Should Sponsors and DSMBs Share Interim Results Across Trials?

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With larger numbers of clinical trials taking place globally than ever before,[1,2] multiple randomized trials are increasingly likely to address similar clinical conditions at the same time, and the interim results of one trial could help protect participants in other studies.[3–5] However, research sponsors traditionally have ethical obligations to participants in their own trials, not participants in other trials. The question of whether the research team from one study is obligated to protect participants from another recently arose in a study of HIV prevention during breastfeeding.

In many developing countries, infant formula and clean water are not available, acceptable, feasible, affordable, sustainable, and safe. Infants receiving formula feeding in these countries face high risks from diarrhea and other infectious diseases. Because these risks outweigh the risk from exposure to HIV through breastfeeding, international guidelines recommend that HIV-infected mothers exclusively breastfeed for 6 months.[6] Preventing HIV transmission during breastfeeding is therefore a critically important global health issue.

The National Institutes of Health sponsors research on preventing mother-to-child transmission of HIV through breastfeeding. One National Institutes of Health (NIH) study compared 6 weeks of infant nevirapine (NVP) versus 6 months of NVP. The sponsor appointed a data and safety monitoring board (DSMB) to oversee this study and evaluate interim results.

The DSMB overseeing the NIH study was also overseeing another study by a different sponsor. This other study had 3 arms: (1) a control of single-dose infant NVP and 1 week of zidovidine, (2) single-dose infant NVP and 6 months of antiretroviral therapy to mothers, and (3) 6 months of infant NVP. After reviewing interim data from this study, the DSMB determined the control arm was inferior to one of the other arms and recommended it be stopped.

This DSMB had duties to protect participants in both studies but also had promised each sponsor to maintain confidentiality of interim results. Along with information from other trials, the data showed that without prophylaxis, HIV transmission during breastfeeding continues after 6 weeks of age. The DSMB thought that these data strongly suggested that the 6-week arm in the NIH study should be stopped. The virtually unprecedented question was whether the DSMB members should breach confidentiality and disclose interim results from another study to the NIH.

This DSMB, in the unique position of overseeing 2 trials at once, was navigating uncharted ethical territory. Here we consider a more generalizable version of this case: what obligations do sponsors and DSMBs have when results are relevant to participants in another trial?

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BACKGROUND

Sponsors have moral duties to protect participants and maintain scientific integrity in research.[7] Sponsors discharge these duties in part by appointing DSMBs (or Independent Data Monitoring Committees or Safety Monitoring Committees).[8] In practice, DSMBs oversee "large, randomized, multisite trials that evaluate interventions intended to prolong life or reduce risk of a major adverse health outcome."[6,9] DSMBs review interim data and can recommend stopping trials (or components of trials) early for harm, futility, or benefit.[3]

DSMBs generally must maintain confidentiality because they insulate researchers and sponsors from information that might prematurely influence the willingness to continue important trials.[10,11] Nevertheless, DSMBs monitoring concurrent trials have communicated with each other to seek independent confirmation before issuing a recommendation for a major change to a trial.[12] Some DSMB members published letters to the editor when they felt that results of a trial they had overseen were reported inaccurately.[13,14]

ETHICAL OBLIGATIONS

DSMBs clearly have ethical obligations for protecting participants in their trials without unduly compromising study integrity. This means that DSMBs should sometimes allow trials to continue even after observing adverse events or poor outcomes, either because the benefits outweigh the risks to participants or because they might be seeing a false signal.[15,16] Nevertheless, DSMBs may determine that interim results are significant enough to merit stopping all or part of a trial and that the results have implications for protecting the participants of another trial. To determine if sponsors and DSMBs have obligations that override the duty to maintain confidentiality, we must consider the broader obligations of sponsors and DSMBs.

We all have general duties to others in society. One such duty is the duty to aid others when we can help them substantially at minimal cost to us. For instance, if someone knew a lake had thin ice, but did not warn children skating on it, we would think this person failed to fulfill a moral obligation. Similarly, sponsors and DSMBs have duties to others whom they can help greatly at limited personal cost.

Additionally, sponsors and DSMBs are a vital part of the clinical trials enterprise, which has the goal of developing knowledge for the benefit of society, and they therefore have duties to help maintain the public's trust in research.[7,9] Sponsors are stewards of resources designated to produce generalizable knowledge through research. DSMBs ensure the public's confidence in the research enterprise by safeguarding research subjects.[13] Without public trust, researchers and sponsors will have a harder time producing socially valuable knowledge to advance the health of future patients. A sponsor who abuses the public's trust is therefore free-riding on the hard work of others conducting responsible research.

For these reasons, DSMBs and sponsors have ethical obligations to disclose information to protect the safety of participants in other trials, depending on the magnitude of the potential harm to those subjects, the consequences of disclosure and whether there are alternatives for protecting subjects. Another relevant factor is whether the results of one trial are relevant to another, given differences in clinical settings, populations being tested, side effects, and/or rates of subject accrual. Preventing significant harm to subjects, even those in other trials, is generally a higher priority than the consequences of breaching confidentiality.

For instance, imagine a large trial testing whether estrogen and progesterone therapy reduce the risks of heart attack and osteoporosis in postmenopausal women. If, contrary to conventional wisdom, interim data demonstrate the therapy caused increased risks of coronary heart disease and stroke, the sponsor and DSMB may have obligations to disclose information to others conducting similar trials. But if a phase III trial of an allergy medication demonstrates increased risks of headache and increased appetite, sponsors and DSMBs may not have this duty.

There may be costs to consider in sharing interim data, but disclosure is not likely to make results less publishable, because even some elite journals are willing to publish information that was previously shared publicly.[17,18] A more significant cost could be the risk of unblinding subjects and investigators in the trial overseen by the DSMB if some portion of the trial will continue. Additionally, if interim results are disclosed prematurely, subjects and clinicians could lose confidence in their trial before it has answered the research question. Although these costs should be taken into account, in many cases, these risks can be minimized by careful disclosure.

Sponsors and DSMBs should therefore communicate interim results when disclosure is not costly, will protect subjects from significant harm, does not have good alternatives, and will help maintain the public's trust. This implies that disclosure should be limited in terms of what is disclosed and to whom.

In practice, some DSMBs have agreed to share information about important adverse events in advance; sponsors sometimes send data to independent groups to analyze adverse events occurring in 2 relatively small trials (Friedman, Personal communication, April 6, 2011). Agencies or networks sponsoring many studies at once can communicate relatively rapidly about interim results across trials. Yet, agreements between sponsors and DSMBs typically require that DSMBs maintain confidentiality and have not recognized that a need may arise for disclosure of information to protect the subjects of another trial.

We propose that sponsors and DSMBs routinely work together in advance to develop a plan for disclosing relevant information in cases where it is necessary to protect the welfare of subjects in other trials. This may include identifying trials for which this information might be relevant and interfacing with those sponsors and DSMBs; developing "disclosing rules", akin to stopping rules, that would indicate when information should be shared; and designating a neutral third party arbiter who could resolve disputes quickly if they arise.

Some commentators have gone further and proposed sharing all interim data publicly to inform treatment decisions.[19,20] However, others have convincingly argued this would make it extraordinarily difficult to conduct clinical

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trials and that it is appropriate not to share interim data routinely provided that subjects understand the terms of participation.[21,22]

CONCLUSIONS

With many more multinational clinical trials studying related questions, research sponsors and DSMBs play more complicated roles than in the past. Sponsors and DSMBs must balance their obligations to maintain the integrity of their trials and to protect subjects in their trials, future patients, and subjects in other trials. When interim results from clinical trials can have significant effects on the conduct of other trials and the welfare of and risks to the subjects participating in them, sponsors and DSMBs have obligations to disclose results to the relevant parties.

In the long term, the research community should develop prospective mechanisms for sharing information. More channels of communication across agencies and institutions will better enable sponsors, DSMBs, and Institutional Review Boards to work together to appropriately protect research subjects.

REFERENCES

1. Thiers FA, Sinskey AJ, Berndt ER. Trends in the globalization of clinical trials. *Nature Rev Drug Discovery*. 2008;7:13–14.
2. Zink A, Silman AJ. Ethical and legal constraints on data sharing between countries in multinational epidemiological studies in Europe report from a joint workshop of the European league against rheumatism standing committee on epidemiology with the "Auto Cure" project. *Ann Rheum Dis*. 2008;67:1041–1043.
3. Hillman DW, Louis TA. DSMB case study: decision making when a similar clinical trial is stopped early. *Control Clin Trials*. 2003;24:85–91.
4. Fisher L, Klibaner M. Regulatory issues for data and safety monitoring committees. *Am Heart J*. 2001;141:536–541.
5. Lavery JV, Singer PA, Ridzon R, et al. In global health research, is it legitimate to stop clinical trials early on account of their opportunity costs? *PLoS Med*. 2009;6:4–7.
6. World Health Organization. Acceptable medical reasons for the use of breast-milk substitutes. 2009. Available at: http://whqlibdoc.who.int/hq/2009/WHO_FCH_CAH_09.01_eng.pdf. Accessed November 20, 2009.
7. Morreim EH. Medical research litigation and malpractice tort doctrines: courts on a learning curve. *4 Hous. J. Health L. & Pol'y*. 2004;4:1–86.
8. Fleming TR, Sharples K, McCall J, et al. Maintaining confidentiality of interim data to enhance trial integrity and credibility. *Clin Trials*. 2008;5:157–167.
9. NIH Policy for Data and Safety Monitoring Available at: http://grants.nih.gov/grants/guide/notice-files/not98-084.html. Accessed June 10, 1998. Further guidance on a data and safety monitoring for phase I and phase II trials. Available at: http://grants.nih.gov/grants/guide/notice-files/not-od-00-038.html. Accessed June 5, 2000 (last visited June 9, 2011).
10. Food and Drug Administration. Department of Health and Human Services. Guidance for clinical trial sponsors: establishment and operation of clinical trial data monitoring committees, non-binding recommendations OMB Control No. 0910–0581. 2006. Available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf. Accessed June 9, 2011.
11. Fleming TR, Ellenberg S, DeMets DL. Monitoring clinical trials: Issues and controversies regarding confidentiality. *Stat Med*. 2002;21:2843–2851.
12. Armitage P. Delta data and safety monitoring committee, data and safety monitoring in the delta trial. *Control Clin Trials*. 1999;20:229–241.
13. Marmor MF. A randomized trial of Vitamin A and Vitamin E supplementation for retinitis pigmentosa. *Arch Opthalmol*. 1993;111:1460–1461.
14. Norton EW. A randomized trial of Vitamin A and Vitamin E supplementation for retinitis pigmentosa. *Arch Opthalmol*. 1993;111:1460.
15. Sydes MR, Spiegelhalter DJ, Altman DG, et al. DAMOCLES Group. Systematic qualitative review of the literature on data monitoring committees for randomized controlled trials. *Clin Trials*. 2004;1:60–79.
16. Pocock SJ, Hughes MD. Practical problems in interim analyses, with particular regard to estimation. *Control Clin Trials*. 1989;10(4 suppl):209S–221S.
17. PLoS Medicine, editorial and publishing policies. Available at: http://www.plosmedicine.org/static/policies.action#copyright. Accessed May 12, 2010.
18. The Lancet, Information for Authors. Available at: http://download.thelancet.com/flatcontentassets/authors/lancet-information-for-authors.pdf. Accessed June 9, 2011.
19. Lilford RJ, Braunholtz D, Edwards S, et al. Monitoring clinical trials—interim data should be publicly available. *BMJ*. 2001;323:441–442.
20. Wells RJ, Gartside PS, McHenry CL. Ethical issues arising when interim data in clinical trials is restricted to independent data monitoring committees. *IRB*. 2000;22:7–11.
21. Miller FG, Wendler D. Is it ethical to keep interim findings of randomized controlled trials confidential? *J Med Ethics*. 2008;34:198–201.
22. Dixon DO, Lagakos SW. Should data and safety monitoring boards share confidential interim data? *Control Clin Trials*. 2000;21:1–6.

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