Industry sponsor influence in clinical trial reporting in Canada: a qualitative interview study

Running title: Industry influence in clinical trial reporting

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HIGHLIGHTS

Industry sponsors in some cases influence decisions on whether to report trials.

Companies may influence reporting through owning and controlling access to data.

Trial agreements may only weakly protect the right of site investigators to publish.

Early phase internal company trials are a source of unpublished clinical trials.

Small biotech firms may cease operations without publishing their results.

ABSTRACT

Purpose: Approximately 40% of randomized controlled trials are not published, leading to publication bias and less informed clinical decision-making. We conducted qualitative interviews to understand whether and how industry sponsors of clinical trials of drugs and biologics in Canada influence decisions to report trial results.

Methods: Participants eligible for an interview included clinical trial investigators and research coordinators with experience in drug research, research ethics board members with at least a year of experience in ethical review of trials, research administrators with knowledge of dissemination of clinical trial findings or relations with trial sponsors, and trial participants who had taken part in a drug trial as an adult in the 5 years prior to their interview. Semistructured interviews were held in person or by telephone between March 2019 and April 2021 with participants in Alberta, British Columbia, and Ontario, Canada. Qualitative analysis included coding of interview transcripts and identification of key themes.

Findings: Interviews were conducted with 34 participants, including 17 clinical trial investigators, 1 clinical research coordinator, 3 research administrators, 3 research ethics board members, and 10 clinical trial participants. Participants involved in the conduct, administration or ethical review of trials represented a range of medical disciplines. Interview participant accounts indicate that in some cases industry sponsors influence whether results are reported. A core theme was that companies have a weaker incentive to publish trials with unfavourable findings and trials for products they have decided not to develop further. Companies may influence reporting in various ways, including stopping trials early and not reporting results of stopped trials, owning and controlling access to data, and negotiating clinical trial agreements in multicentre trials that do not fully protect the ability of investigators to publish. Internal company

trials represent an additional source of unpublished trials. More broadly, the research system creates a dependency on funding from industry sponsors that may weaken the ability of researchers and research institutions to negotiate terms with industry sponsors that would fully protect publication rights.

Implications: Interviews with trial investigators and others connected to trial research indicate that in some cases industry sponsors of clinical trial research in Canada influence whether results are reported. Policies aiming to bring about full reporting of trials could benefit from considering the commercial incentives of companies and the ways in which industry sponsors may influence clinical trial reporting. Future research could examine the generalizability of these findings to other jurisdictions.

Key words: clinical trial, nonpublication, publication bias, sponsor, interview, qualitative study

INTRODUCTION

Many clinical trials and other biomedical studies are either not published or only published after a long delay.[1-3] A recent systematic review, including studies assessing whether clinical studies were published during an average follow-up time of 4.6 years from completion of data collection, found an average of 52.7% of clinical studies were published.[1] A previous systematic review, including studies assessing publication during a minimum of 24 months from trial completion, found 60.3% of randomized controlled trials included in trial registries were published.[3] Similarly, a study of protocols submitted to a Canadian research ethics board (REB) found a high proportion of clinical trials were not published.[4]

As a result of selective publication, the medical literature is both incomplete and characterized by publication bias.[1-3] This has contributed to poorly informed patient care and harm to patients.[5] For example, selective publication exaggerated the efficacy of selective serotonin reuptake inhibitors and other antidepressants,[6] preventing physicians from making fully informed treatment decisions for patients with depression. The harms of incomplete trial reporting have been documented related to several types of drug therapy,[7] including the antibody TGN1412,[7] anti-arrhythmic drugs,[8] and the type 2 diabetes drug rosiglitazone.[9]

In response to this problem, the United States (US) and the European Union (EU) have introduced mandatory registration and reporting requirements applying to many clinical trials.[10-12] For example, US rules require registration of clinical trials and reporting of their results in ClinicalTrials.gov within 1 year of completion of data collection on a trial's primary outcome, except for certain trials such as phase 1 studies and early feasibility trials of devices.[10 12] However, studies examining reporting within ClinicalTrials.gov and the European Union Clinical Trials Register (EUCTR) have found low overall compliance with these reporting

requirements.[10 11] In Canada, the regulator has not adopted mandatory requirements to report clinical trial results within a trial registry.

Many factors appear to contribute to nonpublication of clinical trials. Later phase trials[1 3] and larger trials[2] are more likely to be published, whereas discontinued trials are less likely to be published.[13] A randomized trial of reviewer behaviour suggests that journal reviewers may favour studies with positive findings.[14] In addition, the emphasis on publication in high-impact-factor journals as a measure of researcher merit in academic hiring and promotion[15] may incentivize researchers to focus on novel, significant findings rather than on full reporting of research findings.[16]

While multiple factors contribute to selective publication, the potential influence of the pharmaceutical industry on clinical trial reporting has long been a major concern.[17] In some cases, internal company documents have revealed the intention to suppress unfavourable results.[18-20] The major role of industry in funding clinical research[21] provides potential influence over the reporting of findings. However, the mechanisms through which industry sponsors may influence clinical trial reporting and the experiences of clinical trial investigators in reporting findings in industry-sponsored trials are not well understood.

We conducted a qualitative study of clinical trial reporting in Canada involving interviews with trial participants, trial investigators, and others connected to clinical trial research. Our broader study aimed to investigate factors contributing to nonpublication of clinical trials and ethical issues relating to clinical trial reporting. The analysis reported in this paper aimed to understand whether and how industry sponsors of clinical trials of drugs and biologics in Canada influence decisions to report trial results in journals or trial registries.

PARTICIPANTS AND METHODS

This study used a grounded theory approach to investigate clinical trial reporting in Canada through semistructured, in-depth interviews.[22 23] We aimed to conduct interviews with clinical trial investigators, clinical research coordinators, research administrators, REB members, and clinical trial participants. Strategies to increase reliability of the study included triangulation between different types of participants and reporting detailed context and quotations.[24] The study received approval from the University of British Columbia Behavioural Research Ethics Board and the University of Alberta Health Research Ethics Board. All participants provided informed consent.

Sampling and recruitment

We used purposive sampling to include trialists who had conducted trials in varied fields of medicine, trial participants who had taken part in trials of treatments for a range of medical conditions, and others connected to the conduct, administration or ethical review of clinical trials to provide additional perspectives on policy and practice of clinical trial reporting. Inclusion criteria are shown in **Table 1**.

Recruitment of past trial participants involved newspaper advertising, requesting cooperation from clinical research coordinators and research centres to seek consent for us to contact individuals who had participated in clinical trials at their centres, and following up by email or telephone with individuals who expressed interest or agreed to be contacted. We invited participation from other types of participants through an email with an accompanying cover letter, follow-up emails, and snowball sampling.

Data collection and analysis

Interviews of about 45 to 60 minutes in length were conducted between March 2019 and April 2021. Data collection also included shorter follow-up interviews with 4 of 34 participants. Interview guides developed for each type of participant provided a basis for semistructured interviews. (**Supplementary Appendix**) One of the authors (RM) conducted the interviews and coded the data.

Additional interviews were held until data allowed for identification and in-depth analysis of key themes relating to industry sponsor influence in clinical trial reporting. RM also corresponded by email with the Canadian Institutes of Health Research (CIHR) in May 2021 regarding the agency's policy on using grant funds provided for a clinical trial beyond the initially planned end date of the grant.[25]

Interviews were audio-recorded and transcribed, and transcripts were coded using ATLAS.ti, version 8.[26] Data analysis involved initial coding, focused coding, and memo-writing to elicit key concepts from the collected data.[22] (For additional detail on methods, see the **Supplementary Appendix**.)

RESULTS

The study included interviews with 34 participants from the Canadian provinces of Alberta, British Columbia and Ontario, including 17 clinical trial investigators, 1 clinical research coordinator, 3 research administrators, 3 REB members, and 10 clinical trial participants. (**Table 2**) Trialists represented a range of medical disciplines, including cardiovascular medicine, endocrinology, hepatology, infectious diseases, oncology, psychiatry, and rheumatology.

We identified several key themes in the study data relating to industry influence on clinical trial reporting: (1) sponsor influence on decision making about whether to publish, (2) weaker

incentives to publish trials with negative findings or evidence of harm, (3) stopping trials early and not reporting stopped trials, (4) ownership and control of data, (5) clinical trial agreements and confidentiality restrictions, (6) nonpublication of internal company trials, and (7) dependency on funding from industry-sponsored trials. We elaborate on each of these themes below, including selected quotations from trialists (T1-T17) and research administrators (A1-A3).

Sponsor influence on decision making about whether to publish

Several investigators described cases in which they believed the sponsor had influenced the decision to not publish findings. Following a multicentre phase 1 trial, the company decided not to develop the drug due to its toxicity profile. As a site investigator in the trial, an oncologist had accrued sufficient patients to the trial that he would be coauthor of a publication, but he did not believe the decision to publish was under his control. Asked about when the trial had been completed, he replied: “Probably well over two years [ago]—and I've actually bugged the sponsor to say, are you guys going to publish this?” (T3) A common sentiment in these cases was that site investigators lacked control over reporting of industry-sponsored trials. For example, a cardiovascular researcher who had been a site investigator in unpublished phase 2 and 3 trials sponsored by a multinational drug company said the decision on whether to publish would be made at a high level in the study organization, and added: “I think that in the case of investigational drugs there is a lot of industry influence.” (T8) Another trial investigator in cardiovascular research had also been an investigator in unpublished industry-sponsored trials. However, he emphasized that in his experience as an investigator and steering committee member in large multinational trials, the presumption in pivotal industry-sponsored trials was that the results would be published.

Weaker incentives to publish trials with negative findings or evidence of harm

A core theme was that industry sponsors have a weaker incentive to publish certain studies, including trials with negative findings, trials showing harms or safety concerns, and trials for drugs which the sponsor decided not to develop further. An oncologist who participated in both cooperative group trials and global, multicentre industry-sponsored trials had been a site investigator in two unpublished phase 3, industry-sponsored trials with negative results. She explained that "negative trials tend not to be published." (T12) Other investigators made comments which highlighted the incentives of sponsors. For example, a trialist had conducted both investigator-initiated and industry-sponsored trials and had co-chaired the steering committee of a phase 3 trial sponsored by a large multinational drug company. He reflected: "I would say with the companies, there's so much financial incentive for them to report positive results and not to report negative results." (T15) A few investigators described trials which showed harms or safety concerns and were not published, including a phase 1 trial that was completed and phase 3 trials that were stopped early. In some cases the decision not to publish findings followed from a decision not to develop the drug. For example, a trialist who had served as a site investigator in an unpublished phase 2 cardiovascular drug trial sponsored by a large multinational firm believed the drug worked, but explained: "I guess they determined it was not a business case for further developing and [for] the investment that it required to bring it to market." (T8)

Stopping trials early and not reporting stopped trials

Some trialists had been investigators in trials that had been stopped early and not published. One investigator involved in cardiovascular research as a site investigator described a phase 3 trial sponsored by a large multinational drug company that had been stopped by the data and

safety monitoring board of the trial, which he was not aware of having been published. In his experience this was not unique: “And we've had a lot of trials, actually—that for some safety reason that the trial gets halted, and then the result—I mean, everybody knows, who was involved, that the trial was halted but it actually never results in a publication necessarily.” (T8)

Investigators also described their experiences in unpublished trials which had been stopped due a business decision of the sponsor to halt development of the drug, rather than by a data and safety monitoring board, although in one case a drug was later marketed by another company. It is also possible that a small biotech firm sponsoring an early-phase trial may not only stop a trial but close down as a company without pursuing publication of trial results. As one oncologist described, if the company holds the data and has not shared the data with investigators, this may make it impossible to publish the findings: “I think these small biotechs—because as soon as their drug dies, if they have their negative study, their company dies . . . and then you're kind of left with nothing.” (T1) He added that when a company decides to stop development of a drug, this may lead to stopping not just one trial but multiple ongoing trials within a trial program: “Let's say there's 20 trials going—from one drug across multiple tumour sites—and then if a few of them start to fail, they may just shut down the whole program.” Publishing results from discontinued trials, some trialists noted, may also be of less interest to investigators.

Ownership and control of data

In industry-sponsored trials, the sponsor typically owns the key data from the trial and may control access to data by investigators. As noted above, control of data can be important in the context of trials sponsored by small biotech firms. If the company is reliant on a single drug, it is possible the company may close its operations without proceeding to publish or sharing data with investigators to enable reporting of trial findings. More generally, some trialists considered

control of data to be an important factor differentiating investigator-initiated or cooperative group trials from industry-sponsored trials, and linked control of data to the ability to publish. For example, an oncologist with experience in both types of trials highlighted that a key difference between industry-sponsored trials and cooperative group trials is that "the cooperative group has complete control over the data." (T3) While he had been an investigator in unpublished industry-sponsored trials, he suggested that "most of the time you would see [cooperative group] studies published, because we control the data, we control the output, and . . . we want to publish even if the study results are not what we might have expected them to be." Similarly, a psychiatrist who had been an investigator in multicentre trials sponsored by pharmaceutical companies said he preferred to focus on investigator-initiated trials because in company-sponsored trials "you don't own the data." (T13) He noted a company has a disincentive to publish negative findings, but a site investigator in a multicentre trial would not have a right to access all of the data from a trial to be able to publish the results. In contrast, he felt having control over data in an investigator-initiated trial provided freedom to publish: "You are way better if you can get your own grant, doing your own trial, where you own the data—you can publish what you want."

Alternatives to the sponsor controlling the study data, noted one research administrator who had been a lead investigator in phase 2 and 3 industry-sponsored trials, are models where an academic research organization would either "run the whole trial and have total access to the data analysis" (now less common) or share access to the study database held by the sponsor (a mixed model). (A1) An investigator who was involved in academic research organizations and served on steering committees of large industry-sponsored trials felt that the latter approach not only allowed for more independent validation of findings but also could help protect against

interference with reporting: “Having shared access to the data is another way to protect against industry trying to—or one group trying to—not get the information out there.” (T11) It is unclear to what extent this approach helps ensure reporting of findings, however, and the administrator above felt that the main value of shared access to the study database was to allow for additional analysis and substudies.

Clinical trial agreements and confidentiality restrictions

Several study participants spoke about how clinical trial agreements or confidentiality agreements between researchers and trial sponsors, or contract research organizations, relate to dissemination of research findings. Policies or practices at a research institution may prohibit investigators from entering into contracts that would give up their right to publish, but this might only protect the right to publish results from the local site in a multicentre trial. A university-affiliated investigator with experience on steering committees of large industry-sponsored trials described how this would be put into practice in a clinical trial agreement at his institution:

> It basically said that if X amount of time [has] gone by and the company and/or the lead investigators hadn't published that information, then I as an investigator, at least in the contract, had a legal right to publish my findings. And that was trying to kind of twist the arm and give some time frames to make sure that this information doesn't just get swept under the carpet or buried, particularly if it's a negative result or it's potentially harmful to the stockholders or the company that supported that. The challenge with that is it's not really enough, because if you're doing—as I often do—large multicentre trials, even if I enroll a hundred patients in the study, I can publish my results but I can argue that might not even be ethical because I might have a skewed distribution. I don't have adequate [statistical] power. (T11)

An administrator from another university described similar practices at his institution. In addition, a couple of trialists with experience as site investigators in phase 2 and 3 trials sponsored by multinational drug companies mentioned that confidentiality restrictions could prevent investigators from speaking about or reporting findings from an industry-sponsored trial that has not been published. For example, one investigator noted:

> Sometimes with these trials you're also signing confidentiality agreements . . . and that prevents you, as an investigator, banging out an article kind of in violation of your confidentiality agreement. I know that's happened, where there was some investigator who felt that a particular drug or a device . . . was harmful, and that information is being suppressed by the trial sponsor, so they write a paper that ends up in lawsuits and all kinds of things. (T8)

Although study participants indicated that a clinical trial agreement would not give the sponsor the explicit right be decide whether to publish, clinical trial agreements may only weakly protect the ability of site investigators to publish and confidentiality restrictions may impose additional constraints.

Nonpublication of internal company trials

An investigator who serves on an REB indicated that many early phase, internal company trials are not published. Some of these clinical trials are for drugs the company has decided not to develop further:

> So quite often when a company is developing a molecule—out of probably hundreds or thousands of compounds, they'll get a handful of them that might have some promise. And then they take those into phase 1 and phase 2 . . . . And then either because of lack of efficacy or toxicity, or some problem, they elect to not further develop that compound, and then those studies are usually never published. (T8)

Other internal trials are for drugs the company will continue to investigate in larger trials. When reviewing ethics applications for industry-sponsored trials, this investigator often reads about smaller in-house phase 1 and 2 trials the company has conducted previously, which are described in the scientific appendix of a trial protocol or in an investigator's brochure. He believed these internal company trials for drugs still in development are also typically not published.

Dependency on funding from industry-sponsored trials

The accounts of interview participants reflect that researchers and research centres often depend on industry funding for clinical trial research. Funding from public and nonprofit sources tends to be inadequate to cover all the costs involved in conducting a trial. Industry funding provides opportunities for participating in industry-sponsored trial research and may be used to subsidize other trials. While industry funding provides a range of benefits, dependence on industry funding may make it difficult for researchers or research institutions to negotiate terms which enable full reporting of clinical trials.

Several interview participants contrasted the level of funding provided to a site in industry-funded trials with funding provided by public granting agencies or other nonprofit sources. One oncologist characterized the budgets in industry-sponsored trials as "commensurate with the work", whereas he said that budgets in cooperative group trials are "not high enough to actually conduct the study in a cost-neutral way, so you're usually running a loss in those studies." (T3) Similarly, other trial investigators and a research administrator indicated that funding from nonindustry sources tends to be inadequate for conducting a trial. Comparing funding from CIHR to funding from industry for his investigator-initiated trials, one investigator said he also considered funding from industry to be "safer" in that he would not be at risk of losing funding due to delays in conducting the trial, whereas he might be faced with returning funds to CIHR if

delays continued for an extended period. The investigator described a CIHR policy which states grant recipients are entitled to make use of grant funds for 1 fiscal year after the end of a grant and may apply for an additional extension of 1 year. When contacted, a CIHR representative stated that grant recipients may also request further extensions, although this was not explicit in the policy.[25]

Investigators from various areas of medicine stated that they used funding from industry-sponsored trials to subsidize trials that did not have industry funding. A few emphasized that funding from industry-sponsored trials ensured their research centres were able to operate without a deficit. (**Box 1**) Making use of funding from industry-sponsored trials to fund trials without industry funding appears to represent a common strategy trialists and research centres use to meet funding challenges and carry out their research programs.

Comments from investigators suggest that while industry funding benefits researchers and research centres, depending on funding from industry-sponsored trials may involve trade-offs. First, individual investigators may or may not be able to set the terms of their participation to help ensure that trial results are reported. One investigator with experience on steering committees of trials sponsored by multinational drug companies imagined the situation of an early career investigator aiming to do independent research. He reflected that “if they can bring in some industry funding while they're working on another project to help support those other projects, that's a model that all of us use to try to do the non–industry-funded [trials].” (T11) He imagined what he would want to be in place as a new investigator taking part as a site investigator in an industry-sponsored trial—such as involvement of an independent academic research organization and language in the trial protocol about the responsibility and approximate time frame for disseminating findings—but acknowledged that new investigators may not be in a

position to “pick and choose” which trials to be involved in. Second, research institutions may face difficulties in negotiating terms with industry sponsors that ensure full reporting of trials. When asked whether the university or its REB could take measures to help ensure trials are reported, an investigator with experience in international, multicentre industry-sponsored trials at a university-affiliated research centre responded:

> I guess if the university wanted to take a hard stand on it, they could, but . . . . If it's a big multinational company, then they'll just go somewhere else. And this is where it gets a little bit grey, because to some extent these contracts do bring in money, they do generate revenue for both investigators and for the university. . . . So there is some revenue coming into the university, and . . . if that revenue is supporting research infrastructure more broadly, then . . . there's always kind of potential unintended consequences if you take a completely hard line. (T7)

The above comment highlights that universities may hesitate to adopt policies to help ensure industry-sponsored trials conducted at university-affiliated sites are reported, due to dependency on industry funding.

DISCUSSION

While selective publication may occur for a variety of reasons, accounts of trial investigators indicate that in some cases industry sponsors of clinical trial research in Canada influence decisions on whether to report trial findings. Companies have a weaker incentive to publish trials with unfavourable findings and trials for products they have decided not to develop further. The position of a company as a sponsor allows the company to influence reporting in various ways, including stopping trials early and not reporting results of stopped trials, owning and controlling access to data, and negotiating clinical trial agreements in multicentre trials that do not fully

protect the ability of investigators to publish. Internal company trials represent an additional source of unpublished trials. More broadly, the research system creates a dependency on funding from industry sponsors that may weaken the ability of researchers and research institutions to negotiate terms with industry sponsors that would more fully protect publication rights.

Interview participants spoke about their experiences with sponsors ranging from small biotech firms to large multinational drug companies. An issue specific to small biotech firms was that in some cases a firm might be reliant on a single product and close down as a company when faced with negative results without completing ongoing trials or sharing data with investigators to enable publication of findings. Trialists who had served as site investigators and one trialist who had also served on steering committees of large multinational trials highlighted that site investigators generally lack the ability to publish trial findings based on all data from a large multicentre trial when the sponsor and trial leaders do not proceed with publication.

The accounts of interview participants included examples of unpublished phase 1, 2 and 3 trials. Phase 1 to 3 trials include trials of investigational products and trials for investigational uses of marketed products. In phase 1 to 3 trials, investigators may rely on an industry sponsor to provide not only funding but also access to an investigational product. Industry sponsors may ask investigators to sign contracts with confidentiality restrictions relating to publishing about a product that has not yet been approved.

Comparison with other studies

Our study suggests commercial incentives are an important underlying factor contributing to publication bias in industry-sponsored trials. Similarly, a review of developments in clinical trial transparency highlighted that selective publication of trials of the anti-influenza drug oseltamivir

exaggerated its efficacy for preventing flu complications and affected decisions to stockpile the drug.[27]

Our analysis highlights mechanisms of industry influence on clinical trial reporting, including stopping trials early, not reporting results of stopped trials, and industry ownership and control of data. Aspects of these mechanisms have been explored in previous studies. A study of randomized clinical trials approved by REBs in Canada, Germany and Switzerland found discontinued trials were less likely to be published and that clinical trials were sometimes discontinued due to strategic decisions from companies.[13] In a survey of Canadian trial investigators, a majority of trialists who had participated in industry-funded trials over a 5-year period reported that funders owned the data in all or some trials, and only a minority reported they had access to all data in all or some trials.[28]

Previous studies have explored how clinical trial agreements either protect or restrict the ability of investigators to report trial results.[28-30] Surveys of US medical schools regarding clinical trial agreements indicate that individual sites in a multisite trial may often have the ability to publish local site data.[29 30] Similarly, an academic-affiliated investigator in our study described a policy at his university to protect the contractual right of investigators to publish data from a local site, but he highlighted that the ability to publish data from one site within a multicentre trial may not be meaningful. Among Canadian trial investigators who had signed contracts with an industry funder, a majority surveyed indicated that the contracts included confidentiality clauses, defined as an agreement not to disclose any or all information about a trial without permission from the funding source, in all of their industry-funded trials over a 5-year period.[28]

Previous research has highlighted that academic trials with a nonindustry funding source are often underfunded.[31 32] For example, a review of the activities of a clinical trial research network including cancer cooperative groups in Canada and the US found that insufficient funding represented a threat to the viability of this type of research.[33] Our findings suggest the low level of funding for nonindustry trials may contribute to a dependence on funding from industry sponsors to deliver clinical research programs.

Although phase 3 trials are used for drug approvals and are highly important for providing a more complete understanding of the safety and efficacy of drugs, clinical trials for drugs earlier in their development cycle and drugs a sponsor has decided not to develop further may provide relevant information for future trials and even clinical practice.[34] In 2006, six healthy volunteers in a phase 1 trial of the monoclonal antibody TGN1412 developed cytokine release syndrome with multi-organ failure.[35] However, an unpublished phase 1 trial conducted more than a decade earlier found that a similar antibody had effects which paralleled those of TGN1412.[7 35] If the earlier trial had been published, this might have helped avoid the outcome of six individuals experiencing serious adverse events in the trial of TGN1412.[7 34] In 1980, a small trial of the anti-arrhythmic drug lorcainide in patients with suspected acute myocardial infarction found an increased risk of death in the treatment group compared to placebo.[36] Commercial development of the drug was discontinued.[36] If published earlier rather than after a delay of more than a decade, the trial findings might have discouraged the routine prescribing of other anti-arrhythmic drugs to people with heart attacks, which is estimated to have led to over 100,000 premature deaths.[8 36]

The problem of lack of public disclosure of clinical trial results has been apparent for over three decades.[37-39] The increase in reporting of trial results within trial registries represents one of

the most promising developments in recent years.[40] Industry sponsors have been more compliant than nonindustry sponsors with requirements to report results in trial registries, but nonreporting of industry-sponsored trials continues to be a problem.[10 11] A study of compliance with the requirement to report results in EUCTR within 12 months of trial completion, covering trials completed on or before December 19, 2016, found that close to a third of applicable industry-sponsored trials registered since 2004 had not reported results.[11] Similarly, a study of compliance with the requirement to report results in ClinicalTrials.gov within 1 year of data collection on the primary outcome, covering the period from March 2018 to September 2019, found that about half of applicable industry-sponsored trials had not reported results on time and about a third had not reported results at any time.[10]

Policy implications

While the EU and US have adopted requirements to report the results of many clinical trials within trial registries, the EU has lacked penalties for noncompliance and the US has until recently not enforced potential penalties.[10 11 41] When the EU Clinical Trials Regulation comes fully into force, the regulation will require member states to legislate penalties for noncompliance.[42 43] In April 2021, the US Food and Drug Administration (FDA) issued an unprecedented warning to Acceleron Pharma regarding potential civil monetary penalties which could apply if the company did not report overdue results from a clinical trial, and the agency publicly stated its intention to take action to ensure sponsors comply with reporting requirements.[44-46] If consistently enforced, mandatory requirements to report clinical trial results could help address the incentive of industry sponsors to selectively report clinical trials.[10 11 47] However, most phase 1 trials of medicinal products are exempt from EU reporting requirements,[10 11] and phase 1 trials of drugs and biologics are exempt from requirements to

report in ClinicalTrials.gov.[12] In addition, Canada lacks similar regulatory requirements for reporting of clinical trial results. It is important for reporting rules to cover all clinical trials of drugs and biologics and for Canada to adopt regulatory measures to make reporting of clinical trial results mandatory.

While Canada lacks of a regulatory requirement to publicly report trials within trial registries, it is important to note that Health Canada has in place requirements similar to those in the EU and US for reporting of adverse drug reactions to the regulator.[48-52] Any serious unexpected adverse drug reaction occurring during a clinical trial that has a suspected causal relationship with the medicinal product must be reported to Health Canada by the sponsor in an expedited manner.[50] Sponsors of clinical trials are also responsible for submitting periodic Development Safety Update Reports (DSURs) to Health Canada to provide safety information collected about a drug under investigation, including information collected in clinical trials.[49]

Our study highlights that clinical trials stopped early for commercial reasons are a source of unreported trials. Given that stopping trials early for commercial reasons represents a source of unreported trials and diminishes the social benefit of a trial on which informed consent and ethical approval are based,[53-55] this issue merits further consideration regarding whether regulatory actions should be taken to limit this practice.

When an industry sponsor does not proceed with publishing findings of a multicentre clinical trial, site investigators may lack the ability to report findings from the full trial due to a lack of access to data from the whole trial and a lack of protection of the right to publish in clinical trial agreements. This means that university-affiliated researchers are engaged in research with human subjects they may lack the right to publish in a meaningful way. Conducting clinical research that cannot be reported breaches scientific norms of communication of findings and disinterested

pursuit of knowledge and may violate research ethics by not fulfilling participant expectations that research will contribute to knowledge.[56-58] Consequently, universities and other research institutions in Canada have an obligation to enact policies to better protect the ability of trial investigators to access all data from a trial and the rights of site investigators to report findings based on all data from a trial when the sponsor and trial leaders do not proceed with timely reporting. While research institutions have a responsibility to act, regulatory action may be helpful in this area as Health Canada is better positioned than research institutions to bring about wider reforms.

The research system in Canada and internationally is characterized by a dependency on industry to fund a substantial proportion of clinical research, and it would require much greater public investment to change this. Providing greater support to clinical trial research conducted independently of industry would increase the amount of research that is not subject to commercial incentives to selectively report results. A strategy to lessen the dependence of the clinical research system in Canada on funding from industry sponsors would need to involve a higher level of funding per trial and an overall increase in public funding for clinical trial research. Our study also highlights the importance of stability of funding. For example, CIHR grant recipients may require greater flexibility to continue using grant funds following delays experienced in completing a trial, or at least greater clarity regarding the ability to apply for extensions to use funds over a longer period.

Strengths and weaknesses of the study

Strengths of the study include the use of in-depth interviews, which allowed for a detailed exploration of experiences and views of clinical trial reporting, and the involvement of participants with a wide range of experience in the conduct, administration or ethical review of

clinical trials. The study also has limitations which merit consideration. The study did not include other types of participants who might provide insights into clinical trial reporting, such as representatives of industry sponsors, medical journals or regulators. We relied on interview participant accounts, which may be limited by participants' perceptions or ability to accurately recall events. While participants described a broad range of experiences and views, we cannot disregard the possibility that those who chose to participate might differ in important ways from those who did not. For example, a trialist who had experienced difficulty with an industry sponsor relating to reporting trial results might have had greater motivation to participate. Interview participants provided accounts of unpublished trials from phases 1 to 3, but we lacked data regarding unpublished phase 4 trials.

CONCLUSIONS

Interviews with trial investigators and others connected to trial research indicate that in some cases industry sponsors of clinical trials of drugs and biologics in Canada influence whether findings from clinical trials are reported. Policies aiming to bring about full reporting of trials could benefit from considering the commercial incentives of companies and the ways in which industry sponsors may influence clinical trial reporting, including stopping trials early and not reporting results of stopped trials, industry ownership and control of data, terms of clinical trial agreements that do not fully protect the ability of investigators to publish, and dependency on funding from industry sponsors. Health Canada and research institutions in Canada have an obligation to ensure site investigators are able to report trial findings based on all data from multisite trials, when sponsors and trial leaders do not proceed with timely reporting. Future research could investigate the generalizability of our findings to other jurisdictions.

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Table 1. Types of interview participants and inclusion criteria

Participant type	Inclusion criteria	Rationale
Clinical trial investigator	Conducted ≥1 clinical drug trial	Will have experience relevant to trial reporting
Clinical research coordinator	Coordinated ≥1 clinical drug trial	May have experience relevant to clinical trial reporting
Research administrator	Knowledge of policy and practice related to dissemination of clinical trial findings and/or relations with trial sponsors	Contribute experience, knowledge and views from policy or administrative perspective
Clinical REB member	≥1 year of experience as clinical REB member	Experience in ethical review and familiarity with practice and policy relating to clinical trial reporting
Past trial participant	Participated in ≥1 clinical drug trial while at least 18 years of age; participation in the 5 years prior to interview, but has now ended	Will have experience related to trial participation and trial reporting

REB=research ethics board

Table 2. Interview participant characteristics

(a) Trialists

Characteristic[a]	Trialists (n=17)
Primary appointment	
University or academic teaching hospital	10
Other (e.g., private practice, cancer centre)	7
Experience in role	
<=5 years	0
>5 years	17
Province	
Alberta	0
British Columbia	9
Ontario	8
Types of funding	
Nonindustry only	0
Industry only	0
Both industry and nonindustry	17
Most senior role	
Principal Investigator for site	3
Principal Investigator for trial	14
Trial type	
Single site only	0
Multiple site only	1
Both single and multiple site	16

[a] Classifications were based on those used for an investigator survey by Rochon et al (2011).[28]

(b) Research administrators, research ethics board members and clinical research coordinators

Characteristic	Research administrators (n=3)	REB members (n=3)	Research coordinators (n=1)
Primary appointment			
University or academic teaching hospital	3	1	0
Other (e.g., private practice, cancer centre)	0	2	1
Experience in role			
<=5 years	0	1	0
>5 years	3	2	1
Province			
Alberta	1	1	0
British Columbia	0	2	1
Ontario	2	0	0

Research coordinator=clinical research coordinator REB=research ethics board

Table 2. Interview participant characteristics (continued)

(c) Past trial participants

Characteristic	Past trial participants (n=10)
Sex	
Female	7
Male	3
Age	
<=65 years	5
>65 years	5
Education, highest level completed	
Elementary	1
Secondary	3
Community college	1
University	5
Province	
Alberta	3
British Columbia	7

Box 1. Dependence on funding from industry-sponsored trials

So an industry study usually has a bit of margin in it that you can invest into the other work—so that on the whole, the research unit in a centre is not running a deficit, and you're able to do the important academic work—which is basically subsidized, if you like, by the industry work that you do. (oncologist, T3)

For us in order to not go bankrupt, we have to take on the trials that have adequate funding for us to stay afloat. . . . We get trials sent to us all the time, including those that are grant funded. . . . We have to be very careful about signing on to those lesser funded studies that actually have excellent scientific questions being asked—and necessary questions, because there's no industry interest in this particular thing. (trialist in cardiovascular medicine, T8)

I'm very involved in pharma-sponsored trials, so we run many of those, because as you can imagine, the cooperative groups do not fund [adequately]. And so this is actually a mini-business—in the same sense that you have to hire individuals to run your clinical trials appropriately and in a safe, ethical manner. So that obviously costs money. . . . So these cooperator groups—we don't have a lot of support. It also allows us to run independent or investigator-initiated trials as well. So if you run a whole large clinical trials unit, it tends to fund. It's kind of a give and take. Your industry-sponsored clinical trials—which are usually global, multicentre, large trials—they remunerate much better per patient compared to the cooperative trials. (oncologist, T12)