WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 12, 318-333. Review Article ISSN 2277– 7105

CLINICAL DATA MANAGEMENT(CDM) PROCESS STANDARDIZATION FOR VACCINE TRAILS IN AN INDIAN PHARMACEUTICAL COMPANY UNDER INDIAN REGULATIONS

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Article Received on
02 July 2022,

Revised on 22 July 2022,
Accepted on 12 August 2022

DOI: 10.20959/wjpr202212-25226

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ABSTRACT

Framework that might emerge from establishing CDM procedural paths could improve clinical data management practices and thereby supporting regulatory compliance. India is fast becoming hub for vaccine research and development. Efficient and quality clinical data management remains a challenge. Effective CDM not only support consistent performance desired to meet increasingly tough and an inherently dynamic regulatory compliance requirements but it also drives all stages of drug development economics both prior to and subsequent to product registration and marketing, addressing key challenges not limited to thefollowing. Such clinical scales are also the need for regulatory review to aid in drug development procedures as per GCP. Standardized CDM definitions, the process of developing and implementing technical standards, CDM data formats are needed to optimize data management. 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.

KEYWORDS: Clinical Data Management (CDM), Vaccine Trails, Good Clinical Practices (GCP), CDISC (standards for the interchange of clinical, non-clinical, laboratory, and statistical data) and GMP.

1. INTRODUCTION[1-4]

Clinical Data Management (CDM) is of critical importance in the drug development process and outcome of a clinical trial. Clinical trials, biomedical research studies on human subjects are done under strict ethical and regulatory framework. The data generated from a clinical trial serve to draw scientific inference, therapeutic or prophylactic spectrum, and as evidence that an investigational product is safe and effective for use in human. Data, the clinical information gathered from a trial, 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 could be entered into the database.

Conduct of Clinical Research industry is confronted with a multitude of regulatory constraints. Thus, 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. 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 form national authorities on quality assurance for biological product.

In India, there are two major guidelines which govern trial conduct assuring the ethical and scientific integrity. Indian GCP by CDSCO (Central Drugs Standard Control Organization) and ICMR (Indian Council of Medical Research) ethical Guidelines for Biomedical Research on Human Subjects. These regulatory guidelines demand accurate, reliable and credible data but provide no explicit recommendations on how to adapt them for CDM processes.

The focus of Indian regulatory is more on the site management, clinical trial operations, trial ethics governance and pharmacovigilance (safety data). However, there is no regulatory document that gives step by step clarity on procedures which may be adopted for CDM of drug or vaccine trials. It is the responsibility of the organization to identify, adapt to GCP, implement and document the processes so as to generate regulatory compliant data.

There exists a great diversity in the procedure adopted for data processing and handling in the industry. The provisional CDM processes/criteria adopted are broadly based on opinion of experts. Arguably, there is no universal set of GCP standards or application of GCP

principles, with variation in their implementation and applicable stringency of regulatory agencies. However, having no standardized CDM procedures, variations in procedures adaptation/operating guidelines practices and thereby differences in outcomes, may affect inference from clinical trials and compromise both quality assurance and regulatory compliance.

A vaccine trial aims at establishing, not limited to the following, immunogenicity, reactogenicity, tolerability, safety, and efficacy prior to vaccine being licensed. Vaccine trials are different from other clinical studies as they are done on healthy subjects, and addressed, in particular, pediatric segment. This demands a very low tolerance for adverse event and compliance with high levels of ICH-GCP (International Conference on Harmonization published Good Clinical Practice) and other global regulatory agencies standards such as US-FDA (United States, Food and Drug Administration), EMEA (European Medicines Agency) and WHO, apart from national regulatory agencies before its market approval. Thus generation of quality data is of critical importance.

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.

Indian Pharmaceutical companies, as true globally, are striving hard to streamline its internal procedures so that the time needed 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.

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 definedin protocols/DMP/ study reports and must be validated through audits.

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1.1. Purpose of Study: CDM Standardization in the context of vaccine trials in an Indian Pharmaceutical company[5,6]

Framework that might emerge from establishing CDM procedural paths could improve clinical data management practices and thereby supporting regulatory compliance. India is fast becoming hub for vaccine research and development. Efficient and quality clinical data management remains a challenge. Effective CDM not only support consistent performance desired to meet increasingly tough and an inherently dynamic regulatory compliance requirements but it also drives all stages of drug development economics both prior to and subsequent to product registration and marketing, addressing key challenges not limited to thefollowing.

1) Mitigation of different types of error in the data,
2) Support statistical analysis,
3) Fast regulatory approvals,
4) Assist in marketing the drug,
5) Adaptability and easy redeployment of the CDM processes,
6) Fast study site training,
7) Procedural risk management,
8) Elimination management of technical/procedural hurdles,
9) Consistent and desired quality,

10) No need for database 'unlocking',
11) Prevent duplication of tasks or redo trial and
12) Identification of fraudulent data and malpractices.

A recent study in Europe showed that heterogeneity prevails[11] as there is no common standardized and validated global/ national industry-wide CDM procedural and implementation framework.

Such clinical scales are also the need for regulatory review to aid in drug development procedures as per GCP. Standardized CDM definitions, the process of developing and implementing technical standards, CDM data formats are needed to optimize data management.

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.

1.2. Current practice of CDM: International Trials[7-10]

International CDM guidelines, best practices and standards that must be followed are as listed below[17] but are not mandated under Indian guidelines and regulations:

- Electronic records have to comply with a CFR (Code of Federal Regulations), 21 CFR Part 11.
- GCDMP document by SCDM.
- Clinical Data Interchange Standards Consortium

CDM is a group task and must have the roles listed below, which may be considered as minimum requirements for a CDM team[17]

- Quality Control Associate
- Data Manager
- Clinical Data Coordinator
- Database Programmer/Designer
- Data Entry Associate
- Medical Coder

Team members of CDM actively contribute in all stages of clinical trial right from inception to completion therefore should have satisfactory procedural knowledge to achieve needed quality by applying correct CDM processes resulting into extreme reduction in overall time needed for drug development to its marketing. Various processes in CDM include:

- CRF designing,
- CRF annotation, database designing,
- Data-entry, data validation,
- Discrepancy management,
- Medical coding,
- Data extraction, and database locking

2. Indian regulations for conduct of clinical research[10-13]

The clinical research market in India is likely to grow at a constant rate of 20-25 percent. Although India shows steady increase in clinical trials registered since the introduction of clinical trial registry of India (CTRI), still it lags behind established countries in the field of clinical research. Evolution of modern clinical research in India has occurred with the major breakthrough by ICMR New Delhi, with its guidelines for biomedical research on human subjects in the year 2000. This was updated in the year 2006 'Ethical Guidelines for Biomedical Research on Human Participants.

Schedule Y of the Drugs and Cosmetics Act 1988 has recognized the regulatory guidelines for clinical trial authorization in India. The schedule compelled the industry to carry out Phase III clinical trials for registration of a new drug and supported growth of a primarily generic Indian pharmaceutical industry.

Revision of Schedule Y in January 2005 was an important turning point as it has widen the narrow and restrictive definitions of clinical trial phases, as compared to its previous versions, by providing pragmatic definitions for clinical trial phases I to IV, acceptance of concurrent Phase II-III, as part of global clinical trials.[68] The earlier constraints on number of subjects and study sites in early phases, as specified in schedule Y 1988, were revoked - allowed to grant the freedom to the sponsor company to decide these in relation to protocol requirements.

Indian GCP guidelines of 2001 were legalized in Schedule Y 2005. This schedule detailed GCP obligation of investigator, EC (ethics committee) and sponsor and suggested

templates/formats/structure for critical documents e.g. informed consent, protocol (report), ECapproval, reporting of serious adverse event, but of CDM processes to be followed. These laudable amendments in Schedule Y have been a major step to protect the integrity of Indian clinical trial industry, in conducting ethically compliant trials and providing the much-needed regulatory support to GCP guidelines. CDM as a critical activity of a clinical trial also need to evolve into a standardized procedure.

However, Indian clinical research is at a perilous phase as the execution of local regulations and global guidelines does not seem to be in congruence. These guidelines do not provide explicit recommendations as to how each CDM step should be executed to achieve standardization across industry.

There is also no supplementary or detailed documentary assistance in ICMR (in public domain at the time of writing of this thesis, 2015) to my knowledge. With more number of qualified clinical researchers, data managers and overall scientific developments, there is an immediate need for regulatory processes to be streamlined.

Advancement of clinical research promises new and innovative therapies and vaccines with upgraded technologies. This calls for ongoing need for updation of regulations, guidelines andrecommendations for better safety, efficacy and quality of Intellectual Property with less time to hit the market in a cost effective manner.

These continuous scientific developments will come true with headway progression in instream branches of clinical research like ‘Clinical Data Management’. Overall conduct has to be done within the upgraded robust regulatory and sound ethical framework, necessitating major apprises in current procedures or best practices, followed by subsequent standardization.

Indian regulations are continuously advancing and becoming more and more stringent in order to safeguard the interest of trial subjects and ensure drug safety. One such example is the letter by DCGI (Drug Controller General of India) which says that if there is any delay of more than 6 months in the start of the trial then the same should be brought to the notice ofthe authorities for necessary action.

3. Indian regulatory requirements: CDM for vaccines[12-14]

Each country has its own sets of guidelines to conduct clinical research. The focus of this

thesis is definition, implementation and standardization of CDM activities in the context of vaccine trials in an Indian pharmaceutical company. Indian GCP, the major guidelines available in India, and its application in vaccine trials is discussed below. The details are described of the mandatory regulatory obligations, mentioned by CDSCO in India GCP for stream lining. Indian GCP for streamlining the clinical studies, with reference to CDM, and endorsed for adoption by the DTAB (Drug Technical Advisory Board), the highest technical body under D&C (Drugs and Cosmetics Act).

Inferences drawn from these guidelines depend upon the individual perceptions as there is no standard format, checklist or illustration given in the guidelines, depicting how to fulfil these requirement(s). The universal face of drug development stresses on the fact that both Indian drug regulators and industry pay more attention to world-wide acceptableCDM best practises. Utmost attention is needed for streamlining of guidelines with respect to global standards to evolve into the era of standardize best practises for CDM procedures.

4. Research methodology[15-18]

4.1. Indian pharmaceutical industry survey

A survey was conducted to glean in industry perspective of the needs and challenges of CDM practice in India. The survey indicates lack of industry wide common CDM data standard. The ECRIN data management centers survey was used as a reference for the questionnaire.

Anonymous input was used and the names of respondents are not disclosed to maintain confidentiality. The 46 respondents, 28 in number having more than 5-year of clinical research experience, representing 16 companies having their offices in India (Ranbaxy Laboratories Ltd., Biological E limited, CliniRx Research Pvt. Ltd., PATH Clinical Research, Kinapse Clinical Research, Novo Nordisk, Parexel International, Cognizant Technology Solutions, INC Research, Quintiles, Apcer Pharma, Panacea Biotec Ltd, Glenmark Pharmaceuticals, Venus Remedies Limited, Theorem Clinical Research and Tata Consultancy Services), responded to the questionnaire. The survey data was considered together with verbal discussion with experts from the CDM field, including representatives of various cross-functional teams involved in CDM and related activities at Panacea Biotec Ltd. The survey was related only to CDM practice in general; it was not connected to a specific clinical trial. No ethical approval for the survey was required because no patient data were collected.

4.2. CDM procedural steps

CDM procedural steps were conceptualized to align with industry prevalent best practices. The steps to develop CDM processes for vaccine clinical trials were adopted after evaluating literature, considering expert's opinions (regular telephone conversations and face-to-face discussions with experts both at Panacea Biotec Ltd, and across industry, and conclusion drawn from the outcome the above described industry survey), and calibrated to international guidelines or practices described below, avoiding copyright infringement, to suffice the requirements as per Indian GCP, and also international specifications; none of the below listed documents used as a reference are specific to vaccine trial CDM:

- GCDMP by a SCDM
- ACDM (Association for Clinical Data Management) public website
- ECRIN data management task
- SDTM (Study Data Tabulation Model) , CDASH and other similar CDISCdocuments

The survey described in the section 3.1 highlighted the need for simple, practicable, practical and standardized CDM procedures apart from that there exist limited human and financial resources for CDM, to meet requirements of GCP and thereby GCP compliance. Interestingly to question "Heterogeneity of CDM procedures will lead to non-compliance to GCP, the response was ambiguous. Approximately 53.33% respondents answered 'Yes' and 46.67% answered 'No', reflecting that CDM practices at variance does not equates to non-compliance to GCP in the absence of CDM specific procedural guidelines.

The CDM steps applied in the Myfive™ vaccine trial were audited by QA department. If there were no major or critical auditing findings, the working model established for Myfive™ trial was replicated in NUCOVAC® vaccine study to achieve process standardization. All these activities were carried out at Panacea Biotec Ltd., New Delhi, an Indian Pharmaceutical company, within the scope of Indian regulations after the needed approval as mandated by DCGI, the Indian clinical trials regulatory authority and the Institutional Ethics Committee. Certain information in the following sections and results (Chapter 4) with respect.

Regular verbal discussions within the CDM and cross-functional teams (in particular-Project Management team, Medical Writing team, Clinical Operations Unit, Biostatistics Unit, Quality Assurance (QA), Pharmacovigilance (PVG) etc.) were carried out to gather individual team members perspectives and their understanding of the adopted CDM procedures to bring about company standards in the context of vaccine trials. There were

no differences of opinion within the CDM group. The various CDM parameters considered are listed in the data details ha s not been disclosed tomaintain confidentiality.

4.3.CDM model adopted: Myfive™ vaccine trial

Figure 3.1 depicts the schematic of the methodology adopted for processing (data collection, transformation, analysis and report submission) of clinical trial data for the Myfive™ vaccine trial, performed using paper CRF. The traditional method of use of paper CRFs are still used today in almost 30% of active global trials.

The various CDM team participants, CDM a group activity to effectively deliver its responsibilities, were Project In-charge CDM (Project Manager), Database Administrator, Database Designer, DM (Data Manager), Data Entry Operator, Data Coordinator, SAS Programmer/Statistician, Quality Control Personnel, Quality Assurance Personnel, Medical Dictionary Coder and Trainer.

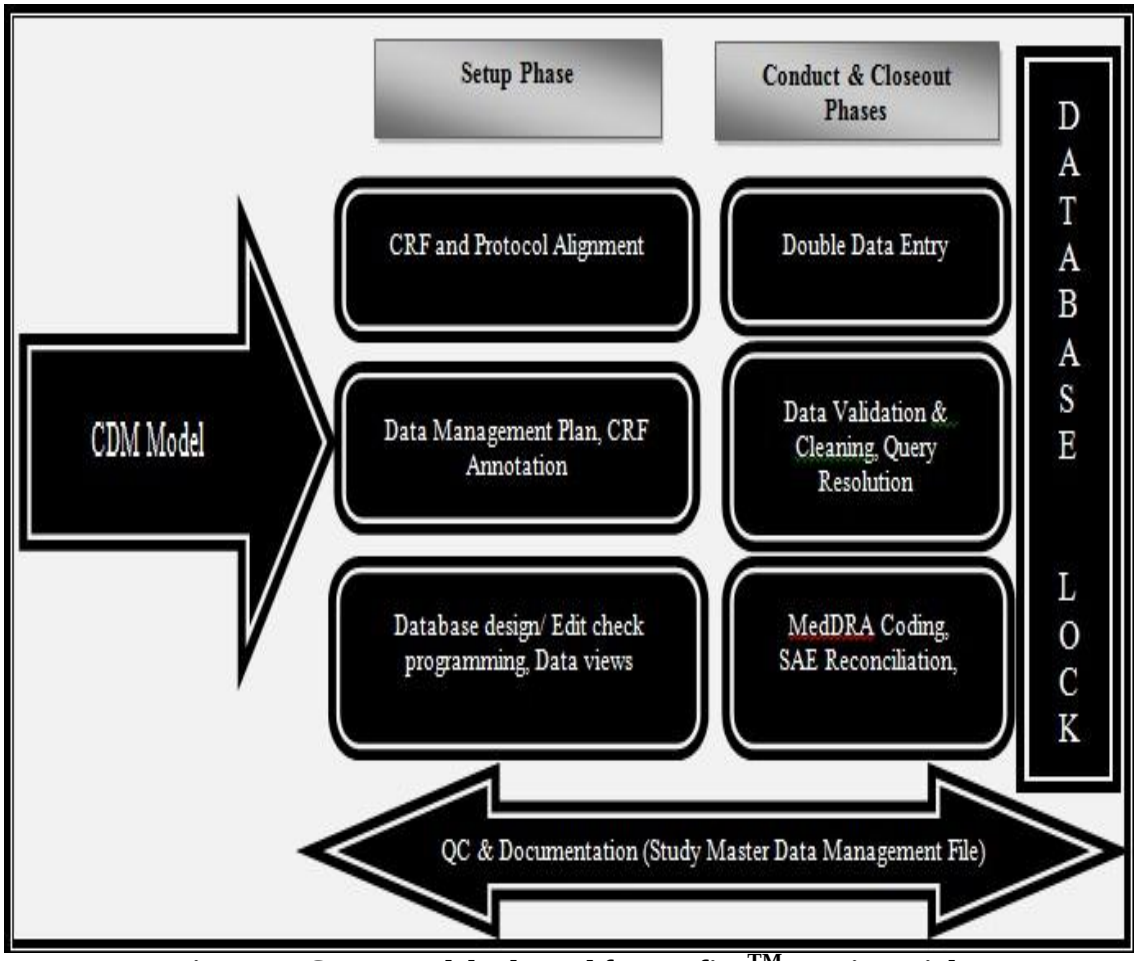

Figure 1: CDM Model adopted for Myfive™ vaccine trial.

Swim lane diagram

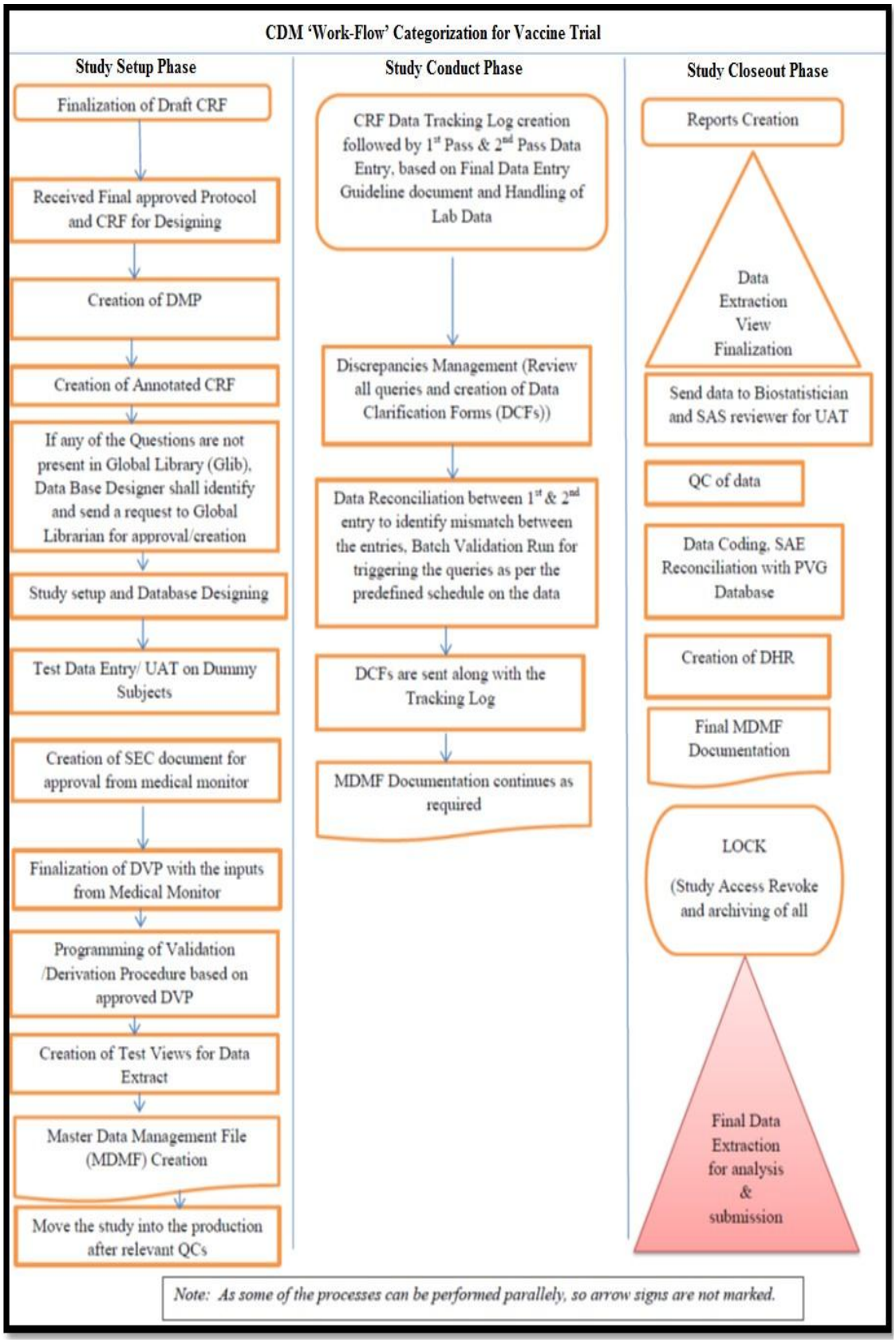

Figure 2: Swim Lane Diagram for CDM Work Flow.

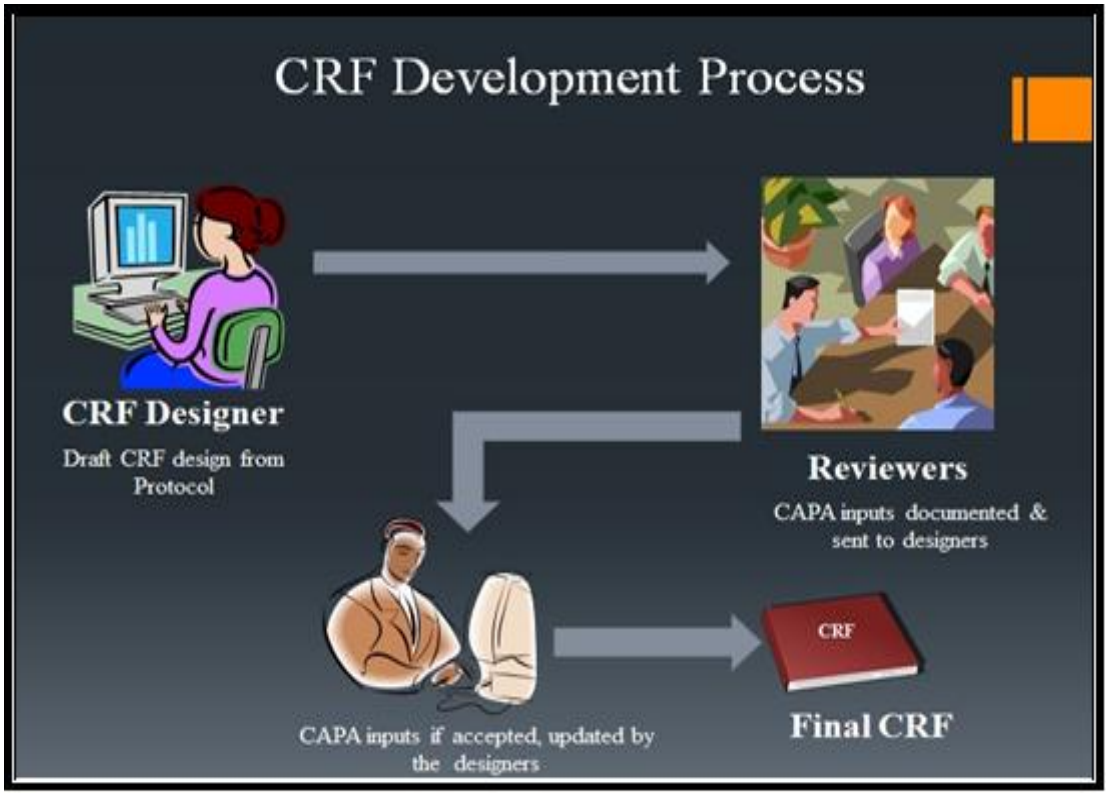

Figure 3: CRF Development Process.

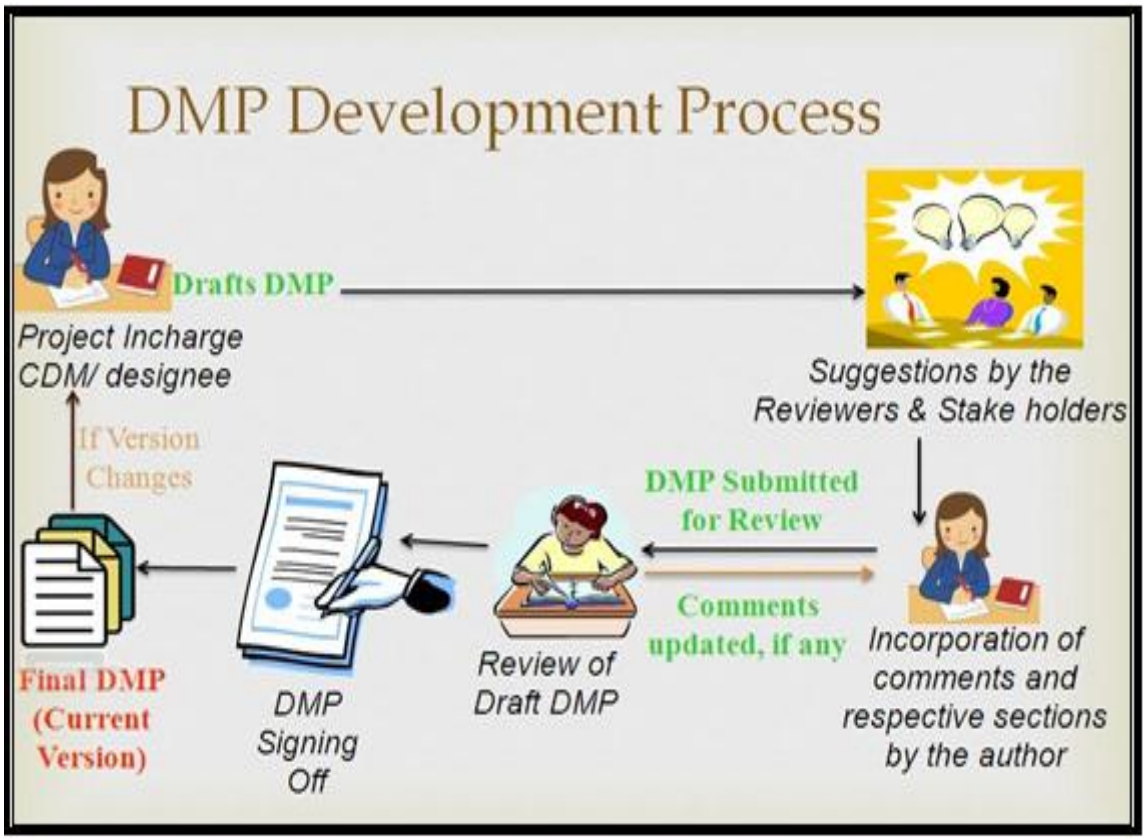

Fig. 4: DMP Development Plan.

Flow chart of finalisation

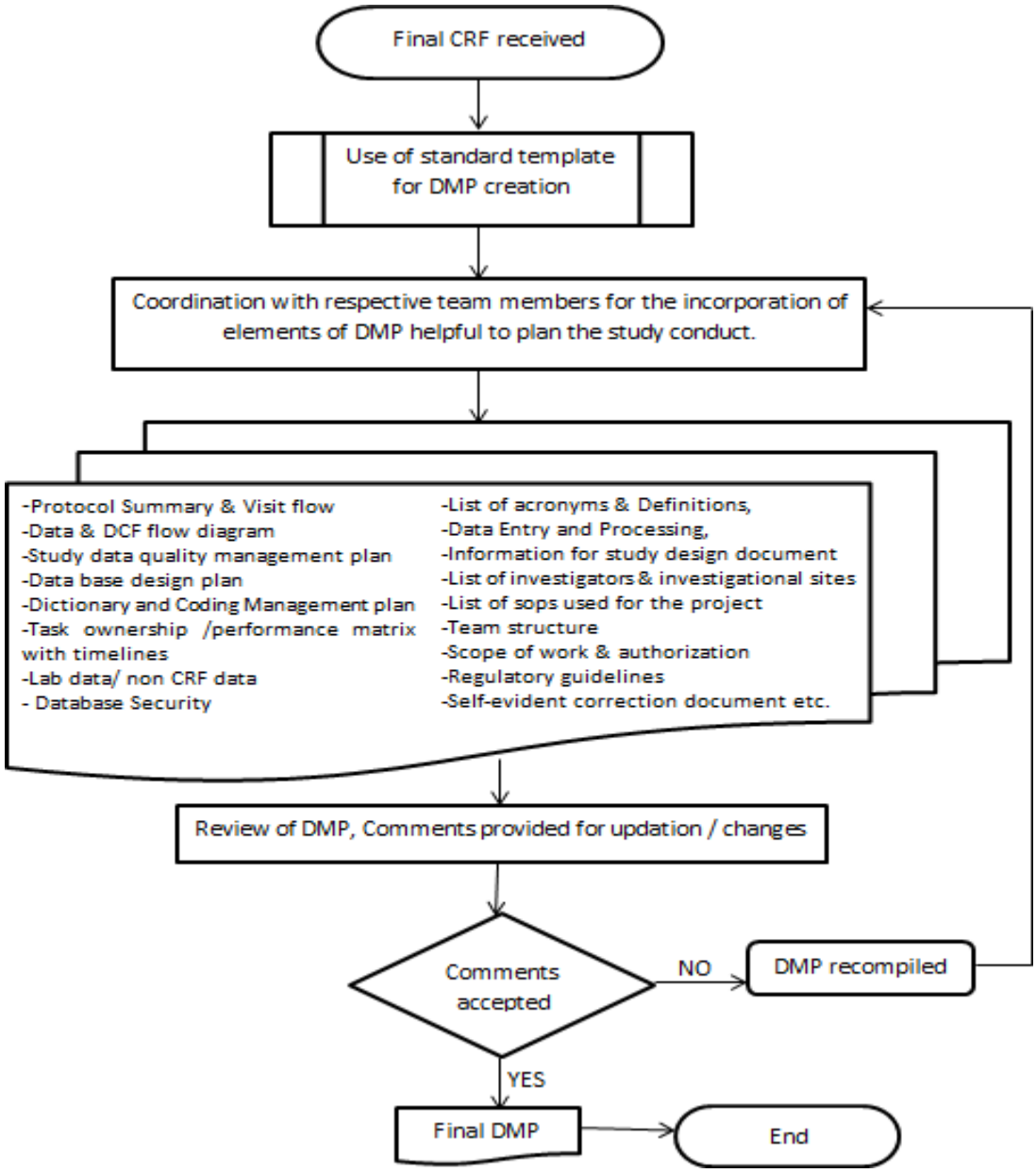

Figure 5: Flow Chart for finalization of DMP.

4.4. CDM Processes: NUCOVAC® vaccine trial

The implemented CDM model for Myfive^{TM} vaccine, QA validated and regulatory compliant (audited) procedures, was replicated in NUCOVAC® vaccine trial (Figure 3.27) to achieve CDM procedural standardization (in-house common data standard, Panacea Biotec Ltd.).

The CDM procedure adopted for NUCOVAC® vaccine trial was audited by QA Department to ensure that there are 1) no deviations in SOPs, 2) no major/critical audit findings in the adopted steps, and 3) no need to 'Unlock' database, thus thereby procedural standardization.

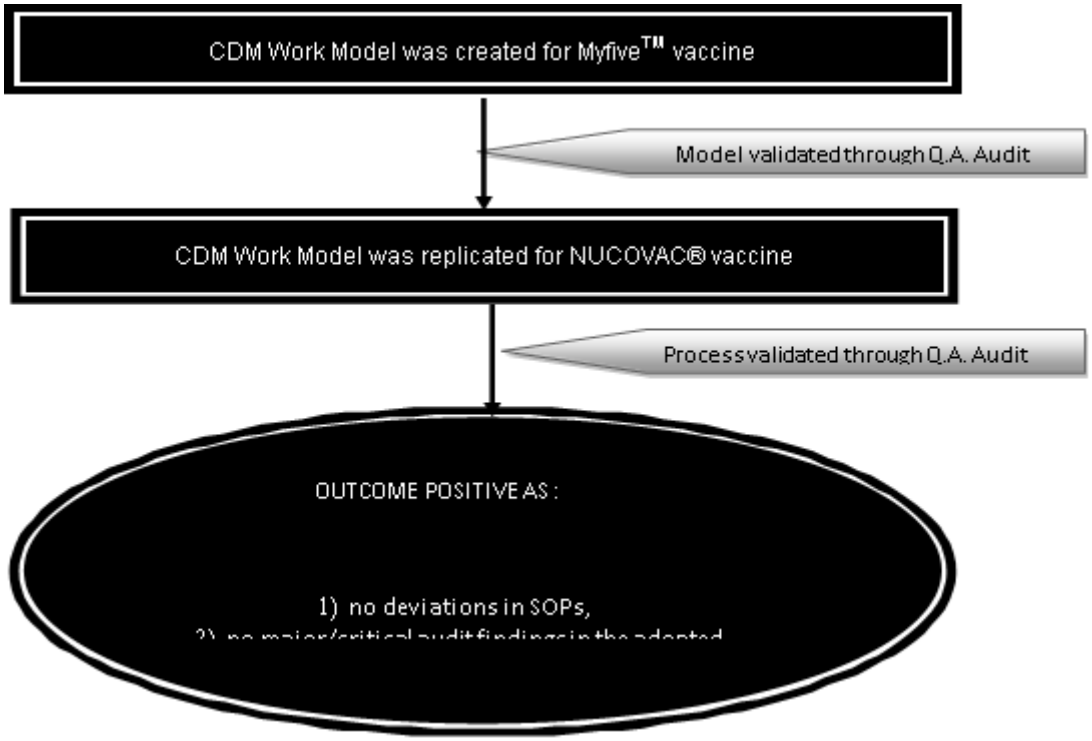

Fig. 6: CDM Model Standardization for vaccine trial, Panacea Biotec Ltd.

5. CONCLUSION

The chapter that follows "Review of Literature" details CDM practices prevalent in industry. The chapter "Research Methodology" 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.

Next is the chapter that describes the outcomes of implemented steps and operational reward that shall facilitate auditing and regulatory compliance. The chapter Future Prospects describes metrics for CDM developed as Next Practice; multi-factor metrics based performance monitoring of critical procedural steps having synergistic impact in boosting overall in-time progression of the project and meeting desired data quality [a way forward to manage increasingly complex and stringent landscape of regulatory compliance. It is acknowledged that the common specification may not be suited to the needs of a given investigational product; it is imperative to establish the functional specifications (based on product type- vaccines/ drugs or therapeutic segment) and scope of the common data standards. Adoption of standard has helped to reduced noise by eliminating operational errors/variations, unnecessary procedures; implement, maintain, and improve common

doctrines/processes to achieve/ensure consistent data quality in reduced time. This not only lowered costs involved but also enhanced competitiveness. Biggest benefit of standardization of CDM steps was achieving data quality that not only satisfied the requirements of applicable statutes and regulations but also supported study outcome in terms of data efficacy and product safety.

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