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STANDARDIZATION OF PROCEDURAL IMPLEMENTATION IN CLINICAL DATA MANAGEMENT WITH REFERENCE TO THE TRIALS: DTwP-HepB-HIB VACCINE (MYFIVE™) vs. PNEUMOCOCCAL VACCINE (NUCOVAC®)

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ABSTRACT

Drug or vaccine safety is the prime concern in clinical trials along with theoverall efficacy. Consequently, it is worthwhile to identify and establish the key processes which ensure consistent outcome in data quality and satisfy applicable safetystandards. This article describes standardization and harmonization of procedures and steps adopted for clinical data management in vaccine studies of Panacea Biotec Ltd. It is expected that the methodological approachmay be adopted as standard operating procedure in compliance with the expectations of Indian Good Clinical Practices.

KEYWORDS : Standardization, Clinical Data Management (CDM), Clinical Data Management System (CDMS)

Adoption of procedural standardization/ harmonization in clinical studies is not new. This has thereby reduced operational errors/variations; helps implement, maintain, and improve common doctrines/processes to achieve/ensureconsistent data quality in reduced time. This not only decreases costs involved but also enhances competitiveness. Biggest benefit of harmonization of CDM steps is achieving data quality that shall not only satisfy the requirements of applicable statutes and regulations but also support study outcomein terms of data efficacy and most importantly product safety. Furthermore, standardization/ harmonization helps 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 (Bajpai et al. 2013). This report describes a comparative study conducted on Clinical Data Management processes adapted for DTwP-HepB-Hib(Myfive™)and Pneumococcal (NUCOVAC®) vaccine trials.

MATERIALS AND METHODS

In this case study we havecompared overall processes adopted for CDM by analyzing the output in conjunction byequating the audit findings for each of the parameters (Table, 3) of Myfive™ and NUCOVAC ® vaccine trials conducted by Panacea Biotec Ltd.. Both studies were conducted after approval from Drug Controller General of India (DCGI) and respective Ethical Committees, with strict adherence to Indian regulatory guidelines, without compromising rights, well being, safety and confidentiality of trial subjects.

Table, 1 provides brief description of the clinical trials. Due to confidentiality reasons complete information about the protocol is not shared.

The clinical data management of DTwP-HepB-Hib (Myfive™) vaccine was done prior to that of Pneumococcal (NUCOVAC®) vaccine study, by implementinga procedural model for ensuring quality in the processes. The same steps were repeated for NUCOVAC® Vaccine Study. This was done with utmost carefulness to avoid deviations in the adopted steps.

CDM Activities: Operation Methodology Adopted

The primary objective of CDM processes is to provide high-quality data by keeping the number of errors and missing data as low as possible and gather maximum reliable and accurate data for statistical analysis (Krishnankutty et al., 2012 and Gerritsen et al., 1993). To achieve the outlined goals and objectives, following steps were performed.

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Table 1:Brief Outline of Study Protocol

Summary	DTwP-HepB-Hib (Myfive™)Vaccine Study	Pneumococcal (NUCOVAC®)VaccineStudy
Study Title	A Randomized, Multicenter, Open Label, Comparative Study to Evaluate the Immunogenicity and Reactogenicity of a Fully Liquid PentavalentDTwP -HepB-Hib Vaccine (Myfive™, Panacea Biotec Ltd.) with PentavalentDTwP-rHepB-Hib vaccine (Pentavac SD/MD, Serum Institute of India Ltd.) in Healthy Infants.	A Randomized, Open Label, Comparative, Single Dose Phase I/II Study to Evaluate the Safety, Tolerability and Immunogenicity of two Formulations (with and without preservative) of 10 -valent Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) NUCOVAC® in Healthy Adults.
Phase of Development	Phase II/III	Phase I/II
Number of subjects	600 (300 in each arm). Initially, the study was conducted in 48 healthy infants.	A total of 48 eligible subjects will be enrolled in the study, 24 in each study arm.
Dose administration	0.5ml per dose by deep intramuscular injection	0.5 ml by deep intramuscular injection
Site of administration	Antero-lateral aspect of thigh	on Day 0 at the deltoid area of arm
Duration of protocol therapy	3 months	Single vaccine dose followed by 24 hours observation.

These steps are depicted in table 2 with the help of the screen shorts of the document and/or Clinical Data Management System (CDMS)Oracle Clinical (OC) Version 4.5.3. These procedures were performed sequentially or in parallel, as applicable.

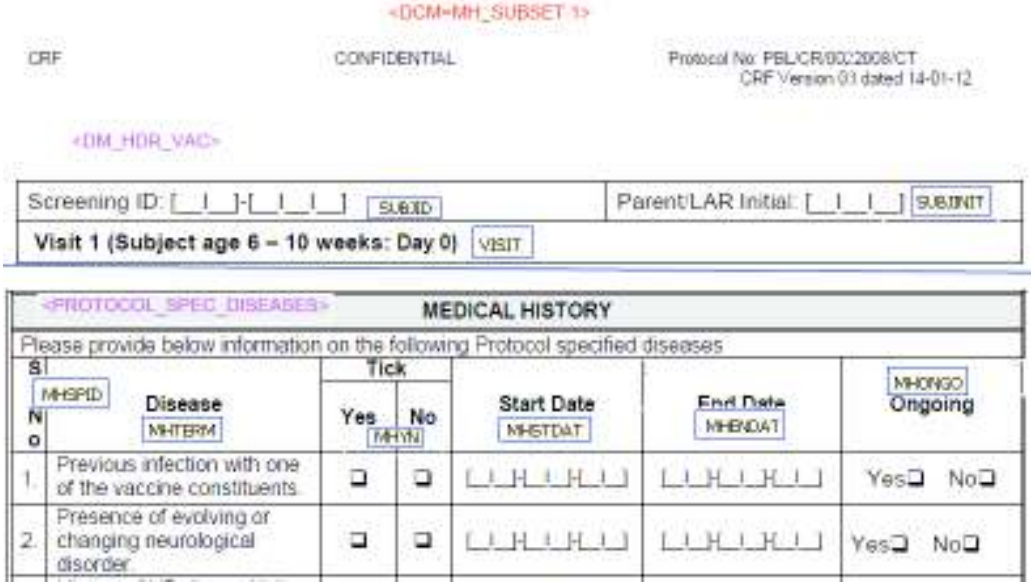
The processes were adopted to suffice Indian regulatory requirements of data handling and processing.

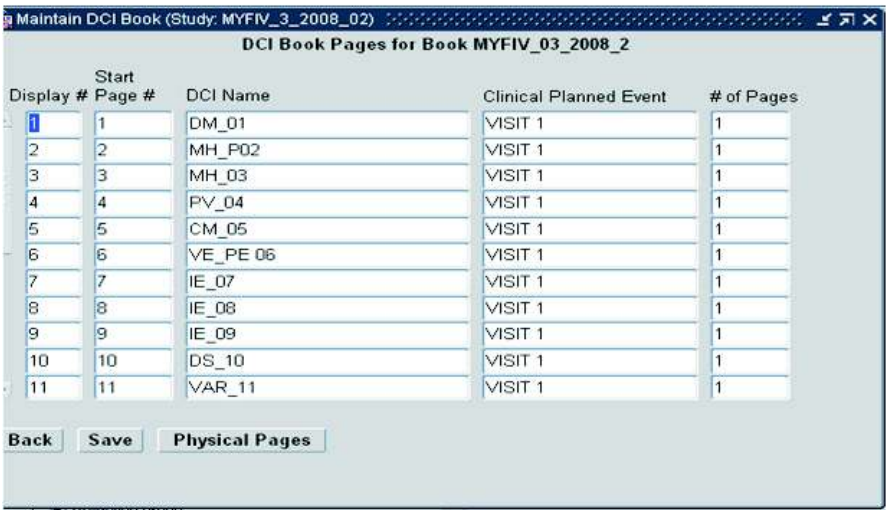
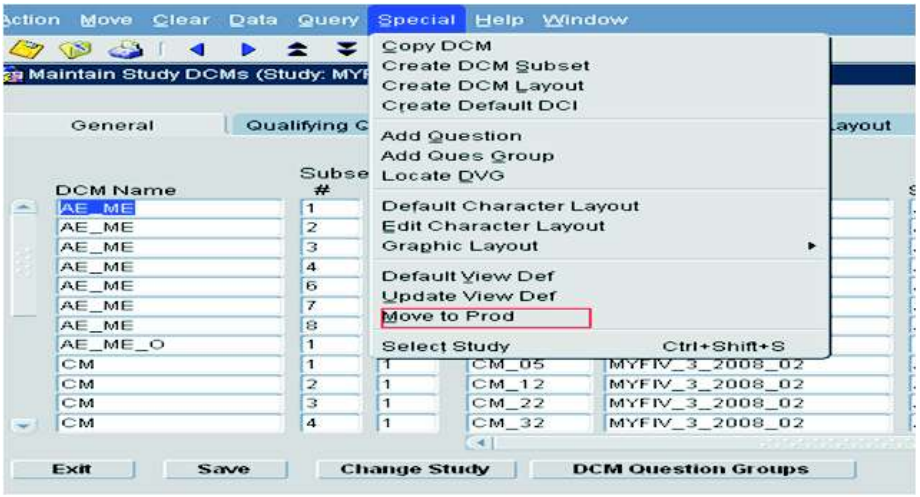
Analysis of harmonization in the CDM procedure for the vaccine studies

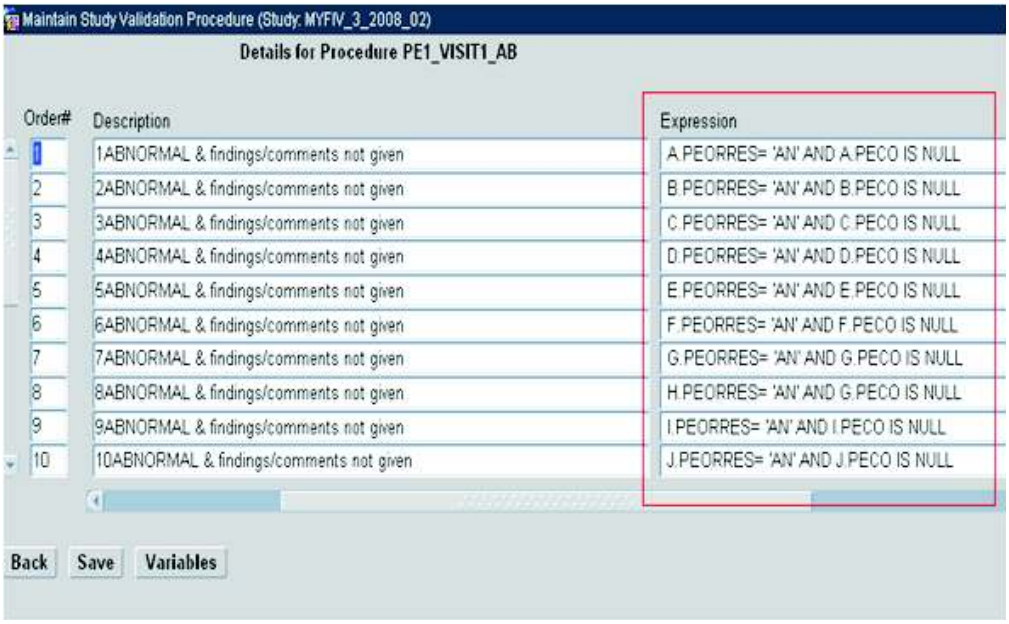
Apparently by inspecting the above process it is reasonable to conclude that harmonizationwas achieved in the method adopted in the management of the clinical trial data and its subsequent processing.

CDM activities are normally categorized into three different stages: Study Start-up, Study Conduct, and Study Closeout (Li F., 2011). In-order to see whether the process for the two trails were similar, let us now analyze the total number of audit findings for each of thesephases. Since there was no difference in the overall findings in the 'Conduct & Closeout phase' therefore we have analyzed the

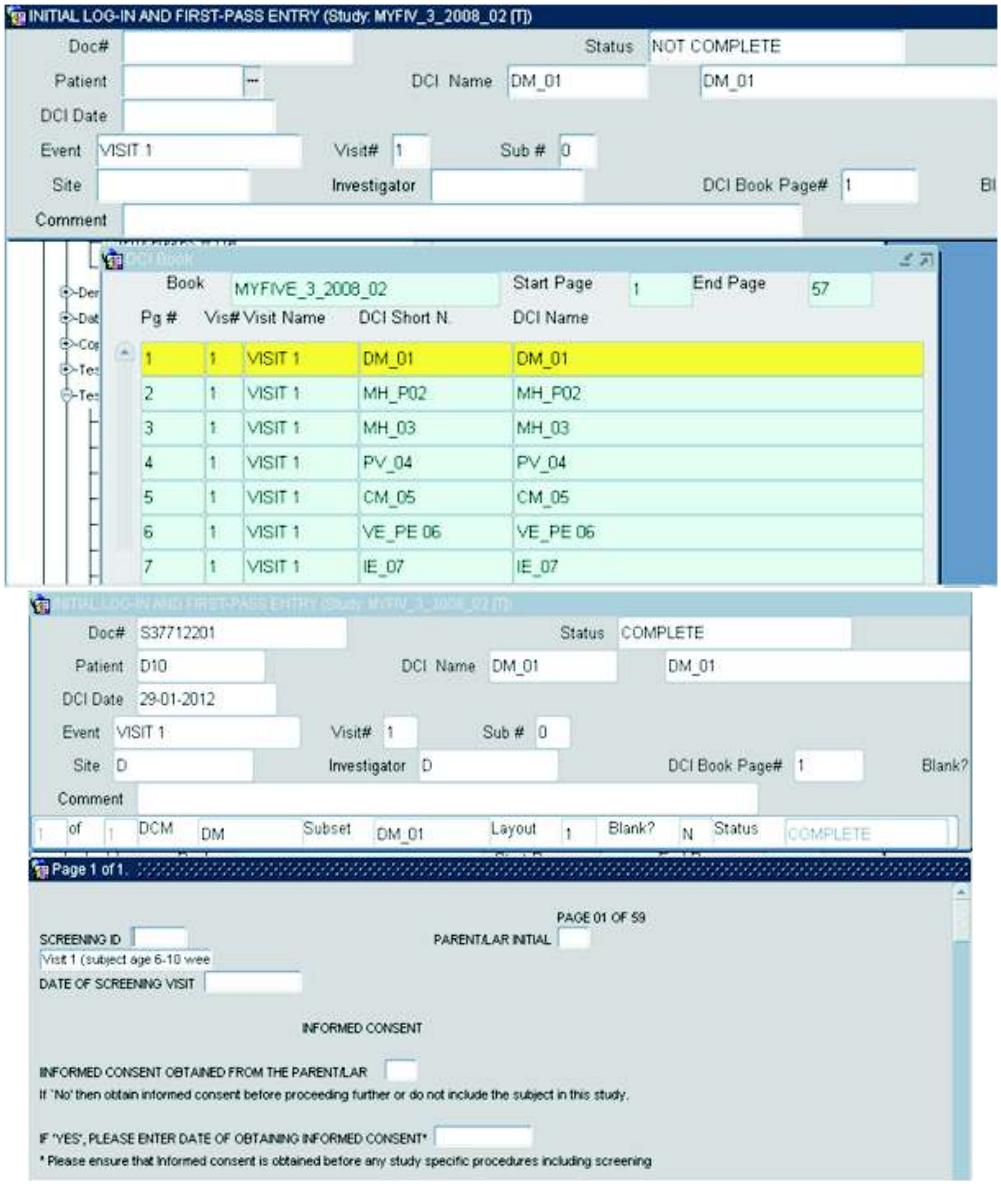
Table 2 : Screenshot of CDM Steps Adopted For Vaccine Clinical Trial

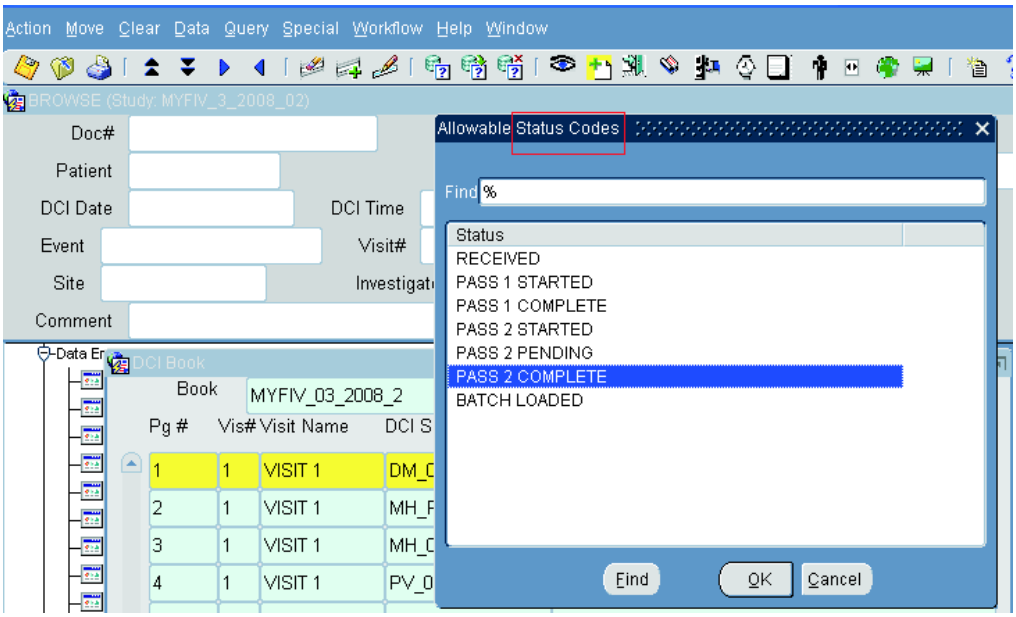
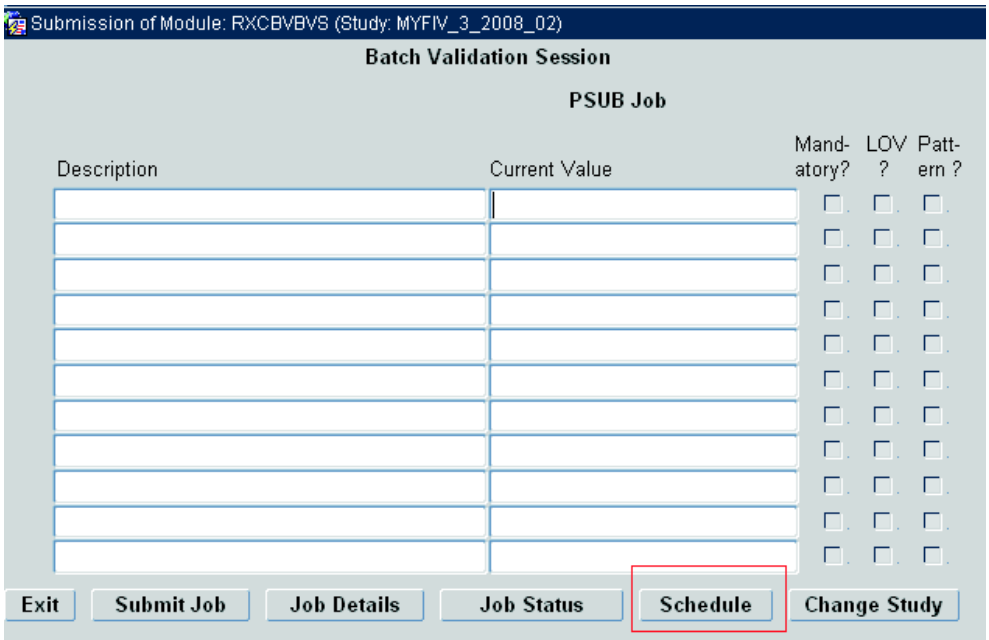
CDM Steps	Myfive™ Vaccine of Panacea Biotec Ltd (Similar procedure was adopted for NUCOVAC®vaccine trial)
Finalization of Case Report Forms (CRF)	CAPA (CRF and Protocol Alignment Document) This document was prepared, keeping in mind the requirements for database designing; some of the example picked from the document are: • Demographic Data: Page numbering is incorrect. • Diary Card: Please check if investigator's signature is required on all the pages of diary card
Annotation of CRF	Final CRF was received by CDM unit for annotations, refer to the screen short below: 
Data Management Plan (DMP)	Data Management Plan included the points not limited to the following: • Project specific information • Distribution List • List of SOPs used for the project • Team Structure , Scope of work & Authorization • Regulatory Guidelines • Self-Evident correction (SEC) Document • Information for Study Designing in OC Following are some of the examples SEC, picked from the document: • If two individuals can deduce interpretation similarly from theambiguous handwriting in the CRF, then query for that data point is not needed. • If all the information in the header is correct and only one is incorrect, then same shall be corrected as SEC, if it is not conflicting with the uniqueness of the CRF page with respect to patient data.

CDM Steps	Myfive™ Vaccine of Panacea Biotec Ltd (Similar procedure was adopted for NUCOVAC®vaccine trial)
Design of Database	Subsequentto CRF annotation, database designing was initiated. After database designing was completed, test data entry was done, some of the common criteria for checking the same are: • 'Length' of fields should be as per CRF • 'Text on the screen'must be the replication of the CRF text • 'Cursor' movement should be correct • Options in the 'Discrete value groups (DVGs)'must be in right order. • SAS Labels must be as per the CRF as they are helpful to biostatistician for data processing Data Collection Instrument Book was prepared as follows:  After successful database designing and validation of all the procedures, the study was moved into production mode. 

<table>
<tr><th>CDM Steps</th><th>Myfive™ Vaccine of Panacea Biotec Ltd
(Similar procedure was adopted for NUCOVAC®vaccine trial)</th></tr>
<tr><td>Edit Checks programming</td><td>
Edit checks may be described as programmed notifications that are created by a database. The purpose of edit checks is to respond to the data points that are inconsistent or may have errors. Following are some of the examples:
<table>
<tr><th>Dataset</th><th>Procedure Name</th><th>Screening Page</th><th>Check type (Programmed/Manual)</th><th>DCF Text/Message</th></tr>
<tr><td>DM</td><td>DM1</td><td>1</td><td>Programmed</td><td>Both age and birth date are blank fields</td></tr>
<tr><td>DM</td><td>DM2</td><td>1</td><td>Programmed</td><td>Refer page 1 of screening form: date of visit must be equal to or greater than date of informed consent. Please check!</td></tr>
</table>
The following shows details of proceduresas seen in database:


</td></tr>
</table>

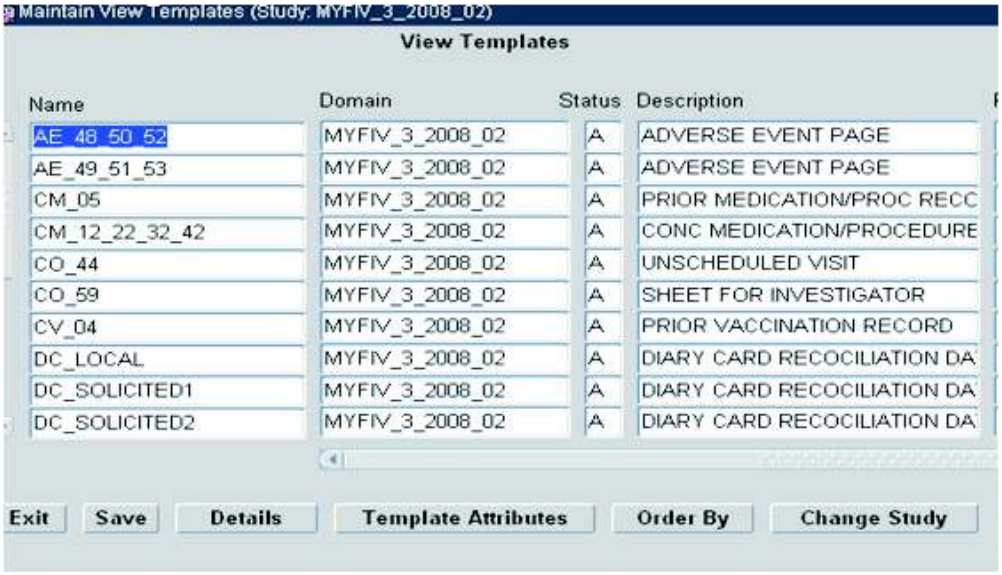
CDM Steps	Myfive™ Vaccine of Panacea Biotec Ltd (Similar procedure was adopted for NUCOVAC®vaccine trial)
Double Data Entry	CRF was received for data entry and double data entry was performed, as per data entry guidelines of the study. Following two screen shows first pass data entry for the study:  Once the first pass entry was done, this was followed by second pass data entry. This ensures that the data was entered correctly and accurately. When both the entries were complete and all CRFs were entered,data reconciliation between first and second pass entry was done. Differences, if any, between the two entries werereconciled. As soon as the reconciliation was complete , page status was checked to confirm the same:

CDM Steps	Myfive™ Vaccine of Panacea Biotec Ltd (Similar procedure was adopted for NUCOVAC®vaccine trial)
	
Validation of Data	Batch validation was done as per the schedule, so that the validation checks can trigger the queries, if any: 

<table>
<tr><th>CDM Steps</th><th>Myfive™ Vaccine of Panacea Biotec Ltd
(Similar procedure was adopted for NUCOVAC® vaccine trial)</th></tr>
<tr><td>Query Management</td><td>
Discrepancy Management/Data Cleaning was started along with data entry.
Few examples of queries that were sent to the site for resolution are:
<table>
<tr><th>Query</th><th>Resolution Received</th></tr>
<tr><td>Refer CRF page No. 1 & 15: Difference between Advised date for next scheduled visit (DD -MM-YY) and Date of Visit1 is not equal to 28 days; please check!</td><td>Date for next scheduled visit is 22 -02-12. It is also corrected in CRF.</td></tr>
<tr><td>Value of 3.10 for PRESENT WEIGHT (KG): DM below expected minimum of 3.3</td><td>Present weight is ‘3.4 kg’ date is verified with source, correction also made in CRF.</td></tr>
</table>
Following is the screenshot of DCF as sent to the site for resolution

Page ID: D2013601
Protocol No.: PBL/CR/0022008/CT (Study of 48 Subjects)
Data Clarification Form
To:SANT DNYANESHWAR MEDICAL EDUCATION RESEARCH CENTRE
Investigator:R.K. DHONGADE
Date:27-FEB-2012
Patient#:A1035
Patient Initials:LSP
Reviewer:Pragati Bais
Form Name / Visit Name | Page # Date | Questions/Comments | Resolution
CRF PAGE 01 OF 59: INFORMED CONSENT & SUBJECTS DEMOGRAPHIC DATA VISIT 1
Disc ID: 122548801
Type: MULTIVARIATE
1, 15
20120216
Closed: N
Refer CRF page No. 1 & 15: Difference between Advised date for next scheduled visit (DD-MM-YY) and Date of Visit1 is not equal to 28 days; please check!
DATE OF VISIT = 20120131
DATE FOR NEXT SCHEDULED VISIT = 20110228
Date for next scheduled visit is "28/02/2012". It is inadvertly written as "28/02/2011".
PUNE 30
Page 1 of 1
DCF ID: 2870901
Revision #: 0
</td></tr>
<tr><td>Data View</td><td>
Preparation of view templates and view definitions was done. Most of the views were prepared after the completion of database designing. Once the views were prepared, these were tested by the biostatistician for detests related requirements.

Following shows a screenshot of view templates in database :
</td></tr>
</table>

<table>
<tr><th>CDM Steps</th><th>Myfive™ Vaccine of Panacea Biotec Ltd
(Similar procedure was adopted for NUCOVAC®vaccine trial)</th></tr>
<tr><td>Data View</td><td>


</td></tr>
<tr><td>Data Coding</td><td>Data coding was done for the verbatim terms in the CRF, using MedDRAVersion 15.0. The coded verbatim terms were later approved by the medical monitor
<table>
<tr><th>MedDRA 15.0 Coding of AE</th><th>SOC</th><th>PT</th><th>LLT</th></tr>
<tr><td>Swelling</td><td>General disorders and administration site conditions</td><td>Swelling</td><td>Swelling</td></tr>
<tr><td>Fever</td><td>General disorders and administration site conditions</td><td>Pyrexia</td><td>Fever</td></tr>
</table>
Common problems faced by medical coding expert while coding medicinal products:illegible verbatim term, spelling errors, use of abbreviations, indication prescribed for the medicinal product is not an approved indication mentioned on prescribing information, local brand available in market and generic/active ingredient is not known, multiple medications recorded together4.</td></tr>
<tr><td>SAE Reconciliation</td><td>There was no Serious Adverse Event(SAE) in both the studies. Same was confirmed from Pharmacovigilance database.</td></tr>
<tr><td>Quality Control (QC) activities</td><td>Each step was followed by QC to ensure that the task was accomplished correctlyand completely in compliance with SOP and regulatory requirements.</td></tr>
</table>

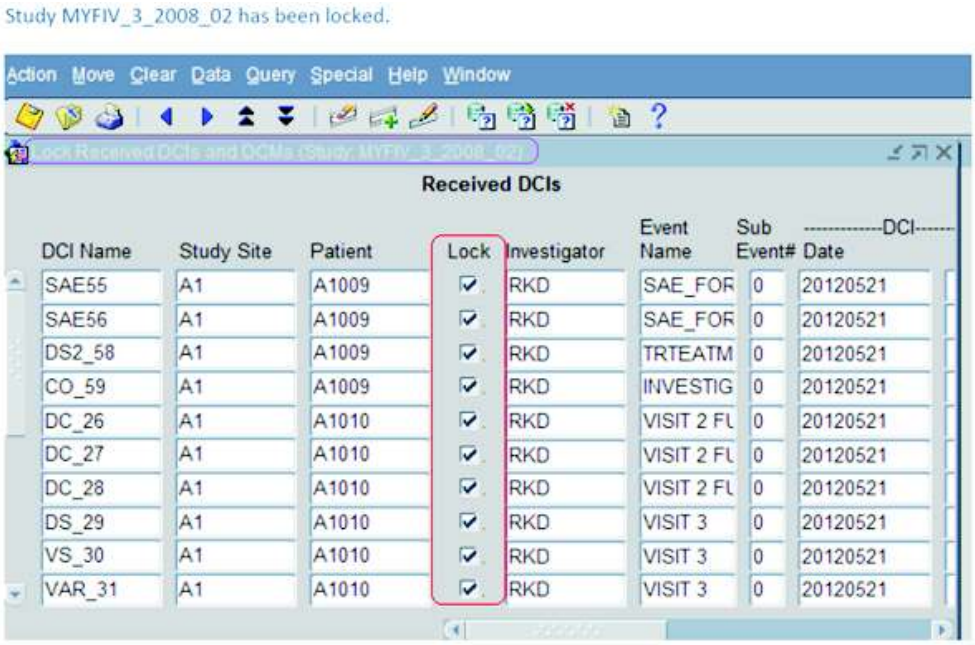
<table>
<tr><th>CDM Steps</th><th>Myfive™ Vaccine of Panacea Biotec Ltd
(Similar procedure was adopted for NUCOVAC®vaccine trial)</th></tr>
<tr><td>Database lock</td><td>Activities related with database lock were initiated.
Before database lock, it was ensured that the task as per database lock check list iscomplete. Some of them are-
It was ensured that all CRFs were received and processed.All DCFs (Data Clarification Forms) were received with resolution and queries were resolved, Data coding was complete, Quality check of all the activities were performed, SAE Reconciliation was done, All documents in MDMF (Master Data Management File) were updated and stored where required as per Standard Operating Procedures etc.
 
</td></tr>
<tr><td>Audit by QA Department</td><td>Both the studies were audited by representative of Quality Assurance Department. Audit agenda was:
<table><tr><th>S. No.</th><th>Activity</th></tr><tr><td>1.</td><td>Review of Master Data Management File and Process</td></tr><tr><td>2.</td><td>Study Database</td></tr><tr><td>3.</td><td>Review of Data Clarification Forms and Query Resolutions</td></tr></table>
The audit was successfully passed and there were no major/critical findings in the study;except for few minor once.</td></tr>
</table>

Table 3 : Gives The Detail About The Number of Findings Observed in Each of The Component of The Set-up Phase

Parameters Under Audit MDMF **Set-Up Phase**	DTwP-HepB-Hib (Myfive™)	Pneumococcal (NUCOVAC®)
MDMF Label	0	1
Data Management Plan (& SEC)	8	6
Protocol Amendments	0	1
Case Report Forms	0	0
CRF Protocol Alignment Document	0	0
Randomization	0	0
Computer System Details : Name of the software/package system used with its version number	0	0
Computer System Details : Description of the hardware platform	1	0
Computer System Details : Location of the database on the system and other details as applicable	0	0
CDMS Software Documentation (as applicable): Annotated CRF	0	0
CDMS Software Documentation (as applicable): Collation list (study specific Glib specifications, in excel sheet)	0	1
CDMS Software Documentation (as applicable): Field to code list association	0	0
CDMS Software Documentation (as applicable):CRF Layout (Screen layout)	0	0
CDMS Software Documentation (as applicable): Database Specifications (Generated from OC) as applicable for the study and Database Design -Data Collection Module Questions for Study - Data Collection Module for Study - DCI Detail Listing	1	0
CDMS Software Documentation (as applicable): Edit Specifications (Data Dictionary)	1	0
CDMS Software Documentation (as applicable): Procedure Details for Study or as applicable	0	0
CDMS Software Documentation (as applicable): Data Entry Guidelines	1	1
CDMS Software Documentation (as applicable): Data Import/Export details	1	0
CDMS Software Documentation (as applicable): Database Closure	0	0
CDMS Software Documentation (as applicable): List of critical and non-critical parameters for the study if applicable	0	0
Total Findings	**13**	**10**

The total number of findings observed for various component of the Set-up Phase for DTwP-HepB-Hib (Myfive™) were=13 in number as compared with that of Pneumococcal (NUCOVAC®) which were=10.

It was analyzedwhether the process adopted for two different studies deviated at the time of its execution- by postulating the following hypothesis. The null hypothesis states that means for both the processes are equal whereas the alternate hypothesis concludes otherwise.

$H_0: \mu_{my5} = \mu_{nucovac}$

$H_A: \mu_{my5} \neq \mu_{nucovac}$

Where μ_{my5} and $\mu_{nucovac}$ are the means for the processes adopted for the management of a clinical data for theDTwP-HepB-Hib (Myfive™) and Pneumococcal (NUCOVAC®), respectively.

The data represents the audit findings for each of the twenty parameters in the sample, for DTwP-HepB-Hib (Myfive™) and Pneumococcal (NUCOVAC®). Paired t-test, was used.

RESULT

From the study conducted it emerged that although there is a harmonization of the processes, however, the need for more studies with larger sample size (observations/parameters) cannot be ruled out.

DISCUSSION

As stated that the p value observed was >0.05. Thus, the data statistic fails to reject stated null hypothesis. It may be reasonably concluded that the process adopted for both studies has not deviated significantly. Of note, the 'auditors' and 'the time frame for the study conduct' were different, thereby minimizing the chances of bias in the observations considered for analysis.

CONCLUSION

Data was acceptable by QA in terms of accuracy, completeness, legibility, timeliness & data was ready to be compiledClinical Study Report (CSR).With this study we were able to implement the procedures of data management for vaccine trials in Panacea Biotec Ltd, andalso achieved standardization in CDM techniques. This enhancedthe benefits of consistent output including but not limited to the following

- Consistent performance
- Effective management of risks
- Functioning in more competent and sustainable manner
- Elimination of technical hurdles
- Demonstrate desired quality consistently
- Almost no SOP deviations

Table 4: t-Test: Paired Two Sample for Means

	DTwP-HepB-Hib (Myfive™)	Pneumococcal (NUCOVAC®)
Mean	0.65	0.5
Variance	3.186842105	1.842105263
Observations	20	20
Pearson Correlation	0.923204333	
Hypothesized Mean Difference	0	
df	19	
t Stat	0.900236936	
P(T<=t) one-tail	0.189631647	
t Critical one-tail	1.729132812	
P(T<=t) two-tail	0.379263294	
t Critical two-tail	2.093024054	

p value is >0.05,

- Less and efficient training time.
- Facilitation exchange of data and dataset
- Easy meta-analysis and roll-out of sister/extension studies

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