

# A PERSPECTIVE OF CLINICAL DATA MANAGEMENT IN THE CONTEXT OF THE APPLICATION OF INDIAN GOOD CLINICAL PRACTICES

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**Abstract**—The focus of this article is on the areas wherein the Indian GCP (Good clinical Practice) interface core themes of Clinical Data Management (CDM). In particular, it highlights evolving trends in CDM and emphasizes the increased necessity to focus on data from a regulatory requirements perspective. To this end, contemplations with respect to CDM activities in context of Indian GCP are reported.

**Index Terms**— Clinical Data Management (CDM), Indian Good Clinical Practices (GCP).

## INTRODUCTION

Research involving human subjects has increased multifold, and emerging markets including India, have become key player in the clinical research space. In India, one of the vital guideline available for conduct of clinical trials is 'GCP for Clinical Research' by Central Drugs Standard Control Organisation (CDSCO)<sup>1</sup>.

To ensure uniform quality and to generate data for the registration for new drugs before use in the population, CDSCO in consultation with experts has formulated the GCP guideline for the generation of clinical data on drugs.

Conformance with GCP not only ensures that clinical trial studies are done in an ethical way but also assures the credibility of data generated. It addresses requirements of overall study conduct at research institutions, investigators, institutional ethics committees and regulators<sup>1</sup> in providing desired track.

The guidelines seek to establish two cardinal principles: protection of the rights of human subjects and authenticity of biomedical data generated.

CDM was once perceived as the set of processes which resulted in a reviewed database. But this very perspective is in a state of dynamic flux today<sup>2</sup>. In today's competitive environment, a drive in CDM activities is reported for

evolving, developing and executing unerringly common principles to achieve required quality data, in time effective manner. The goals of this precision is to set business solution(s) which are process dependent, platform independent, venter neutral, transparent, devoid of duplication and with smooth flow of information between partners, providers and regulatory authorities.

## SUBJECTS AND METHODS

It is vital that all clinical research personnel should comply with GCP, as it is an essential requirement for study conduct. In this review, we have restricted to the sections where the intricacies related with CDM have been expounded. Thus, our focus will only be "CDM in the context of Indian GCP".

## RELEVANT CHAPTERS OF THE INDIAN GCP

Following sections of the Indian GCP give working directives about CDM activities or the inferences drawn from them with respect to its implementation..

### *Validation*<sup>1</sup>

The course of action to adopt procedures for study and data validation, as per the following definitions, depends on the sponsor:

*Validation of Study:* The process of proving, in accordance with the principles of GCP, that any procedure, process equipment, material, activity or system actually leads to the expected results<sup>1</sup>.

*Validation of Data:* The procedures carried out to ensure and prove that the data contained in the final report match the original observations. The procedure is applied to Raw Data, Case Report Forms (CRFs), computer software, printouts, statistical analysis and consumption of Study Product/Comparator Product<sup>1</sup>.

### *Responsibilities of Sponsor<sup>1</sup>*

Sponsor should enter into a formal and legal agreement/contract with the Investigator(s) / Institution(s) on the following terms:

- To comply with the procedures for data recording, and reporting<sup>1</sup>.
- To permit monitoring, auditing and inspection<sup>1</sup>

Under this section how to comply with the terms have not been addressed, leaving the scope to cover the same by the organizational Standard Operating Procedures (SOPs) .

### *Study management, data handling and record keeping<sup>1</sup>*

The Sponsor is responsible for securing agreement with all involved parties on the allocation of Protocol related and other responsibilities including 'Data Processing'.<sup>1</sup>

This section focuses more on the activities related with the data management at site rather than how to manage the same, once CRFs are received in-house by CDM team. It would be much appreciated, if the guidelines incorporated more elaborative information on the approach to accomplish 'Data Processing' activities, related with the off-site data handling at sponsors end.

The section also demands to have in-house Quality Assurance (QA) and Quality Control (QC) systems with written SOPs to ensure that the study data are generated, documented (recorded), and reported – in compliance with the Protocol, GCP and the applicable regulatory requirement(s) <sup>1</sup>. Thus the operational procedures to accomplish the same are left to the discretion of sponsors.

### *Responsibilities of Investigator<sup>1</sup>*

As per Indian GCP, the Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all the required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained<sup>1</sup>.

Any change or correction to the CRF should be dated, signed and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes and corrections<sup>1</sup>.

The suggestions incorporated under this section are not only helpful to get legitimate data in the CRF, but are also useful in getting Data Clarification Forms (DCFs) resolved in the same lines. DCFs are data related queries sent to the site by CDM team members. Guidelines with process detail for discrepancy management would be of immense significance to generate quality data.

Sponsor should provide guidelines to investigators and/or the investigator's designated representatives on making such corrections and should have written procedures to assure that the changes in CRFs are documented and endorsed by the Investigator. The Investigator should retain records of the changes and corrections<sup>1</sup>.

Sample format for the desired facts are expected to be the part of these guidelines and written procedures, if given precisely, would be of immense help, with the benefits of process harmonization.

SOPs should be established to record the laboratory values, with normal reference ranges on a CRF. These SOPs must also cover the aspects to handle the values outside the clinically accepted reference range or values that differ significantly from previous values, along with the method to evaluate and provide comment(s) by the Investigator. Procedures must be in place to handle the superfluous data in the CRF, other than that requested by the Protocol to be marked as the additional findings and their significance must be described by the investigator. Units of measurement must always be stated and transformation of units must always be indicated and documented<sup>1</sup>.

Simplicity in handling laboratory data would be facilitated if we have guidelines to fulfil the requirements, not limited to the following, such as, effective laboratory data exchange by harmonization in its acquisition and use of regulatory defined standard units.

### *Record Keeping and Data Handling<sup>1</sup>*

The basic concept of record-keeping and handling of data is to record, store, transfer, and where necessary convert efficiently and accurately the information collected on the trial subject(s) into data that can be used to compile the Study Report<sup>1</sup>.

The procedures for record keeping and data handling, has to be managed with organisational SOPs. There is no specific method recommended as illustration.

### *Documentation<sup>1</sup>*

All steps involved in data management should be documented in order to allow step-by-step retrospective assessment of data quality and study performance for the purpose of audit. Follows SOPs that shall facilitate documentation<sup>1</sup>.

Documentation SOPs should include details of checklists and forms giving details of actions taken, dates and individuals responsible etc<sup>1</sup>. This section very briefly provides the insight about what has to be the part of the SOP(s), though it is the inevitable fact that if the sample format for the checklist, as an annexure, if provided shall leave no margin for error(s). Addressing the hard core data management documents namely - Data Management Plan, Data Validation Guideline, Edit Checks, Self-Evident Corrections, Data Coding Guideline, etc., is solicited as a part of this section of Indian GCP.

### *Corrections<sup>1</sup>*

All corrections in the CRFs or any other study related documents should be made in a way that does not obscure the original entry. The correct data should be inserted with the reason (s) for the correction (if such a reason is not obvious).

The corrections should carry the date and initials of the Investigator or the authorised person<sup>1</sup>.

This section though comprehensible, should give few examples of reasons which are deemed to be 'not obvious' by regulatory.

#### *Electronic Data Processing<sup>1</sup>*

Requirements mentioned under this section has to be fulfilled with adequate internal SOPs addressing the procedures for electronic data processing including, but not limited to the-system validation, access control, data security, audit trail maintenance and backup recovery.

#### *Validation of Electronic Data Processing Systems<sup>1</sup>*

It is left to the prerogative of organizational SOPs, to address the scenario where the trial data are entered directly into the computer with satisfactory defend to guarantee validation. These procedures must include activities like-taking its printout and backup records with dated signatures<sup>1</sup>. Documented techniques must be established for up-to-date validation of computerized systems, both hardware and software.

#### *Responsibilities of the Sponsor and the Monitor<sup>1</sup>*

The sponsor must ensure that electronic data processing system conforms to the certain documented requirements for completeness, accuracy, reliability and consistent intended performance (i.e. validation). The Sponsor must maintain SOPs for using these systems. The Monitor should take adequate measures to ensure that no data is overlooked. If the computer system automatically assigns any missing values – the fact should be clearly documented<sup>1</sup>.

Sponsor should safeguard the blinding, if any, particularly during data entry and processing. The Sponsor should use an explicit Subject identification code that allows identification of all the data reported for each Subject. Ownership of the data and any transfer of the ownership of data should be documented and intimated to the concerned stakeholders<sup>1</sup>.

The above practice has to be established by the customized processes as adopted by the organizational SOPs.

#### *Quality assurance<sup>1</sup>*

The Sponsor is responsible for the implementation of a system of Quality Assurance in order to ensure that the Study is performed and the data is generated, recorded and reported in compliance with the protocol, GCP and other applicable requirements. Documented SOPs are a prerequisite for quality assurance<sup>1</sup>.

SOPs must address that all the observations and findings are verifiable, for the credibility of the data and to assure that the conclusions presented are correctly derived from the raw data. Similarly for QC, SOPs must be in place to ensure that each stage of data handling has contributed for generation of reliable data, by the use of correct processes.

#### EXPECTATIONS FROM INDIAN REGULATORY AUTHORITIES

Though the Indian guidelines are agreeably framed, but they focus more on the operation aspects, site management, safety data etc. There is crucial need to elaborate the existing guidelines from CDM prospective. With specific method recommended as illustration(s) for data harmonization.

Stepwise approach about - how the data management activities have to be accomplished, would be the welcomed effort from the regulatory bodies. It is expected that more intricate and specific information should be provided about good clinical data management practices (GCDMP<sup>3</sup>). This may contain information, not limited to the following:

- a. Developing Data Management Plans
- b. Project Management-CDM
- c. Steps & procedures for Data Recording, Cleaning and Reporting
- d. Principles for Electronic Data Capture
- e. Handling of Laboratory Data
- f. Steps for Data processing, transmitting and archiving
- g. Data Quality Management Principles
- h. Gauging Data Quality
- i. Data Entry Methods
- j. Medical Coding & Dictionary Management
- k. Database Lock
- l. Development of Data Standardization procedures similar to Clinical Data Acquisition Standards Harmonization (CDASH)/Clinical Data Interchange Standards Consortium (CDISC).

One of the prominent regulatory body outside India, U.S. FDA (Food and Drug Administration<sup>3</sup>), has besides ICH-GCP, electronic data guidance documents like Computerized Systems Used in Clinical Trials and Electronic Records (05/2007); Electronic Signatures - Part 11, Scope & Application (08/2003) while medical devices guidance document includes General Principles of Software Validation: Final guidance for Industry and FDA staff (01/2002). Other important guidelines of the Agency are listed here, though some of them are in draft stage: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring (08/2013), Electronic Source Data in Clinical Investigations (11/2012), Industry Providing Regulatory Submissions in Electronic Format-Standardized Study Data (02/2012).

There is a need for comprehensive guidelines to address the above listed matters under the Indian regulatory frame. However, at the end of the day, it is the necessity for regulatory authorities to develop detailed guidelines aligned with evolving standards (CDISC – Study Data Tabulation Model (SDTM), Analysis Dataset Model (ADaM), Coalition for Accelerating Standards and Therapies (CFAST)), evolving technologies (EDC, e-source, electronic informed consent, risk based monitoring), and the parallelly evolving role of the data manager(s). Also, they may structure their organization internally as well as their inspection systems to focus more upon the data aspects of clinical trials.

The regulatory authorities could reach out to industry forums through bodies such as Confederation of Indian Industry (CII), the DIA (Drug Information Association), ASSOCHAM (The Associated Chambers of Commerce and Industry of India) or Society for Clinical Data Management (SCDM) to name a few, to provide CDM personnel with certified and structured training on the technology and data aspects. They may consider constituting a panel of industry experts to support them to evolve the regulations and guidelines and embed them in the Indian GCP and regulatory guidelines or as applicable, thereby incorporating the criticality of the data aspects in the same.

#### EXPECTATIONS FROM INDUSTRY

Along similar lines with Society of Clinical Data Management (SCDM, Global Headquarters in Belgium<sup>4</sup>) & Association for Clinical Data Management (ACDM<sup>5</sup>, U.K.), Indian pharmaceutical companies/CROs should take an initiative by forming a non-profit organization to create a knowledge forum of CDM professionals or partner with a leading global association. Such a platform shall help to address exclusive need for educational and training requirements keeping pace with technological upgradation.

#### DISCUSSION

Core perspectives on the traditional approach to CDM are rapidly changing and EDC (Electronic Data Capture) and new e-clinical initiatives are redefining the paradigm of data management<sup>2</sup>.

As per the sections from GCP, it is seen that there is limited information provided to explain steps and processes of CDM. This necessitates to have well defined in house SOPs to address the same. Regulatory bodies, industry and CRO's (Contact Research Organisations) need to harmonize CDM related steps to enhance the data quality.

While each study scenario is unique and has to be approached as such, there are several elements in defining strategy and team structure in global CDM that can be applied universally<sup>6</sup>. The existing SOPs of CDM may include following tasks: maintaining data privacy, data acquisition, development of data management & quality control plan, CRF annotation, database design, data/database validation, data entry, comparison reconciliation, tracking log for CRF, query management, dictionary management, data transfers, data quality control, batch data uploads of non-CRF data (e.g. lab data, ECG data), safety data management, serious adverse event data reconciliation, database closure, data archival, etc.

Although CDM professionals should generally follow standard practices to perform these tasks, one should realize that the phase and therapeutic area of a study can lead to differences in tasks and how each task should be performed<sup>7</sup>.

For example; a vaccine trial may have different data management steps than those of an oncology study. With reference to Indian regulations, though GCP gives an overview of CDM activities, but is not therapeutic area specific and lacks step by step clarity on individual CDM tasks. Over the past several years, there has been a gradual shift in focus on the operational model for clinical data management activities in clinical research endeavors<sup>6</sup>. Thus, it is a challenge for CDM personnel to make obligatory changes in the entire processing methodology to conform to GCP and to achieve the common objective of obtaining 'high quality statistically sound data' which is acceptable to the regulatory authorities.

#### CONCLUSION

With the advent of a number of off shore clinical trials and filings of new drugs/biotech based products, it is the need of the hour to have well defined harmonized and standardized CDM steps for its practice, procedure, process & preparation (training). This should be the collaborative effort from regulatory authorities and as well as from the industry. This article aims to serve as the point of inception towards this objective.

#### DISCLOSURE

The opinions, interpretations stated in the article represent individual's viewpoint only, there being no conflict of interest.

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