

Achieving Highest Quality and Usability of SEND through Industry and Regulator Collaboration

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ABSTRACT

This is a time of important change for the CDISC SEND team. We have been producing standards by the heroic efforts of a few, but now need to transform our operation into streamlined processes while we invite, mentor, and engage new membership into active participation. This will enable us to effectively improve our existing standards, expand our portfolio of standards into new important areas and still increase the efficiency with which standards are released, evaluated for implementation, and placed into production. The CDISC SEND team, has created THE world-wide standard for toxicology data exchange. At this very moment more and more data are being transformed into this standard and aggregated into repositories within our companies, within multiple industry consortia, and within regulatory health authorities. These repositories are springing up with the hope that they will enable new insights, better medicines, and result in healthier people all over the world. Let's work together!

INTRODUCTION

The SEND Implementation Guide (SENDIG) is one of the CDISC global foundational platform-independent data standards (1). This paper will provide some history about the CDISC SEND development team, the important changes in the industry that are challenging continued development of standards, and the emerging practices being planned to increase quality and collaboration while also increasing the performance of the rapidly-growing SEND team.

In an attempt to make reading through text with a high volume of acronyms easier, some of the more frequently used ones are listed at the end of this paper.

BACKGROUND

The earliest history of SEND development, including the industry consortium that preceded the formation of the CDISC team and SENDIG development up to the public review period for SENDIGv3.0 has been described before (2). Early in SEND development, there were fewer than twenty regular participants on the SEND team. Today, to the great benefit of development, the majority of those early developers of the standard remain actively engaged in SEND development and, through near heroic efforts, have continued to lead many SEND sub-team efforts, participate in CDISC cross-standards development, and provide essential technical review of multiple standards as part of a growing governance structure within CDISC. While the growth in the use of SEND datasets throughout the industry is essential to bringing the new capabilities and critical gains in delivery of safe and effective medicines that we all hope for, these same varied and important uses of SEND underscore the need for the SEND team to evolve processes to continuously meet new challenges.

CURRENT ACCOMPLISHMENTS OF THE SEND TEAM

Arguably, the first industry-wide acknowledged SEND version, SENDIGv3.0, was released on 17 June 2011. The current published standards for nonclinical are shown in Figure 1 below. These published deliverables of the SEND team can be accessed freely via the CDISC website, www.cdisc.org/send (1). This release of SENDIG v3.0 was recognized as a major milestone in the collaboration between FDA and industry (3) and the SEND team was awarded the FDA Honors Award for successful collaboration on the SENDIG v3.0 at the FDA Center for Drug Evaluation and Research (CDER) Honors Ceremony on 17 June 2011. Both SENDIG v3.0 and SENDIG v3.1 are on the list of standards required for data submission to the US FDA. Details of the requirements for FDA are specified in the FDA's Data Standards Catalog and Study Data Technical Conformance Guide as described in the guidance, "Providing Regulatory Submissions In Electronic Format - Standardized Study Data" (4).

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Figure 1. Current Published Deliverables from the SEND team

SEND Standard	Release Date	Based Upon
SENDIG-DART v1.0 (Provisional)	16 August 2016	SENDIG v3.1, SDTM v1.6
SENDIG-DART v1.1 (Final) (This version is the final version and supersedes the provisional version v1.0)	11 December 2017	SENDIG v3.1, SDTM v1.6
CoDEx 1.0 for SENDIGv3.0	16 Aug 2017	SENDIG v3.0
SENDIG v3.0	17 June 2011	SDTM v1.2
SENDIG v3.1	7 July 2016	SDTM v1.5

CURRENT CHALLENGES OF THE SEND TEAM

In the very earliest discussions of nonclinical data standardization that eventually lead to the development of SEND, the only use case was for US regulatory submission and it was thought that the model could suffice if it properly handled the data within each study, regardless of the variety of lexicons in use in the industry and without regard to use cases outside of regulatory submission. Now as the power of standardized nonclinical data is beginning to be realized, the development of the standard has become more complex than ever. Requirements for SEND come from sponsors, CROs, software vendors, data consultants, academia, and industry consortia. With the federal mandate to provide submissions in electronic form (4), the uptake of the standard for data repositories and data mining within pharmaceutical companies and multiple industry consortia is increasing and SEND data are being produced and analyzed more and more. The analyses of interest now span studies, submissions, product classes and organizational boundaries. The SEND team must assess data usability from beginning to end. For example, in nonclinical today, long standing collection processes and mature systems are now needing to align better with SEND. It is important to gain improvements in all stages of the process and consider all perspectives when developing new versions of the SEND standard. Development including broad perspectives should yield better solutions and minimize the cost of adoption across the collection, analysis, data storage, and metadata needs of the various consumers of the data. The importance of standard controlled terminology and conformant use of the standard is clearly in the forefront of the SEND development conversation now.

The team has also gained new insight into the need for, yet complexities with, establishing conformance rules to apply to SEND data sets. And, with increased use of the SEND standard, comes a deeper appreciation for the impact of the structures of writing within the IG. The SENDIG must be written with the quality and clarity to guide readers at all levels of experience, given that variation in interpretation by readers can result in nonstandard datasets. This becomes even more important as SEND implementation guides are beginning to be used to guide readers in languages other than English, for example the translation to Japanese that is being completed by CDISC Japan User Groups (CJUG).

With the existence of multiple versions of SENDIGs today, there is increasing debate regarding the pace of releases to the industry, with the larger voice being to slow down development. At the same time, sections of the industry that are not yet in the scope of SEND are asking for acceleration. So, the SEND team must gauge readiness to release on both quality and the ability to positively impact industry adoption and usability. A related topic of discussion is the struggle to maintain core competencies to support certain portions of the standards development life cycle, such as: software testing, validation, deployment, due to the cadence of releases today. There are spikes in the need for certain skills followed by periods of inactivity making it difficult to level resources and maintain skill sets.

SEND TEAM PROCESSES REQUIRE TRANSITION

Given the challenges described above and the growth in use of SEND throughout the industry as well as the recent flourish of new volunteers joining the development efforts, the SEND team has reached a turning point. To ensure quality, usability, and therefore longevity of the standard, the SEND Team practices and processes must grow to meet these demands by becoming more disciplined, much more robust, and efficiently repeatable.

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EMERGING BEST PRACTICES FOR TEAM EFFECTIVENESS AND COLLABORATION

COLLABORATION WITH REGULATORS

The SEND team collaboration with regulators is a hallmark of the SEND team successes in the past (7, 8). This collaboration has proven to be essential in making efficiency gains and delivering a standard with both submission purposes and sponsor's operational data purposes in mind. The SEND team continues their successful practice of holding regular face-to-face (F2F) events lasting up to five days, hosting as many as sixty attendees throughout the week's working meetings. The purpose of these meetings is to further our high priority SEND development work and has proven to be a most effective catalyst in lowering barriers and accelerating work. There are currently 13 active sub-teams of SEND. In addition, the collaboration between industry and FDA at the annual PhUSE Computational Sciences Symposium (CSS) is another important venue for initiating work on nonclinical data challenges by focusing on implementation experiences and needs(5). There are eight active SEND-related projects currently underway in the Nonclinical Topics Working Group for 2018 (6). Both the CDISC SEND F2F weeks and the PhUSE CSS events are conducted in locations convenient for FDA representatives to attend.

Through these collaborative efforts, the SEND team has been able to successfully deliver multiple releases and perform the first broad test of usability of the SEND standard, the Fit-For-Use (FFU) pilot of SENDIG v3.0. Important learning points from the FFU generated new SEND requirements that can resolve implementation issues and provide data that is better fit for the purposes of data analyses. This FFU underscores the importance of collaboration between industry and regulators. The need for learning in a collaborative setting can only increase as the use of SEND data is broadening to include additional divisions of the FDA and/or additional global regulators. To meet this demand, the SEND team will continue to hold regular web conferences and F2F events, but has begun to also make better use of the existing CDISC Cross-standards Working Group meetings which are a third instance of F2F events in the DC area. The CDISC Working Group meetings (previously known as CDISC Intrachanges) are annual events that include attendees from all CDISC standards teams and additional global regulators. For discussions of common technical topics, there is a monthly teleconference for FDA and CDISC technical leadership. Beginning this year, the CDISC SEND team leader is participating in these monthly discussions as well.

OVERARCHING PRINCIPLES

Team principles are being developed to more efficiently and consistently guide the development work of all CDISC teams. The SEND team has begun to draft principles to more efficiently guide standards development in our increasingly complex environment. Understanding a set of fundamental principles will help keep teams true to the purpose of developing highest quality deliverables and hopefully, avoid unnecessary or redundant effort. SEND principles include technical development requirements and also establish team development requirements. One technical development principle for SEND requires an assessment and re-alignment to the overarching SDTM model, upon which SEND is based, with each new SEND release. An example of a team development principle is the requirement for the current leadership team to mentor new team members into leadership positions wherever possible, rather than accepting additional leadership positions themselves.

VOLUNTEER ENGAGEMENT

Volunteers are at the heart of CDISC standards development. Without their commitment of time and talents, the standards would not progress. The CDISC organization stresses the importance of truly engaging volunteers in their CDISC procedure on volunteer engagement, COP-019 (7) revised in July of 2017. Towards this end, they provide team leaders with tools and support in assessing the active engagement of team members, including quarterly reviews of team and sub-team activities and time commitments. The SEND team is now beginning to adopt the practices as described in COP-019 (7).

The SEND team leader and CDISC volunteer coordinator recognize the importance of the volunteers in meeting the challenges ahead and are keenly interested in increasing the opportunities for engagement of all volunteers on the SEND team. Beginning in 2018, they have instituted a regular monthly "newcomer orientation" session which can be attended by new members or experienced ones. This orientation, specific to SEND team operations, ensures a better and earlier understanding of team processes and collaboration tools for all new members and also establishes the necessary meeting schedules and account accesses that heretofore could take weeks or months to attain. This provides the new team member with a good start to effectively collaborate in the CDISC website, wiki, and JIRA environments and, perhaps more importantly, to quickly match their interests with the current needs of SEND sub-teams. With the influx of new volunteers and increase in tasks on sub-teams, it is important to establish these relationships quickly.

During the latter half of 2017, a new industry volunteer team leader was named for SEND. This is the first new leadership change for the SEND team in over a decade. The team followed the CDISC procedure for selection of leadership and has begun to establish the structure and responsibilities as outlined in COP-019 (7). In the same timeframe, the CDISC organization provided a much-needed CDISC staff member to support the SEND team leader and team members as a CDISC liaison. The CDISC liaison is embedded with the team and has direct access to tools and CDISC support processes that enable the industry team leader and all volunteers to work more efficiently.

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MANAGING CONCURRENT WORK STREAMS PRODUCING MULTIPLE VERSIONS

The ability to manage multiple concurrent streams of development within the scope of the SEND standard has become more difficult as the team takes on more work. There are currently 13 separate work streams within the SEND team's purview and many cross-standards work streams that generate work on the SEND standard, including concurrently developing multiple SENDIGs and SENDIG versions. We expect this to become even more onerous to manage over time due to increases in the number and kind of stakeholder communities interested in SEND. The CDISC liaison for the SEND team is working directly with CDISC IT support and the SEND Team Change Control Board (CCB) leader to configure the CDISC tools for project, issue, and task tracking and project management. When used consistently, the hope is that all work flows will be tracked concurrently across multiple versions of the standard, with flexibility and transparency across all work streams and accessibility for all SEND team users.

AUTOMATING STANDARDS DEVELOPMENT

The SEND team was an early adopter of the wiki technology within CDISC for team collaboration and document spaces. The team is now adopting the approach of developing the standards within document spaces on the CDISC wiki. Development of the standard on a wiki document space includes automated tools for format checking, automated identification of metadata, and automated document reviews directly connected to the CDISC issue tracking tools for ease of resolving issues and tracking resolution and rationale. Ultimately, the use of the wiki tools lead to more consistent standards within the SEND team, within the family of SDTM standards, and across all CDISC standards.

EMERGING BEST PRACTICES FOR QUALITY AND USABILITY

DEVELOPMENT OF EXAMPLE DATASETS

The SEND team believes that the efficiency with which standards are released, evaluated for implementation, and placed into production to meet the ever-growing need for standardized data will be greatly facilitated by complete full example datasets. The CDISC SEND team has decided to begin creating proof-of-concept (POC) datasets as an integral part of the standards development process. The intent is for these datasets to be designed to be full example datasets broadly covering the use of the standard and to be fully CDISC compliant data packages. Draft example datasets will be made available during the public comment period on the draft standard before it is released, facilitating a more efficient public review resulting in a better standard upon release. Subsequently, along with the final standard, these datasets will be updated and released as final example datasets enabling data receivers to begin creating software to process data when the standard is released. This will also help those creating software to produce datasets to have greater confidence they are implementing the standard correctly and by example may result in more uniform implementations across the industry yielding further improvements to efficiency.

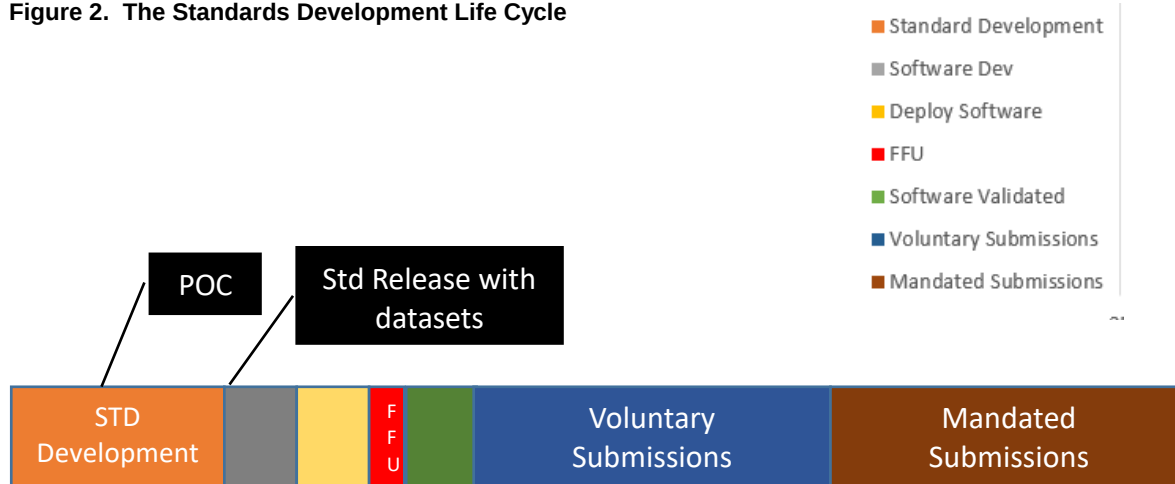
COLLABORATIVE UNDERSTANDING OF IDEAL RELEASE CADENCE

We are exploring ways to meet the challenges to both improve the quality of our standards and to expand the portfolio of standards into new areas. To improve the quality of our standards we are adding components to our releases that result in more work. This additional work competes for the same resources that are working on expanding the portfolio of standards to cover new study types and more study end-points. These same people are also key to the processes following the release of a standard: creating software to work with the new standard, deploying it, and adopting it. Each of these activities are needed intensely for relatively short durations in the life of a single standard, and then not needed again until the release of the next standard. A first step we are taking to meet these challenges is to prepare an idealized release cadence that takes into account the needs of the various stake holders (CDISC, regulators, pharma companies, contract research laboratories, software vendors, consultants, etc.) and the interplay between them throughout the standard development life cycle.

The following diagram (Figure 2) shows the major steps throughout the standard development life cycle. The first step is for the CDISC SEND team to develop the standard with POC datasets, conformance rules, and a listing of the confirmed data end points for exchange. Once the standard is released, software is developed and deployed. At this point we have the opportunity to see how well the standard was implemented in the production-ready software by conducting a FFU pilot. We found this to be extremely valuable with SENDIG v3.0 and enabled the FDA to provide meaningful guidance in the Study Data Technical Conformance Guide to enable the industry to prepare datasets that would be useful to them. This also identified areas requiring improvements in the standard itself. As a result, the SEND team has started identifying long-term solutions to these challenges and are making plans to include these changes in a future release. Given the value of this FFU, the CDISC organization has now added the concept of FFU piloting (optionally) into their standards development process, COP-001(8), for all CDISC teams to consider.

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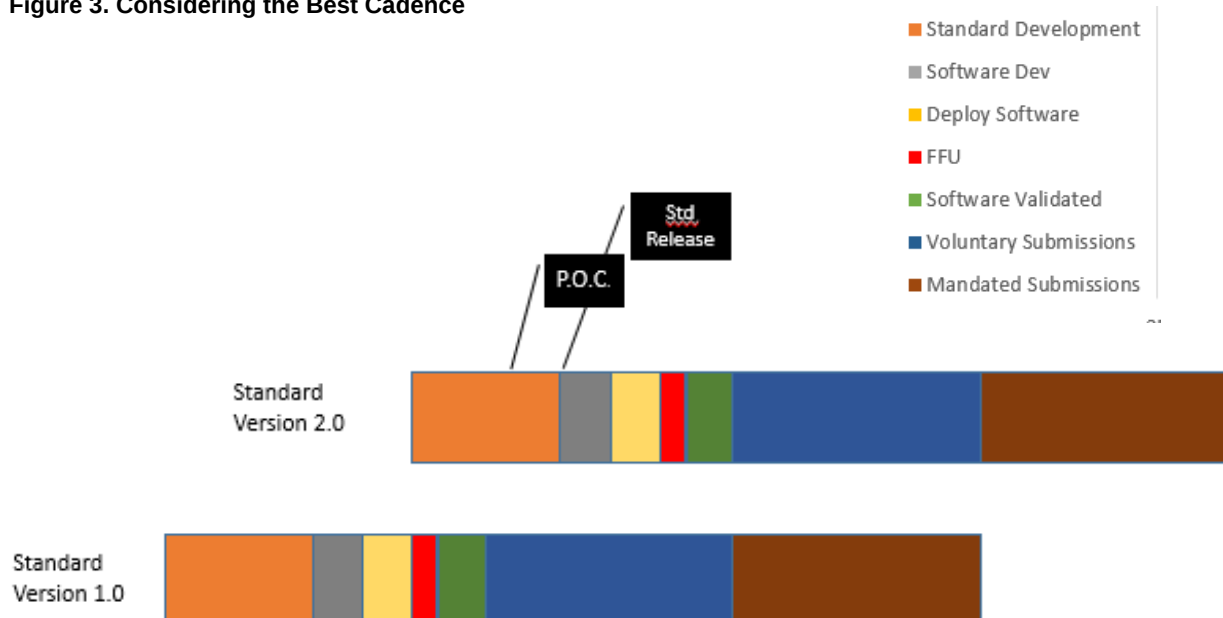
Figure 2. The Standards Development Life Cycle



With the release of a standard accompanied by the example datasets, regulators have the information to determine when they can begin to support the standard; however, it is unknown how well the implementations actually support the regulator's needs until the full usability testing in the FFU pilot. At the conclusion of the FFU pilot, regulators can confidently determine if the standard will improve their operations and if it would be appropriate to require this standard in submissions. This could be the trigger for determining the date this standard is mandated to be used in submissions.

As previously noted, the FFU identifies key areas for improvement. Armed with this information, the standards development team can identify identifying near- and long-term solutions to these challenges and earmark these changes for future releases. When considering the best cadence to aim for in the industry (see Figure 3), the start of development for a subsequent release should depend upon having completed or nearly-completed a FFU pilot. Staggering the development cycles including a reasonable length of overlap in time that old standards are supported while new ones are introduced will allow industry to react in a consistent manner, giving vendors time to adapt software and users time to re-tool their environments.

Figure 3. Considering the Best Cadence



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COLLABORATIVE UNDERSTANDING OF IDEAL RELEASE CADENCE (CONTINUED)

This plan enables the standard to continue to improve and yet sets the pace of advancement at a sustainable rate. However, this would hamper the expansion of the standard into new areas. To overcome this challenge we are intending to release supplements to a standard that introduce expansions into new study types and new types of end-points. These supplements could be released between the releases of the main standard. Their content, once proven to be good and stable, could be incorporated into the main standard in a subsequent release. This approach balances the need to have a good stable base SEND standard that continues to improve and meets the need to more quickly expand the scope of the standard into new areas.

The team is actively evaluating the current standards development work streams to determine how to effectively transition from the current process to the new process.

QUALITY GAINS FROM THE COMBINATION OF EXAMPLE DATASETS AND USABILITY PILOTS

Both the FFU pilots and POC datasets help to establish confidence in a version of a standard, but they also serve distinct functions. The example datasets are released twice. First as draft with the request for public comment on a draft standard. The draft example datasets ensure the standard is more completely considered at this early point in development and enables the standard to be more completely reviewed. This is a key opportunity for the world to give advice to CDISC on how to adjust the standard to more effectively enable the exchange of meaningful data before the standard is released.

The second time the example datasets are released is with the final release of the standard. At this point the datasets promote the efficient adoption of the standard. One of the key distinctions between the FFU pilots and the POC example datasets is that the example datasets are publicly sharable and represent “good practice”.

The FFU pilot is used to test the standard with a specific stake-holder such as the FDA. Sponsor organizations provide data from real studies that are transformed into the standard using production-ready software. Generally, this means the datasets cannot be shared publicly, but they do provide a good representation of how the standard was interpreted and implemented. As a result, they mimic production submissions. Feedback from the FFU pilots are critical to ensure successful production data exchanges.

CONCLUSION

While we cannot guarantee the success of implementing the changes described in this paper, we know that team practices must change and evolve to meet our many challenges. We are hopeful that engaging all industry participants in collaborative discussions about ideal cadence will help evolve our ability to release standards into a more ideal cadence. Basing the decision to mandate a standard on the results of usability testing should improve the quality and standardization of data as well as ensuring FDA mandates are met with the most useful data, ultimately achieving the mission to help safe and effective products reach the market in a timely way.

CALL FOR PARTICIPATION

The SEND Team is a group of passionate volunteers, each bringing their own unique perspectives and potential to the work. We engage in strong debate while valuing all perspectives and, we maintain equally strong relationships throughout. The team invites all interested individuals or companies to reach out to the authors of this paper to participate on the development team. Alternatively, you can join automatically using the “Volunteer” button at the bottom of the CDISC home page (9). You will find the SEND team to be a very dedicated and also enjoyable group of varied personalities who are making their mark on the future of nonclinical research and submissions.

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SOME OF THE ACRONYMS USED IN THIS PAPER

CDER	Center for Drug Evaluation and Research (FDA)
CDISC	Clinical Data Interchange Standards Consortium
CoDEX	Confirmed Data Endpoints for Exchange
CRO	Contract Research Organizations
FDA	Food and Drug Administration (U.S.)
FFU	Fit-For-Use
IG	Implementation Guide
PhUSE	Pharmaceutical Users Software Exchange
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
POC	Proof-Of-Concept
CJUG	CDISC Japan User Group
SDTM	Study Data Tabulation Model
SEND	Standard for Exchange of Nonclinical Data
SENDIG	SEND Implementation Guide

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