Editor's Perspective

Sea Change in Open Science and Data Sharing

Leadership by Industry

Harlan M. Krumholz, MD, SM; Cary P. Gross, MD; Katrina L. Blount, PhD; Jessica D. Ritchie, MPH; Beth Hodshon, JD, MPH, RN; Richard Lehman, MRCGP; Joseph S. Ross, MD, MHS

With remarkable speed, the landscape of open science and data sharing is changing. Fueled by recent evidence that the results of many clinical trials of interventions in common use are never published or reported and that these studies are not missing at random, a persuasive argument has been made that all data from human trials should be available to inform clinical practice.1–4 This would also promote higher quality and higher integrity science, although some urge caution as a result of concerns about unintended adverse consequences.7

In response to these calls for action, some companies have stepped forward and demonstrated leadership. GlaxoSmithKline, in coordination with other companies such as Roche and ViVY, committed early to data sharing.8 Medtronic contracted with our research team, the Yale University Open Data Access Project,9 to conduct external reviews of its clinical trial data for a single product. In addition, we developed policies and procedures to share these data with other investigators. Importantly, Medtronic fully transferred the decision-making authority on how to share the data and who could receive the data to the Yale University Open Data Access Project. Janssen, the pharmaceutical companies of Johnson & Johnson, has now contracted to do the same for the trials under its auspices. Increasingly, other companies are announcing their intention to share data from all published and unpublished clinical trials.

On July 24, 2013, the European Federation of Pharmaceutical Industries and Associations and the Pharmaceutical Research and Manufacturers of America publicly announced the commitment of their member companies to share clinical trial data and results. Specifically, member companies would share patient-level clinical trial data, study-level clinical trial data, full clinical study reports, and protocols from clinical trials in patients for medicines approved in the United States and European Union with qualified scientific and medical researchers on request and subject to terms necessary to protect patient privacy and confidential commercial information.10 In addition, synopses of clinical study reports for clinical trials in patients submitted to the United States Food and Drug Administration, European Medicines Agency, or national authorities of European Union member states will be made publicly available on the approval of a new medicine or new indication. Pharmaceutical Research and Manufacturers of America and European Federation of Pharmaceutical Industries and Associations set a date of January 1, 2014, by which these commitments would be implemented.

It is now an appropriate time to review what these companies have announced and the current mechanisms for data sharing. Industry is developing new models for sharing and setting the pace for others involved in the clinical research enterprise, including public and nonprofit trial funders. Tables 1 and 2 represent a summary of the current data-sharing policies of the top 12 pharmaceutical companies, based on market capitalization.11 This information was obtained from the companies’ public Web sites and organized according to key domains. The data-sharing models continue to evolve in concert with ongoing discussion about the role of funding, the use of trusted intermediaries, the measures needed to protect privacy, and the approaches that are most likely to promote the responsible conduct of research.

It is clear that a sea change in concept and action has occurred, at least in industry. Scientists now have access to data that required billions of dollars to produce. Furthermore, the actions of these pharmaceutical companies are honoring the good faith of subjects who participated in scientific research, providing more opportunity to learn from the data that were generated while taking measures to ensure that the privacy of trial subjects is fully respected.

There is much still to do, and the challenges are considerable. Data sharing allows for replication of results and extension of knowledge from investments in creating data resources. It promotes the engagement of scientists in public dialogue about clinical studies and their interpretation. It is an impediment to fraud and has the potential to expose poorly conducted studies, although it also introduces the potential for false claims and increased litigation resulting from the work of inadequately skilled scientists. In addition, there are the ever-present concerns surrounding violations of subject privacy or abrogation of the spirit of their...
Table 1. Top 1 to 6 Pharmaceutical Companies, Ranked by 2013 Market Capitalization

<table>
<thead>
<tr>
<th>Data-Sharing Parameters</th>
<th>PhRMA EFPIA Guidelines</th>
<th>Janssen Pharmaceuticals</th>
<th>Pfizer</th>
<th>Novartis</th>
<th>Roche</th>
<th>Sanofi</th>
<th>Merck</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trial data available for sharing</td>
<td>• CSR synopses should be available</td>
<td>• Data from interventional trials for products and indications approved in both the EU and United States (older studies may be difficult to access)</td>
<td>• Global trials that ended after September 2007</td>
<td>• January 2014 to present</td>
<td>• January 1999 to present</td>
<td>• January 2014 to present</td>
<td>• September 2007 to present</td>
</tr>
<tr>
<td></td>
<td>• Requests for full CSRs, IPD, and study-level data should be considered</td>
<td>• Trials for which results are posted on ClinicalTrials.gov</td>
<td>• Phase II–III trials for new medicines or indications approved by the EU and US regulatory agencies</td>
<td>• Trials approved by EU and US regulatory agencies and accepted for publication</td>
<td>• Trials approved by EU and US regulatory agencies and accepted for publication</td>
<td>• Trials approved by EU and US regulatory agencies and accepted for publication</td>
<td>• Trials for which results are posted on ClinicalTrials.gov</td>
</tr>
<tr>
<td>Data not available for sharing</td>
<td>• Trials with possibility of reidentification (rare diseases, etc)</td>
<td>• ICF restrictions</td>
<td>• Legal restrictions to sharing, such as partnering agreements</td>
<td>• PhRMA EFPIA guidelines</td>
<td>• PhRMA EFPIA guidelines</td>
<td>• PhRMA EFPIA guidelines</td>
<td>• PhRMA EFPIA guidelines</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Undue resources required to share (i.e., older studies)</td>
<td>• Trials for which results are not posted on ClinicalTrials.gov</td>
<td>• PhRMA EFPIA guidelines</td>
<td>• PhRMA EFPIA guidelines</td>
</tr>
<tr>
<td>Types of data provided</td>
<td>• Clinical trial materials for medicines and indications approved in the United States and EU:</td>
<td>• Anonymous IPD</td>
<td>• Anonymous IPD</td>
<td>• Anonymous IPD</td>
<td>• Anonymous IPD</td>
<td>• Anonymous IPD</td>
<td>• Anonymous IPD</td>
</tr>
<tr>
<td></td>
<td>• Anonymized IPD</td>
<td>• Study-level clinical trial data</td>
<td>• Protocols</td>
<td>• CSR summaries (publicly available)</td>
<td>• CSR summaries (publicly available)</td>
<td>• CSR summaries (publicly available)</td>
<td>• Protocols and supporting documents</td>
</tr>
<tr>
<td>Availability of CRFs</td>
<td>NA</td>
<td>Blank CRF templates available</td>
<td>Blank CRF templates available</td>
<td>Blank CRF templates available</td>
<td>Blank CRF templates available</td>
<td>Blank CRF templates available</td>
<td>Blank CRF templates available</td>
</tr>
<tr>
<td>Data access fee</td>
<td>NA</td>
<td>None</td>
<td>None stated</td>
<td>None stated</td>
<td>None stated</td>
<td>None stated</td>
<td>None stated</td>
</tr>
<tr>
<td>Data application requirements of note</td>
<td>• Research proposal including hypothesis, data requested, and research rationale</td>
<td>• PhRMA EFPIA guidelines</td>
<td>• PhRMA EFPIA guidelines</td>
<td>• PhRMA EFPIA guidelines</td>
<td>• PhRMA EFPIA guidelines</td>
<td>• PhRMA EFPIA guidelines</td>
<td>• PhRMA EFPIA guidelines</td>
</tr>
<tr>
<td></td>
<td>• Plans for analysis, publication and posting</td>
<td>• Scientific purpose is clearly described</td>
<td>• Rigorous statistical analysis plan</td>
<td>• Biostatistician on research team</td>
<td>• Any use of the data by a third party must address a scientific question in the same disease as the original trial unless the informed consent expressly allows broader use</td>
<td>• Biostatistician on research team</td>
<td>• Biostatistician on research team</td>
</tr>
<tr>
<td></td>
<td>• Research team qualifications, experience, and any potential COIs</td>
<td>• Data requested will be used to create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health</td>
<td>• IRB documentation</td>
<td>• Detailed statistical analysis plan</td>
<td>• The names of 3 independent experts whom the independent review panel could consult regarding scientific merit, if requested</td>
<td>• CVs of all researchers</td>
<td>• CVs of all researchers</td>
</tr>
</tbody>
</table>

(Continued)
**Table 1. Continued**

<table>
<thead>
<tr>
<th>Data-Sharing Parameters</th>
<th>Janssen Pharmaceuticals</th>
<th>Pfizer</th>
<th>Novartis</th>
<th>Roche</th>
<th>Sanofi</th>
<th>Merck</th>
</tr>
</thead>
<tbody>
<tr>
<td>Request process</td>
<td>• Review process should include external scientists and healthcare professionals, with identity and existing relationships publicly posted</td>
<td>• All data requests go directly to the YODA Project, which reviews for scientific merit and makes final decision</td>
<td>• Internal Pfizer review committee reviews requests for data first</td>
<td>• Research proposals are checked by Novartis to make sure the information is complete and that they meet the requirements of this initiative and the sponsor’s requirements for informed consent. They are then sent to an Independent Review Panel* that performs a high-level scientific review including qualifications of researchers and biostatisticians, and the scientific rationale and relevance of the proposed research to medical science or patient care. Research may be asked for names of 3 independent experts to perform an additional review.</td>
<td>• Roche reviews requests for data first to determine status of the requested data.</td>
<td>• Independent Review Panel* reviews for scientific merit and value, among other considerations.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Janssen performs a due diligence assessment to determine its ability to make the data available to be shared externally</td>
<td>• Reviewers are publicly named</td>
<td>• They are then sent to an Independent Review Panel* that performs a high-level scientific review including qualifications of researchers and biostatisticians, and the scientific rationale and relevance of the proposed research to medical science or patient care. Research may be asked for names of 3 independent experts to perform an additional review.</td>
<td>• Reviewers are publicly named</td>
<td>• An internal Merck review committee reviews for feasibility, scientific validity of the request and the qualifications of the requesters.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Reviewers are publicly named</td>
<td>• Three of the 4 panel members are on the Pfizer external Biostatistics Advisory Panel</td>
<td>• Independent Review Panel* reviews for scientific merit, feasibility, and advancement of medical knowledge and public health.</td>
<td>• Reviewers are publicly named</td>
<td>• If there are questions regarding scientific validity, the request is forwarded to a non-Merck External Scientific Review Board (ESRB) for further review.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ESRB may also be asked for names of 3 independent experts to perform an additional review</td>
<td>• There is no appeal process</td>
<td>• Reviewers are publicly named</td>
<td>• ESRB members are publicly named</td>
<td></td>
</tr>
</tbody>
</table>

COI indicates conflict of interest; CRF, case report form; CSR, clinical study report; CV, curriculum vitae; EFPIA, European Federation of Pharmaceutical Industries and Associations; EU, European Union; ICF, informed consent form; IPD, individual patient-level data; IRB, institutional review board; PhRMA, Pharmaceutical Research and Manufacturers of America; and YODA, Yale University Open Data Access.

*Independent Review Panel is shared by ClinicalStudyDataRequest.com companies.

**Process for making CSR summaries publicly available is being developed.

†The YODA Project data request website is being developed. Those wishing to submit a request for Janssen data can visit http://www.clinicaltrialstudytransparency.com in the interim.

Informed consent. Other issues related to costs and who will bear them in the long-term are yet to be resolved. The goal of data release ought to be to enhance the likelihood of the benefits and minimize the possibility of the harms—and for the approach to be sustainable and the conditions favorable for attracting scientists to make use of the data. Such issues are being widely discussed in forums such as a focused workgroup of the Institute of Medicine that includes a broad range of stakeholders.

Academia, outside of the basic sciences, remains far from a consensus on data sharing. Findings from many studies are never published or are published after long delays, including a high proportion of those funded by the National Institutes of Health. Trial results often go unreported on ClinicalTrials.gov. Although there are obstacles to be overcome in the academic environment, including funding, academic credit, and privacy issues, the current situation is untenable. It is time for academia to meet the standards that are being established by industry.

For now, scientists worldwide are encouraged to use these data that are being disseminated by industry—data that have the potential to be an unprecedented resource. These data are being made available to facilitate the development and testing of new hypotheses, to confirm or refute existing beliefs, and to advance knowledge in an effort to improve patient outcomes and public health. The success of data-sharing initiatives should be measured not by how many databases are made available but by how much useful knowledge is efficiently produced through their use and whether health and health care are improved as a result. The summary of policies presented here demonstrates that leaders in industry have overcome significant challenges to take the first critical steps toward changing the culture of science.
Table 2. Top 7 to 12 Pharmaceutical Companies, Ranked by 2013 Market Capitalization

<table>
<thead>
<tr>
<th>Data-Sharing Parameters</th>
<th>GlaxoSmithKline</th>
<th>Bayer</th>
<th>Bristol-Myers Squibb</th>
<th>AbbVie</th>
<th>Eli Lilly</th>
<th>AstraZeneca</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trial data available for sharing</td>
<td>• CSRs synopses should be available</td>
<td>• January 2014 to present</td>
<td>• All global interventional clinical studies</td>
<td>• January 2008 to present</td>
<td>• All data for medicines and indications approved in the United States and the EU</td>
<td>• Interventional clinical studies for approved indications of medicines on the market in the United States and EU</td>
</tr>
<tr>
<td>Types of data provided</td>
<td>• Anonymized IPD</td>
<td>• Anonymized IPD</td>
<td>• IPD</td>
<td>• Anonymized IPD</td>
<td>• IPD</td>
<td>• Not stated</td>
</tr>
<tr>
<td>Availability of CRFs</td>
<td>• Blank CRF templates available</td>
<td>• Blank CRF templates available</td>
<td>• Not stated</td>
<td>• Not stated</td>
<td>• Not stated</td>
<td>• Not stated</td>
</tr>
<tr>
<td>Data access fee</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Data application requirements of note</td>
<td>• None stated</td>
<td>• None stated</td>
<td>• None stated</td>
<td>• None stated</td>
<td>• None stated</td>
<td>• None stated</td>
</tr>
</tbody>
</table>

(Continued)
Table 2. Continued

<table>
<thead>
<tr>
<th>Data-Sharing Parameters</th>
<th>PhRMA EFPIA Guidelines10</th>
<th>GlaxoSmithKline</th>
<th>Bayer</th>
<th>Bristol-Myers Squibb</th>
<th>AbbVie</th>
<th>Eli Lilly</th>
<th>AstraZeneca</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data request review process</td>
<td>- Review process should include external scientists and healthcare professionals, with identity and existing relationships publicly posted</td>
<td>• Research proposals are reviewed by GSK to determine technical feasibility, make sure the information is complete, and that they meet the requirements of this initiative and the sponsor’s requirements for informed consent</td>
<td>• Research proposals are reviewed by Bayer to determine technical feasibility, make sure the information is complete, and that they meet the requirements of this initiative and the sponsor’s requirements for informed consent</td>
<td>• All requests are reviewed internally by a qualified panel of Bristol-Myers Squibb experts and then passed to an Independent Review Committee (IRC) of external experts for review and final decision</td>
<td>• All requests managed by AbbVie, who may either grant or deny a request after reviewing the requestor’s proposal</td>
<td>• Researcher first completes a request for availability of clinical study data form</td>
<td>• AstraZeneca considers requests for patient level data from other parties on a case-by-case basis, following consistent criteria to establish if and how the information provided will be used for valid scientific purposes and to benefit patients</td>
</tr>
</tbody>
</table>

C0I indicates conflict of interest; CRF, case report form; CSR, clinical study report; CV, curriculum vitae; DUA, data use agreement; EFPIA, European Federation of Pharmaceutical Industries and Associations; EU, European Union; GSK, GlaxoSmithKline; ICF, informed consent form; IPD, individual patient-level data; IRB, institutional review board; and PhRMA, Pharmaceutical Research and Manufacturers of America.

*Independent Review Panel is shared by ClinicalStudyDataRequest.com companies.

Sources of Funding

This work was supported by grant U01 HL105270-04 (Center for Cardiovascular Outcomes Research at Yale University) from the National Heart, Lung, and Blood Institute. Dr. Ross is supported by grants K08 AG032886 and K08 AG038336 from the National Institute on Aging and by the American Federation for Aging Research through the Paul B. Beeson Career Development Award Program.

Disclosures

H.M. Krumholz, C.P. Gross, K.L. Blount, J.D. Ritchie, B. Hodshon, R. Lehman, and J.S. Ross disclose that they are recipients of research grants from Medtronic and Johnson & Johnson, through Yale University, to develop methods of clinical trial data sharing. H.M. Krumholz discloses that he chairs a cardiac scientific advisory board for UnitedHealth, and J.S. Ross discloses that he is a member of a scientific advisory board for FAIR Health.

References

Sea Change in Open Science and Data Sharing: Leadership by Industry
Harlan M. Krumholz, Cary P. Gross, Katrina L. Blount, Jessica D. Ritchie, Beth Hodshon,
Richard Lehman and Joseph S. Ross

Circ Cardiovasc Qual Outcomes. published online June 2, 2014;
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272
Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7705. Online ISSN: 1941-7713

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circoutcomes.ahajournals.org/content/early/2014/06/02/CIRCOUTCOMES.114.001166.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Circulation: Cardiovascular Quality and Outcomes can be obtained via RightsLink, a service of the
Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for
which permission is being requested is located, click Request Permissions in the middle column of the Web
page under Services. Further information about this process is available in the Permissions and Rights
Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Quality and Outcomes is online
at:
http://circoutcomes.ahajournals.org//subscriptions/