to prepare for the next global health crisis

CHÉOS
Centre for Health Evaluation
& Outcome Sciences

In 2020, a novel coronavirus began to rapidly spread across the world, and saving lives meant acting quickly. New vaccines, diagnostics, and therapeutics had to be identified and tested in record time.

Today, the world of Clinical Trials is experiencing rapid and exciting developments as international collaborations and new technologies help transform research.

For the first in a symposium series dedicated to exploring the future of Clinical Trials in Canada, and around the world, the Centre for Health Evaluation and Outcome Sciences (CHÉOS) led a conversation about lessons learned, challenges faced, and potential opportunities to mobilize a rapid response for the next global health crisis.

Contents

Overview 1

1) Data sharing 2

- Biobanking 3
- Privacy Concerns 3

2) Increase Clinical Trial Flexibility 4

- Shortening Evidence Generating Timelines 5
- Adaptive Platform Clinical Trial Study Design 6
- COVAXHIV Study Example 7

3) Streamline Approval & Ethics Processes 7

- UK Versus Canada Study Approval Timelines 8
- E.A.R.L. Framework 8

4) Education Opportunities 9

- General Public 9
- Clinicians 10

5) Network Value 11

- The CIHR Canadian HIV Trials Network 11

High-Level Takeaways 12

- What's mine is yours: data sharing for better research 12
- Increasing flexibility and efficiency in clinical trials to create opportunities 12
- Engaging the public to improve health overall 13

Overview

CHÉOS is proud to be recognized as one of Canada’s foremost health outcomes research organizations. Bridging the gap between data, research, and care, CHÉOS is a collaboration between cross-disciplinary scientists and expert research staff. Our backbone is our staff, who are dedicated to providing research support services to over 200 projects in both health outcomes research and clinical trials. CHÉOS supports 11 research programs that produce more than 300 publications annually and hold over $21 million in funding. The Centre influences change and improves patient care and health systems by empowering decision-makers to find evidence-based solutions to positively impact public health.

On May 10th, 2022, CHÉOS hosted the first in a symposium series, titled “Clinical Trials at the Speed of COVID-19.” The purpose of the event was to bring together clinical trial experts to discuss the lessons learned and challenges faced during the COVID-19 pandemic. Clinical trials are an integral part of evidence-based medicine, used to inform the implementation of novel interventions in health care. They are needed to scale and sustain innovation and provide the evidence required to directly impact and improve public health and health care practice. Several ideas to improve Canada’s current clinical trial climate were discussed, including facilitating data sharing in a central database, supporting adaptive clinical trial formats, creating a single portal system for ethics applications, and improving public education and engagement. In light of lessons learned from the COVID-19 pandemic, there is an opportunity to improve Canada’s clinical trial infrastructure to support responsive and adaptive clinical trials that provide pertinent, timely, and generalizable data to improve health for everyone.

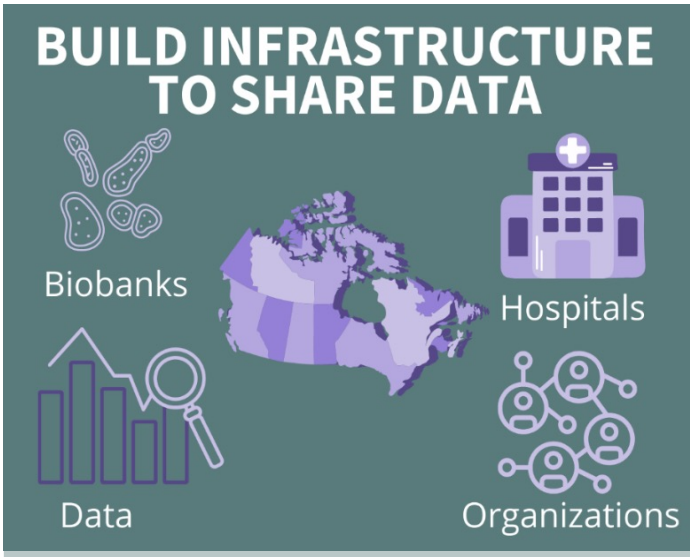
> **Clinical trial platforms are very much a part of biosciences innovation platforms, because you not only have to manufacture and produce diagnostic and therapeutic interventions, you also have to show they work.**
>
> *Dr. Peter Singer*

1) Data Sharing

A recurring theme throughout the event was the importance of sharing data. There is little value in conducting clinical trials if the data aren't shared and readily available. Essentially, the resources put into these studies are wasted and any benefit to patients or researchers is prevented. Barriers to data sharing were a significant challenge faced by the COVID-19 Immunity Task Force (CITF). The inability to access data, especially between provinces, prevented important information from being shared across borders and between jurisdictions during the pandemic. The concept of data ownership does not improve clinical research, it only impedes progress and broader collaborative efforts. There is a genuine need for real-world data and evidence to inform strategic decisions. Sharing data helps inform clinical trials and move innovation forward.

A Health Canada-funded example of impactful data sharing is found within the Marathon of Hope Cancer Centres Network, which shares data and harmonized patient consent forms. They provide a core data set that highlights the collection of pre-determined data points, which can be used to inform Health Canada and reimbursement decisions. Sharing data is not novel within national funding bodies either. Part of the contract to receive funding from the CITF stipulated that the data collected would be made available to CITF to share with other investigators. CIHR has also recently adopted a policy on disclosure of results, consistent with WHO requirements; however, that only specifies that data be made available a long time after the trial has ended. There needs to be emphasis on sharing data earlier on in studies and making data openly available to researchers across the country. Sharing of data could be made mandatory as a condition of being funded, similar to how the CITF included this stipulation in their conditions of funding.

Building a central database for all the CIHR-funded clinical trials in Canada would enable investigators to use a web-based system to access data. Once data are collected, data sharing cannot be left up to the investigators, but should be enforced by funding bodies. This would help reduce redundancies. A central hub for Canadian clinical trials could also include Canadian collaborations on international clinical trials. In order to be able to address public health concerns on a global scale, platforms including hospital networks, biorepositories/biobanks, and shared phenotyped and geocoded study populations need to be created and openly available to use in collaborative research endeavours. The availability of the data is more important than which researcher "owns" the data. The goal is to improve global health and, ultimately, very little is required to invest in improving care and positively impacting health for everyone.



> **If there's one thing that blocked, and frankly harmed us in this pandemic, it was our inability to expeditiously, clearly, and transparently transmit data across the provincial borders.**
>
> ***Dr. Gina Ogilvie***

BIOBANKING

Biobanking is an essential component when sharing information, as clinical samples are a crucial and limited resource across all medical science research sectors. After waiting 11 months for ethics approval, the BC COVID-19 Biobank Network is currently functional and collecting and hosting several different blood and types of blood samples. The goal of this network is to build connections across the province, including Northern and Interior Health Authorities, who are utilizing biobank networks and support storing biological samples beyond blood. Establishing biobanks will facilitate impactful clinical research across the province, especially as they are central to the growing field of precision medicine. The BC COVID-19 Biobank Network is collecting samples using shared platforms and software that allows them to be accessed anywhere within the province. This includes rural and northern communities who do not normally have access to larger sample sizes and data repositories. The Canadian Tissue Repository Network is a nationwide representative of Canada's leading biobanks, showing that nationwide biobanking infrastructure is already in place; however, more can be done to increase education and streamline sample accessibility across different health centres and provincial jurisdictions.

> **The single biggest way we can make a difference to patients and their journey through the health care system is to understand disease. We are not doing a good job of understanding the mechanisms that drive disease because they are different in different people, even if they present with the same disease. Biobanks are central to precision medicine and to understanding disease.**
>
> ***Dr. Darryl Knight***

> **We only consider the risk of sharing, not the risk of not sharing. If there are data that has a signal that was missed, we need to have a good reason not to have had that data.**
>
> ***Dr. Gina Ogilvie***

PRIVACY CONCERNS

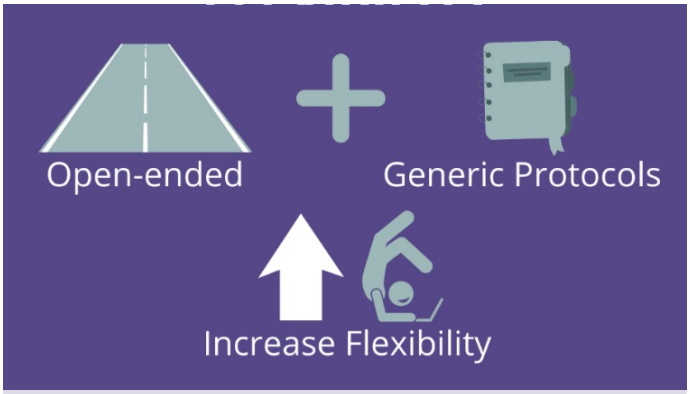
A significant barrier to data sharing involves concerns about privacy. However, consequences of inaction need to be weighed against the perceived consequences of conducting and implementing impactful research that uses the shared data. There is very little discussion about the consequences of privacy and the risks of not sharing information versus the risks associated with sharing information. There needs to be good reason not to share data, not just during a pandemic response, but also post-pandemic, as research data are assets that can help improve the health of Canadians. We need to re-evaluate privacy concerns to understand how we balance privacy and data sharing when there is an urgent need to share valuable health information. The mindset needs to consider the risks of not sharing data. There needs to be efforts to change legislation around privacy and data sharing, as there may be situations where it is unethical to not share potentially life-saving data.

> **The consequences of inaction need to be weighed up against the consequences of really doing something.**
>
> ***Dr. Darryl Knight***

2) Increase Clinical Trial Flexibility

The traditional way of designing clinical trials focuses on one-shot trials with a fixed sample size. This design is effective, in theory, if the nature of clinical research was predictable; however, this is certainly not true. As illustrated by the dynamic nature of both the COVID-19 virus and the rapid development of various interventions to both prevent and treat COVID-19, clinical trial research, especially during a pandemic, can be unpredictable. In fact, of over 3,000 trials registered to study various COVID-19 interventions, most were one-shot trials that did not finish recruitment.

Adopting novel clinical trial designs that are flexible and adaptive to accommodate the nature of the ever-changing research landscape are important to ensure that clinical trials contribute meaningfully to future health challenges in a timely, cost-effective manner. Funding bodies should provide an environment to support research in all its forms. For example, hybrid trials are effective in reaching rural, remote, and isolated populations as study participants can either be involved in clinical trials from home or via rural clinic outposts. In collaboration with the CITF, the Public Health Agency of Canada's National Microbiology Laboratory developed blood sample self-collection kits that were mailed to more than 10,000 study participants across the country to test for COVID-19. This novel sample collection method allowed researchers to better understand the spread and impact of the coronavirus without participants having to leave their home or see a health care provider.



> **Research Ethics Boards should be encouraged to be more accepting of more generic, less-focused protocols during times of pandemics and rapid evolution. In addition, funding agencies should accept more open-ended study designs given the evolving nature of pandemics.**
>
> ***Dr. Cecilia Costiniuk***

SHORTENING EVIDENCE-GENERATING TIMELINES

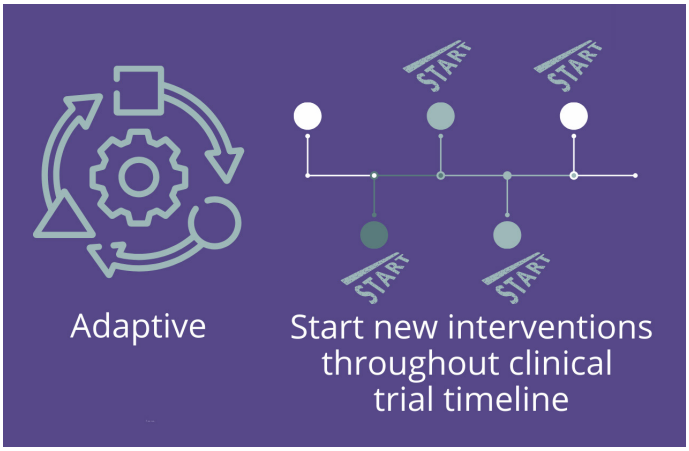
Another important aspect to consider when increasing clinical trial flexibility is the time it takes to generate evidence to determine whether or not a treatment should be put into practice. For example, trials for cancer drugs take ~13 years to generate evidence. To counter this lengthy timeline, there has been a rise in master protocol trials, include umbrella and basket trials and adaptive trial designs, especially within precision oncology. The flexibility of having adaptive randomized controlled trials within master frameworks speeds up trials and shortens the multi-year gap in treatment development. Furthermore, clinical trial design should with in parallel with the learning within health care systems, as they are an ever-changing cycle that constantly influence each other and impact the health of Canadians and related research needs.

When looking back at evidence generated from clinical trials assessing the outcomes of COVID-19 globally, more work was done on COVID-19 within the first 12–18 months of the pandemic than in the preceding decades for several other diseases and conditions, including sepsis. Although this was possible due to the international focus on a single disease, there was also an alignment between private industry and academia, leading to effective prevention and better ICU care. Shortening evidence-generating timelines for other diseases is possible if resources and interests are appropriately aligned, allowing for flexibility in clinical trial design.

> **To have more efficient evidence-generating mechanisms, we need to standardize trial and real-world designs for the appraisal, reappraisal, and the adoption of novel technologies in our [health care] systems and... really leverage our learning health care systems in parallel to clinical trial design.**
>
> ***Dr. Dean Regier***

ADAPTIVE PLATFORM CLINICAL TRIAL STUDY DESIGN

Adaptive platform clinical trials are designed to allow multiple interventions, introduced at different time points, to be evaluated simultaneously against a common control group. These trials are adaptive because they accommodate the addition of new interventions and control group updates throughout their duration. This enables multiple interventions to be evaluated faster and can be used to assess a range of areas, from pharmaceuticals to health management practices. Although the initial set-up time and cost would be greater, due to developing a master protocol with trial plans and ensuring standard operating procedures are in place to evaluate multiple interventions, adaptive trials designs are more efficient as they reduce sample size requirements, time, and cost in the long run by avoiding redundancies in set-up and close out of multiple trials. Clinical trials must evolve. Adaptive trials are faster, more efficient, and ultimately better for patients and the public than traditional trials. Funding agencies must accommodate flexibility in order to facilitate these these types of trials and expedite innovation.



Adaptive trial designs are clinical trial designs that have data-driven approaches, allowing the trial to adapt to the accumulating information in a formal way. In adaptive trial design, everything is planned and specified in the design and in the protocol then, at scheduled interim analysis, we review the data and make an adaptation *if* the data says we should.

Dr. Jay Park

COVAXHIV STUDY EXAMPLE

COVAXHIV is a multi-centre nationwide clinical research study evaluating the immunogenicity, safety, and effectiveness of COVID-19 vaccination in diverse people living with HIV. This study uses an open-ended design with broad recruitment parameters. Due to the urgent nature of the study, investigators requested an expedited review that allowed for patient recruitment to start without having contracts finalized. Other important considerations to facilitate this research included avoiding the use of traditional "study visit windows" to maximize data collection and retain participants. The ongoing need for research protocol flexibility was emphasized because the introduction of booster doses and the uncertainty around who will get COVID-19 meant there was no knowing how many participants would be in each subgroup until the analyses was underway. With so many moving targets for other diseases and circumstances, funding agencies should accept more open-ended clinical study designs with generic protocols, especially during a rapidly changing clinical health research landscape.

3) Streamline Approval & Ethics Processes

During a health emergency, when clinical research constantly has to adapt to the current circumstances, especially at a global scale, there is a need to expedite administrative and approval processes to prevent unnecessary loss of life. As mentioned earlier, ethics approval of the BC COVID-19 Biobank Network took nearly 11 months, which is an unacceptable timeline when responding to an international health crisis. Currently, to conduct a Canada-wide clinical study, protocols need to be approved by several Research Ethics Boards (REBs) across multiple institutions. After receiving initial REB approval from the sponsor site, protocols must be approved by both provincial and local REBs, all with different submission portals, consent form formats, and other location-specific administrative requirements. Having multiple approval and ethics processes and submission portals significantly slows down the clinical trial approval process. This delay is not acceptable when responding to an international health emergency nor ideal when investigators want to conduct timely clinical trials for other important health concerns.

> **A key takeaway from the pandemic is that it's important to have a stable, common trial infrastructure with dedicated funding and opportunities to train and maintain methodologists and research staff.**
>
> ***Dr. Jay Park***

> **Clinical trials are hard. We shouldn't make them hard; we should make them easier so that we can randomize more patients.**
>
> ***Dr. Srinivas Murthy***

UK VERSUS CANADA STUDY APPROVAL TIMELINES

In the UK, a nationwide COVID-19 study protocol was submitted to the national UK Clinical Research Network, with the first clinical trial participant enrolled seven days later. By contrast, in Canada, there were 169 days between the CATCO protocol being sent to sites and its first patient enrolment. This delay was a direct result of having to go through multiple REB submissions and approvals, and contract submissions and executions. The fastest turnaround was nine days, which happened at the sponsor site where no contracts with other institutions were necessary. Research is an internationally competitive space, and even though Canada has the expertise and motivation to lead high-impact national and international clinical trials, the administrative and ethics approval process is a significant barrier to efficiently executing timely research.

E.A.R.L. FRAMEWORK

The E.A.R.L. framework highlights solvable barriers to streamline Canada's clinical trial approval process:

Ethics: This highlights the redundancy of the clinical trial approval process. There multiple REBs resulting in multiple opinions as well as duplicated work when submitting the same protocol through different portals, each needing reformatting of questions and answers to align with each REB's requirements. Having a single portal with a universal form submission standard would significantly expedite this process.

Administration: Negotiating clinical trial contracts among different sites often highlights concerns around liability, data ownership, and funding. Implementing a one-size-fits-all contract suitable for clinical trials that does not need to change between platforms and institutions would decrease the administrative workload.

Regulatory: Pragmatic clinical trials are embedded within care as much as possible; however, the extensive paperwork and logistics required by Health Canada to approve novel pharmaceutical-focused clinical trials are incompatible

with the pragmatic trial approach. A possible solution is highlighted by the international Good Clinical Trials Collaborative, which reframes clinical trials going forward to reduce regulatory confusion while still conducting safe clinical research.

Logistics: Currently, local capacity to conduct research is lacking, but tackling issues highlighted by the E., A., and R. of the framework will improve logistics and enable more groups to be involved in clinical trials, especially in more rural and isolated areas, which are often under-represented in research cohorts.

> **If we embed clinical trials in care as much as possible, a lot of the local capacity issues will be solved.**
>
> ***Dr. Srinivas Murthy***

4) Education Opportunities

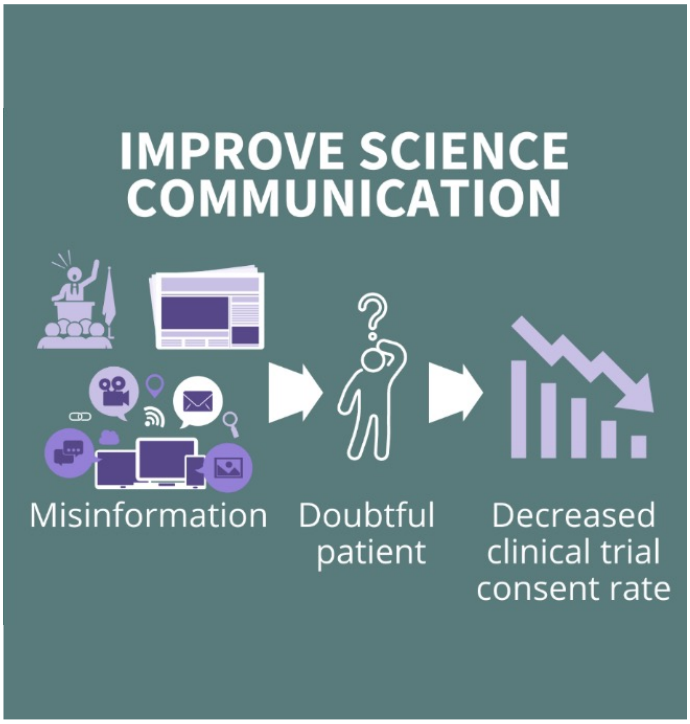
GENERAL PUBLIC

Throughout the pandemic, doctors have encountered patients who confidently deny their COVID-19 diagnosis despite overwhelming evidence of its existence. These patients are often not interested in participating in clinical trials or acknowledging peer-reviewed academic research. This phenomenon is happening worldwide as a result of misinformation and disinformation shared by both traditional and social media, resulting in the spread of harmful ideas that impact public health efforts. The trend of declining consent rates in COVID-19–focused clinical trials was observed internationally as the pandemic continued. This is especially problematic when conducting clinical trials because if researchers are not able to recruit patients, clinical trials cannot finish, and thus needed answers cannot be found. More investment and improvement is needed to effectively communicate with the public and patients, in order to prevent the spread of harmful information and improve trust and engagement within the health care research ecosystem.

There is also the need to empower patients as part of increasing engagement because it will lead to better health outcomes, better clinical trial compliance, and better overall activity in the health care system. Another consequence of educating the general population is the willingness to donate samples to biobanks. Having access to healthy tissue is just as important as having access to disease tissue, as it provides the necessary controls to conduct physiologically relevant medical research. The best models of human disease are humans. If health research is not engaging with patients and the public to break down knowledge barriers and include them in the research journey, then the clinical trial research ecosystem is doing everyone a disservice.

> **We know that social media drove the vaccine hesitancy and anti-vaccination movement and that it increased personal and community COVID-19 risk. [Misinformation] is a huge issue going forward and the rate of anti-vaxxers will be higher if we don't have smart people addressing this.**
>
> ***Dr. Jim Russell***

Diversifying clinical trials and rewarding patient empowerment will also improve clinical trial participation in both sample size and diversity. Everyone has a right to participate in research and it is not the role of researchers to be gatekeepers. This speaks to a clear institutional bias, often a result of racism and colonialism, which needs to be addressed to stop discriminatory clinical trial practices. Enabling broad community participation makes clinical trial results more representative and generalizable to larger populations. Clinical trial findings need to be meaningful and actionable. Part of the role of researchers and funders is to make sure clinical trials are open and designed for the broad population. This means funding must support opportunities and research centres based outside of densely populated urban areas and encourage active diverse patient enrolment. Patient involvement is paramount to improve clinical trial recruitment and support rapid clinical uptake of therapies and interventions validated by clinical trial research.



> **It would certainly be easier, from a clinician's perspective, to have organizations like CHÉOS, which provide that infrastructure and support to clinicians that don't necessarily have [clinical trial] experience.**
>
> ***Dr. Natasha Press***

CLINICIANS

Clinician perspectives are imperative in clinical research, but more support, funding, and time is needed for interested clinicians, which can be achieved through training and collaboration. Support from CHÉOS allows front-line physicians to carry out important, timely research by working with Project Managers, Clinical Research Officers, and volunteers to help navigate the clinical research infrastructure. To prepare clinicians for future health emergencies, divisions with clinical faculty should take the initiative to identify physicians interested in participating in clinical trials and nurture these relationships with ongoing collaborations.

5) Network Value

Having networks that can provide immediate and ready clinical trial support and resources is crucial when responding to a health crisis. In a situation like COVID-19, results need to be generated quickly and having existing networks with access to important resources can help expedite research. Networks are also valuable when facilitating communications with other places around the world, especially when responding to an emergency situation. Networks are easily recognizable entities that can leverage infrastructure and funds to support pandemic-related research before receiving official study funding.

> **Networks can leverage research infrastructure and funds to support pandemic-related research before official study funding is received.**
>
> ***Dr. Cecilia Costiniuk***

THE CIHR CANADIAN HIV TRIALS NETWORK

The COVAXHIV study was able to get a head start on patient enrolment without waiting for funding because it was part of the CIHR Canadian HIV Trials Network (CTN). Investigators were able to access resources, funds, and infrastructure to finance the COVAXHIV study costs upfront while still assembling the protocol. While the CTN is traditionally an HIV and STBBI research network, affiliated investigators and staff were contacted early on in the pandemic with requests to support some of the largest institutions across Canada who lacked coordinated infrastructures and faced many projects being put on hold. The CTN is an excellent model of a multi-disciplinary coordinated group of staff and investigators that can support crucial, timely research in rapidly changing times.

> **The pandemic taught us a lot of lessons about things that should be in place... The CTN started getting calls from colleagues at the largest institutions across Canada. They were coming to us because they had ideas for clinical trials and had developed protocols, but they didn't have the infrastructure support. They were coming to the CTN because we are coordinated.**
>
> ***Dr. Joel Singer***

High-Level Takeaways

A national clinical trial network can invest not only in tackling the burden of disease aligned with national health priorities, but also capacity building, training for research, engaging with the lay public, collecting knowledge to share among stakeholders, including providing data to inform policy, and supporting innovation. This involves investing in comprehensive solutions to reduce health burdens by considering the continuum of care, populations and individuals, biological and social determinants, integrated, team-based, multidisciplinary care and research, research into policy translation, building networks and collaborations, and working with patient partners with lived experience.

> **If academic investigators and private companies are offered the chance to participate after we build long-lasting clinical trial infrastructure, I believe they will come.**
>
> ***Dr. Jay Park***

WHAT'S MINE IS YOURS: DATA SHARING FOR BETTER RESEARCH

The prevailing attitude towards sharing data can often be one of protectionism. The concept of data ownership does not improve clinical trial research, it only impedes progress and broader collaboration efforts. There is no value in conducting clinical trials if the data aren't shared and available. Resources would be wasted, which is not beneficial for patients or researchers. There needs to be a re-evaluation of privacy to understand how we balance privacy and data sharing when there is a need to share valuable health information. Data sharing can also be facilitated by the creation and support of strong networks that connect key research staff with researchers nationwide.

> **Clinical trials are designed to be very rigid and follow protocols, but here's a situation where the world has been turned upside down and we are just one step behind everything that's happening. We have to be flexible and evolve, which requires funding agencies accepting this flexibility as it's better for our patients who are our most important asset.**
>
> ***Dr. Aslam Anis***

INCREASING FLEXIBILITY AND EFFICIENCY IN CLINICAL TRIALS TO CREATE OPPORTUNITIES

Clinical research is a highly competitive space internationally, and even though Canada has the expertise and motivation to lead high-impact national and international clinical trials, the administrative and ethics approval process is a significant barrier to efficiently executing timely research. Creating a national clinical research hub with standardized and centralized infrastructure to expedite national clinical trial research applications is a crucial step in ensuring Canada's potential as a leader in health care innovation. An important part of nurturing an innovative space is providing flexibility in clinical trial design. For example, having adaptive randomized control trials within master frameworks speeds up trials and shortens the multi-year gap in treatment development. Furthermore, clinical trial design should parallel the learning within health care systems, as they are an ever-changing cycle that constantly influence each other and impact the health of Canadians and related research needs.

ENGAGING THE PUBLIC TO IMPROVE HEALTH OVERALL

Distrust in medical research and health care is a phenomenon happening worldwide as a result of misinformation and disinformation shared by both traditional and social media. Unlimited access to information is a defining feature of this era in humanity, but it has resulted in the spread of harmful ideas that significantly impede public health efforts. This is especially problematic when conducting clinical trials because if researchers are not able to recruit patients, clinical trials cannot finish, and thus needed answers cannot be found. The public are patients, or will become patients, so establishing trust between health authorities, medical researchers, and the public is imperative in ensuring a healthy population. Effective communication and education are essential in that effort so actions must be taken both to promote good science and to understand why misinformation spreads to forcefully combat it. Not only will this establish, re-establish, and improve trust with Canada's health care system, but engaging the public about research will improve clinical trial understanding and recruitment.

> **We need to empower patients a lot more than we are. By empowering patients we are going to get far greater engagement from them. Empowering patients is the single biggest secret source for empowering research on patients.**
>
> ***Dr. Darryl Knight***

> **Science is reductionist but solutions have to be holistic.**
>
> ***Dr. Prabhakaran Dorairaj***

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