Putting CDISC Standards to Work

How Converting to CDISC Standards Early in the Clinical Trial Process Will Make Your CDISC Investment Pay

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While the FDA will shortly mandate the use of the CDISC data standards for most clinical data submissions, for most pharmaceutical companies and Contract Research Organizations, the conversion to CDISC standards is done after the close of a clinical trial; sometimes long after the study completion. By waiting until late in the process to incorporate mandated standards, however, research organizations are missing out on enormous time, quality, and cost efficiencies that could be found from integrating CDISC standards at the very beginning, as part of their standard workflow.

With the goal of improving medical research through the development of platform-independent data standards, The Clinical Data Interchange Standards Consortium (CDISC) has set forth standards to support the acquisition, exchange, submission, and archiving of clinical research data and metadata.[1] Recognizing that standardized study data would enhance a reviewer's ability to more fully assess the efficacy and safety of a product, FDA chose to issue guidance in December 2014 requiring study data be submitted in conformance to CDISC standards.[2] For NDA, ANDA, and certain BLA submissions, FDA now mandates the use of the CDISC SDTM, SEND, ADaM and Define-XML standards as well as CDISC Controlled Terminology.[3]

To meet this regulatory requirement, most research organizations will—upon completion of a clinical trial—take the data from their Electronic Data Capture (EDC) database and/or reporting systems and perform a large conversion process into CDISC standards prior to submitting the results to the Agency. Some companies will even wait for confirmation that a particular study will be submitted before beginning the data conversion, which could mean years passing between the study close and the conversion of the data to CDISC standards, with the requisite re-learning of the study specifics and peculiarities this invariably incurs.

Organizations that put off the conversion of data to CDISC standards until late in the clinical trial process are robbing themselves of the major advantages that can come from putting the CDISC standards to work early on within a study. By integrating CDISC standards at the very beginning of a clinical trial, research organizations can leverage powerful analysis tools to cut through much of the tedious, time consuming, and expensive manual work typically associated with collecting, cleaning, analyzing, quality controlling, and reporting clinical study data.

Interactive data analytics software is available today to take clinical study data and quickly and easily generate reports for risk-based monitoring, data quality and fraud detection, program validation, pharmacovigilance, pattern discovery, predictive modeling, subgroup analysis, or P-value operations. Because these modern data analytics tools are embedded with the CDISC standards, the sooner data can be taken from a clinical trial's EDC system and converted to the CDISC standards, the sooner researchers can leverage the power of these analytics tools and put the data to work.

Term	Definition of CDISC Term
SDTM (Study Data Tabulation Model)	A standardized, predefined collection of domains for clinical data submission
SEND (Standard for Exchange of Nonclinical Data)	An implementation of SDTM for nonclinical studies
ADaM (Analysis Data Model)	Defines standards for analysis datasets derived from SDTM domains
Define-XML	A machine readable version of the regulatory submission

Monitoring Prioritization and Risk-Based Monitoring

From the very start of a clinical study, data collected in an EDC system can be periodically exported and automatically put into the CDISC standards structure. The data can then be easily read by a data analytics tool to generate reports that shine a light on areas that might be unusual and require attention. For example, the reports could highlight a site where patient-reported outcomes are being rated significantly higher or lower than other sites, which could indicate some flaw in the way the staff at that site are interpreting the rating scale.

More powerfully, data analytics reports from CDISC standard data can be used to implement risk-based monitoring by flagging sites reporting data that stands out from the norm or is otherwise questionable. While ICH E6 states that clinical trial data should be actively monitored to ensure data quality, it allows that "statistically controlled sampling may be an acceptable method for selecting the data to be verified.4 Riskbased monitoring leverages a central computerized review of clinical trial data and site metrics to determine the clinical sites requiring more extensive quality review or intervention.[5] Data analytics reports can show where monitors are needed most urgently and arm the monitors with the information they need to ask the right questions so that they can quickly identify problems and address them before they become uncorrectable and compromise the study.

Safety System Integration

When data is converted into the CDISC standards throughout the course of the trial, an immediate benefit can be realized in terms of the safety data that has been received in the trial. Importation of ongoing safety data utilizing standardized parameters within a safety database has many advantages. For example, when Serious Adverse Events (SAE) are reported and submitted, they fall under defined regulatory guidance. Standardization of the data allows the safety team to evaluate the severity of the information, determine possible causality related to the product, and begin processing the report. Standardization also allows a safety team to develop a profile related to the product being studied.

Other benefits of supporting the safety team with standardized data include the ability to weed out non-useful data and false assumptions, streamlining of processes to ensure regulatory timelines are met, and the ability to reconcile on an ongoing basis the data that is provided, allowing for early review and analysis to identify potential signal generation related to safety. Not only are these advantages beneficial in terms of cost containment for trial sponsors, safety-conscious regulatory reviewers appreciate the ability to receive timely information regarding the safety of investigational products as well as new information on approved products.

Quality Control

Automated reports should not replace customized analysis as a means for determining the efficacy and safety of a product within a clinical study report. Statistical programmers remain a vital part of the team, with the hands-on task of organizing, deriving, and interpreting the analysis data and putting it into the proper ADaM and Define-XML standards for use in reporting. But because it is essential to validate these customized statistical programming activities, many research organizations will spend extra time and resources performing what is called "double programming," in which two sets of programmers will perform identical functions in order to compare the results for consistency.

By leveraging interactive data analytics software, the customized work of statistical programmers can be more efficiently verified by comparing and cross checking their work against the outputs of the automated reports. This approach both speeds up and simplifies programming validation activities, producing higher quality results with less manpower, available almost immediately after the close of the study.

The ability to analyze data on an ongoing basis throughout the course of a trial further serves to provide a quality control function by rooting out incidences of fraud. While incidences of site and patient fraud is generally considered to be a rare occurrence, its prevalence is likely to be significantly underestimated due to limited assessment tools and training or an underlying fear over negative publicity.[6] The potential for data fraud and misconduct is an unfortunate reality of clinical research, but with the aid of sophisticated data analytics tools that leverage CDISC standards, incidences of fraud can be immediately identified and stamped out before the integrity of an entire clinical trial is jeopardized.

Conclusion

A CRO that integrates CDISC standards at the beginning of a clinical trial has an opportunity to provide powerful information to guide the execution and monitoring of the clinical operations team, to support the review and reporting efforts of the safety team, and to streamline the data cleaning activities of the statistical programming team. Further, the CRO is able to provide sponsors with a constant flow of information and insights throughout the course of the trial and provide a final analysis within days of database lock.

The full scope of what advanced data and analysis tools can offer is broad and includes:

1. Monitoring reports and patient profiles to arm monitors with the collected data
2. Risk-based monitoring reports and fraud detection analysesto target monitors to suspect sites
3. Safety analysis reports for Safety & Pharmacovigilance teams, sponsors, and project managers
4. Full interactive data review capability for blinded safety meetings, patient classifications and in support of the Data and Safety Monitoring Board
5. General study progress reports for project managers and sponsors
6. Automatic generation of Patient Narratives for SUSAR and SAE case reports in safety processing
7. General on-demand analysis reports for demographics, findings, events, etc. to populate and validate clinical study reports

The early creation of FDA-ready CDISC submission deliverables opens up enormous opportunities for research organizations. Leveraging the data within today's powerful analytics tools brings efficiencies to work processes that translate to faster reporting, faster submission-ready data, and higher quality outputs at a lean and predictable cost.

1. CDISC Mission and Principles. Available at http://www.cdisc.org/about/mission. Accessed 5/11/2016.
2. Study Data Standards for Regulatory Submissions Position Statement. Available at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm368613.htm. Accessed 5/11/2016.
3. FDA Final Binding Guidance on Standards Now Available. Available at http://www.cdisc.org/FDA-Final-Binding-Guidance-on-Standards. Accessed 5/11/2016.
4. ICH E6 (R1) Guideline for Good Clinical Practice: 5.18.3, Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf
5. Zink, Richard C (2014). Risk-Based Monitoring and Fraud Detection in Clinical Trials Using JMP® and SAS®. ISBN 978-1-61290-991-2.
6. Buyse M, et. al., (1999). The Role of Biostatistics in the Prevention, Detection and Treatment of Fraud in Clinical Trials. Statistics in Medicine 18: 3435-3451.

About the Authors

Jon Roth

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Jon Roth has more than 25 years of practical experience working in the life science industry, within the statistical programming, biometrics, and data sciences areas. On a global level, he has been involved with the CDISC development of the analysis data model since the earliest days of the ADaM Development Team. A CDISC-authorized ADaM trainer since 2008, Mr. Roth was responsible for the first FDA submission to include analysis data in the ADaM format, and, as a consultant, speaker and trainer, continues to assist organizations in successfully implementing the CDISC models in a way that brings both regulatory compliance and business advantages to the pharmaceutical and biotechnology industries. Now tasked with growing a world class Data Sciences & Biometrics Division at Biorasi, Mr. Roth is leveraging his years of management and technical experience in pharmaceutical drug development life-cycle projects, with a special emphasis on clinical data standards, data management, drug safety reporting, statistical programming, and analysis.

For more information on Biorasi's CDISC Expertise please scan the QR code to the left or visit:
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As Vice President, Safety and Pharmacovigilance, Mark Vieder develops policies, methodologies, tools, and templates to manage drug safety and pharmacovigilance within Biorasi. He brings a unique set of skills to the role, having most recently served in the U.S. Food and Drug Administration (FDA). Mr. Vieder's experience with the FDA began as a contractor to the Agency in the receipt, triage, processing, and review of all case safety reports. He also became a known presenter and lecturer at DIA conferences, chairing and co-chairing sessions and speaking on such subjects as drug safety, narrative writing, and compliant submissions to the FDA. In addition, he has conducted training sessions involving MedDRA and the WHO Drug Dictionary at numerous pharmaceutical companies in the U.S. and abroad. He then became the Program Director for the FDA's post-marketing adverse event database (FAERS), which processed more than one million safety reports on a yearly basis. Moving from contractor status into the FDA, Mr. Vieder continued to oversee the FAERS program and was a resource for many centers in the Agency, including the Office of Surveillance & Epidemiology, Office of New Drugs, Office of Generic Drugs, Office of Regulatory Affairs, and the Office of Compliance.

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