

‘CLINICAL DATA MANAGEMENT (CDM) PROCESS STANDARDIZATION’ for VACCINE TRIALS IN AN INDIAN PHARMACEUTICAL COMPANY, UNDER INDIAN REGULATIONS

Synopsis submitted in fulfillment of the requirements for the Degree of

DOCTOR OF PHILOSOPHY

By

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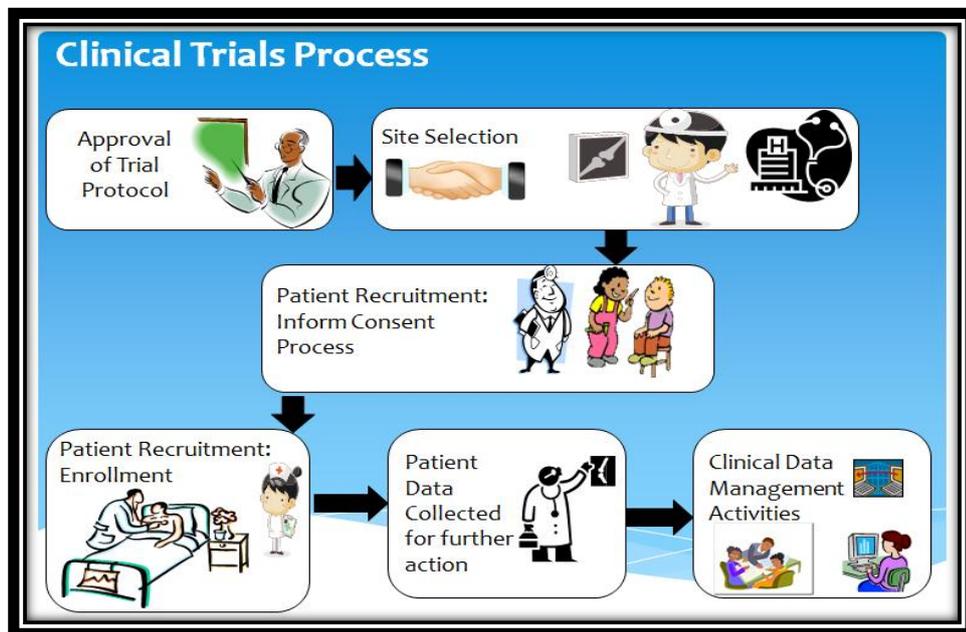
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BACKGROUND AND RATIONALE

Clinical data management (CDM) is an important component and of critical value in the process and outcome of a clinical trial. Clinical trials, research studies involving human subjects, are necessary to establish the safety and effectiveness of specific health and medical products and practices [1]. Clinical trials aim to find new methods of prophylaxis, quality of life analysis, diagnose or treatment of diseases. Once the trial design protocol gets finalized in the organization, the procurement of approvals by regulatory authority and ethical committee occurs, this is followed by the process of site selection. Subsequent to patient recruitment, study conduct starts at the site by the investigator. Data, ‘the clinical information gathered from each patient enrolled in study’ is the most valuable information and its handling and management is the most critical step of a clinical study. CDM group keeps the database ready so that the clinical information collected at the site could be entered into the database [2].



Source: Dureja, N., Bajpai, N., “Patient Recruitment and Retention Strategy in Clinical Trials: Data-driven and Evidence-based Approach”. HCL: White Paper, pp. 01-18, Dec. 2014.

Data is validated as per the protocol requirements and reviewed thoroughly. Any discrepancy identified in the data, is sent to the site in the data clarification form (DCF) for corrections. Only valid resolutions obtained from the site in response to the queries, are updated in the database. Once there are no discrepancies and database is clean, database is locked to prevent any unauthorized access [2].

Analysis ready data is sent to the biostatistician through secure network to ensure its validity and reliability. Biostatistician creates the data tables and listings; this becomes the part of clinical trial study report. Once the report is finalized internally, same is submitted to the regulatory authorities for product related approvals. Study data may be published as applicable [2].

Poor management of data may lead to the wrong outcomes. Irrespective of the big investment of time, resources, money and effort for the conduct of the trial, if the quality of data is not as per the required standards, a meaningful analysis of study outcome may not be possible [3].

CDM: Current Regulatory Scenario

Clinical trials industry is confronted with a multitude of regulatory constraints and standards that govern the conduct of the industry itself and the individuals who participate in it.

Regulatory requirements have advanced the necessity of CDM as science. Therefore the processes used to support the clinical data must be clearly defined and documented [4]. Over the last decade the clinical research industry has attempted to work toward a common data standards with the goal of accelerating the drug development process by improving the data collection, transformation, analysis and submission [5].

Currently the World Health Organization (WHO) has the following guidelines and requirements that are relevant to the evaluation of vaccines: Good Clinical Practice (GCP) for trials on pharmaceuticals products, Good Manufacturing Practice (GMP) for pharmaceuticals, GMP for biologicals, regulation and licensing of biological products in countries with newly developing regulatory authorities and Guidelines for national authorities on quality assurance for biological products. Guidelines and

recommendations for the production and control of specific vaccines are reviewed in detail in a series of WHO technical reports. However, there is no WHO document that provides guidelines or standards for CDM conduct including planning [6], and data formats for the standardized representation of data and process implementation. It is recommended that the practice of CDM should be grounded to Good Clinical Practice (GCP); overall the steps adopted for CDM should adhere to principles of good trial design and practices; though opportunities remain for further improvement. There is a need that the data format should be standardized and the protocol/Data Management Plan (DMP) should provide clear guidance about CDM procedure implementation. Methods of assessing standardization or definition of standardization criteria and the design considerations to be applied in CDM, or operational benefits should be defined in protocols/DMP/ study reports and must be validated through audits. The use of consistent standards in CDM procedures and implementation could facilitate comparison of trials by meta-analysis.

Major Indian guidelines available for conduct of clinical trials are

- GCP for Clinical Research & Schedule –Y: Central Drugs Standard Control Organization (CDSCO)
- Ethical Guidelines for Biomedical Research on Human Subjects By ICMR

Development of robust CDM procedures and implementation plans with assessable endpoints are the urgent unmet clinical/regulatory need of every Indian Pharmaceutical company. Regulatory guideline has the overall requirement of credible, trustworthy, dependable, correct and authentic data. Data must have an underlined audit trail and should not be subject to unauthorized access. The focus of Indian regulatory documents is more on the site management, clinic trial operations and pharmacovigilance. However, there is no regulatory document that gives step by step clarity on procedures which may be adopted for clinical data management of vaccines. It is totally left to the organization to identify, adopt, document and implement the processes so as to generate data compliant to regulatory. Procedures adopted to achieve the same must be robust enough to pass audits and inspections.

However, there are still fundamental problems in clinical data management practices. There exists a great diversity in the procedure adopted for data processing and handling. The provisional CDM processes/criteria adopted are based on expert opinion. Depending upon the phase of study and investigation product under test, specific set of clinical data management activities may be needed. Framework that might emerge from establishing CDM procedural paths could improve the quality of clinical trials thereby supporting regulatory review. Of note, a recent report have highlighted regulatory non-compliance as a major issue among Indian life sciences companies; gaps exist pertaining to data management and quality control practices (GCP), apart from others (GMP, GLP) [7].

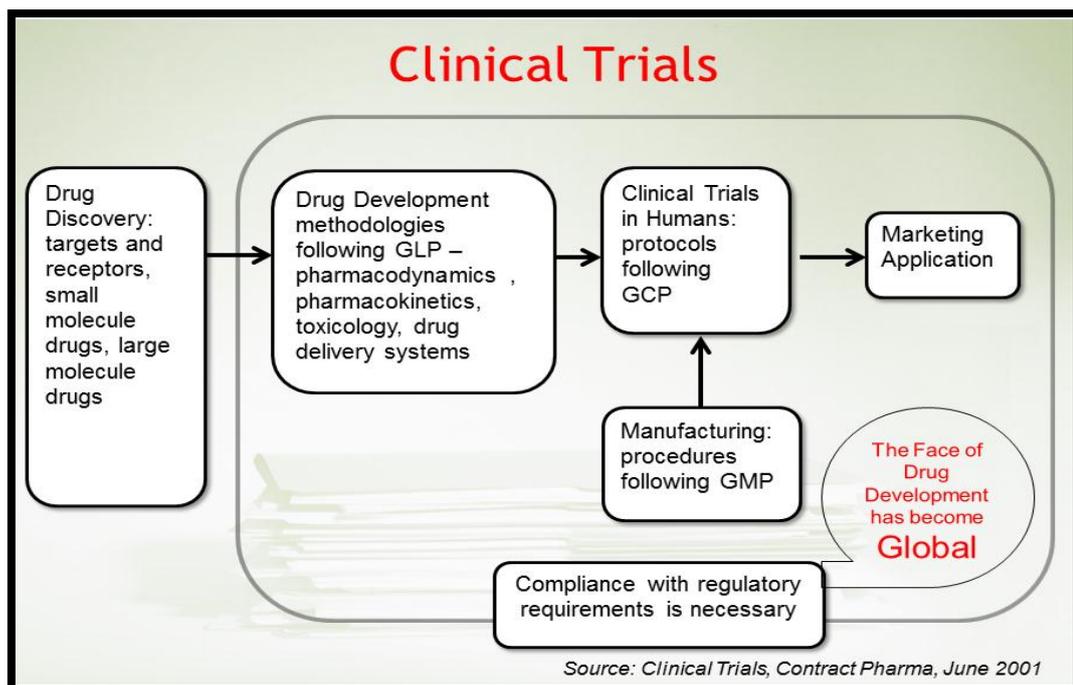
Purpose of Study: CDM Standardization: -Vaccine Trials

India is fast becoming hub for vaccine research and development. Efficient and quality clinical data management remains a challenge. Heterogeneity prevails [8] as no common standardized and validated global/ national industry-wide CDM procedural and implementation framework has been developed for drug or vaccine trials. Such clinical scales are also the need for regulatory review to aid in drug development procedures as per namely GCP. Standardized CDM definitions, the process of developing and implementing technical standards, CDM data formats are needed to optimize data management and facilitate comparisons between results of different trials.

With advent of new genre of vaccine biopharmaceutical products, biosimilar, the CDM task need to be streamlined and the guidelines need to be implemented in an effective manner so as to achieve process standardization. In the past, Excel® spreadsheets (invalidated) were the only tool for data management. Every single step of the process was manually driven, thus error-prone, resulting in decline in overall efficiency. Unless these tools are used appropriately (i.e. properly validated), the integrity of the data may be questioned and the information may be deemed inaccurate or possibly even perceived as fraudulent activity [9].

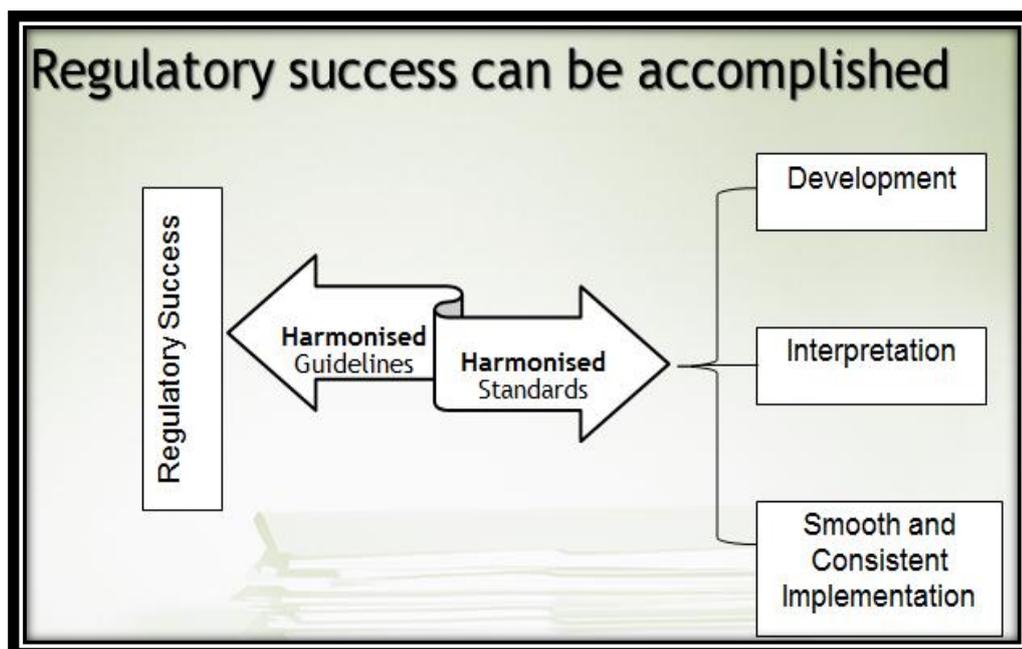
Of particular note, vaccine trials are different from other studies as they are usually done on healthy subjects. Unlike other studies where the focus is on the outcome of the treatment, in most vaccine trials antibody titers are measured to check the immunogenicity for prophylaxis. A vaccine trial usually aims at establishing at least one of the following-immunogenicity, reactogenicity, safety, tolerability and efficacy of a vaccine prior to it being licensed. A new vaccine must pass three hurdles before its approval by the national drug regulatory authority. Sufficient data as evidence is required to show the new-vaccine-to-be is of required quality standards, is effective for its prophylaxis use and is safe to use. As mandatory by Indian GCP, once the required data is generated and brought for processing, it has to be handled in a manner so that it is complete, accurate, reliable and validated. Therefore, the role of CDM has become an essential component for vaccine development.

The safety concerns and effectiveness of specific health and medical products and practices differ between countries and hence national governments regulatory norms/industry must accommodate (harmonize) them when committing to global standards. The un-harmonized national and international standards increase the cost of doing business apart from other hurdles. The global face of drug development demands that both government and industry pay more attention to internationally acceptable technical standards and conformance tests.



In today's competitive world, as true globally, all Indian Pharmaceutical companies are striving hard to streamline its internal procedures so that the time required for its research related obligatory regulatory requirements can be drastically reduced with almost no hurdles for the product to reach market. These procedures must be established in such a way so that every time when the company wants to launch the product in a country different than that of its origin, the regulatory authorities of the new place must accept its original work, and as far as possible, must not mandate the company to do the task again, only because there have been gaps with respect to the implementation of the logical steps. Thus all the processes, steps and procedures adopted must always be in a way to satisfy demanding legislation, rules and regulations [10] [11].

There are concerted efforts in the pharmaceutical industry to adopt a common data standard in various aspects of clinical studies and product development, for example, CDISC (standards for the interchange of clinical, non-clinical, laboratory, and statistical data) and GMP. However, a widely adopted common CDM procedural standardization/harmonization does not exist. The proposed study is an attempt to develop and implementation of analogous standards for CDM, leveraging existing GCP framework for vaccine studies conducted by Panacea Biotec Ltd. It is also important to acknowledge that the common specification may be unsuited to the needs of the product; it is imperative to establish the functional specifications (based on product type- vaccines/ drugs or therapeutic segment) and scope of the common data standard. Adoption of standard has helped to reduced noise by eliminating operational errors/variations; implement, maintain, and improve common doctrines/processes to achieve/ensure consistent data quality in less time. This not only decreases costs involved but also enhances competitiveness. Biggest benefit of standardization of CDM steps is achieving data quality that shall not only satisfy the requirements of applicable statutes and regulations but also support study outcome in terms of data efficacy and most importantly product safety.



The proposed study intends to define various steps of CDM of vaccine trials for Indian Pharmaceutical Company under the framework of Indian regulations. It is envisaged to set the stage for much needed progress in the establishment of procedures that might be used for the evaluation and mapping of procedural paths that could support regulatory review for market approval.

Standardization will help to develop a business solution which is process dependent, platform independent, vender natural, transparent and devoid of duplication. This may also mean reduced training time, and flawless transmission of information between partners, providers and regulatory authorities [12]. Moreover, the lessons gained, if applied at the project commencement stage, may be helpful to improve the study design, conduct, documentation, reporting and interpretation by serving as a blueprint for forecasting project performance.

Aim/Purpose of study:

Standardized CDM procedural and implementation steps supporting Good Clinical Practice (GCP) are needed in the context of vaccine trials that facilitate meeting audit requirements and enable regulatory compliance.

Objectives:

1. Define and implement CDM procedural steps in the context of vaccine clinical trial (MyfiveTM vaccine) in an Indian Pharmaceutical company, within the scope of Indian regulations.
2. Effective documentation of CDM procedural steps in compliance to meet audit requirements, to ensure implementation and data quality; expected outcome that:
 - i) there are no major/critical deviations or findings,
 - ii) no need to unlock database so that the data are adequately safeguarded
 - iii) procedural steps suffice, operating in conformance with desired practices, to achieve the data quality expected by Indian GCP validated by QA.
3. Replication of audited CDM procedural steps to NUCOVAC[®] vaccine trial to achieve standardization

Methodology

CDM steps were conceptualized to align with industry best practices adopted from literature review, expert opinion, and parallel to GCDMP (Good Clinical Data Management Practice), a Society of Clinical Data Management (SCDM) [13]. The steps were implemented in the context of MyfiveTM vaccine trial and audited by QA department. If there were no major or critical auditing findings, a working model developed for MyfiveTM trial was replicated in NUCOVAC[®] vaccine study to achieve process standardization. All these activities were carried out at Panacea Biotec Ltd., an Indian Pharmaceutical company, within the scope of Indian regulations [14].

Objectives were enumerated through surveys (internal and industry), to check the feasibility of the CDM processes based on the CDM parameters not limited to the following:

- Compliance to Regulatory
- Quality for very small quantity of Data
- Quality for large quantity of Data
- Randomization & Blinding

- Support to multi-arms study
- Subject Confidentiality maintained
- Double Data Entry
- Data access by authorized person
- Data security system maintained
- Recorded audit trail
- Hardware & software – validation, Adequate backup
- Credibility of the data based on the study design
- Data discrepancies handling

The industry survey revealed that heterogeneity in CDM procedures exists across Indian industry. There is a need for standard CDM procedural and implementation steps meeting the requirements of audits and/or inspections, and facilitating increasingly stringent and complex regulatory approvals.

Results and Discussion

Following are the major steps adopted and their outcome:

Annotation of CRF

Each field was assigned a name in the Case Report Form (CRF) to meet the requirements of data base design. Annotations were consistently used, where feasible, with an objective of quick rollout of extension/sister studies and to facilitate meta-analysis, thereby to achieve standardization.

Data Management Plan (DMP) Standardization

Distribution list, study specific milestones, team structure, task ownership matrix, list of applicable SOPs/ guidelines, list of self-evident corrections etc. were defined in terms of its contents and format, and incorporated in DMP to ensure consistency and thereby compliance.

Database Design

Oracle Clinical (OC, Version 4.5.3.) was used as Clinical Database Management System (CDMS). To achieve performance consistency and a step towards creating global standard pages, use of Questions, Questions groups was adopted from global library of OC. Following tasks were accomplished, based on the study requirements:

- Use of Correct/consistent SAS Labels
- Correct/consistent use of code list and controlled terminologies
- Flagging of mandatory fields
- Applying upper and lower ranges (bounding)
- Hard Coding of fields as applicable
- Use of repeat questions groups, indicator and qualifying questions
- Conditional branching navigations on screen
- Correct order of Cursor movement
- Use of subsets in Data Collection Module (DCM) for consistent page layouts
- User Acceptance Test (UAT) i.e. test data entry was done before release of the database into production

Edit Checks programming

For global standard pages, edit checks were copied to have consistency of output in terms of the text language used in the data clarifications forms. However, new PL/SQL program was developed for study specific unique pages as per the input from study medical monitor.

Double Data Entry

Double data entry was done followed by reconciliation(s) and rectification(s) of data points with differences in the value, a desired practice not possible to perform in traditional Excel® spread-sheets (invalidated). Any change in the data values was updated with proper audit trail with time stamp, as audit trail documents the history of every single task for all the pieces of business transaction.

Validation of Data

Live data was incrementally scanned for its correctness as per the protocol requirements by triggering the scheduled batch validation or by running a single procedure.

Query Management

Discrepancy management was done to provide accurate and credible data by creation of Data Clarification Forms (DCFs). DCFs were sent to the investigator's site to seek query resolution. DCF tracking logs were maintained to monitor DCF flow and to keep the track of turn-around-time (TAT) by the site.

Data View

Views were created to facilitate analysis by the biostatistician. SAS format was used to generate system views. View template was copied for subsets of DCMs (Data Collection Modules) to have consistency and to achieve process standardization.

Data Coding

Verbatim terms for Serious Adverse Events (SAE) and Adverse Events (AEs) were manually coded with the help of Medical Dictionary for Regulatory Activities (MedDRA) to achieve consistency and facilitate data analysis.

SAE Reconciliation

Registry of SAEs was maintained at CDMS and Pharmacovigilance (PVG) safety database. SAEs were reconciled to have the same and consistent information. All discrepant data points were identified and if needed DCFs were created to seek resolution from the site.

Quality Control (QC) activities

QC measures including, but not limited to the following were applied [15]:

- QC Report of CRF annotation
- QC Report of Database Designing and Entry Screen Layout
- QC report of 1stand 2ndPass Test Data Entry
- QC Report of Validation Procedures

- QC Report of View Definitions, View templates and Data Extraction
- QC Report of Subject Enrollment
- QC Report of MedDRA Coding
- QC Report of Discrepancy Status in OC
- 100% QC of Critical Data Points
- 100% QC of Random sample size using $\sqrt{n+1}$
- QC Report of DCFs

QC findings were resolved / updated as required and all the signed QC reports were documented in the Master Data Management File (MDMF)[15].

Database lock

Database lock process was initiated once all the activities were complete as per database lock check list to prevent unauthorized access and thereby data integrity. Some of the activities that were completed to ensure that the database is now ready for lock are listed below including but not limited to the following:

- All Study Data Entered
- MedDRA coding done
- SAE reconciliation accomplished
- All discrepancies reviewed, resolved and closed with the appropriate resolutions
- Final data QC completed
- QA activities completed
- Approved and signed documents placed in specific folders in MDMF

Consistent performance in the CDM processes achieved has resulted in the following operational/strategic rewards that shall facilitate auditing requirements and regulatory compliance, which are enumerated below with the examples not limited to the following:

Effective management of procedural risk:

- CRF pages were not misplaced, as this problem occurs if tracking is not done properly
- System status for the CRF pages strived to be achieved as 'passes two complete'. No page was omitted for second pass data entry, by establishing robust data entry tracking procedure
- All validation checks were in Active stage and no one was inadvertently left with the Provisional status demonstrating effective QC.

Elimination of technical/procedural hurdles:

Procedures were in established to handle the situations such as following business scenarios [16]-

- Version change of CRF: before the start of study at the site
- Version change of CRF: for an ongoing study
- Use of different versions of the CRFs at different sites for the same study.

Demonstrate desired quality consistently:

High volume of data collection i.e. data scalability can increase the error rate and compromise the quality. Thus all the procedures which are implemented can be translated easily for addressing the requirements by multiple regulatory agencies and health authorizes. Established procedures are likely to minimize scope for malpractices or redundant action as it is easily possible with Excel® spread-sheets (invalidated).

Almost no SOP deviations:

Unlike previous studies, audit findings have revealed that there was no SOP deviation with respect to the procedures, documentations, formats etc.

Less time required for training:

Standardization of CDM procedures has contributed to the domain knowledge enhancement, decreased training time for subsequent projects and thus decrease in the overall time to market.

Facilitation exchange of data and dataset:

Standardization of CDM procedures has not only helped in easy exchange of data but other extended benefits which was identified was: Bio-statistician Unit can use pre-written programs, Marketing department can use the inputs from the trial outcome soon for clinical communication, care planning, identifying the correct healthcare practitioners and thus for overall better serving for patient healthcare.

No need for database unlocking

Implementation of efficient procedures, validated by QA, as helped to eliminate 'Unlocking of database' for both the studies.

Prevent duplication of tasks

The CDM model for the said vaccine trials are expected to give compliance not only as per Indian regulations but may help to adhere to international norms thereby avoiding retrial/duplication of work.

This is because the steps address the following dimensions to create mass impact for CDM of vaccine studies:

- leverage of best practices
- technology driven research work
- successful adoption as validated by QA
- conforms to government, policies and regulations which impact and define the implementation and roll outs. [17]

THESIS CHAPTERS

The outcomes of the above listed objectives are detailed as described below:

Chapter 1: Introduction

Indian pharmaceutical companies are still struggling to achieve standardization of processes for clinical data management of vaccine trials. This chapter will provide background information focusing on the existing practices and need for standardization of CDM activates for vaccine studies.

Chapter 2: Review of Literature

State-of-art of current practices followed in industry and procedural gaps resulting in regulatory non-compliance.

Chapter 3: Research Methodology

This section outlines approach adopted towards identification, definition, implementation and standardization of easy-to –follow and practical CDM procedures, validated by QA. Each task is explained in a stepwise manner for the following vaccines: Myfive™ (DTwP-HepB-Hib) and NUCOVAC® (Pneumococcal) manufactured by Panacea Biotec Ltd.

Chapter 4: Result and Discussions

This section describes the outcomes of implemented steps and operational reward that shall facilitate auditing and regulatory compliance.

Chapter 5: Future Prospects

This section describes a way forward to manage increasingly complex and stringent landscape of regulatory compliance.

i) Future Trends

Metrics for CDM as Next Practice

During the course of development, implementation and standardization of CDM procedures in the context of vaccine trials in an Indian pharmaceutical company, it emerged that multi-factor metrics based performance monitoring of critical procedural steps have synergistic impact in boosting overall in-time progression of the project and meeting desired data quality [18].

ii) *CRF Design Imperative for CDM*

The design of the CRF is imperative not only from the viewpoint of clinical research operations and the study site staff, but the perspective of data management team should not be ignored. A well designed CRF with correct layouts can aid in study conduct by enhancing the performance, as the data collected is expected to be credible and accurate with minimum errors; thus depicting the importance of good CRF designing practices for CDM [16].

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