Sharing and Reporting the Results of Clinical Trials

The principle of data sharing dates to the dawn of scientific discovery—it is how researchers from different disciplines and countries form collaborations, learn from others, identify new scientific opportunities, and work to turn newly discovered information into shared knowledge and practical advances. When research involves human volunteers who agree to participate in clinical trials to test new drugs, devices, or other interventions, this principle of data sharing properly assumes the role of an ethical mandate. These participants are often informed that such research might not benefit them directly, but may affect the lives of others. If the clinical research community fails to share what is learned, allowing data to remain unpublished or unreported, researchers are reneging on the promise to clinical trial participants, are wasting time and resources, and are jeopardizing public trust.

Across public and private sectors, the United States has increasingly focused on data sharing, including through directives from the White House to ensure that valuable scientific data generated with federal funding are publicly available and useable. As the largest public funder of biomedical research in the world, the National Institutes of Health (NIH) has a special responsibility to share data while safeguarding the interests of researchers and research participants.

Today, the US Department of Health and Human Services (HHS) proposed a rule to implement the requirements of the Food and Drug Administration Amendments Act of 2007 (FDAAA), to require public sharing of summary data from certain clinical trials of FDA-regulated drugs and devices. Such summary data would need to include demographic and other baseline characteristics of participants, data on primary and secondary outcomes, and information about adverse events. Although the FDAAA, with such a requirement, has been in place for several years, the proposed regulation will, when finalized, clarify the requirements and extend them in ways permitted by law. HHS is seeking public comment to inform the final content of the regulations.

The scientific community has a disappointing track record for dissemination of clinical trial results. Numerous factors may contribute to these poor publication rates, including some that are beyond the control of researchers. Despite the best efforts of investigators, the results of some trials may never reach the threshold deemed necessary to merit the attention of journal editors and readers. Even published results may focus only on the findings of most interest to the investigators. Other means to share such data are necessary because both real and potential harm can result from failure to fully disclose the results of clinical trials. However, difficulty with achieving publication in scientific journals for negative results cannot be blamed entirely. A recent analysis of 400 clinical studies revealed that 30% had not shared results through publication or through results reporting in ClinicalTrials.gov within 4 years of completion. This is a serious issue and the proposed rule underscores the intent of NIH to take strong action to promote timely dissemination of clinical trial results.

Without access to complete information about a particular scientific question, including negative or inconclusive data, duplicative studies may be initiated that unnecessarily put patients at risk or expose them to interventions that are known to be ineffective for specific uses. If multiple related studies are conducted but only positive results are reported, publication bias can distort the evidence base. Incomplete knowledge can then be incorporated into clinical guidelines and patient care. However, one of the greatest harms from nondisclosure of results may be the erosion of the trust accorded to researchers by trial participants and, when public funds are used, by taxpayers.

The efforts to make information derived from clinical trials public has been under way for nearly 2 decades. In 2000, following passage of the FDA Modernization Act of 1997, NIH established ClinicalTrials.gov, a public database operated by NIH’s National Library of Medicine. In 2007, the FDAAA expanded the subset of clinical trials required to register within 21 days of enrolling the first participant. Registration involves submitting important information about the condition under study, the interventions tested, recruitment criteria, and location of trial sites into ClinicalTrials.gov. This information allows patients and clinicians to find currently enrolling trials focused on conditions of specific interest; more than 57 000 unique visitors access the site every day. The FDAAA also mandates, with some exceptions, that basic summary results from registered trials of approved products be submitted to the database generally within 1 year of the trial’s completion of collection of primary outcome data. More than 14 000 results records have already been posted, but reporting of results has not yet become routine across the clinical research enterprise.

The subset of clinical trials subject to the FDAAA proposed regulation includes certain controlled interventional studies of drugs, biological products, and devices that are regulated by the FDA; excluded are phase 1 studies of drugs and biological products and small feasibility studies of devices. Data from covered clinical trials must be submitted irrespective of who funds or conducts the trial. Although the FDAAA currently requires results only of trials of approved products, it allows HHS to broaden the scope to unapproved products. Given the importance of data from trials of drugs or devices that never result in FDA clearance, licensure, or approval, HHS...
is proposing to exercise this option and expand the scope of results submission to trials of unapproved products.

According to the FDAAA, failure to comply with its provisions may result in civil penalties of as much as $10,000 per day (assessed by the FDA) and could affect funding for federally funded trials that are out of compliance. The immediate goal is to have NIH-funded trials be 100% compliant under this act, and the NIH is committed to working with NIH-funded investigators to ensure they understand their responsibilities regarding submission of research results. We understand that reporting the results of clinical trials takes time and effort. Data for all prespecified outcomes must be analyzed and required information must be submitted in a structured format to the ClinicalTrials.gov data submission system, which is being refined to make the process as simple as possible. The NIH is committed to supporting the clinical trial community; for example, ClinicalTrials.gov is increasing the availability of individualized, one-on-one staff assistance during the results submission process. Thus, with the implementation of clearer requirements, augmented support materials and resources, and facilitated reporting, the NIH expects that investigators and sponsoring organizations will have the necessary tools to provide accurate, complete, and timely trial results submissions. However, for grantees who are subject to the amendments act and fail to comply after sufficient notification, the law is clear that NIH and other federal funders of clinical trials must then withhold further funding for the grant and any future grant to the grantee. In addition, the timely reporting of clinical trials will be taken into consideration during review of subsequent applications for funding.

These requirements of the FDAAA relate to the public disclosure of summary data, rather than data from individual research participants. The value of greater access to such participant-level data is likely considerable, and other steps are being taken to develop approaches to make that access possible in the future, while protecting patient privacy and respecting proprietary information. The Institute of Medicine, with support from the NIH, plans to issue a report at the beginning of 2015 with recommendations about sharing participant-level data from clinical trials. Some NIH institutes have already begun to require that participant-level data from certain funded studies be made publicly accessible. The European Medicines Agency has also been working toward broader access of participant-level data. In January 2014, members of the Pharmaceutical Research and Manufacturers of America and the European Federation of Pharmaceutical Industries and Associations began reviewing research access requests for patient-level clinical trial data. A number of pharmaceutical manufacturers have or are developing mechanisms to provide access to anonymized participant-level data from clinical trials.

The NIH is committed to ensuring transparency around every NIH-supported clinical trial. Therefore today, NIH has also announced a proposed policy for registration and results reporting for all clinical trials (interventional studies, not observational) funded by NIH, including phase 1 studies of FDA-regulated drugs, small feasibility studies of devices, and clinical trials of interventions not subject to FDA regulation such as behavioral interventions. Timely reporting of clinical trials will be taken into consideration during review of subsequent applications for funding.

It is time to embrace an era in which transparency and responsible data sharing are common values. Research participants trust that the data they provide will be used to advance the health of many. It is the responsibility of investigators and funders to guarantee that obligation is fulfilled.