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In the next issue of  
**EDC Today:**

EDC and Data Entry  
Systems: What  
Systems Developers  
Really Need to Know

## EDC's Impact on Clinical Data Management: Metrics, Best Practices, and Decision Making

*Welcome to our sixth issue! EDC Today is an independent publication on current information and issues in Electronic Data Capture (EDC) strategies and technologies for the Biotechnology and Pharmaceutical (biopharma) industry. Each month we examine topic areas related to EDC theory, technology, practice, or implementation.*

*Continuous quality improvement is an important business goal for biopharma companies. Our sixth issue details the various tools (i.e., metrics) used to evaluate quality, monitor performance, and track process improvement in the pharmaceutical industry. We also provide an overview of how EDC improves both processes and process monitoring.*

Average development costs for a new drug were \$30,000 per day in 2000 and rising by 10% to 12% every year.<sup>1</sup> With development cycle times ranging from about 3 to more than 12 years, the financial consequences of even minor delays can be significant. Given research that shows each day of delay to market can cost from \$1 to \$13 million in sales, the ability for a company to achieve reliable, consistent results is crucial to the organization's effectiveness. Consistent results are best achieved through rigorous quality control.

With increased pressure to improve quality control, biopharma companies are expanding their definition of quality and beginning to look at data management criteria from perspectives established in other industries. The American Society for Quality (ASQ) defines this broader view of quality (Table 1).

Two of the most highly regarded quality methodologies in use today have sprung from the automotive industry. The first is the Taguchi Method, which helped the Japanese auto industry to thrive in the 1970s and 1980s. Sometimes referred to as Robust Design, the Taguchi Method involves a system of experimental functions focused on improving fundamental functions of the product or process, thereby facilitating flexible designs and concurrent engineering. The Taguchi Method defines "expensive" as deviations from ideal rather than exceeded threshold limit or maximum/minimum values. The idea is to reduce "scrap" to arbitrarily low levels, rather than performing no corrective actions until "batches" exceed tolerable margins of deviations from ideal. The Taguchi Method is widely regarded as the most powerful method available to reduce product cost, improve quality, and simultaneously reduce development interval.<sup>2</sup>

Six Sigma is another quality methodology recognized as a powerful business process innovator. Named for a statistical measure of negligible error, (six standard deviations from the mean in a control chart) Six Sigma is a term used to indicate that a business process is well controlled. By focusing on increasing performance and decreasing variation within processes, the methodology leads to reductions in defects and improvements in profits and product quality. Six Sigma is usually associated with Motorola, which named one of its key operational initiatives Six Sigma Quality.<sup>2</sup>

**About EDC Management:**

EDC Management was founded to assist biopharma companies plan, prepare for and implement Electronic Data Capture (EDC) strategies according to their data management goals and objectives. We do not sell or endorse any specific EDC software application or vendor.

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**Table 1. Key Features of Quality<sup>2</sup>**

- Quality is not a program; it is an approach to business.
- Quality is a collection of powerful tools and concepts that is proven to work.
- The customer defines quality through his/her satisfaction.
- Quality includes continuous improvement and breakthrough events.
- Quality tools and techniques are applicable in every aspect of the business.
- Quality is aimed at performance excellence; anything less is an improvement opportunity.
- Quality increases customer satisfaction, reduces cycle time and costs, and eliminates errors and rework.
- Quality isn't just for businesses; it works in non-profit organizations like schools, healthcare and social services, and government agencies.
- Results (performance and financial) are the natural consequence of effective quality management.

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Clinical research trials are even more ideally suited to the mindset of these quality control methodologies than automotive components. Automotive components are designed to “work” as long as they are within tolerance ranges.

However, the notion of “errors” being arbitrarily small (essentially zero) is, in principle, already the assumed goal of clinical research. There are instances of data values that may be missing because they were never collected, but any and all errors that can possibly be found and corrected are expected to be. This is significant because generally there is a much less established notion, especially in data management, that the goal should be zero errors in the data set. For example, statisticians can typically establish some margin such that there can be M errors in a data set of size N, but the data are still significant. In clinical trials, this is sometimes considered when there is an issue of excluding from analysis the data collected by a “bad site”. However, the usual assumption is that data management strives to make the data perfect.

Given these goals, the Taguchi Method and Six Sigma Quality translate well to the biopharma environment. But before biopharmas can implement quality improvement strategies borrowed from other industries, they must first assess their existing quality standards.

### Measuring Data Quality

As in the automotive industry, quality can be measured and tracked in the clinical trials process with statistics called metrics. A *metric* quantitatively represents a characteristic or a component of a business process. Metrics in clinical data typically represent quality, productivity, speed, or cost of one or more clinical data management activities.<sup>3</sup> Companies routinely track certain key metrics on every project as indicators of success. The collection and reporting of standard metrics enables the biopharma industry, like other industries, to quantitatively assess its business practices.

An important first step in using metrics for quality assessment is standardizing the definitions of basic terms. This is a challenge for biopharma companies, as clinical data management practices vary from organization to organization. For example, there are a variety of interpretations of the term “locked database”. For some organizations, locking a database may be a major milestone that involves resolution of all outstanding queries, resolution of all missing data values, performance of a comprehensive quality assurance audit, and a review and signoff of all documentation by management. For other organizations, locking the database may be a more casual event: they may lock the database after processing the “last” query and may unlock and relock the database as frequently as necessary.<sup>4</sup>

In keeping with this goal of standardizing definitions of “useful” metrics, participants in a Drug Information Association (DIA) roundtable conference on metrics have begun discussions that could lead to standardization and publication of important clinical data management and biostatistical metrics (Table 2).

**Table 2. Common Metrics in the Clinical Trials Process<sup>4</sup>**

#### Productivity metrics:

- Mean number of case report form pages entered per hour per operator
- Mean number of data fields or keystrokes entered per hour per operator
- Mean number of CRF pages processed to completion, per person hour
- Mean cost of processing a data clarification query

#### Performance metrics:

- Mean elapsed time from receipt of last patient’s data until database lock
- Mean elapsed time from last patient visit until database lock
- Mean elapsed time from receipt of response to last query until database lock
- Mean elapsed time from approval of final protocol and CRF until the data management plan is approved
- Mean elapsed time from approval of final protocol and CRF until the clinical data management system/operational database is approved as ready to process study data
- Mean elapsed time from database lock until key efficacy results are available
- Mean elapsed time from database lock until all data displays (listing, tables, figures) are approved for use by study report authors

#### Data quality metrics:

- Estimated error rate of an analysis database in comparison to paper CRFs
- Mean number of times per study the database is unlocked due to critical data errors
- Mean number of times per study that final tables must be reproduced due to critical programming errors

#### Data management cost metrics:

- Total cost of clinical data management processing through database lock, per CRF page
- Total cost of designing, programming, and producing data displays (listings, tables, figures)
- Mean number of data clarification queries per CRF page, or per data field

Once defined and measured, company metrics are generally compared to two industry benchmarks: best practices and current practices. *Best practices* describe the “best” values of metrics, such as the highest quality, highest speed, greatest productivity, or lowest cost of a specific clinical data management activity. *Current practices* describe the “typical” values of metrics, such as the median, mean, or range of value reported by biopharma companies.<sup>3</sup>

Preliminary surveys are beginning to gather data on best practice metrics in clinical data management. In a study published by the *Drug Information Journal*, 14 pharmaceutical companies participated in a telephone survey of production, cost, quality, and performance metrics. Following are some of the survey findings:

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- For database development (defined as elapsed time, including edit checks), the mean cycle time was 51.5 days.
- The average time to resolve one query was 8.4 days, with a range of 5 to 49 days. Queries from electronic data capture trials took less time to resolve.
- The mean (i.e., average) time from last subject/last visit to database lock was approximately 36 days, with a range of 20 to 60 days. This metric was based on processing paper CRFs. The one company that reported using EDC exclusively for its clinical studies stated that its cycle time metric was 48 hours.
- The mean cycle time for database lock to primary statistical analysis is 9 days, with a range of 2 to 20 days.
- The mean cycle time from database lock to final statistical tables was 15.4 days, with a range of 2 to 20 days.<sup>3</sup>

During a clinical trial, there are a number of things to be measured that are inherent in the business process. On a sampled basis, it would make sense to track system use during actual operation. Tracking keystrokes and mouse movements would allow feedback on what features are used the most, which are efficient, and which require too many keystrokes and mouse movements.

However, measuring and tracking such items presents problems of both privacy and logistical difficulty. Logistical issues are easier to address, and may be overcome with some technical solutions. In contrast, privacy concerns likely preclude tracking such information on a widespread basis during normal operation. Many workers are uncomfortable with being monitored on a detailed level during work. There is a fear among employees that mundane personal habits could be viewed as issues for poor work reviews. There is also a general discomfort with activities that resemble “big brother” monitoring of any aspect of daily life. Sponsors may choose to address these concerns by communicating with employees about the importance of metrics.

### Improving Data Quality

Once baseline quality metrics have been assessed, efforts to improve operations can be tracked and progress can be measured. Improved operations may result in improved quality and greater return on investment. Biopharma companies may employ a variety of strategies borrowed from other industries and designed to improve operations, including process intelligence and high-yield throughput.

*Process intelligence* is a comprehensive methodology that incorporates an understanding of key business data in the context of its relationship to strategy, organizational priorities, and work process momentum. Several attributes identify process intelligence: integration, aggregation, transformation, communication, and orchestration. Exercising process intelligence is just one way organizations can maximize business throughput and quality.<sup>5</sup>

The most effective approach is *high-yield throughput*, another quality initiative which focuses on improving both the pace and concurrent volume of new drug development across many concurrent projects. For biopharma companies, achieving throughput across concurrent

projects is a fundamental challenge. Each project may operate under unique conditions and present management challenges that span organizational boundaries.

The ability for a company to avoid errors is crucial to the organization’s effectiveness. Philip Holt, Vice President of Life Sciences in Chantilly, Virginia, describes delay as the most common enemy of effective throughput. In his experience, origins of delay include:

- “Duplication of data and data entry efforts
- Failure to translate data into understandable, usable formats
- Failure to disseminate information in a timely manner to all the right people — getting even good information too soon or too late or to the wrong place
- Miscommunication between site managers, physicians, and others involved in trial management and administration
- Failure to identify drugs that are not viable before expending significant resources that could have been used on another project
- Lack of globalization and harmonization between countries causes a duplication of effort that wastes resources.”<sup>5</sup>

Efforts to overcome these problems are critical to any process improvement plan. Whether high-yield throughput, process intelligence, or another data quality improvement strategy is employed, the plan should be tailored to each company’s unique challenges.

### EDC and Best Practices: Improving Quality and Return on Investment (ROI)

Depending upon their use, EDC systems may have a significant impact on both quality assessment and quality improvement. Some organizations may use EDC systems to streamline the calculation and tracking of company metrics. Other companies may choose to implement EDC in an effort to improve performance, productivity, quality, and cost metrics and to achieve industry best practices. Many organizations choose EDC systems to achieve both goals.

The use of EDC changes the processes for ensuring data integrity, affecting the activities of clinical research associates, site coordinators, and safety monitors. While conducting studies that use EDC, investigator sites enter clinical protocol data directly into an electronic system that is designed to maintain the integrity of paper Case Report Forms (CRFs). A major advantage of EDC is that the clinical protocol data are immediately in electronic form, without the delays and traditional data cleaning processes of standard clinical data management data entry departments. It is believed that the use of EDC will lead to faster completion of studies, with cleaner data at an earlier stage, yielding lower costs and more effective in-time response to safety issues.

The changes in work processes and project dynamics brought about by the introduction of EDC can lead to disorientation and lack of effectiveness in clinical study operations, at least until the individuals involved become

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acclimated to the new system. The variety of EDC systems, and disagreement about what constitutes good design, has led to additional dissatisfaction with EDC and has slowed adoption of this transformation to electronic systems in the clinical workplace.

A variety of issues affect data quality in EDC studies. Both technical design and global project processes have an impact on the collection of accurate data in an effective and timely fashion. Such issues include:

- Consistent user-oriented presentation and navigation of electronic forms
- System response time performance and delays
- Harmonious presentation of secondary entry forms (e.g., entry change reason)
- Effective balance of front-end validation checks and back-end query checks
- Changes in quality assurance (QA) focus and priorities due to EDC implementation
- User training and satisfaction issues
- Project management issues
- Organizational change management during adoption/transition process
- Effective sponsor-site communication tools
- Assessment and monitoring of data quality throughout the project life cycle

Human factors and the impact of technical and organizational decisions inherent to the adoption of EDC are also important factors. The impact of these factors on data quality should be considered, with an emphasis on best practices in implementing new EDC systems and studies.

Cost metrics are an important indicator of company success. As with other metrics, cost statistics may be significantly affected by the implementation and use of EDC systems. In ROI calculations, some factors have become moot points as paper-based offices have already largely evolved to electronic workplaces. At this point, computers, networks, Internet access, and so forth are part of the standard work environment. Only the incremental costs of implementing EDC should be included as actual costs. Some of these costs include:

- System setup. Systems using EDC technology potentially could be more expensive if a more powerful machine is required.
- Validation costs. With a clinical data application operating from the desktop, there are regulatory implications and costs, so validation costs could be increased.
- Help Desk costs. An unfamiliar application would introduce additional cost to a help desk, although most of the cost should be directly borne by the EDC/study helpdesk services, rather than by the corporate IT infrastructure helpdesk. This is one cost that may be cleanly and directly measured.

Once they have been implemented, EDC systems have the potential to achieve three types of benefits:

- Accelerated time to market
- Operational savings

- Improved decision making support due to the availability of clean data<sup>6</sup>

Though these benefits definitely exist, they can be difficult to measure reliably in order to create quantitative justification for EDC. Potential benefits reaped from accelerated time to market stem from the notion that a product that goes through clinical research faster may be approved and sold on the market sooner, creating revenues for a longer time, and possibly creating additional revenues due to the competitive advantage of being first to market. This potential benefit is more speculative, as time saved at one point of the process does not necessarily translate into faster approvals. Still, EDC promises to improve product development time.

One measure of time, the cycle time from last subject/last visit to the database lock, is the most frequently assessed metric in clinical trials. In part, this is due to the fact that this cycle time is “non-value added” time and provides an opportunity to reduce the time for drug development by a significant amount for most companies. Companies processing paper CRFs report a mean cycle time of 36 **days**, whereas companies using EDC report a 48-**hour** cycle time.<sup>3</sup> One can only presume that time saved in collection of protocol data would reduce overall time-to-approval.

Operational savings stem from the elimination of data entry from paper CRFs. With the implementation of EDC, departments that have a large number of lower-paying jobs are replaced with a small gain of more skilled and professional positions with new job descriptions. Some of the data entry tasks are moved to sites as well. After allowing time for personnel to be trained and adjust to the new system, the overall operation can be more efficient with EDC than with paper systems. However, a fair and accurate accounting is not always intuitive or easy. In addition, many clinical research operations have only approximate cost estimates for existing paper studies for comparison.

A third benefit stems from the advantage of having data in electronic form and in a “clean” form with less delay. In many companies, there is a constant internal competition for resources, as departments must make large decisions about product development choices. Better knowledge of safety and efficacy on a real-time basis, brought about by the availability of “clean” data, may allow companies to make faster and more accurate decisions about when to “backburner” or even cancel projects that show less promise or are even failing. Just one such decision, if it is correct, can override the savings in the other areas, and can allow resources to focus in more productive areas.

## Conclusion

As drug development costs continue to rise, it is becoming increasingly important for biopharmas to maximize quality to maintain a competitive advantage. Biopharmas are taking their cue from other successful industries and embracing a more comprehensive approach to data management and quality control.

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Assessing performance, productivity, quality, and cost measures is key to evaluating the strengths and weaknesses of any business process. In the pharmaceutical industry, company metrics are measured against industry best practices and current practices to help identify places where improvement is needed.

Some companies are turning to systems of electronic data capture to improve data quality, shorten time to market, and improve the bottom-line.

The use of EDC has a two-fold effect on quality. First, using EDC improves some metrics. As an example, companies using processing paper CRFs report a mean cycle time of 36 days, whereas companies using EDC report a 48-hour cycle time.<sup>3</sup> Secondly, using EDC streamlines the process of quality tracking itself. Because so many data management functions occur within the electronic environment, events such as entry of erroneous data can be automatically tracked and measures such as time to database lock can be automatically calculated.

EDC's effects on quality may translate to significant cost savings. First, faster time to market may bring competitive advantages that translate to financial gain. Second, because EDC streamlines the data collection and management process, operational costs may be reduced in the long-term despite significant initial start-up costs. Third, by making data available in real time, EDC allows management to make faster and more accurate decisions.

Regardless of the industry, individual companies universally strive for the same business goals: better products, greater customer satisfaction, and long-term financial stability. Rigorous quality assessment and improvement methods are critical to achieving these goals.

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### Who's behind the research?

Our lead researcher, Kirk Mousley, PhD received BS and MS degrees in Electrical Engineering from MIT and a PhD in Computer Science from Lehigh University. He has been the President of Mousley Consulting, Inc. since its founding in 1993 and has directed the company's efforts in the areas of clinical database design, data editing/cleaning, document management, and submissions.

Karl Mousley received his BS in Mechanical Engineering from Rose-Hulman Institute of Technology and a MS in Computer Science from Villanova University. He has been a senior member of the technical staff at Mousley Consulting, Inc. since 1993. Among his significant accomplishments are the investigation, evaluation, and implementation of new computer technologies for clinical data management systems and developing strategic plans for integrating these technologies into current systems. He has extensive experience preparing Standard Operating Procedures (SOPs).

**Robert Pearsall** received his BS in Electrical Engineering from MIT and his MS in Nuclear Engineering/Biomedical Instrumentation from The Ohio State University. He is Senior Consultant and Vice President for Business Development at Mousley Consulting, Inc. He has been involved with a variety of clinical data system projects for biopharma, including data management systems, electronic data capture (EDC), electronic submissions, validation compliance, and knowledge management. He was team leader and design architect for pilot projects in FDA/CBER electronic submissions.

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## Available **EDC In Depth** Research Reports related to this issue:

### 6.1 "Identifying and Tracking Data Processing and Quality"

As indicators of success, biopharma companies routinely track certain key productivity, performance, quality, and cost metrics on every project. In this report, we detail the advantages and disadvantages of different approaches to tracking data processing and quality.

### 6.2 "Financial Issues – Data Collection and Interpretation"

The financial considerations relevant to data collection and interpretation are far reaching, ranging from start-up costs to returns on investment. In this report, we guide biopharma companies in assessing both the costs and financial gains that can be achieved with EDC.

### 6.3 "Best Practices in EDC – Improving Operations for Quality and ROI"

EDC systems allow biopharma companies to achieve a fundamental business goal: producing better data faster. In this report, we examine how sponsors can use EDC to improve operations for enhanced quality, realize industry best practices, and achieve better return on investment.

See back for order information.



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