Canadian Journal of Medicine 4(2022) 4-12

Canadian Journal of Medicine

WWW.CIKD.CA

journal homepage: https://www.cjm.cikd.ca

Review Article

A Beginner's Guide to Clinical Trials

Sarah Keyes[1*], Philippa Hawley[2]

[1]Department of Medicine, University of British Columbia, Vancouver, BC, Canada
[2]Pain and Symptom Management/Palliative Care, Vancouver Cancer Centre, BC Cancer Agency, Vancouver, BC, Canada

Keywords:
Clinical trial, Study design, Randomized controlled trial, COVID-19

Received
30 December 2021
Received in revised form
05 February 2022
Accepted
08 February 2022

***Correspondence:**
smkeyes@student.ubc.ca

ABSTRACT

Evidence-based medicine rests upon the pillars of scientific evidence, clinical expertise, and patient values. Evidence comes from various avenues including clinical trials; a branch of experimental research studying interventions in human participants. Clinical trials evaluate the safety and efficacy of interventions, including medications, devices, and procedures that are administered according to a detailed plan. A control group such as no-treatment, placebo, or standard-of-care is used for comparison. A clinical trial determines whether one intervention is better, worse, or no different than another in the specific context and demographics of enrolled participants. Safety and efficacy are established by measuring clinically significant outcomes. Ultimately, the goals of clinical research are to advance medical knowledge and improve patient care through the development of preventative measures, diagnostic and screening tools, treatments, and supportive care. In the rapidly evolving landscape of medical literature, clinicians increasingly consult clinical trials to guide their practice. As such, medical students and trainees stand to benefit from developing a strong understanding of research design and logistics during their training. This article presents a general overview of key elements and practical considerations in clinical trials.

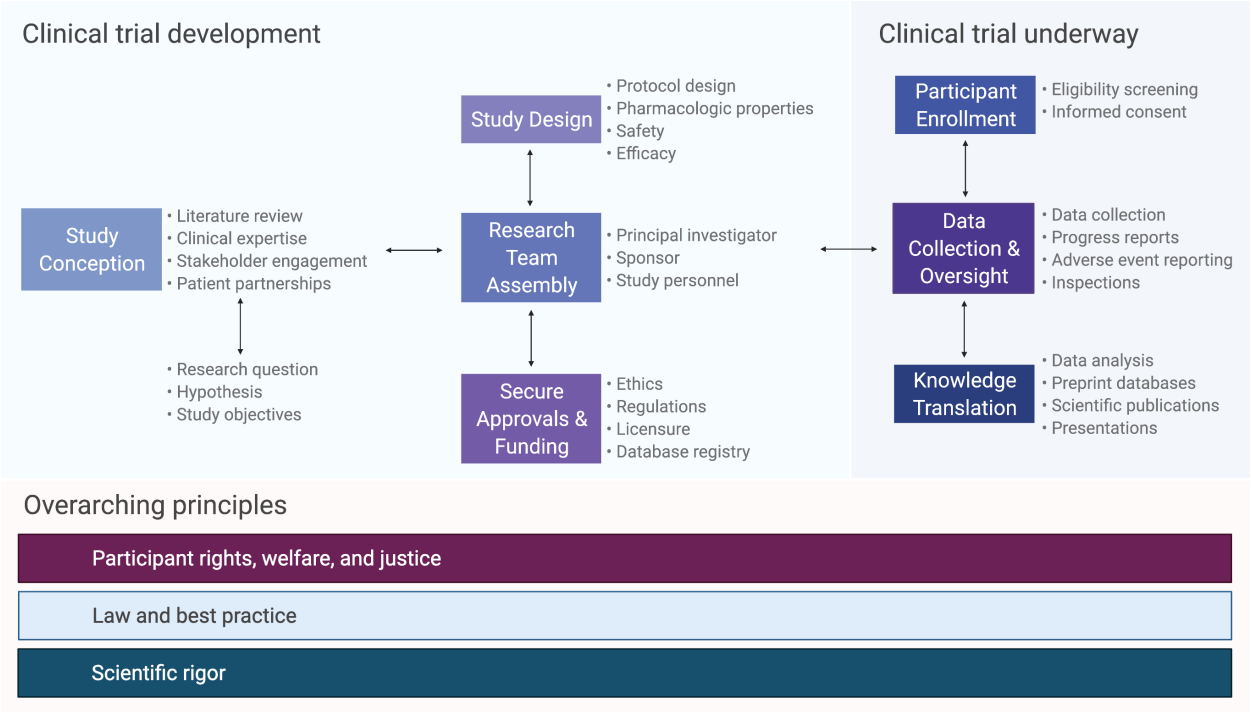
©CIKD Publishing

Study Conception

Each clinical trial starts with a question. Research questions are created in response to knowledge gaps, often identified through clinical practice and extensive literature review [1]. Early and ongoing consultation with multiple stakeholders and patient partners provides guidance, with formal needs-based assessments augmenting the process [2, 3]. Once identified, general research questions are refined to define the population of interest, intervention, comparator, outcome, and time frame [1]. Subsequent consideration of which research questions to pursue ensures that resources are appropriately invested, and efforts provide a benefit to society. Productive questions are those that are feasible, interesting, novel, ethical,

and relevant [1]. From the research question, a hypothesis and set of study objectives are formed. The hypothesis proposes an anticipated outcome for the research question and informs what methodology is used. Objectives outline the aims of the study and describe how the research question will be answered. This provides a crucial framework around which the study is designed and carried out (Figure 1) [1].

Figure 1. Outline of the clinical trial process from design to implementation, with overarching principles that guide



Study Design

Interventions such as medications are studied through a series of phased trials (Table 1). Therapeutics are first introduced in humans after years of preliminary laboratory and animal testing. Initial trials (phase 0-III) evaluate and establish the pharmacologic properties, safety, and efficacy of a new therapeutic modality. If trials demonstrate overall benefit, the therapeutic may then be approved for market by regulatory authorities. Approved therapies are continuously monitored through phase IV trials, which inform their optimal use [4]. From pre-clinical studies to post-market surveillance, monitoring and assessing adverse events and medical errors, collectively known as pharmacovigilance, protects patients from undue harm. Together, the escalating phases of study ensure that therapies are backed by high-quality evidence.

Table 1. Clinical trial phases in drug development

Phase	Purpose	Description
Phase 0	Evaluate pharmacologic properties	Optional exploratory studies. Intervention is given to ~10 participants, usually at subtherapeutic doses. Pharmacokinetic and pharmacodynamic properties are assessed.
Phase I	Evaluate safety	First-in-human studies. Intervention is given to ~20-100 participants, usually at a range of doses. Dosing information, common/short-term side effects and adverse events, and toxicities are identified.
Phase II	Evaluate efficacy	Therapeutic exploratory studies. Intervention is given to ~100-300 participants and compared against a control (e.g., placebo). Therapeutic range is determined.
Phase III	Confirm safety and efficacy	Therapeutic confirmatory studies. Intervention is given to ~1000-3000 participants and compared against a control (e.g., standard-of-care). After this stage, the intervention may be approved by health authorities.
Phase IV	Monitor safety and effectiveness	Ongoing for approved therapeutics. Optimal use and dosing, rare/long-term side effects and adverse reactions, and cost-effectiveness comparisons are considered.

A trial's design is carefully crafted depending on the phase and what best serves its study objectives. For example, a common type of phase III clinical trial is the comparative efficacy trial, often called a randomized, double-blind, placebo-controlled trial [5]. This design is generally considered gold-standard to evaluate treatments for approval. These trials directly compare an intervention against a comparator, such as standard of care or placebo. Participants are enrolled after fulfilling eligibility criteria, and randomly assigned to the treatment or control group (with an equal chance of either; both the participant and investigator are blinded to the assignment). Participants receive their allocated intervention and are followed for outcomes. Consideration of intervention allocation concealment, randomization strategy, degree of blinding, and analysis strategy is made to balance intervention groups prognostically and to mitigate potential confounding factors and bias [5, 6]. When comparing against a control, every effort is made to prevent the identification of the interventions (e.g., placebo pills are prepared to look, smell, and taste indistinguishable from study medication). Various intervention models exist outlining how a study intervention is given to participants [7]. This careful planning protects the integrity of downstream data collection and analysis.

Research Team

Clinical trials require considerable oversight and support. Trials are led by a principal investigator (PI), often a physician or scientist, who is supported by a sponsor [8]. Sponsorship refers to intellectual responsibility for a study and generally falls to the pharmaceutical/biotechnical company, academic/hospital center, organization, or federal agency that conceives the trial. The PI may also be the sponsor, as in the case of investigator-initiated clinical trials [9]. The PI oversees the trial and ensures compliance to ethical, scientific, and regulatory standards [10-12]. This includes protecting participant rights and welfare, delegating tasks, supervising staff, maintaining study approval and licensure, reporting adverse events and protocol deviations, and beyond. The PI is also accountable for any infraction during the study [8, 11]. With help from the clinical trial coordinator, the PI and sponsor create a set of documents outlining how the study will be carried out: the protocol, investigator's brochure, consent forms, standard operating procedures, case reporting forms, and others (Table 2) [11, 13]. These documents are crafted to ensure the study is based on scientific evidence and best practice, with procedures in place at each anticipated step.

Table 2. Key clinical trial documents

Document	Purpose	Description
Protocol	Outline how the study will be carried out	Includes study title, administrative details, background, methodology, oversight procedures, operational/ethical considerations, and supporting documentation/annexure. It is frequently subject to amendment as the study is planned and carried out.
Investigator's Brochure	Summarize current literature about the study intervention	Includes physical, chemical, pharmaceutical properties; pharmacodynamic, pharmacokinetic, physiological effects; therapeutic use and dosing; indications and contraindications; established safety and efficacy; and toxicology. It is prepared by the sponsor and should be updated at least once annually.
Informed Consent Forms	Provide an overview of the trial to educate and enroll participants	Includes background information, enrollment criteria, methodology, participants' responsibilities, risks, benefits, alternatives, length of participation, early end to participation, confidentiality, costs, and compensation. Language should be suitable for participants and contact information available for questions.
Standard Operating Procedures	Describe how each step of the study will be carried out and by whom	Includes clinical trial team roles and responsibilities; trial initiation, activation, close-out procedures; subject recruitment, screening, informed consent processes; and methods of managing investigational products and biological specimens. These are made for a specific organization's personnel to use in carrying out a study.
Case Reporting Forms	Present a template for collecting data during the trial	Includes participant questionnaires, concomitant medication logs, toxicology report forms, serious adverse event forms, and deviation report forms.
Others	Documentation of trial participant and staff activities	Includes randomization lists, subject logs, delegation logs, and training documentation. These are checked carefully in every audit or monitoring visit.

Research teams usually form through group entities, such as clinical trial units within academic institutions and hospitals. Depending on study needs, staff may include clinical trial assistants and coordinators, nurses, social workers, pharmacists, and statisticians. There will also be data monitors, auditors, finance personnel, and other professionals making sure everything runs smoothly. Staff roles and responsibilities depend on individual expertise and clinical setting. The clinical trial coordinator works closely with the PI to conduct the study and ensure protocol compliance. They may recruit participants, enforce timelines, maintain documents, and liaise with the PI, sponsor, and ethics/regulatory committees [14]. The study nurse and/or research assistant interact with the participants, delivering care and coordinating follow-up [15]. The pharmacist may prepare study product, carry out safety reviews, and supervise the safe disposal of unused product [16]. The statistician may carry out safety data monitoring, interim and end-of-study analyses, and results reporting [17]. Effective communication and collaboration from all team members is imperative for the trial's success.

Approvals and Funding

Clinical trials require ethical approval to proceed. Research ethics boards (REB) aim to protect the rights and welfare of participants, and ensure approved studies are ethical, scientifically sound, and clinically relevant [12,18]. Applications may be submitted by the PI to public REBs, such as those of academic and medical centers, or to private REBs, which may offer expedited services [18]. Trials are evaluated based on internationally accepted standards and core principles of respect for persons, concern for welfare, and justice [10-12]. Specifically, in Canada, this often means compliance with the Tri-Council Policy Statement [12], a standard put forth by a council bridging three federal agencies. REB-approval is a dynamic process; the application and corresponding study documents are subject to ongoing review and amendment before and after approval.

In hand with ethics, in Canada, federal approval is needed for phase I-III clinical trials. A clinical trial application is submitted by the study sponsor to Health Canada [19], and approval

is indicated by the receipt of a No-Objection-Letter. Additional specific research licensure may be required, depending on the study intervention [20]. Like ethics, federal approval is an ongoing process that may be facilitated by regular audits. Once approval is achieved, general information about Canadian trials is made publicly available by Health Canada through the Clinical Trials Database [21]. Sponsors are responsible for registering their studies with other databases, such as ClinicalTrials.gov [22] and the ISRCTN registry [23], to provide the public and other researchers with a more comprehensive overview.

The cost of a clinical trial is often in the millions [24], so securing funding is a significant hurdle to overcome. Funding may be supplied internally, such as by the sponsor, or acquired externally, such as from governmental grants, charitable foundations, or private-for-profit organizations [25]. In Canada, a large provider of funding for clinical trials is the Tri-Council. Funding agencies generally support projects that reflect their mandate and that they deem important, feasible, and well planned [26].

Participant Enrollment

Following regulatory approval, trial staff can begin recruiting and enrolling participants. Enrollment is carried out by the investigator or delegated to staff with relevant training [11]. Prospective participants are screened with pre-defined eligibility criteria. Inclusion and exclusion criteria are carefully created to ensure safe and appropriate enrollment of participants. For example, in clinical trials evaluating therapeutics, one exclusion criterion may be taking medications that interact with the study medication and cannot be switched to a different, non-interacting medication. After having understood all the necessary information (e.g., purpose, methods, risks, benefits, and alternatives to the study), informed consent can be obtained from the competent volunteer who has freely agreed to participate [11, 12]. This ethical and legal necessity is an ongoing process, meaning staff should confirm participants' consent throughout the study. Importantly, participants should understand their right to refuse or withdraw consent to participate at any time for any reason without consequence [10, 12].

Data Collection and Oversight

Comprehensive documentation and monitoring are central to any clinical trial. Trial data may be in the form of participant logs, questionnaires, chart notes, laboratory results, imaging reports, and the like. As such, information must often be extracted and encoded into an electronic database [27]. To maintain investigator blinding, preliminary data is often analyzed by a statistician. Depending on the study question, design, and outcome measures, different statistical methodology may be applied to the data. Commonly used statistical tests include t-tests, chi-square, analysis of variance, and regression modeling [17]. Interim analyses help guide the fate of a clinical trial, as a trial may be ended early according to pre-specified stopping rules [12].

Continuous data and safety monitoring during a trial maintains the fidelity and integrity of the research while protecting the safety and wellbeing of participants; this is the responsibility of the research team but may be augmented by an independent Data and Safety Monitoring Board [12]. Progress reports, amendments, unanticipated events, and new information pertaining to the study must be documented and communicated to the sponsor and REB. New information relating to participants' welfare or consent (e.g., newly discovered risks) must be

communicated to the participants, as well [12]. For example, through pharmacovigilance, pharmaceutical trials continuously monitor for adverse events and adverse drug reactions. These are documented, assessed for severity and causality, and followed as appropriate. Safety concerns like serious and unexpected adverse drug reactions must be reported immediately by the PI to the sponsor, REB, and regulatory agencies according to specified criteria [11, 28].

Additionally, regulatory agencies monitor clinical trials for compliance to standards of best practice and law through audits and inspections. Generally, site selection for an inspection is determined using a risk-based approach and pre-defined criteria. Inspections may occur at the sites of investigators, sponsors, or other delegated parties. To assess how a study is conducted, investigators may evaluate documentation, personnel qualifications, standard operating procedures, inform consent processes, and adverse event reporting. Observations of deficiencies or deviations from regulations are recorded, classified by risk, and used to determine whether the trial is deemed compliant or not. Following the inspection, sponsors are required to address deficiencies [29]. Clinical trials may be prematurely concluded should safety, efficacy, futility, and/or ethical concerns arise [12]. Regardless, all Canadian clinical trials are required by law to store study records responsibly and securely for a minimum of 25 years [28].

Knowledge Translation

Clinical trials require knowledge translation to advance medical knowledge and, ultimately, improve patient care. There is also a broader ethical obligation to study participants and society, as a whole, to communicate results regardless of whether they are positive, negative, or inconclusive [10, 30]. Results may be used to gain approval of a new intervention, change clinical practice guidelines, or inform governmental legislation and policy. Therefore, knowledge translation can come in many forms, though commonly in scientific papers and conference presentations. In academic and medical settings, value may come from departmental and institutional rounds. At a minimum, study sponsors can update clinical trial registries with a summary of the results [26]. An important consideration is the dissemination of study findings to the participants, themselves [31]. After the study is completed, it may be appropriate to issue unblinding letters to participants along with words of gratitude and further information for their benefit.

Exceptional Circumstances

Though there are some examples of exceptions to traditional clinical trial processes due to specific circumstances, such as testing of new HIV treatments, the landscape of clinical trials generally changed dramatically in the coronavirus (COVID-19) pandemic. At the onset of the pandemic, there was a rapid effort to research the SARS-CoV-2 virus with the aim of developing vaccines and evaluating potential treatments [32]. As case numbers and deaths climbed, there was an obvious need to expedite clinical trials without compromising scientific rigor or regulatory oversight. This allowed for the introduction of new therapeutics into human testing at an unprecedented rate. Key lessons emerged from successfully accelerated trials, including streamlining bureaucracy, coordinating the ethical and regulatory review, investing in health data systems, and simplifying patient consent processes [33]. Further, the need for increased scientific transparency and rapid communication led to a surge in the number of open

access and preprinted articles [34]. Medical journals accelerated publishing timelines for COVID-19-related articles by decreasing the time allotted for peer-review and editing [35]. However, expediting the scientific process led to concerns about the quality of evidence produced [36]. To provide the greatest overall benefit for patients, the infrastructure surrounding clinical trials may continue to evolve to ensure the efficient study of potentially beneficial therapeutics, while protecting the integrity of scientific rigor, ethical conduct, and participant safety.

Conclusion

Clinical trials are no simple undertaking. Successful trials result from careful planning and diligent oversight. A strong research question, robust study design, dedicated research team, effective participant enrollment, and thorough documentation are essential elements in a trial. Gaining regulatory and ethics approval is an extensive and ongoing process, but is essential to protect the welfare of the participants and the integrity of the study. Securing funding and support are additional hurdles to overcome, especially for newer investigators [37]. Investigators bear the responsibility of ensuring that their trials provide value for investment, not only by answering relevant questions but also in financial terms and patient volunteerism. Every trial will have some limitations that restrict the generalizability and validity of results (e.g., relatively short duration of study, underpowered sample size, or strict eligibility criteria) [5]. As such, continued safety and effectiveness monitoring of approved interventions closes the loop from discovery to safe applications in clinical settings. Finally, the unbiased dissemination of results is needed for progress to be achieved. Recent events have revealed that this may benefit from streamlining of processes and improving infrastructure.

Declarations

Acknowledgements

The authors thank Ms. Narsis Afghari for sharing her expertise in clinical trial design and logistics for the preparation of this manuscript.

Disclosure Statement

No potential conflict of interest was reported by the authors.

Ethics Approval

Not applicable.

Funding Acknowledgements

Not applicable.

Citation to this article

Keyes S, Hawley P. A beginner's guide to clinical trials. Canadian Journal of Medicine. 2022 Feb 08;4(1):4-12. doi: 10.33844/cjm.2022.60615

Rights and Permissions

© 2022 Canadian Institute for Knowledge Development. All rights reserved.

Canadian Journal of Medicine is published by the Canadian Institute for Knowledge Development (CIKD). This is an open-access article under the terms of the Creative Commons Attribution (CC BY) License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

[1] Farrugia P, Petrisor BA, Farrokhyar F, Bhandari M. Practical tips for surgical research: Research questions, hypotheses and objectives. Can J Surg. 2010;53(4):278-281.

[2] Boaz A, Hanney S, Borst R, et al. How to engage stakeholders in research: design principles to support improvement. Health Res Policy Syst. 2018;16(1):60.

[3] Sacristán JA, Aguarón A, Avendaño-Solá C, et al. Patient involvement in clinical research: why, when, and how. Patient Prefer Adherence. 2016;10:631-640.

[4] Mahan VL. Clinical trial phases. Int J Clin Med. 2014;5:1374-1383.

[5] Umscheid CA, Margolis DJ, Grossman CE. Key concepts of clinical trials: a narrative review. Postgrad Med. 2011;123(5):194-204.

[6] Sil A, Kumar P, Kumar R, Das NK. Selection of control, randomization, blinding, and allocation concealment. Indian Dermatol Online J. 2019;10(5):601-605.

[7] Evans SR. Clinical trial structures. J Exp Stroke Transl Med. 2010;3(1):8-18.

[8] Baer AR, Devine S, Beardmore CD, Catalano R. Clinical investigator responsibilities. J Oncol Pract. 2011;7(2):124-128.

[9] Konwar M, Bose D, Gogtay NJ, Thatte UM. Investigator-initiated studies: Challenges and solutions. Perspect Clin Res. 2018;9(4):179-183.

[10] World Medical Association. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. JAMA. 2013;310:2191-2194.

[11] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Efficacy Guidelines, https://www.ich.org/page/efficacy-guidelines; [accessed 25 Aug 2021].

[12] Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council. Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, https://ethics.gc.ca/eng/documents/tcps2-2018-en-interactive-final.pdf; 2018 [accessed 25 Aug 2021].

[13] Bellary S, Krishnankutty B, Latha MS. Basics of case report form designing in clinical research. Perspect Clin Res. 2014;5(4):159-166.

[14] Davis AM, Hull SC, Grady C, et al. The invisible hand in clinical research: the study coordinator's critical role in human subjects protection. J Law Med Ethics. 2002;30(3):411-419.

[15] Hastings CE, Fisher CA, McCabe MA, et al. Clinical research nursing: a critical resource in the national research enterprise. Nurs Outlook. 2012;60(3):149-156.e1563.

[16] Brown JN, Britnell SR, Stivers AP, Cruz JL. Medication safety in clinical trials: Role of the pharmacist in optimizing practice, collaboration, and education to reduce errors. Yale J Biol Med. 2017;90(1):125-133.

[17] Adams-Huet B, Ahn C. Bridging clinical investigators and statisticians: writing the statistical methodology for a research proposal. J Investig Med. 2009;57(8):818-824.

[18] Dunne C. Research ethics board approval: what, why, when, how? BCMJ. 2021;63(4):149.

[19] Health Canada. Clinical Trial Applications (CTAs), https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/applications.html; 2015 [accessed 25 Aug 2021].

[20] Health Canada. Application requirements for cannabis research licences, https://www.canada.ca/en/health-canada/services/publications/drugs-health-products/cannabis-research-licensing-application.html; 2020 [accessed 25 Aug 2021].

[21] Government of Canada. Clinical Trials Database, https://health-products.canada.ca/ctdb-bdec/newSearch-nouvelleRecherche.do; 2021[accessed 25 Aug 2021].

[22] U.S. National Library of Medicine. ClinicalTrials.gov, https://www.clinicaltrials.gov/; 2021 [accessed 25 Aug 2021].

[23] BioMed Central Ltd. ISRCTN registry, https://www.isrctn.com/; 2021 [accessed 25 Aug 2021].

[24] Sertkaya A, Wong HH, Jessup A, Beleche T. Key cost drivers of pharmaceutical clinical trials in the United States. Clinical Trials. 2016;13(2):117-126.

[25] Hakoum MB, Jouni N, Abou-Jaoude EA, et al. Characteristics of funding of clinical trials: cross-sectional survey and proposed guidance. BMJ Open. 2017;7(10):e015997.

[26] Kanji S. Turning Your Research Idea into a Proposal Worth Funding. Can J Hosp Pharm. 2015;68(6):458-464.

[27] Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-381.

[28] Health Canada. Guidance Document: Part C, Division 5 of the Food and Drug Regulations "Drugs for Clinical Trials Involving Human Subjects" (GUI-0100), https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/compliance-enforcement/establishment-licences/directives-guidance-documents-policies/guidance-drugs-clinical-trials-human-subjects-gui-0100/GUI-0100-v1-EN-version.pdf; 2019 [accessed 25 Aug 2021].

[29] Health Canada. POL-0030: Compliance and enforcement approach and inspection strategy for clinical trials of drugs involving human subjects, https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/compliance-enforcement/good-clinical-practices/guidance-documents/inspection-strategy-clinical-trials/inspection-strategy-clinical-trials.pdf; 2021 [accessed 3 Feb 2022].

[30] Brassington I. The ethics of reporting all the results of clinical trials. Br Med Bull. 2017;121(1):19-29.

[31] Bruhn H, Cowan EJ, Campbell MK, et al. Providing trial results to participants in phase III pragmatic effectiveness RCTs: a scoping review. Trials. 2021;22(1):361.

[32] Dillman A, Zoratti MJ, Park JJH, et al. The landscape of emerging randomized clinical trial evidence for COVID-19 disease stages: A systematic review of global trial registries. Infect Drug Resist. 2020;13:4577-4587.

[33] Mather N. How we accelerated clinical trials in the age of coronavirus. Nature. 2020 Aug;584(7821):326.

[34] Fraser N, Brierley L, Dey G, et al. The evolving role of preprints in the dissemination of COVID-19 research and their impact on the science communication landscape. PLoS Biol. 2021;19(4):e3000959.

[35] Horbach PJM. Pandemic publishing: Medical journals strongly speed up their publication process for COVID-19. Quant Sci Stud. 2020;1(3):1056–1067.

[36] Besançon L, Peiffer-Smadja N, Segalas C, et al. Open science saves lives: lessons from the COVID-19 pandemic. BMC Med Res Methodol. 2021;21(1):117.

[37] Bentley C, Sundquist S, Dancey J, Peacock S. Barriers to conducting cancer trials in Canada: an analysis of key informant interviews. Curr Oncol. 2020;27(3):e307-e312.