

## HEALTH LAW, ETHICS, AND HUMAN RIGHTS

Mary Beth Hamel, M.D., M.P.H., *Editor***Preparing for Responsible Sharing of Clinical Trial Data**

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Data from clinical trials, including participant-level data, are being shared by sponsors and investigators more widely than ever before. Some sponsors have voluntarily offered data to researchers,<sup>1,2</sup> some journals now require authors to agree to share the data underlying the studies they publish,<sup>3</sup> the Office of Science and Technology Policy has directed federal agencies to expand public access to data from federally funded projects,<sup>4</sup> and the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) have proposed the expansion of access to data submitted in regulatory applications.<sup>5,6</sup> Sharing participant-level data may bring exciting benefits for scientific research and public health but may also have unintended consequences. Thus, expanded data sharing must be pursued thoughtfully.

We provide a suggested framework for broad sharing of participant-level data from clinical trials and related technical documents. After reviewing current data-sharing initiatives, potential benefits and risks, and legal and regulatory implications, we propose potential governing principles and key features for a system of expanded access to participant-level data and evaluate several governance structures.

## INITIATIVES TO EXPAND ACCESS TO DATA

For more than a decade, policymakers have sought to expand public access to information about planned, ongoing, and completed clinical trials. Recently, several initiatives have broadened the focus from the registering of trials to the sharing of protocol details, enrollment opportunities, and study results, and now to providing access to participant-level data.

The 1997 Food and Drug Administration Modernization Act (FDAMA) mandated public registration of trials involving drugs for serious

and life-threatening conditions in an online database, called ClinicalTrials.gov. The registry included studies that were privately and federally funded and was expanded in 2002 to include most controlled clinical trials after phase 2 for drugs in the FDA approval process. Pharmaceutical companies and their trade associations also made voluntary commitments beginning in 2002 to share clinical trial results.<sup>7,8</sup> In 2005, the International Committee of Medical Journal Editors (ICMJE) began requiring previous registration of studies as a precondition for publication.<sup>9</sup> In the FDA Amendments Act of 2007, Congress expanded registration requirements to cover most controlled clinical trials (excluding exploratory, early phase 1 drug trials and small feasibility studies of devices, even though the ICMJE requires registration of these trials for publication) and mandated that summary results, including frequent adverse events, be reported and posted.<sup>10</sup>

Researchers and other observers have demanded access to raw (i.e., participant-level) data,<sup>11-19</sup> reflecting concern about the completeness, timeliness, and accuracy of sponsor-reported summary results<sup>20-24</sup> and investigators' reticence about sharing data sets.<sup>13,25</sup> Companies have responded: pharmaceutical associations in the United States and Europe have recently published commitments to expanded access to trial data and summaries,<sup>2</sup> Roche and GlaxoSmithKline have adopted policies allowing researchers access to participant-level data from trials of approved products,<sup>26-28</sup> and Medtronic partnered with Yale University to provide access to Medtronic's data on recombinant human bone morphogenetic protein 2.<sup>29</sup> Several other voluntary initiatives are planned or under way.<sup>1,30</sup> In addition, in January, the *BMJ* began requiring that anonymized, participant-level data from drug and device trials be shared with other researchers "on reasonable request" (although a detailed definition of "reasonable" was not elucidated) as a condition of publication.<sup>3,31</sup>

The EMA, which approves drugs for marketing within the European Union, announced in a draft policy in June that it will provide public access to some of the data in marketing dossiers, including participant-level data.<sup>5</sup> Historically, the EMA has declined to release participant-level data because they contain “confidential commercial information.” In response to criticism from the European Ombudsman in 2010,<sup>32</sup> the EMA began allowing access to certain clinical trial data that were submitted to the agency,<sup>33</sup> prompting litigation by objecting companies that has yet to be resolved.<sup>34,35</sup> The EMA’s new policy expands access further, and although the agency will not release documents that it determines contain confidential commercial information, it has also stated that “in general,” clinical trial data “cannot be considered confidential commercial information.”

The new policy applies to data submitted to the EMA after March 1, 2014, and covers a range of study types. The policy requires disclosure of certain raw data, clinical study reports, and individual case-report forms, among other items. Some data and documents will be posted online, but access to data that the EMA deems would endanger participants’ privacy will be controlled. Requesters must promise to use data only to address a question of public health importance that is consistent with the purposes for which participants gave informed consent. They must also pledge not to use the data to reidentify par-

ticipants or to obtain a marketing authorization outside the European Union and not to publish the identities of the participants. Finally, requesters must agree to publish the results of their analyses.

The FDA has long treated participant-level data that are submitted in product applications as confidential commercial information, though the agency has routinely disclosed summaries of data from trials of approved products. In June, the agency signaled a potential change in policy (albeit one that is less dramatic than the EMA’s), requesting public comments on a proposal to release deidentified participant-level data that are pooled within a product class and masked so that they do not identify particular products.<sup>6</sup>

#### POTENTIAL BENEFITS OF EXPANDED DATA ACCESS

The rationales for expanded access to participant-level clinical trial data are numerous (Table 1). Although some benefits of data sharing can be achieved to some extent through sharing of summary data, access to participant-level data may enable a much wider range of analyses.<sup>36</sup>

First, data analyses by independent researchers can detect important findings concerning product safety and effectiveness,<sup>1</sup> thus serving as a check on a sponsor or investigator’s characterization of the risks and benefits of a treat-

**Table 1. Potential Benefits of Sharing Clinical Trial Data.**

Benefit	Primary Beneficiaries				
	Public or Patients	Research Participants	Scientific Community	Regulators	Trial Sponsors
Encourage accurate characterization of the benefits and risks of drugs in research reports, improving public confidence in clinical research and pharmaceuticals	X		X	X	X
Improve surveillance of drug safety and effectiveness	X		X	X	
Facilitate secondary analyses of clinical trial data to explore new scientific questions	X		X		X
Speed innovation	X		X		X
Enable patients and advocacy groups to learn more about their specific medical problem	X				
Ensure that research participants are not exposed to unnecessary risk		X	X		
Ensure that research subjects’ participation advances science		X	X		
Achieve operational efficiencies in conducting clinical trials			X		X
Inform strategic decisions about potential avenues of research and development			X		X

ment and the assessment of a regulatory agency.<sup>37</sup> Inappropriate analytical methods, selective use of data, and other problems may be exposed through review of analysis files and attempts to replicate analyses with the use of patient-level data; weak trial designs and deficiencies in trial operation may be identified through review of patient- and summary-level data, protocols, and clinical study reports; and new lines of analysis of patient-level data may expose issues obscured in study reports or omitted in approved product labeling. With greater transparency of data, there could be greater accountability for design, conduct, analysis, and reporting of clinical trials and more vigorous monitoring of products over their life cycle, as two Institute of Medicine committees have recommended.<sup>38,39</sup>

A second benefit is the potential effect on scientific discovery. Independent researchers may use aggregated participant-level data to explore questions of public health significance that have not been addressed in individual trials. Pooling of these data may increase the precision of estimates of treatment efficacy, detect safety problems unobservable in smaller samples, allow exploration of subgroup effects, and permit analysis of how therapeutic effects vary in different geographic settings because of such factors as population genetics and health care delivery systems.

Because of the public health benefits of well-designed analyses of participant-level data, the responsible provision of access to data to enable such analyses is ethically indicated. It is consistent with the commitment of both health researchers and industry representatives to improve health and with the obligation of physicians to ensure that they and their patients have information sufficient for good treatment decisions. Expanded access to data can also help researchers meet their ethical obligations to participants in research studies.<sup>1,15,40</sup> Maximizing the scientific benefit derived from each trial honors participants' contributions and furthers their interest in advancing new therapeutics.<sup>11,41</sup> Data sharing can also ensure that patients are not exposed to the risks of a trial if sufficient certainty about the research question can be reached on the basis of existing data.

Finally, sharing summary- and participant-level data may help research sponsors and investigators make more informed decisions about

where to invest resources. Companies often know which of their competitors' trials appear promising, but greater access to data from completed trials may enable them to examine subpopulations with lower participant accrual and refine recruitment, retention, and site-selection strategies.<sup>1</sup>

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#### POTENTIAL RISKS AND UNINTENDED CONSEQUENCES

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A leading concern in expanding access to participant-level data is whether the privacy of research participants can be guaranteed.<sup>1</sup> It is difficult to effectively deidentify certain data — especially data from trials concerning rare diseases or other small trials — without rendering them useless.<sup>42</sup> Data on the sex, age, and geographic location of participants are often important for research purposes but can reveal participants' identities when triangulated with other databases. Revelations that the results of genome sequencing can be reidentified with relative ease with the use of publicly available information<sup>43</sup> have called into question whether deidentification is ever completely reliable.<sup>44</sup> The fact that specific trial sites are disclosed on ClinicalTrials.gov and other trial registries increases the risk of reidentification. Although a discussion of informed-consent issues is beyond the scope of this article, the risk of breach of privacy raises critical questions about how to ensure that participants understand the potential ramifications of data sharing.

Public access to participant-level data could also lead unskilled analysts, market competitors, or others with strong private agendas to publicize poorly conducted analyses. Rather than advancing public health, a flood of methodologically flawed analyses could mislead health care providers and patients, potentially damaging patient care and treatment adherence.<sup>1,45</sup>

Another concern is that mandatory disclosure of clinical trial data could affect incentives to invest in research to develop new medical products. As courts have noted in upholding the FDA's traditional refusal to disclose clinical trial data submitted in new drug applications, requiring disclosure in a jurisdiction in which a product has been approved could allow competitors to use the data to seek approval of competing products elsewhere “without incurring the time, labor, risk, and expense involved in developing them independently.”<sup>46</sup> Competitors also benefit

from learning about other companies' scientific or commercial strategies, gleaning information to shape their own decisions about developing products for the same condition or with similar mechanisms of action. Requests for clinical study reports that have been presented to the EMA over the past few years have been filed mostly by competitors,<sup>47</sup> buttressing concerns about competitive harm and long-term risks to investment in research.

Finally, operating a system to receive and respond to data requests involves costs. Depending on the system that is adopted, these costs may include the expense of establishing a team of clinical and statistical experts to evaluate data requests, forming a legal team to draft and negotiate agreements regarding data use, monitoring of data requesters to ensure compliance with data-use conditions, and hiring of technical staff to set up databases and facilitate the use of data sets.

#### LEGAL AND REGULATORY IMPLICATIONS

Broader data sharing — particularly if mandatory — raises important legal and regulatory issues. First, requirements regarding the public disclosure of data and detailed regulatory filings may affect sponsors' ability to patent inventions. This problem arises even if disclosure requirements are limited to approved products, because marketing and patent approvals are staggered across different jurisdictions and sharing of data in one country can affect what happens in others. Moreover, disclosed data from approved products could still pose an obstacle to obtaining patents on further claims.

Patent law creates disincentives to make information about an investigational drug public early in development. Such publication could jeopardize patentability, because early disclosure may be considered "prior art" that could prevent companies from filing for patents on inventions. Premature publication can also trigger the initiation of the period of patent protection and data exclusivity that the inventor enjoys. A shorter exclusivity period after the product is marketed can result in decreased return on investments in research and development. Public disclosure may also arm competitors with information they could use to beat the disclosing

company to be first to file a patent application. Consequently, data-sharing requirements may spur sponsors to file patent applications earlier with less fully developed information and thus a higher risk of denial.

Second, expanding access to participant-level data increases the risk that already overburdened regulatory agencies may become inundated with additional data analyses and petitions for reconsideration of agency decisions. Competitors or advocacy groups could more easily challenge decisions to deny or restrict marketing licenses, for example. Regulators' decisions may be second-guessed with a fervor hitherto unknown, and over time this may profoundly affect agencies' operations and increase demands on their limited human and technology resources.

Many of the participants in this new information marketplace could contribute rigorous analyses and discoveries of sentinel importance. The histories of the drugs rofecoxib and rosiglitazone demonstrate this possibility, since analyses of summary-level data by expert academic scientists highlighted important safety concerns.<sup>11,37,39</sup> However, the need to evaluate the significance and strength of a barrage of external analyses could strain regulators' resources.<sup>48</sup> On the other hand, it may push regulators toward a "life cycle" approach to product approval that includes open, robust, ongoing monitoring of safety and effectiveness.<sup>38,39</sup>

#### CORE PRINCIPLES OF EXPANDED DATA SHARING

Any system that is ultimately adopted for expanded access to participant-level data should promote several core principles. It must provide sufficiently broad access to achieve the sought-after benefits for scientific innovation and public health that constitute the main justification for data sharing. Therefore, at a minimum, it should prospectively apply to trials of all approved prescription drugs, medical devices, and biologics. If there is sufficient protection of critical intellectual-property interests, it should apply to products approved in any country. Because poor-quality analyses can harm rather than advance public health, it must ensure responsible use of data. It must protect the privacy of research participants and treat all qualified data requesters and trial sponsors evenhandedly.

The system should also ensure accountability on the part of both data generators and requesters. Data requesters should commit to safeguarding the privacy of participants and to conducting analyses that meet accepted standards of scientific rigor and integrity. If the system permits data generators to influence when data are released, data generators should demonstrate their adherence to the letter and spirit of the sharing scheme.

Finally, the system must be practicable. It must respond to data requests in a timely manner, avoid undue burdens on those generating or requesting data, and accommodate the volume and diversity of clinical trials being conducted. It should minimize compliance costs by applying standards that are harmonized internationally.

These principles suggest some essential elements for a well-functioning system. To ensure accountability, access, and evenhandedness, some means of ensuring that all sponsors and investigators participate in data sharing in a manner that adheres to some minimum standards is desirable. Regulatory mandates could create a level playing field, although inconsistent regulations across jurisdictions could create substantial costs and loopholes that favor one group or another. In place of mandates, some sponsors and data generators would prefer voluntary commitments with mechanisms for accountability. Specificity about how data must be shared (including when and what types of information) can prevent underreporting, concealment, and incomplete or uninformative disclosures. Any data-sharing requirements that are adopted should apply to all trial sponsors, including academic, government, and not-for-profit entities.<sup>49</sup> Some effective mechanism must enforce compliance with conditions of data use, including participants' privacy. Whether voluntary initiatives can provide sufficient accountability, or whether regulatory imperatives will be needed, remains to be seen.

Transparency will help to ensure accountability on the part of data generators and users. Any system that allows data generators to make or influence data-release decisions case by case must limit discretion to deny legitimate research requests and require an explanation of the rationale for denials. Explicit, reasonable decision criteria should be applied, and the reasons for the decision in each case should be disclosed.

Although this is a point of contention, we

think that data requesters should be required to publicly disclose certain information, including the identity of persons accessing data, hypotheses to be explored, an analytical plan sufficient to understand the requester's ability to address the hypotheses, and the specific data that are needed. Requiring requesters to pre-commit to a rigorous analytical plan promotes adherence to sound scientific methods, enables whoever evaluates data requests to weigh the risks and benefits, and minimizes risks to participants by limiting releases to the minimum necessary data set. Data requesters should also be required to attest that they have the necessary scientific expertise to carry out the analyses and will not attempt to reidentify participants.

To facilitate responsible use of shared data, a system must require data generators to provide users with the information needed to understand and work with the data sets. Requiring collection and reporting of data with standardized field definitions and formats would help considerably,<sup>1,50</sup> but data generators should also provide database manuals, clinical study reports, analysis files, and other documentation necessary to address research questions, interpret data, and replicate analyses.<sup>51</sup> Even the most sophisticated users will probably need some level of direct technical support,<sup>1</sup> which could impose a considerable new workload on data generators.

Existing data-sharing initiatives have some of these elements but are limited to particular types of trials, sponsors, or journals and do not guarantee access to all necessary materials and technical support. Some do not require public disclosure of decisions about data requests or include a mechanism for enforcing conditions of data sharing. The current EMA and FDA proposals, too, lack some attributes of an optimal system, such as assessment of requesters' scientific expertise and analytical plans and general applicability to all data generators.

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TOWARD AN ETHICALLY SOUND  
DATA-SHARING SYSTEM

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What form might a more comprehensive data-sharing system take? At least four potential models are foreseeable (Table 2). In a pure open-access model, data sets and accompanying documentation could be freely downloaded. This would vigorously advance the principles of trans-

parency and broad access but at the cost of magnifying risks. In particular, an open-access model provides no way to ensure that analyses are consistent with accepted scientific methods or that the minimum necessary data set is released.

A more restrictive approach would be to retain custody of the data and have requesters submit research questions they would like answered. In this database-query model, the data holder — the trial sponsor or, perhaps, an intermediary — would construct and run the analyses for requests that are deemed to have scientific merit and return results to the requester. This model would be resource-intensive for data holders and could involve considerable wait times for requesters. Moreover, its lack of transparency would preclude requesters from verifying that the results they receive are based on valid analytical methods and complete data.

A third alternative is to release data but allow the trial sponsor to control decisions about data releases, with some mechanism for appeal and oversight. In this sponsor-review model, the sponsor’s discretion to deny requests could be bounded by requiring it to apply a specified set of criteria. These decisions could be appealed to an independent board. This model allows spon-

sors to resist attempts to conduct inappropriate or low-quality analyses. However, a system in which sponsors fully control data-release decisions may fail to quell public distrust.<sup>52,53</sup>

A fourth model would use an independent board, or “learned intermediary” entity, to evaluate data requests and impose and enforce conditions on use. The entity would be independent of the sponsor and research institutions that conducted the trials at issue, as well as the involved regulatory agencies. In addition to assessing the scientific soundness of each data request, the intermediary would confirm that requesters have expertise sufficient to conduct proposed analyses and determine whether public health benefits to be gained from the research outweigh likely adverse effects on data generators and research participants. Trial sponsors would have an opportunity to submit information concerning benefits and risks. The intermediary would ensure that only the minimum data necessary to answer the study question are released and obtain a data-use agreement from the requester. Existing initiatives demonstrate some aspects of the learned-intermediary approach.<sup>28,54,55</sup>

A key premise of the sponsor-review and

**Table 2. Four Possible Models for Expanded Access to Participant-Level Data.**

Variable	Open Access	Database Query	Sponsor Review	Learned Intermediary
Decision maker	None	Independent review board or trial sponsor	Trial sponsor	Independent review board
Process	Trial sponsor routinely posts data and supporting documentation when trial results are publicly reported or submitted to regulatory agency; researchers download the material	Requester submits a research query to the data holder, who then runs the query and returns results, not data	Trial sponsor reviews request, decides, and publicly documents rationale for the decision, which may be appealed to an independent board, whose decision is final	Board reviews request, collects input from trial sponsor, decides, and publicly documents rationale for decision
Criteria for releasing data	<i>Responsible-use attestation:</i> Full access as long as requester attests that data will not be used inappropriately (e.g., to reidentify research participants)	<i>Sound science:</i> Is there a reasonable scientific hypothesis, sound analytical plan, and adequate plan to disseminate findings? <i>Benefit–risk balancing:</i> Do the potential public health benefits of answering the proposed questions outweigh the probable adverse effects on the trial sponsor (e.g., intellectual-property interests, competitive concerns, technical-support burden) and the potential risks to research participants?	Same criteria for sound science and benefit–risk balancing as in database-query model <i>Expertise:</i> Does the research team have expertise sufficient to carry out the proposed analyses?	Same criteria as in sponsor-review model

learned-intermediary models is that the balance of benefits and risks of each data request should be assessed. This framework may seem an uneasy fit with a simple desire for complete data transparency. However, in some instances, transparency can do more harm than good, and a trustworthy process is needed to assess and modulate risk case by case.

Both trial sponsors and learned intermediaries would be well situated to ensure that data users comply with the conditions of data release. Their staff could manage the execution and monitoring of legally binding data-use agreements and enforce adherence. As needed, they could issue cease-and-desist letters, post public notices of violations and report them to data users' institutions and journals, demand return of the data, deny future data requests, and seek injunctions or money damages in court.

It would need to be determined how a learned-intermediary entity would be organized and financed, whether its decisions could be appealed, how its operation might be coordinated with voluntary data-sharing initiatives of sponsors, and how implementation would be phased and assessed. It seems likely that a consensus around these issues — and in favor of a system or systems embracing key aspects of the learned-intermediary model — could be reached among major stakeholders. Such systems promise to ensure accountability on the part of data generators and users and allow trial sponsors a voice while precluding them from denying access to data for reasons the public would not consider legitimate. They also appear to be practicable and advance the values of protecting research participants, evenhandedness, and avoiding undue restrictions on access to data.

As in other areas of health care, the push for greater transparency in the area of clinical trial data appears inexorable. The question is not whether, but how, these data should be broadly shared. The potential risks to research participants and trial sponsors must be thoughtfully addressed in the design of any new data-sharing system but need not block progress toward achieving the promise of “big data” in the clinical trials context.

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