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How Transparency is Changing the Way an Entire Industry Thinks about Data

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ABSTRACT

Clinical trial data transparency implementations have been moving at extraordinary speed throughout the industry, with almost 10 top tier biopharmaceutical companies at some stage of implementation as of April 2014. Decisions to implement transparency systems were initially guided by proposed EMA regulations, and are now proceeding under their own momentum as biopharmaceutical companies strive to show that they have nothing to hide regarding their clinical research programs. Additionally, many of the companies that have launched their corporate transparency implementations are going one giant step further, and offering independent researchers the opportunity to readily investigate clinical trials data that spans multiple manufacturers. Fewer than 18 months ago, most biopharmaceutical companies viewed their clinical trial data as strictly proprietary. Today, these companies are actively enabling independent researchers to explore the trial data directly. During this session, you'll learn more about this important industry initiative, and how your organization can support its success.

INTRODUCTION

In early 2013, virtually every biopharmaceutical company, CRO and anyone involved with clinical trials viewed patient-level clinical trial data as information to be shielded from anyone outside of the sponsoring organization, except as a formal part of the regulatory approval process. Some clinical trial content was being shared through *clinicaltrials.gov* and similar sites, but this information was only at an aggregate level – summary results, synopses, etc. Patient-level clinical trial data was not even part of this discussion.

By mid-2014, that viewpoint had been turned upside-down. If biopharmaceutical companies were not already sharing clinical trial data outside their organization, they had agreed to it and were working out the details, or they were considering it at the executive level within the organization. As if that wasn't staggering enough for an industry typically perceived as hyperconservative with regard to changing business practices and technology, a critical subset of these companies had additionally agreed to support the pooling of clinical trial data across multiple biopharmaceutical companies. While there have certainly been obstacles to overcome, the momentum to share data continues. Those companies that have not yet announced plans to share their clinical trial data are feeling mounting pressure to participate in this process, and are struggling to find reasons to abstain.

BRAVE NEW WORLD

The dramatic change regarding patient-level data sharing was driven by several related factors. In June 2013, the European Medicines Agency (EMA) released a policy document titled "*Publication and access to clinical-trial data*"[1]. This document explained that the EMA intended to create a mechanism whereby patient-level clinical trial data would be made available to interested parties not directly affiliated with the biopharmaceutical manufacturer. As initially published, the document did not make any significant statement regarding controls around this patient-level data, and certainly created the impression among manufacturers that very limited controls would be provided. In effect, the patient-level clinical trial data would be publicly available.

Shortly after the EMA policy document was published, the Pharmaceutical Research and Manufacturers of America (PhRMA) and the European Federation of Pharmaceutical Industries and Associations (EFPIA) brought together leaders from their respective member organizations and drafted a set of principles to address the proposed EMA policy. The "*Principles for Responsible Clinical Trial Data Sharing*" [2] was published in July 2013 – just one month after the EMA's policy document.

The joint PhRMA/EFPIA *Principles* document described the means by which the biopharmaceutical industry intended to enable the sharing of patient-level clinical trial data. While it didn't directly conflict or compete with the EMA policy document, it appeared to be clearly intended to describe similar data sharing goals, but managing the data sharing process via tighter controls.

Under the EMA policy document, patient-level data was going to effectively be available to anyone. The PhRMA/EFPIA document simply took a more managed approach, describing how interested parties could apply for access to patient-level data in order to address specific research interests. The publication of the *Principles* document enabled the biopharmaceutical industry to, in effect, support the EMA policy but under its own terms.

At about the same time, GlaxoSmithKline was in the process of implementing a patient-level data sharing solution. The decision to implement such a system was made by GlaxoSmithKline months before the publication of the EMA's policy and the PhRMA/EFPIA *Principles* documents, and the implementation was well under way. GlaxoSmithKline was thus able to prove out industry's ability to support the PhRMA/EFPIA principles associated with this emerging initiative.

The convergence of these three events triggered an industry-wide launch into the brave new world of patient-level clinical trial data transparency. Beginning in the late summer of 2013, interest in patient-level data transparency grew exponentially. A series of data transparency calls were held between leading biopharmaceutical executives, face-to-face cross-company meetings were hastily organized and, before long, additional companies beyond GlaxoSmithKline were making announcements about their

[1] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/06/WC500144730.pdf

[2] http://phrma.org/sites/default/files/pdf/PhRMAPrinciplesForResponsibleClinicalTrialDataSharing.pdf

commitment to the patient-level data sharing initiative. Mainstream media publications like Forbes, the New York Times and the Wall Street Journal were publishing articles about the initiative, as were medical publishers, like the New England Journal of Medicine.

By April 2014, more than 10 top biopharmaceutical manufacturers had publicly announced their commitment to sharing patient-level clinical trial data, and virtually all biopharmaceutical manufacturers had put together internal teams to investigate this further.

THE COMMON APPROACH

The other early adopter biopharmaceutical manufacturers recognized the value in addressing patient-level clinical trial data through a common methodology, and built upon GlaxoSmithKline's initial approach. This approach, depicted in Figure 1, relies upon a series of interdependent applications and business processes.

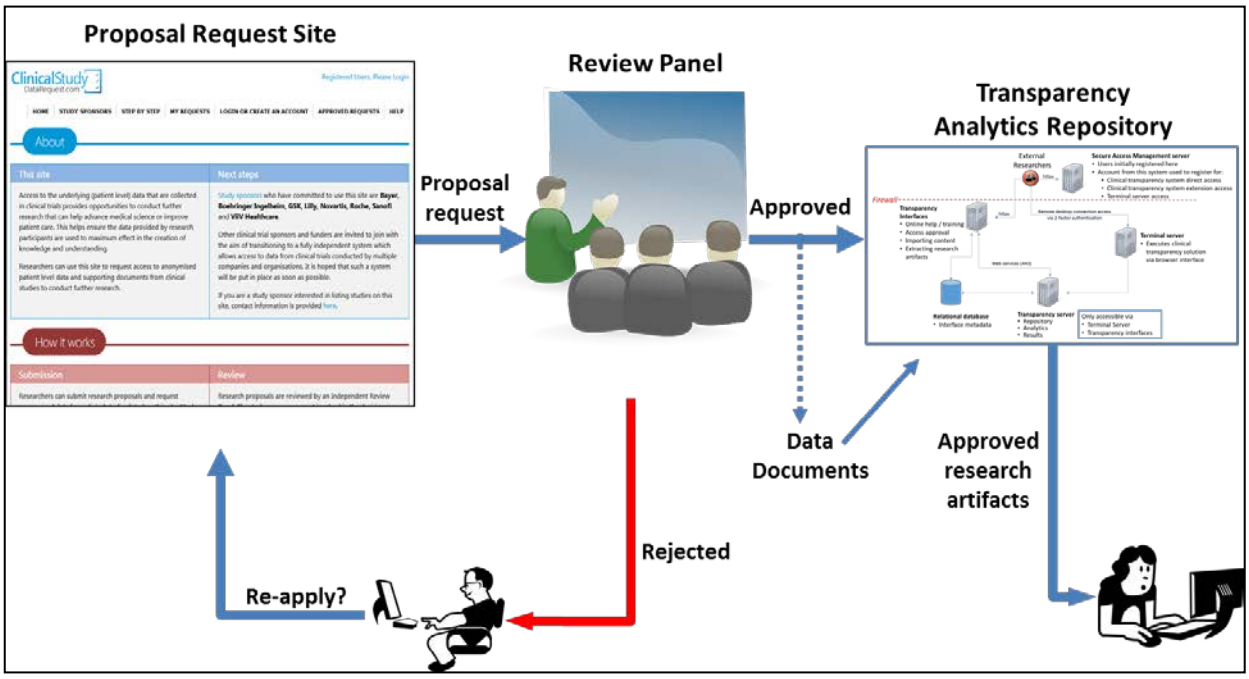


Figure 1. Common business process flow for transparency systems

PROPOSAL REQUESTS

Requests from researchers to gain access to the patient-level data are managed through a request site. From this site, a potential researcher can provide contact information, research credentials, the trial or trials for which data access is being requested, as well as the planned intent of the analyses associated with the request. Depending upon the manufacturer, the request site may be populated with all of the trials available for access, or it may be populated with a combination of those trials for which data is available as well as other trials for which data could be made available.

There is a significant effort involved in identifying what trials will be included within the overall transparency system and making that data available. Manufacturers are taking varied approaches in this regard. Some, for example, are including trials dating back to 1999 or even earlier. Others are including trials only on a go-forward basis. These decisions are based upon the need for the manufacturer to balance a series of complex issues:

- Informed consent. Many manufacturers believe that a patient provides consent to a clinical trial for a particular purpose. If they haven't consented to making their data available on a broader basis, it may not be appropriate for it to be shared. Other manufacturers take a more liberal view of informed consent, and believe that the patient is consenting to have their data applied to a certain field of research. Regardless of their interpretation of the consent rules associated with historic trials, most biopharmaceutical companies are modifying their informed consent forms to support the sharing of a patient's data beyond a single clinical trial.

- Locating data. For older trials, patient-level data may be stored offsite, in archives, or on media and/or devices that are not readily accessible.

- Data structure. Modern clinical trial data is typically structured to align with the CDISC SDTM and/or ADaM standards, but older data is likely to follow a corporate standard or no standard at all. Manufacturers must balance the time and effort to provide data "as is" versus standardizing the data.

- Competing corporate priorities. While providing data for transparency initiatives is certainly important, it is, in many ways, a diversion of resources that may need to be targeted on prospective drug development activities. In this era of leaner corporate staffs, the individuals most qualified to prepare data for transparency may be committed to other projects.

REVIEW PANEL

The review panel is responsible for determining whether to accept or reject the proposed research project. In general, most manufacturers are staffing the review panel with members independent from their organization. In some cases, their panel is composed of a group of individual scientists, while in others, a more structured organization such as Yale University Open Data Access (YODA) is being used. Regardless of how the review panel is staffed, the goals of the review panel are fairly clear. They are to provide an unbiased assessment regarding whether to approve or reject the research proposal. Reasons for rejection may include the fact that the data available is not appropriate to answer the research question, or the researcher's credentials may not align with the research request. There have also been discussions as to whether a research proposal should be rejected if it is put forth by a biopharmaceutical competitor.

The long-term composition of the various review panels will ultimately need to be addressed via a sustainable model. It is unlikely that different review panels for the same therapeutic indication, but

sponsored by multiple manufactures, can be sustained. More likely, review panels that support a specific therapeutic area across multiple manufacturers will emerge over time.

TRANSPARENCY ANALYTICS REPOSITORY

After having their research proposal approved, the researcher(s) are given access to an application that not only houses that data available for review, but the analytical tools to conduct that research. The data is typically de-identified before it is made available to the researcher. That is, the data has been modified to prevent a researcher from linking an individual patient record back to an actual named patient. De-identification is an emerging process within the industry, and requires adherence to a variety of governing rules around the world. Examples of published de-identification rules include changing PatientID numbers, converting all dates to new dates while maintaining the relative timeliness of the corresponding records, or redacting "sensitive terms" such as "HIV" or "Mental Illness" from the available data.

From an analytical tool perspective, SAS and R have typically been provided as part of the analytics repository, although there is the potential to include other tools as necessary. Critically, the researcher only has access to the data inside the application. It cannot be readily extracted from the system for any reason. This restriction is in place by design, and is intended to limit research access to only the approved research team.

The repository is also designed to manage the ability to extract analysis results and artifacts from the system. While the intent is to not prevent researchers from extracting the results, the management of the extraction process creates several benefits for the manufacturer:

- The manufacturer can review the researcher's results with the researcher to ensure the proper data fields, data sets and analytic methodologies have been used. In general, the researcher is likely to be naïve to the research data structure, and may not make the same data choices as the manufacturer did when forming their analysis.

- In cases where the researcher's results contradict the manufacturer's published or submitted results, both parties can discuss their methodologies to ensure the correct approaches have been taken. Additionally, the manufacturer will then have some opportunity to prepare to answer questions from shareholders, as well as the patient and healthcare communities, regarding differences in the results.

The process for extracting analysis results and artifacts from the system is not to be viewed as an obstacle. It is designed to ensure the accuracy and quality of the results being extracted. The researcher will ultimately be permitted to extract their work regardless of their findings.

ANALYSES ACROSS TRIALS FROM MULTIPLE MANUFACTURERS

Biopharmaceutical companies have surprised many audiences with not only their willingness to begin sharing patient-level data, but with the remarkable speed in which such sharing decisions and implementations have occurred. More surprising to many is the biopharmaceutical companies' interest in enabling researchers to conduct research projects using data from multiple manufacturers.

Many manufacturers are already using a common proposal request application[3] as shown in Figure 2. From this site, a researcher can request data from an individual manufacturer, or from multiple manufacturers (depending upon the formal agreements that are in place between manufacturers). These multiple manufacturer requests add a significant layer of complexity to the research request, as the data is unlikely to be in a common structure across manufacturers. The emergence of the CDISC standards will help in that regard, but many trials included in the proposal request system are not likely to initially be available as CDISC-structured data. And, even those that are, will have been subjected to each company's interpretation of the CDISC standards. Additionally, it will be important to implement de-identification rules consistently across all trial data that is being analyzed together. De-identifying multiple studies with different rules may create subsequent difficulties in reliably analyzing the pooled research data.

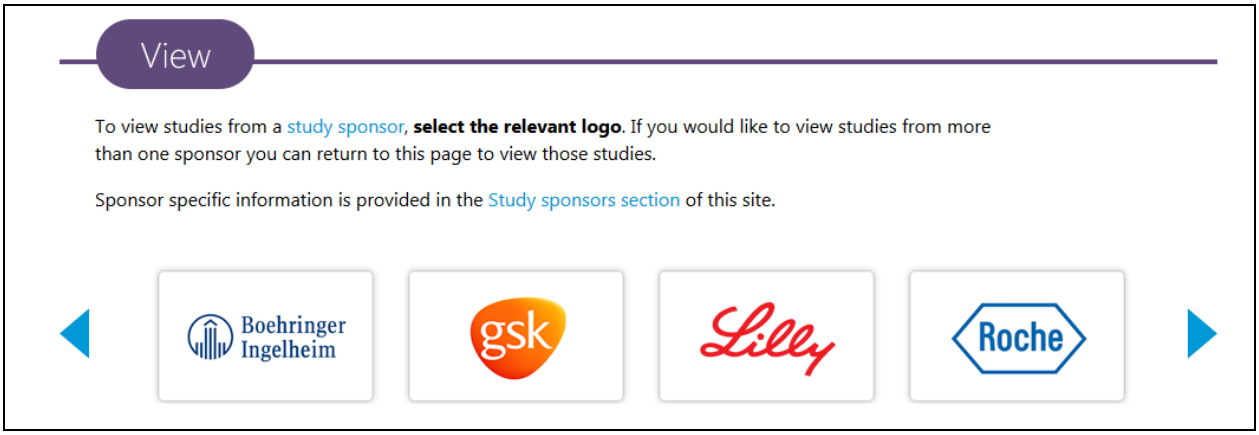


Figure 2. Cross-Manufacturer proposal request application

CONCLUSION

The rise of patient-level clinical trial data transparency interest has been swift, and the speed with which transparency solutions have been implemented has been extraordinary. Multiple top biopharmaceutical companies already have live transparency solutions and processes in place just 12 short months after the initial buzz regarding transparency started to build. There is still much work to be done, however, from both a regulatory and manufacturing perspective.

Since the EMA's initial policy document was drafted, thousands of comments on the document were received, and the EMA has delayed issuing a final version of the policy. The most recent scheduled date of July 2014 has been pushed to the fall of 2014, and, as of the writing of this document, there is rumor

[3] https://clinicalstudydatarequest.com/

that a decision will be pushed further still into 2015. The content of that final document will greatly influence the next steps for biopharmaceutical companies. If the EMA dials back its initial intentions regarding the public availability of clinical trial data, and is satisfied that the manufactures are on the right path, the capabilities associated with existing transparency solutions will need to evolve to match the needs of the researchers and manufacturers. If, on the other hand, the EMA decides that the biopharmaceutical companies are not doing enough to support the ideas behind patient-level data sharing, it may be back to the drawing board as industry works to meet the regulators' expectations.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

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