Participant-Level Data and the New Frontier in Trial Transparency

Deborah A. Zarin, M.D.

Medical progress is possible only because altruistic volunteers put themselves at risk in clinical trials. The results of those trials are then used to inform medical decisions. The traditional system of relying on investigators, sponsors, and journal editors to decide whether, when, and how to report trial results was based on trust. There was no way to know what trials had been conducted, what data were collected, how they were analyzed, and whether the reported data were complete and accurate. Policies mandating the registration of trials and the reporting of summary results were instituted to provide greater transparency. In turn, this greater transparency brought greater awareness that the aggregated, or summary, data used to report results were not always a valid or sufficient reflection of the underlying data. As a result, the trial-transparency movement was broadened to include a focus on the participant-level data.

Summary data are an efficient way to communicate trial results and conduct common statistical analyses. However, the transformation from participant-level data to summary data involves the loss of information.[1] For example, a magnetic resonance imaging scan may need to be interpreted and then coded; emergency department notes may need to be used to determine whether a trial participant met the criteria for a heart attack. Inconsistent data for a given participant need to be resolved, the analysis population established, and a descriptive statistic calculated (e.g., mean or median change in response). It is not surprising that different ways of summarizing the same data may lead to substantially different conclusions. Commonly used statistical analyses are based on the presumption that these decisions were prespecified before the data were examined,[2] though in practice the degree of specificity varies and subjective judgments are inevitable. The trial-transparency movement argues that by opening up participant-level data, along with the protocol and other documents, the underlying decisions become part of the public record, providing accountability and allowing scientific debate. Proponents also argue that the availability of such data will allow interested parties to use participant-level data for additional analyses as a preliminary test of a new idea or to combine data from multiple studies to seek previously unidentified associations.

Two articles in this issue of the *Journal* reflect this new frontier.[3,4] GlaxoSmithKline (GSK) offers detailed information about its policy of providing controlled access to deidentified participant-level data from certain trials of approved drugs to "qualified" researchers for research proposals that meet certain criteria.[4] In contrast, the article by investigators from the Immune Tolerance Network (ITN) of the National Institute of Allergy and Infectious Diseases on treatments for vasculitis (the Rituximab in ANCA-Associated Vasculitis [RAVE] trial)[3] is accompanied by open public access to participant-level data without the need for a specific research plan or approval of the qualifications of the investigators.[5] These policies reflect different methods of balancing the benefits, risks, and costs of disclosure. GSK has appointed an independent review committee to consider research proposals[6] but retains control over who uses the company's data and for what purpose, as well as how the results are disseminated; GSK is looking for a third party to host the data and manage the proposal review function. The ITN allows any user to conduct and download analyses. Both approaches are limited to published studies, thereby minimizing academic and commercial risk, and include access to key documents. As discussed in the GSK article, careful consideration has been given to issues of informed consent, participant privacy, and uses of the data. It is clear that both groups had to go to considerable length to ensure that the data format and documentation are sufficient for use by external researchers.

These two very distinct approaches are just pieces of the "open data" picture. In recent months, the Institute of Medicine[7] and others have fostered discussion about the pros, cons, and practicalities of providing access to participant-level data, and the European Medicines Agency[8]

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has proposed a proactive policy of making the participant-level data in its possession publicly accessible in either an open or a controlled manner, depending on the need for privacy protections.

Historically, each proposed increase in trial transparency has elicited concerns, including the possible loss of competitive or commercial advantage; the potentially negative implications of increased public access, including the possibility of invalid secondary analyses; and the associated costs. Release of participant-level data elicits these and additional concerns related to the potential identification of participants.

As we consider the path ahead, key questions to ask of each new data-disclosure policy include the following. First, for which trials will participant-level data be available? In particular, will the policy perpetuate a dissemination bias by increasing the amount of information available for some trials while keeping other trial results inaccessible? Second, exactly what data and supporting documents will be available? Third, what will the process be, and how transparent will it be? For example, who will get access, who will decide, and what criteria will be used? What types of analyses of the participant-level data will be allowed, and what ongoing role would the trial sponsor have?

The GSK and ITN data policies are bold attempts to modify and improve the process by which research is reported. We have to learn as much as we can from these experiments about the benefits, risks, costs, and appropriate role of disclosing participant-level data, in service to the ultimate goal of honoring each trial volunteer's altruism.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the National Institutes of Health (NIH)–Lister Hill National Center for Biomedical Communications, National Library of Medicine, NIH, Bethesda, MD.

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DOI: 10.1056/NEJMe1307268
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