Standardization in clinical trial data analysis and reporting

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INTRODUCTION

- Drug development is a multidisciplinary and highly regulated process that could last as long as ~ 10-15 years from discovery to market.
- It requires heavy investment (~ 800 million USD), majority of which (>60 %) is directed for conducting clinical trials.

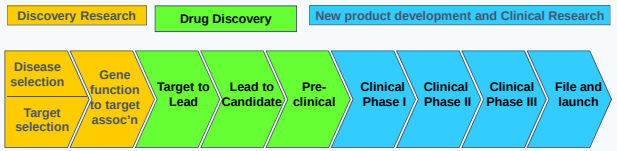

Figure 1. Schematic demonstrating the drug development process (above).

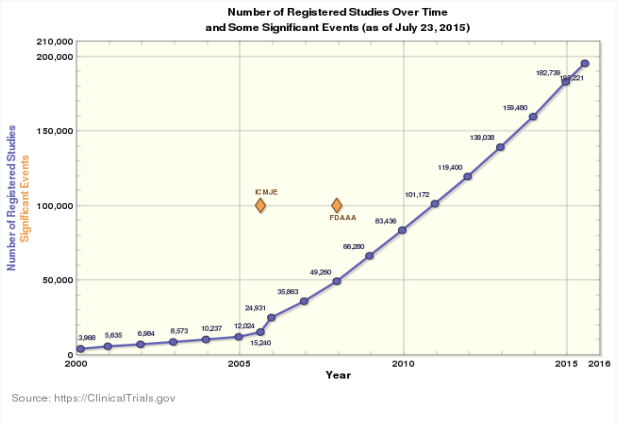

Figure 2. Graphical representation of the total number of studies registered on ClinicalTrials.gov since 2000 [1].

In order to sustain the number of studies being registered over the years it is important to improve productivity of the clinical trial processes.

THE PAST CHALLENGES

- One of the main ways to improving the efficiency and reducing costs of trial processes is by introducing clinical data standards (and standards for handling data).
- in late 1990s and early 2000 many CRO's, pharmaceutical and biotech companies started implementing company specific data standards and formats to improve their efficiencies.
- The FDA statistical reviewers however still had to bear the brunt of completely different internal data standards from sponsor to sponsor. The simplest example that explains this challenge is the definition of gender of a subject within a clinical study (Figure 2)

Study 1
- Variable name: Sex
- Values: M, F

Study 2
- Variable name: Gender
- Values: Male, Female

Study 3
- Variable name: SEX01
- 1, 2

Study 4
- Variable name: GEND01
- 0, 1

Figure 3. Differences in clinical data collection

- These challenges became particularly cumbersome for the reviewers at the FDA especially after the reauthorization of PDUFA (Prescription drug user fee act) which required increased transparency in the drug review process and mandated 12-month review cycles (now down to 10 months) [2].

BIRTH OF CDISC

- All the challenges discussed above lead to the FDA's support of data standards and the introduction of Clinical Data Interchange Standards Consortium (CDISC) in 1997.
- CDISC is a "global, open, multidisciplinary, non-profit organization that has established standards to support the acquisition, exchange, submission and archive of clinical research data and metadata" [3].
- The CDISC mission is to "develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of healthcare" [3]

Model	Application/Purpose
Protocol Representation Model (PRM)	To support the generation of a protocol document, research study registration and tracking and regulatory oversight
Clinical Data Acquisition Standards Harmonization (CDASH)	To standardize the look and feel of CRF, i.e. to standardize the variable names of data elements being captured in clinical database
Laboratory data model (LAB)	To develop a standard content model for the acquisition and interchange of clinical trials laboratory data
Study Data Tabulation Model (SDTM)	To support a standard structure for human clinical trial data tabulations for submission of data to the FDA
Standard for Exchange of Nonclinical Data (SEND)	To guide the organization, structure, and format of standard nonclinical tabulation datasets for submission to the FDA
Analysis Data Model (ADaM)	Built on the nomenclature of the SDTM standards for collected data, and has added content required for statistical analyses
Study Design Model in XML (SDM-XML)	To provide rigorous, machine-readable, interchangeable descriptions of the designs of clinical studies
Operational Data Model in XML (ODM-XML)	To facilitate the regulatory-compliant acquisition, archive and interchange of metadata and data for clinical research studies
Define-XML	For transmission of metadata for a clinical study (including SDTM, SEND and ADaM datasets)
Dataset-XML	To support the interchange of study data for clinical research applications in an XML-format
Controlled Terminology	CDISC Controlled Terminology are the set of CDISC-developed or CDISC-adopted standard expressions (values) used with data items within CDISC-defined datasets.

Table 1. Summary of some CDISC models

PRESENT DAY

- The FDA has supported CDISC initiatives not just at various conference podiums, but it has also released a number documents that have openly supported these standards.
- Even managers and software vendors are preaching the data standards confirming with CDISC.

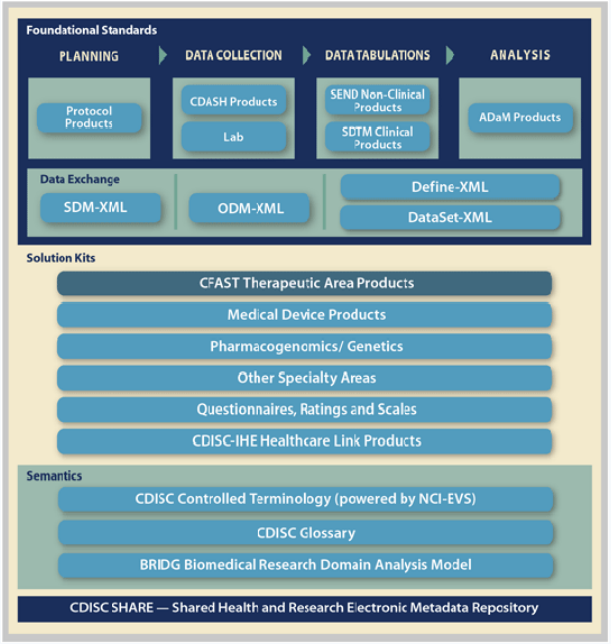

Figure 4. CDISC Foundational Standards shown above are the basis for supporting standardization of clinical and non-clinical research process [3].

MOVING AHEAD

- With that being said there is no doubt that CDISC has done an excellent job of laying clinical data standards however, getting the largely lethargic clinical research industry to implement these would be a daunting task

NEWER STANDARDIZATION INITIATIVES: Among the newer standardization initiatives the two that specifically need mentions include:

- The Coalition for Accelerating Standards and Therapies (CFAST): To accelerate clinical research and medical product development [3].
- Therapeutic Area Standards: These data standards would describe the most common research concepts relevant to each therapeutic areas and should also enable and enhance the ability to integrate, analyze, and report regulatory information about therapeutic areas [3].

CONCLUSION

- Despite the clear-cut benefits of data standardization the implementation of such standards still largely depends on the study phase, organization size and technical know-how and the amount of resources.
- For larger organizations with plenty of resources (like CRO), implementing standards may not be an issue however, the bigger question for them is whether it is worth it given the stage the study us in
- The other challenge is that there are many different groups addressing data standardization and it is important that they all come unified under CDISC initiatives to play a more common central role in this direction.

REFERENCES:

[1] https://clinicaltrials.gov/
[2] http://www.fda.gov/
[3] http://www.cdisc.org/

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