Industry-sponsored pharmaceutical trials and research ethics boards: Are they cloaked in too much secrecy?

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When the research ethics board (REB) of hospital Z reviewed a phase II clinical trial protocol for an investigational drug, several ethical concerns were raised. The REB did not approve the protocol as submitted because of concerns regarding patient confidentiality. The REB wrote a letter to the clinical investigator at the hospital with its decision. The clinical investigator spoke to colleagues at other hospitals and discovered that 2 other REBs had approved the study. Did these other REBs document the same issue and ask for changes? Did they make an error of fact with respect to this issue by misinterpreting the information given to them? Or, did hospital Z's REB commit such an error? Unfortunately, hospital Z's REB will probably never know the answers to these questions. Of equal concern, the other hospitals' REBs will probably never know of the concerns of hospital Z's REB and its eventual decision.

REBs, including hospital, university and independent REBs, have a duty to protect the rights and welfare of research subjects participating in studies associated with their institution. The problem for hospital Z is that our system does not allow REBs to share confidential information about matters before them, and there is no formal system for coordinating REBs' concerns and decisions. Whereas some REBs may communicate informally with one another about a protocol, such communication is sporadic at best. Such sharing of information may be hazardous, given the absence of clarity about industrial or intellectual property rights and legal direction about how much can be revealed and to whom. Some pharmaceutical companies may be willing to have REBs communicate with each other, but this has not been systematically examined. Ashcroft and Pfeffer argue that the secrecy that surrounds REBs and their decision-making is not justified, although they state that there may be some justification for it in early stage clinical research.[1] They argue for openness and accountability, such that private discussion is the exception and not the rule. Although many may agree, we do not have a legislative framework that would offer legal immunity for the sharing of information in good faith.

At present, our REBs do not benefit from the expertise of other REBs that are reviewing, or have reviewed, the same protocol. Research suggests that when reviewing multicentre trials, individual REBs may weigh factors differently resulting in variation in decisions made.[2–5] Even after the United Kingdom introduced multicentre research ethics committees to approve multisite studies before their review by local REBs, variability in the decisions made persisted among local REBs.[6,7] There is likely to be additional variation in decision-making when a protocol involves new issues, such as the interpretation and use of data from new technologies concerning human genetic material, because there may be an absence of appropriate guidelines or regulations to help an REB. Thus, whether a patient may enter a study and, if admitted, the terms and conditions of that involvement may reflect local differences. Moreover, sponsors who have applied to Health Canada's Therapeutic Products Directorate (TPD) to run a clinical trial could "shop around" their protocol to multiple REBs until enough of them agree with their terms and conditions.

The issues of lack of communication among REBs and the lack of centralized mechanisms to coordinate REB discussions and decisions are not restricted to industry-sponsored pharmaceutical trials, and these issues should be considered for all kinds of studies. However, there are special aspects of drug trials that warrant particular attention in that they are subject to both federal legislation and regulation. Canada's Food and Drugs Act[8] mandates that drugs (both prescription and over-the-counter), medical devices and other therapeutic products be tested for their safety, efficacy and quality. Whereas the TPD regulates pharmaceutical drugs (and other therapeutic products and medical devices) and sets out rigorous clinical trial requirements before such agents can be marketed in Canada. The REBs are responsible for independently reviewing these study protocols to determine whether the proposed research should be permitted to proceed in their institutions. However, the REBs function without formal communication and coordination among the REBs, the TPD and the sponsors.

We need to develop mechanisms that will increase communication and coordination and offer legal immunity for doing so, as long as a communication is made in good faith. Any process that changes the duty of confidentiality must include a regulated and appropriate procedural framework for exercising the duty of disclosure. This framework should stipulate what is to be disclosed, to whom and when, and it must reflect the general duty to act fairly. The framework must be in place before we remove any of the protections of protocol confidentiality that may now exist.

Creating a centralized system to track REB decisions

Some of these issues could be addressed by having a centralized system that required REBs to report their decisions to the TPD. A centralized Canadian system might also facilitate our involvement in international pharmaceutical trials. Such a system would be different from the British multicentre research ethics committees in that it would be associated with the governmental regulatory body for pharmaceutical devices, it would serve as the national centralized body, it would not change the authority of the REBs and it would have a legislative framework for regulated disclosures of REB discussions and decisions. However, we can still learn from the British experiences and solutions.[6,7,9,10]

In the proposed system, REBs that are considering giving their approval to an industry-sponsored pharmaceutical trial could access the decisions of other REBs. Once an REB made a decision, it would report it to the TPD, and if approval was denied, the reasons would also be reported. In reality, most REBs will ask for changes to a protocol and will grant approval if the requirements are subsequently met. A centralized system could share protocol changes with other REBs. The REBs would be required to continue to act in good faith and be accountable to their institutions because of the need to consider local contexts (e.g., other trials using the same population).

Such disclosure may highlight issues in clinical trials in which ethical principles, regulations or laws fail to guide REBs adequately. Once these issues are identified, the new centralized program will need to address them. It is conceivable that this may give rise to policy statements or require an interpretation of legal or ethical principles that apply, or can reasonably be assumed to apply, so that REBs have some guidance to help them make their decisions. For example, REBs may question whether a trial's exclusion criteria fail to recognize equal treatment as a fundamental right, leading to the need to have a legal and an ethical opinion about the clinical trial under review.

There would need to be an appeal process within the centralized system for sponsors. (Clinical investigators would appeal REBs' decisions locally.) Applying the rules of law, an appeal process would need to determine whether substantive review or only review of procedural fairness was allowed.

Conclusion

These recommendations are not problem free. Costs and increased bureaucracy are at issue. Sponsors might pay an administrative fee to help support the new system. Such a fee would be levied not to pay for the centralized service but, rather, to offset some administrative costs. The TPD must remain independent of industry, as must our REBs.

As with any recommendations, the devil is in the implementation. Although many will agree to the principle of disclosure to a regulatory body (and some may also want public disclosure), it is the details as to how to do it both legislatively and practically that can turn good intentions into bad deeds. In the meantime, we must continue to discuss this issue, because our REBs need assistance in protecting the rights and welfare of patients in their institutions and in doing their duty to protect the public interest, while facilitating important trials that could improve the health of Canadians.

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