

Data Integrity in Clinical Trials: Current Trends and Future Directions

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Questioning the Unquestioned

The backbreaking work done by an inventor, researcher and scientist to get innovative molecules to the market is incomplete without the underlying support of clinical research. While a multitude of factors are critical in successful completion of any clinical trial, it largely depends on the conduct of trial sites that recruit patients, and under the direction and guidance of a multi disciplinary team that ensures that the prerequisite protocols and procedures are regularly followed, monitored and adhered to.

During a site monitoring visit, it becomes the core responsibility of a Clinical Research Associate (CRA) to be vigilant for the outlined priority areas for most patients, especially for sites that happen to be the highest and fastest recruiters and ensure that observations such as the following are diligently reported: In the case of Signed Informed Consent Forms (ICFs), observations such as completely neat and clean ICFs and use of the same ink for all signatures must be reported immediately. Medical and Laboratory records of patients are imperative in deciding Patient Eligibility, however, if every Medical Record of any patient is easily available or all the reports are from the same laboratory, an alarm must be raised instantly. Availability of identical Laboratory Reports such as same electrocardiograms is extremely suspicious and thus should be reported on the spot! In the case of Drug Accountability Reconciliation, 100% compliance for visits and IP schedule is quite a rare sight, hence, if observed, it should be reported at once.

Moreover, as the study progresses, the CRA has to also, periodically, ascertain that all safety issues are adequately reported during the entire clinical trial duration. Based on this continual monitoring activity performed by the CRA, one can attest, if the data generated at each site is robust and will be acceptable by regulatory agencies across globe.

Questionable data can lead to a study losing its entire credibility. Worse than that, if not identified at the right stage, it may pave the way for entry of ineffective or harmful treatments in the market and possibility of patients being kept away from effective therapies – situations that are definitely avoidable and uncalled for.

“In God we trust, all others must bring data”. So, if you are a CRA responsible for monitoring a clinical trial site, any deviations or scenarios even partly similar to those mentioned above, should be enough to ring a bell! It is your lookout to observe these trends in the data collected by the site and report any discrepancies, whatsoever.

The Genesis and Evolution of Quality in Clinical Trials

Who can forget the famous thalidomide disaster that scathed the history of clinical trials? The so called “clinical trials” of thalidomide involved distribution of more than two and a half million tablets of thalidomide to approximately 20,000 patients across the nation—amongst which, approximately 3,760 women were of childbearing age and at least, 207 of whom were pregnant! More than one thousand physicians participated in these trials, but, to our dismay, only a few tracked their patients after dispensing the drug, leading to the biggest disaster scarring the history of clinical trials.

However, on a positive note, the negative effects of thalidomide led to the development of more structured drug regulations and control over

drug use and development. The tragedy surrounding thalidomide helped motivate profound changes in the FDA. By passing the Kefauver-Harris Drug Amendments Act in 1962, legislators tightened restrictions surrounding the surveillance and approval process for drugs to be sold in the US, a significant move that shaped the future of drug approval process.

History authenticates that it was always these “clinical tragedies” that made us realize the importance of having an independent evaluation of medicinal products, before allowing them to come to the market. The Nuremberg Code was one of the initial research ethics principles that got established in 1949. The drafting of Nuremberg code was the outcome of critical observations during the Nuremberg War Crime Trials at the end of the Second World War. This Declaration is an important document in the history of research ethics, as it is the first significant effort of the medical community to regulate research itself, and forms the basis of most of the subsequent documents.

Another example is that of the Belmont Report, issued in 1978, that summarizes ethical principles and guidelines for research involving human subjects. Prompted, in part, by problems arising from the Tuskegee Syphilis Study, the Belmont Report was first written by the National Commission for the Protection of Human Services of Biomedical and Behavioral Research, to safeguard research in human subjects.

As International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) puts it forward as “For most countries, whether or not they had initiated product registration controls earlier, the 1960s and 1970s saw a rapid increase in laws, regulations and guidelines for reporting and evaluating the data on safety, quality and efficacy of new medicinal products. The industry, at the time, was becoming more international and seeking new global markets; however the divergence in technical requirements from country to country was such that industry found it necessary to duplicate many time-consuming and expensive test procedures, in order to market new products, internationally.” This forms the basis of International Conference on Harmonization-Good Clinical Practice(ICH-GCP).

Data Integrity and Its Importance

The historical mishaps and the subsequent efforts aimed towards safe guarding the right and safety of human subjects in clinical trials have helped carve the much needed niche for “Data Integrity” in clinical trials. Data integrity in generic terms can be defined as “maintaining and assuring the accuracy and consistency of data over its entire life-cycle, and is a critical aspect to the design, implementation and usage of any system which stores, processes, or retrieves data”.

Let us now try to understand what this means in the clinical trial setting. The data generated for any clinical trial needs to be valid, sufficient and of highest-quality. This is of utmost importance in order to interpret the results of any clinical trial. It becomes our ethical obligation to make good use of participants’ involvement in studies, and that requires making every effort to ensure that our data meets the highest standards.

ICH lists the elements right through designing to conduct to performing to monitoring to auditing to recording to analyses and lastly reporting of clinical trials, which require focus in order to maintain data

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integrity. Traditional ways to ensure data integrity are quality control and quality assurance, which are implemented throughout the stages mentioned above. However, we often see that the focus largely is on the conduct phase. The sole reason for this is the fact that the data collection takes place in the conduct phase.

FDA Guidelines for Ensuring Data Integrity

FDA has given comprehensive advice on prevention of fraud in order to maintain data integrity. Some of the salient points are mentioned below:

Sr. No.	FDA guidance on prevention of fraud
1.	Make sure all study staff have the necessary resources and support needed to accomplish their tasks
2.	Don't place needless requirements or unreasonable demands on the site
3.	Monitor sites closely and pay attention to complaints from site personnel
4.	Minimize the use of enrollment incentives

Additionally, FDA has also given guidance on detection of serious misconduct. Here are some important pointers from the guidelines:

Sr. No.	FDA pointers on detection of serious misconduct	What you need to do
1.	Get technical	Read x-rays, EKGs, lab results, don't just inventory
2.	Fill in the blanks	Question missing dates, times, information, offer to retrieve records yourself
3.	Don't be intimidated	Tell the emperor he has no clothes
4.	Don't shoot the messenger	Believe the monitor, put the burden of proof on Investigator
5.	Be suspicious of blame shifting	Tell investigator he is totally responsible for study conduct
6.	Expect fraud	Start from the assumption the records are bogus and the study is a fraud, and work back
7.	Cultivate whistleblowers	Establish rapport with study staff, be approachable and available, listen to grievances, observe working conditions
8.	Be prepared	Have a system in place to capture, document and deal with complaints of misconduct in a timely fashion Follow SOPs

Ways to Ensure Data Integrity in Clinical Trials

If we review the above direction from the FDA closely, we understand that all these aspects needs to be covered and qualities, as outlined, needs to be cultivated in person and implemented at the investigator site.

On-site monitoring, the conventional approach

Traditionally, data monitoring in clinical trials is being done through on site monitoring visits as part of quality control and on site audits/inspections as part of quality assurance.

On-site monitoring has proven to be critical to:

- Identify data entry errors (e.g., discrepancies between source records and case report forms (CRFs)) and missing data in source records or CRFs;

- Provide assurance that study documentation exists;
- Assess the familiarity of the site's study staff with the protocol and required procedures; and
- Evaluate compliance with the protocol and investigational product accountability.

On-site monitoring can also provide a sense of the quality of the overall conduct of the trial at the site (e.g., attention to detail, thoroughness of study documentation, appropriate delegation of study tasks, appropriate investigator supervision of site staff performing critical study functions). On-site monitoring is therefore required particularly early in a study, especially, if the protocol is complex and includes novel procedures with which investigator may be unfamiliar.

Revolutionized monitoring approaches

The globalization of clinical trials was done with the aim of cost and time saving. However, variation in regulatory processes and differences in clinical practices and infrastructure between the developed and developing countries has made compliance to global quality extremely difficult. Thus, the global pharmaceutical industry is facing challenges of increase in cost and delay in drug development. The increase in the number and complexity of clinical trials in past two decades has further complicated the scenario.

On the other hand, increasing use of electronic systems and records and improvements in statistical ways of assessments present opportunities for alternative monitoring approaches (e.g. centralized monitoring), that can improve the quality and efficiency of sponsor oversight of clinical investigations.

Risk-based monitoring

FDA encourages sponsors to develop monitoring plans that manage important risks to human subjects and data quality and address the challenges of oversight, in part, by taking advantage of the innovations in modern clinical trials. A risk-based approach to monitoring does not suggest any less vigilance in oversight of clinical investigations. Rather, it focuses sponsor oversight activities on preventing or mitigating important and likely risks to data quality and to processes critical to human subject protection and trial integrity. Moreover, a risk-based approach is dynamic, more readily facilitating continual improvement in trial conduct and oversight. For example, monitoring findings should be evaluated to determine whether additional actions (e.g., training of clinical investigator and site staff, clarification of protocol requirements) are necessary to ensure human subject protection and data quality across sites.

Centralized monitoring

Centralized monitoring is a remote evaluation, done at sites other than those where the clinical investigation is being conducted. Monitoring of this type need not be necessarily carried out by clinical monitors but can be done even by data management personnel or statisticians. Centralized monitoring processes have the potential to provide many of the capabilities of on-site monitoring as well as some additional capabilities. FDA encourages greater use of centralized monitoring practices, where appropriate, than has been the case historically, with correspondingly less emphasis on on-site monitoring. The types of monitoring activities and the extent to which centralized monitoring practices can be employed depend on various factors, including:

- The sponsor's use of electronic systems;
- The sponsor's access to subjects' electronic records, if applicable;
- The timeliness of data entry from paper CRF, if applicable; and
- Communication tools available to the sponsor and study site.

These may vary by study and by site. Sponsors who plan to use centralized monitoring processes should ensure that the processes and expectations for site record keeping, data entry, and reporting are well-defined and guarantee timely access to clinical trial data and supporting documentation.

The Evolving Role of Clinical Data Managers in Safeguarding Data Integrity

Clinical Data Managers play a vital role in detecting issues relating to data integrity and quality. In order to assess data integrity, clinical data managers evaluate data collection tools, confirm the environment is controlled, viz., access restriction, 21 CFR compliance and audit trail, at every step of the process. Data integrity is imposed during study start-up phase viz., database designing, by implementing standard operating procedures and can be maintained through electronic edit checks and SAS/SQL programming.

Embracing intelligent technology of the new era holds promise to address complex issues like clinical documentation, identifying outliers, query data and analytic reports such as data listings to validate data thus ensuring data is real, accurate and safeguarded from any manipulation. Having a single, well-defined and well-controlled data integrity system facilitates stability, performance, reusability and maintainability. Therefore, it is of utmost importance that any application providing data assurance should focus on data integrity, data availability, data authentication, data confidentiality and data non repudiation.

Not only this, today's Data Manager is changing the face of clinical trials. The arrival and adoption of eClinical trial, is no longer a buzz-word, but a business and scientific reality! As defined by the Clinical Data Interchange Standards Consortium (CDISC), an eClinical trial is a study "In which primarily electronic processes are used to plan, collect (acquire), access, exchange and archive data required for conduct, management, analysis, and reporting of the trial". One component of this is Electronic Data Capture (EDC), and this technology is increasingly being adopted by various sponsors, healthcare providers and regulators, reflecting a transformation of the data application in clinical research.

Centralized Risk-based Monitoring (RBM) to improve the efficiency of clinical monitoring is altering the mind-set of all stakeholders with growing body of evidence to certify that "blanket" Source Data Verification (SDV) is not necessary but should be applied to "critical" data points, thus, reducing the frequent visits of the CRA to each clinical trial site. Newer methods facilitating collection of eSource data to generate eClinical Trial Record (eCTR) will involve Direct Data Entry (DDE) in EDC system which will allow collection of data electronically at the time of the trial visits and procedures, thereby simplifying the entire process of data collection and management.

Future directions and way forward

In the near future, with the advent of integration of RBM and DDE, which allows acceptance by regulators of eSource data, traditional monitoring will be complemented by Clinical Data Manager's new role. This will include a revolutionized approach of understanding sponsor needs, setting expectations and anticipating challenges, guiding sponsor on technology and processes to develop innovative economical solutions, developing resource management strategies, collaborating with other stakeholders and creating automated metrics to proactively drive the study in the right direction.

Online GCP training, audit trails, data management reports, trend analysis and batch edit checks, continuous and automated Serious Adverse Event (SAE) reconciliation with email alerts will play a major role in routine review of data in real time along with electronic Trial Master File (eTMF).

Nevertheless, there is a huge difference between saying and doing, and harmonization of RBM and DDE among the regulatory authorities in the different ICH and ICH-like countries is an aspect that needs to be addressed. Implementing the eClinical vision will take more effort and planning than simply flicking a switch in this ever-evolving risk landscape. Combining these tools and technologies with on-site monitoring visit has definitely provided the CRAs that additional edge to ensure that the data retrieved by them is valid and can sustain any audit and inspection in future.