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Strategic implementation of CDISC across pharmaceutical companies- an integrated approach

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Abstract: *Strategically planned implementation process across pharmaceutical organisations will ease the submission process. It results in increased efficiency, cost effectiveness, avoid unforeseen surprises and it reduces stress for the employees. Although it is a challenging task for implementation and execution of CDISC (Clinical Data Interchange Standard Consortium) compliant dataset, a well-planned submission process will lead to successful regulatory submissions. This avoids re-opening of data bases and helps in smoother submission processes. There is a need for technical expertise and effective cost management implementation process. CDISC vision is to enlighten patient care and safety through higher class of medical research. CDISC mission is to improve medical research and healthcare related areas. The major goal is traceability from collection of data till analysis. Food drug and administration (FDA), Pharmaceuticals and Medical Devices Agency (PMDA), Prescription Drug User Fee Act (PDUFA) has mandated the electronic common technical document (eCTD) format for regulatory submissions. Sponsors need to reconsider whether they need to convert and standardize the data when the study data goes for submission approval or efficiently adapt from the beginning of the trial with the collaboration of global study team. This paper will help sponsors to adapt the strategical implementation process from the beginning of the trial and helps companies to overcome the challenges faced during the implementation. This paper also discusses how feasible is to invest internally or outsource to contractors or consultants considering the cost effectiveness and the skilled resources and validation of work being carried out.*

Keywords:*CDISC; Strategy; Implementation; Pharmacompanies; integration; Pharmaceuticalcompanies; Strategicimplementation.*

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I. Introduction

CDISC has proposed the ideal data flow model which is the conversion from raw data to SDTM to ADaM and then conversion to TLFs (table shells or templates to specify outputs for statistical display). The prime purpose of CDISC is the conversion of SDTM and ADaM standards and is to build datasets for analysis that supports analysis and reporting the data in the field of clinical research. The major goal of submitting clinical research results to regulatory authorities is to determine the efficacy and safety of the product or medical device. These models are not always easy for implementation and not result in the most effective data structure for day-to-day operations. These can be done by going from phase to phase implementation which includes setting up of CRF library, aCRF tool, standard controls, controlled terminology, SDTM and ADaM implementation. The unified approach helps in quality of deliverables and savings of cost. This helps in standardization across cleaning cycles. The quality review must be done consistently and will help in resolving mapping issues, programming issues, validation data issues and following up of SDTM domains set. We need to implement proper quality control plan and documentation based on the submission requirements. This helps in ease of integration process produced with high quality at very low cost.

We need to strategically implement CDISC compliant dataset processes across companies else if implemented incorrectly it results in delay in submission to regulatory agencies. We need to know the importance on evolution of CDISC and the building blocks for implementation of this process for submission readiness.

CDISC evolution, purpose and need for strategic implementation

The need for CDISC is to be compliant with regulatory requirements and to control the need of emerging standards. The major purpose includes data collection, data compilation and manipulation and the data

analysis for statistical and medical inferences on the grounds of efficacy, safety and traceability from protocol to analysis.

In 1980's, case report tabulations were originated for the submission of CRFs. Since 1997, CDISC has recognized the need for establishment of standards across pharmaceutical companies worldwide. After which during dec 2006, FDA announced to make the submission datasets to be compliant with CDISC. During 1999, electronic common technical document (eCTD) mandated SDTM submissions to be accompanied by data document definition and replacement of define.pdf by define.xml. The major submission requirements include CDASH (Clinical data acquisition standards harmonization), CRF design standards, SDTM raw study data tabulation for data management purposes, ADaM (Analysis Data Model) analysis dataset design and define .xml.

CDISC helps in creating the major specifications, plan required implementation, check for validation, standard operating procedure (SOP) updates and changes to specific organisational management (15).

The data flow of CDISC compliant dataset process includes from CRFs via electronic data capture to submission of metadata repository.

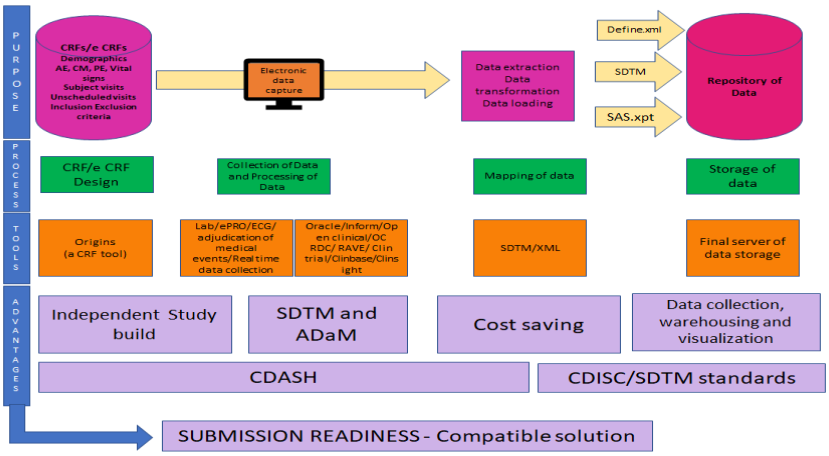

Fig. 1*CDISC Data Flow Process, Repository Of Data (11)*CDISC Standard Model Of Domains

The components of CDISC includes raw data, SDTM datasets, ADaM data and TLFs. Interventions, Events, Findings and special purpose are the major class of domains.

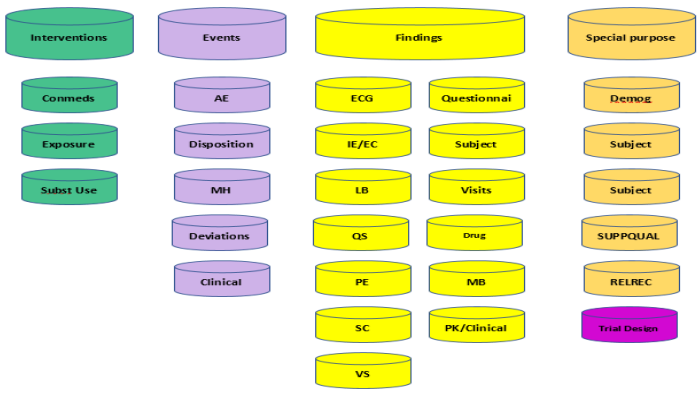

Fig.2*CDISC Domain Model (3)*

SDTM

SDTM **(**Study Data Tabulation Model**)** is the standard for submitting data to regulatory agencies (4). SDTM was originated in 1999 which is developed by CDISC team with a collaboration across pharmaceutical industries and clinical research organisations. This was developed with the help of small to midlevel service providers regularly by email communications, quarterly face to face meetings and teleconferences. The annotated CRFs provides the traceability from SDTM data. SDTM v1.1 serves as the conceptual model. SDTM v3.1.1 were later created which includes domain descriptions, examples and assumptions.Figure 3 explains the

origin of SDTM implementation guide. It is built based on domain models and real data examples, assumptions and interpretation, trial design domains or table, relationship across datasets for submission.

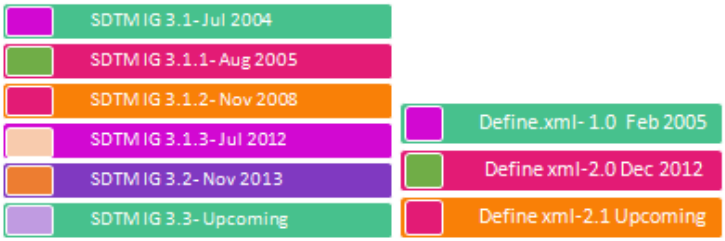

Fig.3 Sdtm Implementation Guide (12)

Trial Design Domains

Trial design domains are created for planned conduct of studies in a standardized way. It includes trial elements, trial arms, trial visits, epochs, trial inclusion exclusion criteria and trial summary dataset implementation. It serves as a building block for comparison with varied trials and actual and planned treatments (3).

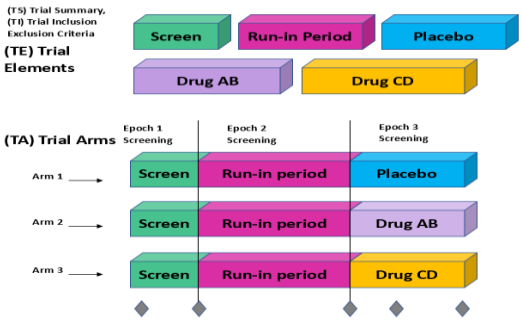

Fig.4 Trial Design Domains (3)

Define .xml

CDSIC define .xml study data specification is a replacement for traditional pdf. It provides quick and easy access to reviewers. The major purpose is to support metadata dataset in a machine-readable format. It supports clinical trial data submission to regulatory authorities. It represents with enhancements including CDISC controlled terminology support, value level metadata flexibility, origin or source data documentation enhancement, ADaM metadata improved support and comment handling (9).

ADaM

It is for documenting analysis results. It makes traceability of data easy. It identifies columns included for analysis data results. It includes ADaM data in SAS transport format (xpt files), Analysis Data Reviewer's Guide (ADRG) and result metadata including Define.xml. The major differences between SDRG and ADRG includes Validation level, SI unit conversion, Conformance issues, Unexpected specification. SDRG will update the reviewer about the standards being used, traceability, datasets being submitted and data validation (8).

TLFs

TLF is an industry reporting approach to generate table shells or templates to specify the outputs for statistical display.

The other standards developed by CDISC includes:

Clinical Data Acquisition standards (CDASH),
The Lab Model (LAB),
Operational Data Model (ODM),
CDISC Terminology (CT),
Protocol Representation Group (PRG),
Standard for Exchange of Non- Clinical Data (SEND) Implementation for pre-clinical or nonclinical studies (1).

With the help of CDISC standards we need to strategically plan and implement the processes more accurately considering the final submission goals.

Strategic planning and implementation of CDISC

When should organisation consider to strategically implement the CDISC processes?

The optimal way to implement CDISC process is based on the stage of the study whether it is a legacy (locked) trial or the trial is ongoing or a new prospective study.

The major implementation steps include:

1.Source data
2.generate SDTM
3.generate ADaM from SDTM
4.Result analysis
5.Trial documentation.

There are various approaches being carried out across companies for the implementation of CDISC. Strategical planning helps the company for submission readiness and meet the regulatory requirements. This enunciates organizations growth, progress and successful submissions.

Electronic data capture (EDC) makes SDTM compliant datasets submission readiness faster and easier. However, on the other hand, considering the collection of data including laboratory, (Electro cardio gram) ECG, Event adjudication, electronic paper reported outcome (ePRO) Questionnaires, real time hypo event collection, (Interactive voice response system) IVRS randomisation data must be standardized for submission readiness.

For legacy trials, meta-analysis must be made considering the cost and based on the submission requirement. This should be an added value for a standard database as mapping has been complex for completed trials. These trials are not CDISC structured and are not per principles of ADaM. The CRFs collected for these trials are per CDASH requirements and are tabulated using SDTM and the analysis had been done using ADaM compliant analysis. If non-compliant datasets are created it must be rebuilt completely however it is a challenging task to reproduce figures, tables and listings of raw data (6).

Especially longer duration trials including oncology trials are getting impacted with SDTM 3.1.3 (Define 1.0) to SDTM 3.2 (Define 2.0) (5). Study teams should not delay in implementation of SDTM and must choose to implement CDISC data flow which could ease the submission for regulatory authorities.

In case of any changes during the conduct of the trial can be easily tracked with the use of CDISC e share (shared health and research electronic library) downloads. These are developed for accessing the CDISC standards metadata electronically. It is a curated resource that makes it easier to implement CDISC standards in electronic systems such as clinical data management systems, mobile apps, and learning health systems. It also increases accessibility of these standards to programmers, data managers and biostatisticians. Implementing these standards can facilitate collecting, aggregating and analysing standardized data from early design to end analysis. Apart from this, SAS program, SAS macro or SAS spreadsheet compare can also help to find the changes. This helps in good clinical practices (GCP) and 21 CFR compliant and traceability for data analysis and integration (13). Hence, the best way to implement CDISC is to plan from the initial phase of the trial by deigning the CDASH compliant CRF pages, mapping into SDTM datasets thereby creation of ADaM compliant datasets and this would increase overall efficiency (7).

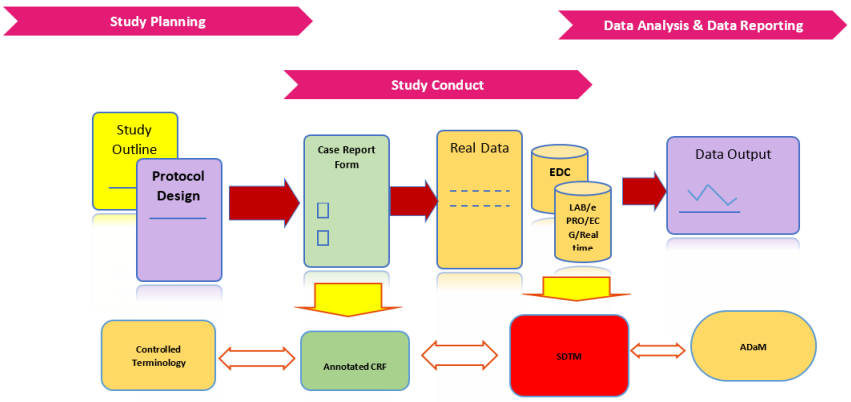

FIG.5Strategic Planning And Implementation Of CDISC (7)

Strategic planning and implementation of CDISC helps in time saving, cost effectiveness and more efficient

way of data submissions by a sponsor or CRO to regulatories (14).
With the defined processes, we need to strategically implement CDISC-compliant study data across the trials.

Successful implementation of CDISC processes

How can the implementation process of CDISC be successful?

This can be made successful with a team of knowledgeable experienced experts in both standards and processes. The implementation team must be dedicated and enthusiastic be it small scale or large-scale pharmaceuticals or a full service CROs. Clinical data management team plays a key role in the SDTM implementation and need to understand the downstream effects of TLs and analysis datasets.

The implementation team should make sure there should not be any delay and should start during protocol initiation phase itself. The team should have thorough knowledge of CDISC standards and Therapeutic standards. They should also have commitment towards accomplishing within the timeline.

Contractors who are data standard experts can also be a solution for successful implementation for a tight deadline. Knowledgeable contractors should be hired based on networking and recommendations considering the long-term goals of an organisation. Independent contractors, CDISC experts can also be hired based on the organisations requirement and make choices of remote work considering the secure data.

For successful implementation, final validation of data checks and review must be done thoroughly considered based on the company specific requirements. In context to ethical aspects resources must be efficient and continue to work towards achieving the goal for new standards (15).

Importance of strategic implementation of CDISC

The importance of having implementation process in place is to help companies in data acquisition. This unified approach for both SDTM and ADaM will help in creating a standard repository and help in submissions across organisations (7).
This helps in risk assessment and impact analysis which thereby helps in task orientation and increases the quality and timelines for deliverables with traceability. This is to create standard SAS global and therapeutic area specific codes including standard reporting and efficient analysis. There is no benefit directly for larger groups but there are benefits considering SDTM and ADaM challenges.
This helps in the reduction of trial set up cost. This increases customer interaction and prepare organisation for submission readiness (8).

Risk analysis during strategic implementation of CDISC

The risk management process plan includes:

1. Strategic quality planning,
2. Design,
3. Specifications,
4. Configuration,
5. Integration,
6. Regression and
7. Reporting.

With strategic quality planning and design specifications, we need to analyse the risk involved during the implementation process.
Analysing the risk helps in proper configuration, integration and regression for reporting. This maximizes efficiency and reusability. This standardizes therapeutic standard requirements, standard metadata and efficient future standards (11).

Challenges to strategic implementation of CDISC

Evolving standards with constant changes in vocabularies, severity identification are the major challenges followed by mandate or suggestion on standard terminology and timeline coordination. This constant change results in having major challenges on transitional period issues and legacy trial updates. This also has resulted in frequent changes to controlled terminology updates, variables, supplemental, parent, label changes, added variables and communication and timeline issues for submissions. Not only limited to this, in future there is possibility of updated define versions hence with proactive communication we can plan better, timelines for implementation.

If the study team is not having sufficient upgrade in knowledge sharing and lessons learnt with experiences and findings will have a major impact. We need to discuss upfront with various stakeholders and timelines and cost will not be impacted. This will reduce the possibility of any milestones and planning and execution and discussion with stakeholders. As data managers or project manager having an expertise on

different phases of trials is important as even if a team lacks expertise they should be able to guide internally for the successful implementation. Thinking outside the box will help in choosing the CRO and ensure the task is being done (15).

The other major challenging reasons for companies not having unified CDISC-compliant dataset includes EDC data integration issues. There is no specified model being followed across companies for unified metadata or ADaM repository. There is no end to end driven approach. So, we need to have end to end data driven approach. There are discrepancies across companies apparently it is different to relay with differences as systems are completely different and adapt the harmonized repository. This also includes the adjudication issues of clinical events. This would help in strategic implementation of CDISC standards across organisations. This helps in ease of processes and saves lot of money and time being invested in resources and outsourced processes (13).

These challenges can be overcome when startup and large pharmaceuticals/ full service or boutique or specialty CROs look forward as a study team. If they plan strategically to consider inhouse expert team efficiently with adequate training the CDISC complaint process can be implemented correctly. The selection of CRO for outsourcing should be based on quality of services, contract flexibility, open cooperation, global reach and resource capacity including experience level and reputation. Budget related issues to be considered while choosing a CRO. Based on budget limitations and constraints there are CROs which quotes five times costlier than any other CRO. When we have a study with minimal feasibility of budget requirement we may be forced to select a CRO. Project bidding plays a vital role considering the monetary benefits. Companies must upgrade on the guidance documents considering the CDISC standards, processes and validation must be considered.

Self-learning and knowledge sharing experiences internally across organisations helps in effective implementation of CDISC-compliant dataset. This helps in archival, retrieval of data and increases transfer. The implementation team should be able to implement the required skills. The team should have desire to participate and support the study set-up, conduct and closure with quality and awareness to know the regulatory aspects to have CDISC compliant dataset.

II. Conclusion

The clinical trials need to consider CDISC compliant datasets and adhere to standards for regulatory submissions.

Strategic planning for the CDISC submission from the commencement of the trial will increase in the efficiency and avoid last minute issues at the time of database locks.

This will support ease of submission processes for integrated and clinical study reports. This must be implemented in a cost-effective manner considering the timelines across deliverables.

Careful planning at an earlier stage of the trial phase will facilitate ease of the process. We need to have simplified eCRF designing capability, robust CDISC compliant dataset process, all in one cloud solution including e PRO for efficient patient engagement with unified and seamless data integration. This adds value and more efficient way of data submissions by a sponsor or a CRO to regulatory authorities. This way it saves cost and time and have greater effect on budget.

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