

Data Quality and the FDA

See DQRI's website for information on:

- New Projects
- Sponsorship Opportunities
- Recent talks
- Upcoming Events

www.dqri.org

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Regulatory Authority
 FDA has a broad public protection mission to ensure the safe use of regulated products that are themselves safe and efficacious. To accomplish this mission the FDA makes decisions on product applications and labeling based on complete and accurate information from well-designed, ethically-conducted, and well-monitored clinical research.

ICH E6 2.10 and 13 state that "All clinical trial information should be recorded, handled,

and stored in a way that allows its accurate reporting, interpretation, and verification" and "systems with procedures that assure the quality of every aspect of the trial should be implemented". In 5.1.1 quality of data is addressed as follows "the sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported

in compliance with the protocol, GCP, and the applicable regulatory requirement(s)." E9 further states that timely and reliable processes for recording data and rectifying errors and omissions are required.

Background

Issues and components of data quality in clinical trials research are of interest to all those involved in biopharmaceutical research. These have been discussed and addressed in various forums for the past two decades. The

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Recent Activity in DQRI

Within the first quarter of 2007, DQRI plans to refocus its efforts, initiating additional projects and securing sufficient resources to permit its continued operation. While two of its projects have made progress, over the course of the past year DQRI activities have been fairly low-key. It has presented at several meetings on

topics related to data quality, however the initiation of new projects has been slow. In response to this, DQRI is reassessing its approach, structure and resourcing, and is redesigning its early phase project methodology. DQRI thanks you for your patience as this process proceeds.

Have a pet peeve about quality?

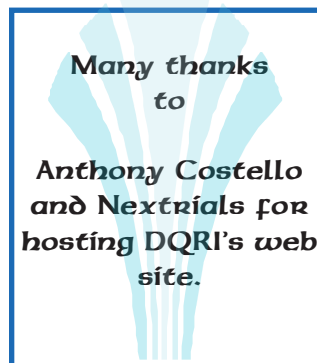
Suggest a project!

Go to

www.dqri.org

and click on Projects then

Propose a Project!



Many thanks to

Anthony Costello and Nextrials for hosting DQRI's web site.



Data Quality and the FDA (cont.)

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1988 Format and Content of the Clinical and Statistical Sections of an Application was the source of guidance concerning clinical trials data for many years. The 1997 IT Day at the DIA Annual meeting in Montreal laid the foundation for defining data quality in Information Technology terms. In 1998 the industry began focusing on standards with the advent of CDISC and the SCDM GCDMP. The 1999 IOM Workshop on Data Quality and the resulting paper reintroduced the more theoretical approach. By 2002 CDISC was established as a 501(c)3 non-profit organization and version 1 of the GCDMP published. Both of these efforts have moved forward resulting in the recognition by 2005 of the importance of issues of data quality by both regulatory agencies and clinical practice leadership. Clinical data quality in the regulatory setting is addressed by BIMO.

FDA Announces New Initiative to Modernize the Regulation of Clinical Trials and Bioresearch Monitoring

In December 2004 the FDA began working on a series of new policy and regulatory developments to strengthen the Agency's oversight and protection of patients in clinical trials and the integrity of resulting data in an effort

to modernize the agency's approach to bioresearch monitoring. On November 4, 2005 Dr. Janet Woodcock, Deputy Commissioner for Operations, Food and Drug Administration announced the FDA's New Bioresearch Monitoring Initiative at the FDA Science Board meetings. "As clinical trials continue to evolve, in particular becoming increasingly large, decentralized and global, the FDA's approach to bioresearch monitoring and human subject



protection must also evolve and modernize," said Janet Woodcock, at the 2005 Drug Information Association annual meeting.

Janet Woodcock, M.D., Chairs the steering committee and Rachel Behrman, M.D. is the scientific lead with Terrie Crescenzi the Project Manager. Representatives

from the Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), Center for Food, Safety, and Nutrition (CFSAN), Center for Veterinary Medicine (CVM), Office of Regulatory Affairs (ORA), and the Office of the Commissioner (OC) are included on the committee. Dr. Janet Woodcock issued a call for more research and a greater emphasis on data quality and efficiency in clinical research stating that "we need consensus on the definition of high quality data". She further stated that "BIMO is responsible for Protect human subjects in trials of FDA-regulated products and Ensuring high-quality and integrity of data used to: Support marketing applications, Support regulatory decision making, and Provide evidence base for clinical use of regulated products". Recognizing DQRI representatives in the audience, Dr. Woodcock further stated that "we need data integrity in the data from large clinical trials and . . . (the DQRI) is working on ways to assess the quality."

With the formation of the Agency-wide steering committee on Human Safety and Bioresearch Monitoring in 2005, the need for research into methods to build data

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Data Quality and the FDA (cont.)

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quality into the research process was acknowledged. In the first presentation to this committee in the fall of 2005, Kaye outlined the state of the understanding of data quality, the progress that has been made in this arena in the recent past and an agenda for research needed. Now that CDISC has made progress in developing transfer and content standards for clinical trials research data and the SCDM GCDMP Committed has made significant progress in developing process standards for Clinical Data Management, the research needed to further define and assess

data quality is possible. It is important to continue to assess these standards and their contribution to data quality since it is understood that consistently inappropriate standards can produce poor data quality.

Current issues in clinical trials data quality include establishing a common definition of data quality, developing Methods to assess this quality, and an Assessment of current system for data quality, and incorporating Continuous improvement processes in the data quality assessments. High quality in clinical trials research data is required to support the integrity of the entire clinical research enterprise.

FDA needs better methods to evaluate level of data quality problems across all studies/development programs. It is likely that a risk management approach will be incorporated into these methods along with the QA procedures currently in use. Given the large number of resources expended on ensuring data quality the overall system needs to be explicitly examined.

DQRI Role

Working with Industry, Academia, and the FDA, the DQRI research agenda

is coordinated to support the work of this steering committee to define how each aspect of the overall system impacts the quality of the data upon which decisions are based, to identify the critical control points where the quality if data are impacted, to develop methods to assess and improve the quality of these data. The Data Quality Research Institute serves as the catalyst promoting the collaboration to advance the quality of clinical data and develop the world of data quality moving forward by providing an international scientific forum for academia, health care providers, industry, government, and other stakeholders to provide research, education, and documentation to support the achievement of the best results.



DQRI Project Update

A Critical Examination of Database Audits

The DQRI project team participating in “A Critical Examination of Database Audits” have been making good progress toward their goal of establishing the usefulness and applicability of traditional database audits in paper and EDC environments. To date, several of the project objectives have been achieved. A summary of their findings to date follows.

- Defined the terms “database audit” and “error” in the context of this project
- Compiled a bibliography of published references
- Created typical maps for paper and EDC processes identifying the points where the introduction of error is most likely

- Developed a rationale for determining the goals of an audit, including defining the types of samples that are appropriate for different types of audits (e.g., sampling an entire database will not identify data management process errors)
- Defined the appropriate “source” and “target” data for an audit, identifying where gaps currently exist

Subteams are currently completing the tasks of developing an approach for sampling critical vs non-critical data (and the definitions thereof), and defining how to address threats to the perceived clinical vs statistical credibility of the database in which some errors remain. Once these deliverables have been completed, the team will develop the rules for drawing audit

samples, and the statistical tools for assessing the corresponding error rates.

Following these final activities, the entire project will be synthesized, and a white paper will be produced that outlines a recommended approach to database audits, along with tools and guidelines that will step the user through the process, from defining the audit goals and strategy to calculating and interpreting the results. This white paper will provide the insights to allow each organization to determine how to apply the tools in a way that fits their corporate culture. Results to date, presentations delivered, and a list of team members can all be found on the DQRI website, www.dqri.org, under Projects, on the Database Audits page.



New DQRI Data Quality Project: Detecting Fraud in Your Data

Ensuring the integrity and comparability of clinical data drives a significant amount of activity in the clinical trials endeavor. Techniques for identifying out-of-range and inconsistent data errors are well-established, and are in place in most organizations, and are generally detected using within-subject checks. Other types of issues, such as site bias, consistent data recording misunderstandings and fraud, are not as easily detected. To address these latter concerns, running aggregate cross-subject, cross-site and cross-time checks can identify patterns that may indicate

data integrity problems. Some of these checks are a standard part of statistical analyses, but by the time the analyses are run, it may be too late to salvage the data.

There are several different types of data examination techniques that could be of use, a few of which include:

- Looking for outliers within and/or across sites
- Identifying sites that have too much (or too little) variability in given data points
- Continuous measures (such as blood pressures) that end in consistent numbers (such as 0 or 5)

Detecting Fraud (cont.)

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- Efficacy parameters that appear very different at one site
- Data that seem too clean
- Too few AEs or concomitant medications as compared to other sites

A few organizations already utilize this approach, but the majority do not, and there is currently no generally available recommended list of checks nor tools to use. This project will create a



catalogue of these techniques, including examples, pseudo-code, and possible causes for unusual values. The project will also define a decision-making approach for determining what techniques to apply in what situations, and how to determine when findings are significant enough to warrant action.

The project is expected to progress relatively quickly, and will result in the catalogue and an associated white paper, and may include opportunities to participate in the publication and presentation of the results. The commitment will consist of attending a two-hour telecon-

ference every other week, and between 2 and 3 hours of work outside of the telecons.

DQRI is seeking volunteers for this project. The ideal team will consist of individuals with a variety of backgrounds, including statistics, programming, data management, quality assurance, monitoring, clinical, and site management. There is particular interest in leveraging the new kinds of metadata available from EDC and eDiary applications in this field. If you are interested in participating or co-leading the project, please contact Kit Howard at khoward@dqri.org.



Participating in DQRI Projects

DQRI achieves its goals by sponsoring research projects that seek to define aspects of data quality in clinical research. Rather than driving the results, it seeks to promote open collaboration between interested individuals and organizations, drawing expertise from the clinical research community and making the results freely available to all. Projects range from large to small, and long-term to rapid. The individuals who participate are volunteers who work with a DQRI representative to define, conduct and summarize the research questions. Each project team is comprised of several roles, with responsibilities as follows:

- **Team lead:** one or more individuals who take ownership of the project, tracking the progress, ensuring telecons happen and the project goals are achieved. This role is expected to facilitate discussions rather than provide answers
- **Team support:** a team participant who ensures the agendas are sent out, and takes and distributes notes from each meeting, in effect the project archivist
- **Team participants:** the individuals who attend the telecons, do the external tasks, and contribute their expertise to achieving the project results
- **DQRI liaison:** an individual on the team who acts as the link to DQRI, providing updates

to and guidance from the organization.

On the DQRI website there is a list of potential projects. Any project can be initiated by a motivated leader/facilitator with enthusiasm for the topic and a desire to research the question. DQRI can help with identifying additional team participants, defining the project goals, and producing and disseminating the results. Additional resources may be available, depending upon the nature of the requirements. Please consider participating - it is an opportunity to make a real difference in our field.



“I have offended God and man because my work didn’t reach the quality it should have.” Leonardo da Vinci, on his deathbed



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The **Data Quality Research Institute (DQRI)** is a non-profit organization that provides an international scientific forum for academia, health care providers, industry, government and other stakeholders to research and develop the science of quality as it applies to clinical research data.

DQRI is run through an Operating Board drawn from industry, academia, regulatory agencies and support services. The Institute also has been assigned an FDA liaison, Dr. Steve Wilson.

DQRI Projects Seek Funding

In addition to DQRI’s on-going activities, there are a number of projects that are seeking funding. These include:

- Assessing and improving data quality in patient data repositories
- Developing statistical tools for defining and measuring data quality
- Data quality assessment in pediatric process improvement projects
- Defining the nomenclature of data quality

Any organization interested in the results of any of these initiatives and willing to provide funding is urged to contact DQRI. In addition, DQRI is always open to proposals for quality projects that are in alignment with its goals. 