Commentary

Clinical trial registration and results reporting: a call for transparency, coordination, and meaningful enforcement

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Thirty years ago, David Moher made the case for mandatory registration of clinical trials in the pages of *CMAJ*.[1] In Canada, requirements to both register trials and report their results were added to the Tri-Council Policy Statement (TCPS) in 2010 and were made a condition of funding for clinical trials from the Canadian Institutes of Health Research (CIHR).[2] However, requirements for registration and results reporting are still poorly followed in Canada, especially for trials that are run exclusively in Canada. Fewer than three-quarters of trials completed in 2019 were preregistered and fewer than two-thirds of trials completed by 2014 had been published by 2022.[3] Only 5% of trials sponsored by Canadian academic institutions register, report, and publish their findings, compared with 36% of industry-sponsored trials.[3]

Trial registration and timely reporting are critical safeguards against data manipulation, cherry-picking of results, and persisting biases in favour of publishing only positive findings. Withholding clinical trial findings is not only wasteful of research resources, but also leads to the risk of misinformed clinical decisions and dishonours the contributions of participants who agreed to take part in the trials — at times at serious risks to themselves — to help generate new knowledge about an intervention's safety, effectiveness, or both.[4] Every set of trial results that fails to see the light of day compromises trial participants' investment and trust in the knowledge generation process.

Several countries have enshrined registration and results reporting requirements into national law over the course of the last decade or so, and any Canadian initiatives to do so would not be unique.[5] Notably, in 2007, the United States made nonregistration of clinical trials and failure to report trial results an offence under the *Food, Drug, and Cosmetic Act*, punishable by a fine of as much as $10 000 per day for as long as the violations remain unaddressed.[6] However, effective compliance and enforcement requires institutional resources and the will to act. Compliance with and enforcement of transparency requirements are not easy and limited resources are likely a major contributor to academic centres' poor record of enforcing registration and reporting of trials. Despite the 2007 legislation, the US Food and Drug Administration (FDA) took more than a decade to issue guidance about when it would act on failure to comply with the law's transparency requirements. Despite data showing that trial sponsors often fail to report results, to date, the FDA has initiated enforcement action for non-compliance on only 1 occasion.[6]

Key points

- A substantial number of clinical trials that take place in Canada still do not meet standards for registration and results reporting.
- The duty to publicize clinical trial information under the *Food and Drugs Act* has not been implemented by Health Canada.
- Improved coordination among research ethics boards, medical journals, research funding bodies, and Health Canada, as well as a strengthened enforcement strategy, are needed to ensure all clinical trials in Canada are registered and their results reported for the benefit of patients.

A core part of the problem of enforcement concerns who is best positioned to do this thankless work. Under the TCPS, all trials funded by the CIHR 2022–2023 Clinical Trials Fund competition or conducted by researchers at institutions funded by the tri-agencies (Social Sciences and Humanities Research Council, Natural Sciences and Engineering Research Council, or CIHR) are required to be registered, in a publicly accessible registry, before recruitment of the first trial participant. Some research ethics boards (REBs) require proof of trial registration upon submission of trial protocols; however, REBs are notoriously under-resourced and do not track approved trials to see whether investigators follow through on their commitments to report trial results.[7]

Given researchers' interest in keeping in good standing with the primary source of health research funding in Canada, CIHR may be better placed than REBs to ensure adherence to transparency standards. The first round of recipients of CIHR's Clinical Trials Fund included 17 projects, at least a few of which are registered on https://clinicaltrials.gov/. However, CIHR-funded trials represent only a fraction of those conducted in Canada each year. Even if CIHR had the appetite to enforce conditions of trial registration and results reporting, its oversight would be only partially helpful.

Health Canada — without whose authorization no clinical trial involving a new pharmaceutical drug or vaccine can lawfully proceed in Canada — may be better suited to enforce trial registration and results reporting for health products. However, a closer look at Health Canada's track record reveals consistent disinterest in the issue.

When drug safety legislation known as *Vanessa's Law* was first introduced in Parliament in 2013, it contained no measures to improve the transparency of the evidence base behind health products, in marked contrast to reforms enacted in the US and elsewhere.[8] Health Canada officials reworked the draft legislation in concert with Members of Parliament, adding several provisions intended to enhance the transparency of evidence generated through clinical trials, as well as the regulatory system as a whole. This legislation later became part of the *Food and Drugs Act*. However, the provision relating specifically to trial registration and results reporting proved to be an empty measure. Rather than mandating trial registration and results reporting, like in the US, section 21.71 of *Vanessa's Law* simply added the power to make such regulations — at some unknown point in the future. Nearly 10 years since the law was passed, regulations prescribing what and how trial information should be publicly available have never been published by the regulator. In the interim, Health Canada has endeavoured to modernize its oversight of clinical trials.[9] In February 2023, it published draft guidance on trial registration and public disclosure of trial results, which stated that trial sponsors should register their trials and publish their results.[10] A year later, whether Health Canada will finalize this policy — which encourages, but does not require greater clinical trial transparency — remains to be seen.

Given Health Canada's slow action and the limitations of other actors involved in the oversight and publication of clinical trials — including scientific journals, REBs, and research funding organizations like CIHR — 2 key actions are required to improve trial registration and results reporting. First, a more coordinated and transparent approach, in which those actors share information related to clinical trials registration and reporting directly with Health Canada, needs to be put into place. To facilitate its tracking of phase 1–3 trials, Health Canada should transparently list trial opening and closure dates. Similarly, trial publication in a journal or public reporting of results on trial registries should be relayed to Health Canada, easing the regulator's burden. Second, to ensure Health Canada's authority is clear, Parliament should revisit the wording of section 21.71 of *Vanessa's Law*. Rather than tying the duty to publicize clinical trials to the holder of a therapeutic product authorization, the provision should be amended to oblige all sponsors who have been authorized by Health Canada to conduct a phase 1–3 clinical trial to register the trial before participant recruitment begins and publish the trial results within 12 months of the trial's completion or approval of the product by Health Canada for clinical use, whichever comes first. Absent proof of trial registration and results reporting, Health Canada should not be allowed to grant product approval. Given that the financial penalties available under US law have seldom been used by that country's regulator, a penalty of delayed market entry seems much more likely to encourage compliance in Canada.

Only by reducing information silos by facilitating communication between journals, REBs, research funders, and Health Canada, and by reinforcing the regulator's authority under the *Food and Drugs Act*, does trial registration and results reporting stand to substantially improve.

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