



PhUSE US Connect 2019

Paper SA08

Identifying Hurdles for Submission of Electronic Non-Clinical Data (SEND)

Janice M Fiori, Eli Lilly and Company, Indianapolis, IN, USA

Bob Friedman, Xybion Corporation, Lawrenceville, NJ, USA

Lou Ann Kramer, CDISC, Greenfield, IN, USA

ABSTRACT

The Pharmaceutical Industry is continuing to evolve processes to meet the regulatory mandate for submission of non-clinical study data using the SEND format. The PhUSE Non-clinical group has undertaken an annual survey to understand the status of industry readiness and the issues that sponsors are encountering.

A survey of sponsors and other involved parties has been taken to gather this information for each of the past five years. The results include information about what complications are being encountered in the data preparation process and the coordination amongst the parties responsible for different parts of the dataset in one submission. The industry is making progress in readiness to meet the new standards, though significant hurdles are being encountered. The survey is helpful in informing the PhUSE collaboration members as to where they can focus their efforts to best help the industry in meeting this obligation and provide the stakeholders with metrics of how their progress and possible solutions.

INTRODUCTION

As the mandate for SEND 3.0 electronic data submission has been put into effect by the FDA, and updated with the SEND 3.1 implementation guide (SEND IG), the Pharmaceutical Industry has had to devise and implement new processes to meet these submission requirements. The PhUSE Non-clinical group serves to help the industry meet these needs and to give feedback to the standards bodies on the practical aspects of implementation. In order to gather information to understand the status of industry readiness this group has conducted an annual survey of the involved organizations. This has been done for each of the past five years.

The content of the survey is intended to gather information on the successful deployment as well as stumbling blocks and barriers to the implementation of the standards.

This is helpful in informing the PhUSE collaboration members and project teams as to where they can focus their efforts to best help the industry in meeting this obligation. It also provides the stakeholders with metrics of how their progress compares with the industry and possible solutions to questions they have with their own processes.

METHODOLOGY

Survey questions were developed and then the survey was implemented using SurveyMonkey.co.uk. The survey questions are updated each year based upon the previous surveys and updated to include questions pertinent to current submissions and regulatory expectations.

Invitations to complete the survey were then sent to members of the CDISC and PhUSE non-clinical mailing lists. Answers were anonymous with the opportunity to include the respondent's organization.

The survey has been conducted annually, beginning in 2015. The number of respondents has increased steadily with a total of 99 participants in 2017, the latest survey.

RESULTS

Results were tallied and graphed to show distribution of responses and trends of study submissions using the SEND standards. Challenges are described in a longer free form response format, and hence these are collated and summarized to be presented in the survey results. The results include information about what complications are being encountered in the data preparation process and the coordination amongst the parties responsible for different parts of the dataset in one submission.

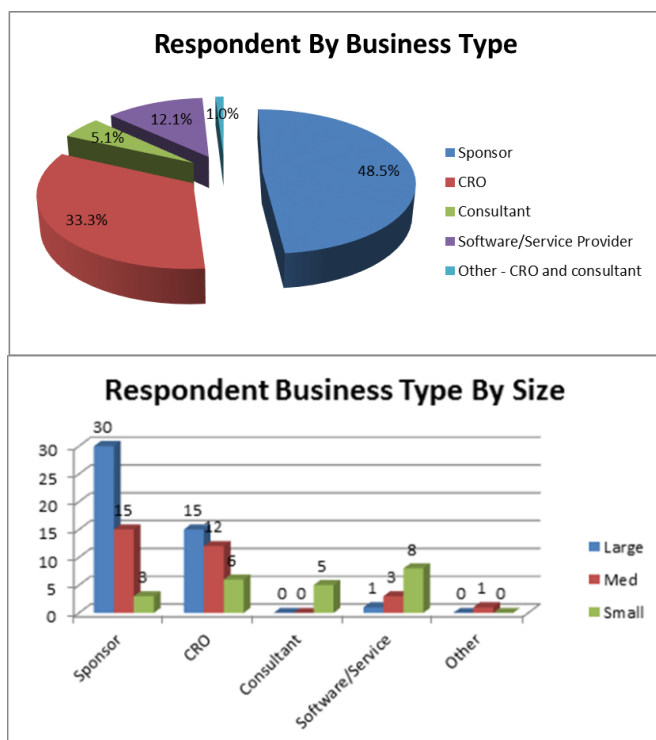


DEMOGRAPHICS OF RESPONDENTS

Ninety-nine people responded to the survey. The largest portion of respondents identified themselves as sponsors at 48.5%, followed by CROs (33.3%), software/service providers (12.1%), consultants (5.1%), and other (1.0%).

Respondents further characterized their organization as large (46.5%), medium (31.3%), or small (22.2%). The graph Respondent Business Type by Size graph demonstrates that a good cross-section of business types and sizes are represented in the survey.

Location, identified by three-fourths of the respondents, included many US sites. Twenty-three participants were located in non-US countries, including France, Germany, Japan, Switzerland, and the UK.



The implementation of SEND is a multi-disciplinary task. All the respondents picked one of the eight pre-designated options. Professionals with diverse expertise are required, including Regulatory Operations/Data Managers (32%), IT programmers (16%), Nonclinical Scientist/Toxicologist/Study Director (15%), IT/Operations (11%), biostatisticians (10%), Consultants (8%), Quality Assurance (4%), and Regulatory Affairs/Scientist (3%).

IMPLEMENTATION READINESS

With the initial survey in 2015, the PhUSE organization was keenly interested in measuring the readiness of the key players across industry to supply SEND compliant data in regulatory submissions.

In response to the question "What stage of SEND readiness are you in?", 60% of respondents indicated they had implemented a solution and are capable of creating SEND submissions. The remaining 40% were evenly divided between "implementing a solution (i.e., in-house, external services, commercial systems)" and "have not started/education phase".

Respondents were asked about the SEND solutions they have implemented. Commercially available software was selected by 65%. The second most popular option (47.5%) was "Studies conducted at CROs who will provide SEND datasets". All additional choices were selected by over 20% of the respondents including in-house software (32%), commercially available software in a hosted (cloud) environment (22%), external consultation services (29%), and



study conversion services (26%). Even though 80 respondents replied, multiple options were frequently selected, resulting in total responses counted greater than 100% of respondents. This suggests that multiple solutions are being implemented within organizations, possibly due to supporting multiple business processes for which a single solution is not adequate, limited internal resources, or multiple uses of the SEND data.

To access the degree of implementation, the survey asked “What actions are you currently taking/have taken towards implementation? (Select all that apply)”. The question was more relevant to end-users/sponsors than other groups; two-thirds of the participants responded to this question. Over 80% had provided training internally. The majority of responses indicated they had produced SEND datasets and had sent test datasets to the FDA. Since the question is more relevant to end-users/sponsors than other groups, the survey saw two-thirds of the participants replied overall. Over 80% had provided training internally. The majority of responses indicated they had produced SEND datasets and had sent test datasets to the FDA. While this latest survey showed that only 28% had included SEND datasets in IND or NDA submissions, the requirement to do so was not in effect at the time of the survey. See the specific responses in table 1.

What actions are you currently taking/have taken towards implementation? (Select all that apply).

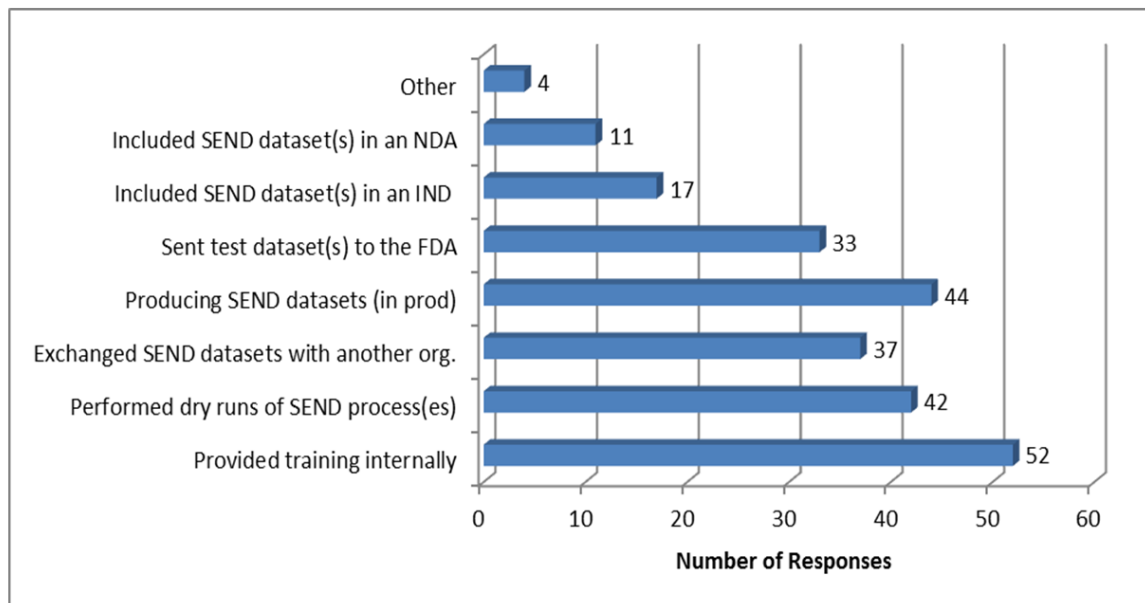


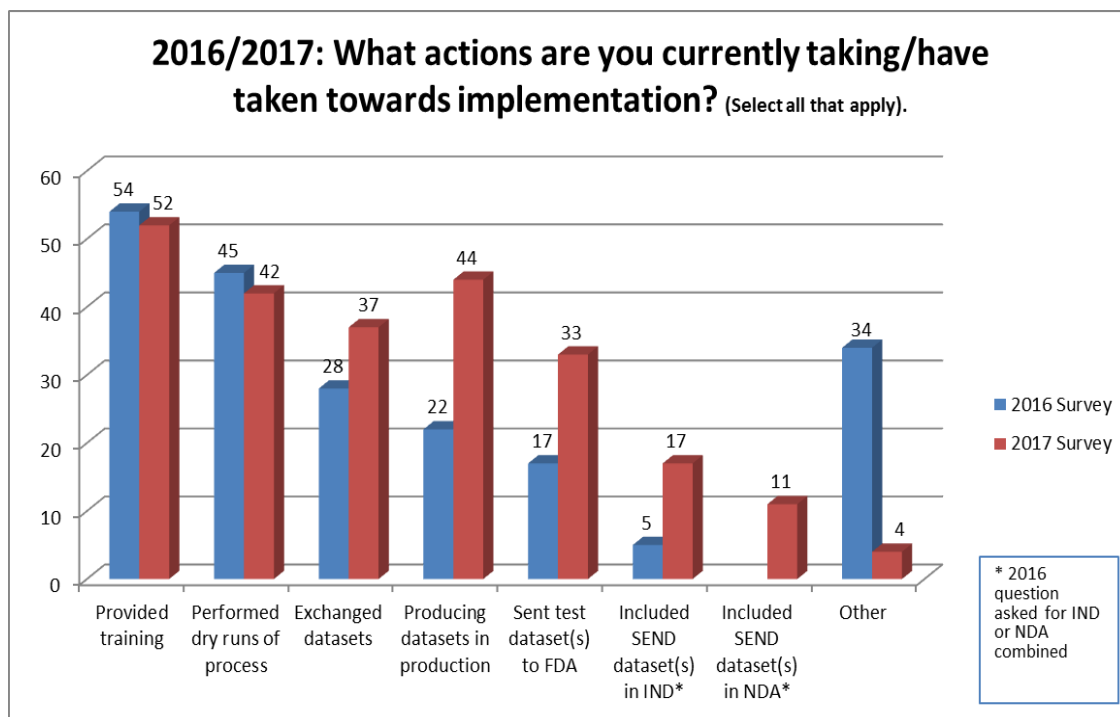
Table 1
What actions are you currently taking/have taken towards implementation? (Select all that apply).

ANSWER CHOICES	RESPONSES
Have provided training internally	80.95%
Have performed dry runs of envisioned SEND process(es)	66.67%
Have exchanged SEND datasets with another organization	57.14%
Already producing SEND datasets (in production)	69.84%
Have sent test dataset(s) to the FDA	52.38%
Have included SEND dataset(s) in an IND submission	26.98%
Have included SEND dataset(s) in an NDA submission	17.46%
Other (please explain)	6.35%



Total Respondents: 63

It is also important to look at the amount of progress in the industry in preparation of the requirement. This data suggests a significant increase in readiness over 2016 survey results with twice as many respondents in production mode (see graph). In the 2015 survey, the number of responding organizations who had included a SEND dataset(s) in an actual IND or NDA submission was only 5%. There has been an increase from 5% of responders to 28% in two years. The SEND Survey team has and will maintain the exact (or nearly exact) same verbiage for this particular question to continue to use the data as a barometer to gauge readiness over time.



Timing of SEND dataset generation relative to study finalization was also investigated. Approximately one-third (31%) of respondents (total of 61) generate SEND data after finalization while 25% generate SEND only if needed for a submission. A sizable proportion generate SEND data prior to finalization (39%) for purposes of data visualization or for study monitoring or interim submission (28%). Additional comments on timing noted that the timepoint of preparation may differ between in-house and CRO studies, that some datasets are created at the audited draft report stage, and that some are created after finalization for legacy studies. For CRO respondents, the timing was reported to differ from sponsor to sponsor, and that for some the preference is that it be done before study finalization.

Organizations plan to use SEND datasets in additional ways other than submission to the FDA, including data warehousing (57%) and visualization (58%). A smaller number will create report tables and/or graphics for submission (15%), and 17% will use SEND data for archiving. Additional uses were consistency checking against the study report and data sharing with BioCelerate.

ANSWER CHOICES	RESPONSES	
Data warehouse	56.67%	34
Visualization	58.33%	35



Report table/graphics creation for submission	15.00%	9
Archiving	16.67%	10
Not applicable	21.67%	13
Other (please describe)	13.33%	8
Total Respondents: 60		

For organizations implementing a SEND computer system, the majority will validate/qualify the system (69%). An additional 15% will perform testing but not at the validation level. One respondent mentioned qualification of the vendor and internal processes. The remaining 14% reported as undetermined.

ANSWER CHOICES	RESPONSES	
Validate/qualify the system	68.97%	40
Perform testing of the system but not at the Validation/Qualification level	15.52%	9
Do not intend to test the system	0.00%	0
Undetermined at this time	13.79%	8
Other (please describe)	1.72%	1
TOTAL		58

To ensure the dataset completely and accurately represent the study data, 43% cited study testing/validation with random data checks for all datasets. Other approaches to quality assessment included 100% datapoint QC of all datasets in a submission (11%, n=7), less than 100% datapoint QC of all datasets (i.e. military standard) (15%, n=9), undecided (18%, n=11). Various hybrid approaches also mentioned (see table) range from manual to automated machine-learning tools.

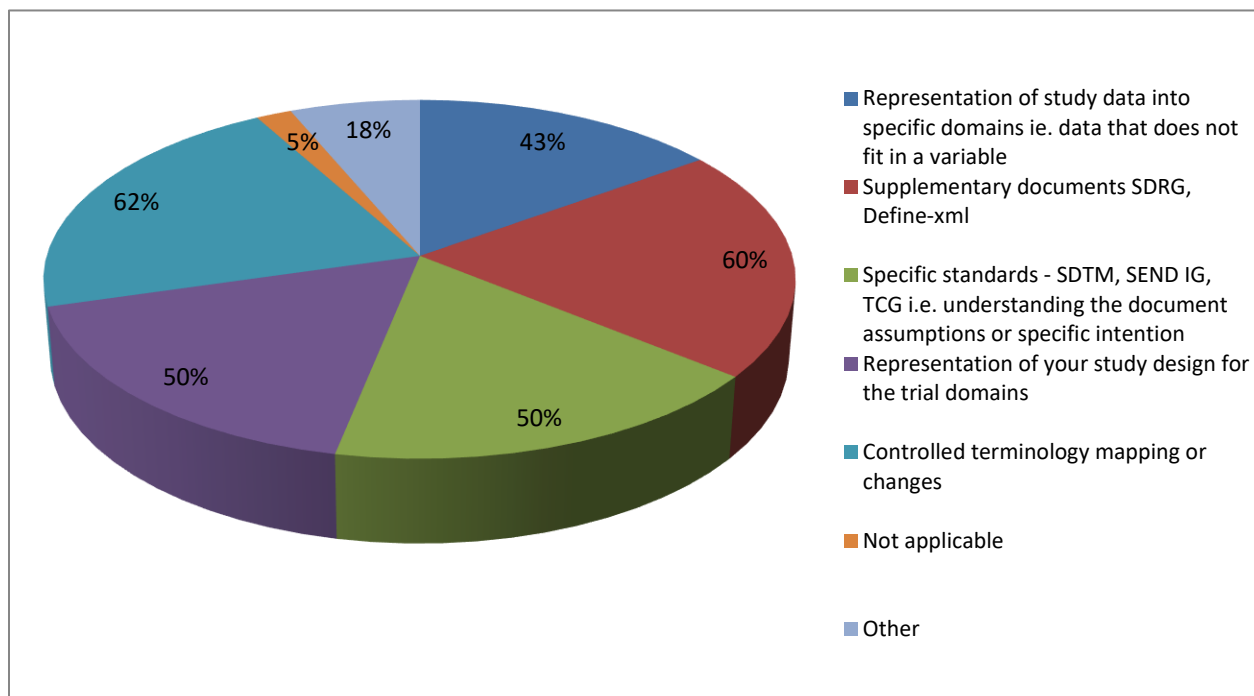
Other approaches to ensuring completeness and accuracy of the SEND data relative to the study report.
100% all manually created domains, %10-25 for validated system output of non-manual domains
100% QC or System testing/validation and then random data checks. It depends on kind of data.
Automated 100% comparison of data against Study Report; and use of machine learning algorithms
External QC, somewhere between military and 100%, depending on SEND creator
Full QC for the first studies then random checks
QC performed by the CRO
System testing / validation and QC checks for less than 100 % datapoints
Visualization tables based on SEND datasets are compared to the study report



HURDLES FOR SUBMISSION

When asked where in the process stumbling blocks were encountered, respondents noted that they occur in all areas that were asked about. The largest problem areas are control terminology mapping, representation of study design in the trial domains, and creating the non-clinical study data reviewer's guide and the define.xml file.

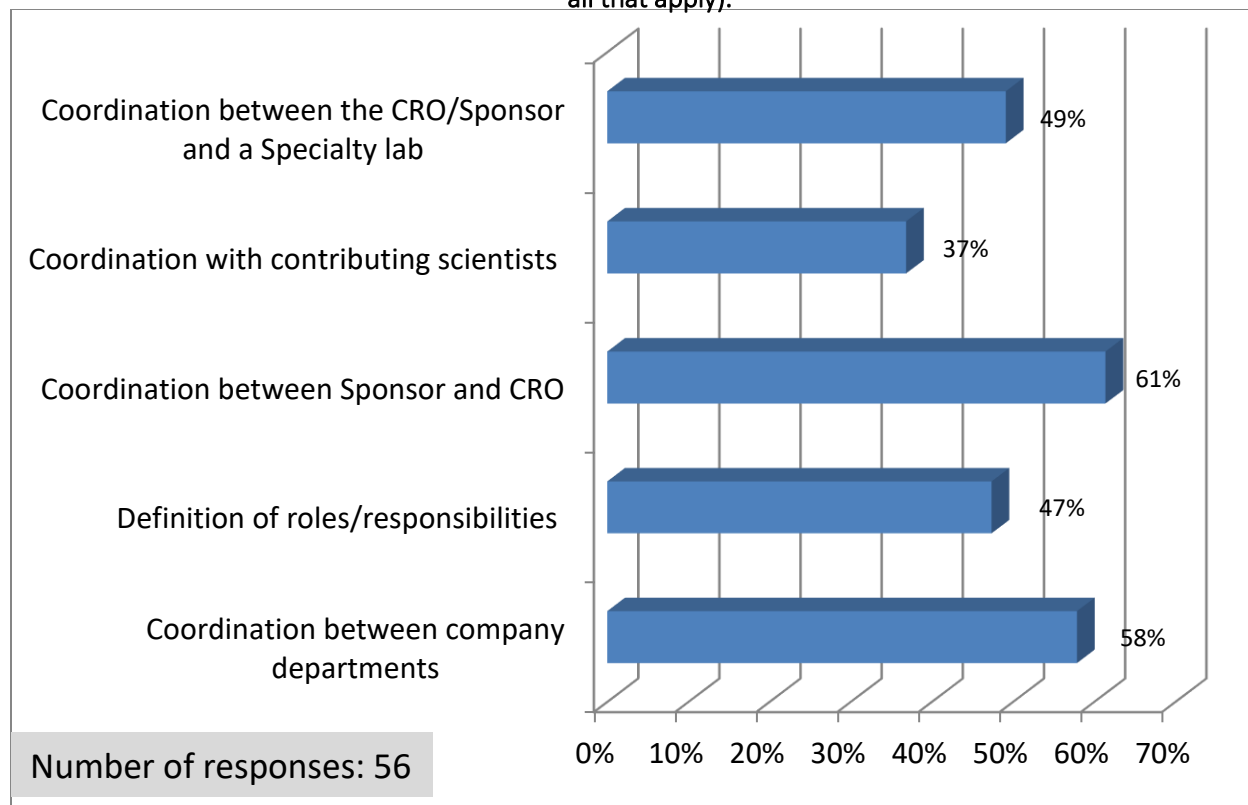
What did you find were stumbling blocks or barriers during your implementation efforts for SEND? (select all that apply)



In addition to asking about the problems in created the different parts of the submission, it was asked about problems with inter-company and intra-company processes. Respondents offered that many of these areas were causing problems in the creation of the datasets as well:



What were the process problem areas that you encountered during the implementation of SEND? (Select all that apply).



The hurdles in creating the submission components is therefore multifaceted, including issues of both scientific and technical standards understanding as well as process and responsibility issues that need to be worked out as this process matures.

STUMBLING BLOCK COMMENTS FROM THE SURVEY

A wide variety of comments accompanied these answers and it is instructive to see examples of these comments, these are shown in the next sections. They are organized here into general categories of the types of problems. They have been edited for clarity where necessary. Note that most comments came from just one organization and therefore they need to be understood as potential problems a company may encounter rather than an indication of their prevalence across all companies.

COMMENTS ON SUBMISSION MECHANICS

File format required to be a proprietary SAS transport binary file format.

(Note – the SAS transport binary file format is in fact a publicly published standard).

Uncertainty on where to place legacy TS domain file during submissions

Timing of the SEND sets relative to final report.

Where to put the TUMOR dataset of carcinogenicity studies in the eCTD as it is not a standard SEND dataset?

COMMENTS ON FDA FEEDBACK

Lack of FDA feedback and expectations and guidance.



Without regular feedback from the FDA, it is challenging to know if, i.e., the trial design and/or define file represents the study as expected.

(Note that after the survey that completed early in 2018, there is anecdotal information that FDA feedback on SEND submissions has been more common in the latter part of 2018 and we expect this to be reflected in the next survey results.)

COMMENTS ON PREPARING STUDY DATA INTO SEND DATASETS

Found it very challenging to extract sufficient protocol information with the source data.

The best approach for legacy data conversion, etc.

Representing collected data that does not fit in SEND variables & data listed as expected in the SEND datasets according to the Implementation Guide, but this data was not collected

Sponsors mapping 4 scale severity grades to 5 scale severity grades resulting in the study report for these findings not matching the SEND datasets

Although the PhUSE wiki page for SEND implementation is very helpful, additional information is needed regarding the PC and PP datasets

SENDIG timing variables are scarce and may not match the manner of GLP data collection, this leads to implementations where variables must work together in unintended ways in order to present the data collected in the SEND expected format.

There is a conflict between the core intention to tabulate data in the SEND datasets and the inherent need to have analysis grade data presented. This leads to basic conflicts in the degree of processing from original data capture systems designed for creating pdf tables versus the SEND dataset organization of raw data and complications to provide both types while maintaining traceability.

COMMENTS ON GUIDELINES AND STANDARDS DOCUMENTS

With issuance of the various documents, there are sometimes conflicts in requirements/recommendations

Different interpretations of the Implementation Guides by different sponsors

Learning how to decipher the documents and apply to the understanding to dataset validation reports, data standards and guidelines.

It is burdensome to follow the Control Terminology changes which are published every 3 months

There are so many "rules" in addition to the SENDIG, including FDA validator rules, the Technical Conformance Guide, FDA Business Rules, etc. It is hard to follow all of them, especially for entities based in non-English speaking countries.

There exist gray areas on the rigor of implementation of standards.

There is a steep learning curve for people new to SEND. There are poor examples in the SENDIG. It seems that there is a constantly changing nature of the SEND standards.

COMMENTS ON SOFTWARE AND SYSTEMS

Even with a software system made by the same company that makes our data collection and reporting systems, there are big gaps in the process of creating the SEND datasets that require substantial manual effort to complete the process.

Limitations of data capture systems to align with SEND format.



Software vendor issues with their assumptions made for the SEND system. We did not find barriers but definitely encountered a few stumbling blocks.

It is difficult to assess different SEND conversion service providers and software providers.

Some commercial IT systems are hard coded to SENDIG variable structure making it difficult to include other variables allowed by the SDTM model.

COMMENTS ON MANAGEMENT COMPLEXITIES

The biggest stumbling block was the inability of upper management to comprehend the intricacy of work involved in the creation of the SEND submission datasets and documents.

There are 3 elements that have been challenging:

- 1) Get our internal studies SEND compliant (technical component)
- 2) Get SEND data from CRO
- 3) Process from start to submission involves many parties

Limited pre-clinical budgets, SEND requirements are not sufficiently clear yet to set aside accurate budgets.



NEXT STEPS

Areas where hurdles to SEND submissions were identified will be discussed with PhUSE non-clinical teams to see where help can be offered in education or exploration of projects to improve upon submission examples and to share success stories.

The CDISC non-clinical group can also explore problem areas to identify where the standards need to be updated or expanded. CDISC is also working with the FDA on pilots for the submission of new study types.

All stakeholders are invited to examine these issues to see where they can help with consulting, improved software and processes to improve the submissions and the drug approval process in general.

A new survey is being prepared to begin in January 2019 and conclude in February 2019. Based upon the previous survey, some questions will be repeated to compare to previous results and new questions are being added where elaboration is desirable on known stumbling blocks. Also new questions are being formulated to ascertain information on the next steps in SEND submissions now that they are becoming routine for some study types.

CONCLUSION

The survey shows progress in SEND readiness and actual submissions from the previous year. However, most respondent organizations are experiencing challenges in both the technical aspects of preparing submissions and intra- and inter-company processes. This points to the need and importance for sustained efforts by the PhUSE non-clinical group to help companies overcome these challenges.

REFERENCES

2017 SEND Survey Results: http://www.phusewiki.org/wiki/images/7/70/2017_PhUSE_SEND_Survey_Results_-_CSS_Final_%281%29.pdf

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Author Name: Bob Friedman
Company: Xybion Corporation
Address: 2000 Lenox Drive, STE 101
City / Postcode: Lawrenceville, NJ 08648
Work Phone: 973-538-5111
Email: bfriedman@xybion.com
Web: www.xybion.com