Benchmark Your SEND Readiness!

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In the course of providing SEND-ASSURE services for checking Conformance, Consistency and Quality of SEND data sets we continue to see significant gaps in readiness on the part of preparers such as CROs and sponsors who need to stand behind these SEND datasets when submitted to the regulatory agencies. We have compiled metadata about these three KPIs for a dozen (12) studies we have assessed under our SEND-ASSURE program over the past couple of months. These are normal operational results from our SEND-ASSURE program and do not include any "first-time" studies that were assessed to benchmark a client or data preparer. The summary is included below. The numbers indicate the number of egregious conformance, consistency or quality issues that will affect the submit-ability or reviewability found. The actual number of issues reported in the SEND-ASSURE reports may exceed the numbers shown here.

Number of Conformance, Consistency, or Quality Issues Found per Study Checked

	Highest	Lowest	Average
Conformance	3	0	1.3
Consistency	4	1	2.3
Quality	4	0	1.4

The three indicators we consider are, together, an indicator of how ready a sponsor or data preparer is to meet the mandate in place today. While some of the studies had "0" Conformance issues, or "0" quality issues – NO studies were without Consistency issues. One study that had "0" Conformance and Quality issues, in fact, had the highest number of Consistency issues.

Watch for periodic updates on our website as we share the latest statistics on these quality indicators and use it to benchmark your organization and process. We have provided a description of the three indicators and what steps can be taken to improve performance in each.

Conformance

We consider Conformance as the lowest, but necessary, bar that must be met. This is about ensuring that the rules specified in the SEND IG are met structurally, in format, in CDISC schema, and meets published business rules. It is also about ensuring the terminology used conforms to the version of the Controlled Terminology, and that the Define.xml and nSDRG are complete and true to the data in the SEND files.

Improving Conformance

Use of SEND Validators along the process helps conformance to an extent, but not sufficiently - because some of the IG rules are complex and conditional on the actual study data. CDISC training,

disciplined following of IG and use of validators will improve the statistics for non-conformance.

Consistency

We have regarded Consistency with Study Reports as vitally important since early 2015. The Study Director signs the PDF Study Report after the audit, and the Principal Investigators sign off on any study domains that were done at other laboratories or CROs. This PDF is the authoritative reference for the study. It is produced, under GLP, from the as-collected data by the Study Director or Investigator's team. The SEND data set uses the same source of as-collected data but then gets processed by a SEND qualified team.

SEND requires that the same source of as-collected data is transformed, mapped and re-organized into SEND formatted data sets. Trial design for SEND is not the same as the sponsor defined dose groups in the Study Report. Terminology used in the SEND data set needs to be mapped to the chosen Control Terminology version. Unstructured qualitative observations as-entered by veterinarians, pathologists and histopathologists need to be parsed into SEND IG defined structures. All of these are fraught with potential for introducing inconsistencies with the Study Reports - and we are seeing plenty of these.

Since the Study Report and the SEND data set are "end products" generated by two independent processes from a common source it is easy to see why the two end-products end up with inconsistencies. When we see Trial Summary fields being entered differently in the PDF versus the SEND TS.xpt it signals that there was no check against the Study Report while the SEND data was being prepared. The more substantial issues we typically see include (some of these may be esoteric so please check with your SEND experts):

- Blocks of data are offset to the wrong grouping (this is less common with automated adaptors connected to LIMS).
- Missing domains in SEND data sets compared with Study Report
- Errors in Measurement values in subject level data for a visit day and parameter (usually caused by manual packaging)
- Errors in Visit-days compared with Report
- Inconsistent parsing of qualitative observations (ORRES) resulting in differences in incidence counts reported for sponsor dose groups.
- Missing exclusion flags in the SEND data or caused by missing flags in the as-collected LIMS source
- Discrepancies in reporting units between SEND data and the study report
- Test Article ID used in SEND is not the same as specified in the report

The consequences of submitting SEND studies that are not consistent with Study Reports are easy to imagine. As reviewers re-combine Trial Set (TX) data to make clubbed groups that have

significance to them, they will check trends they see against the less granular dose group behavior in the Study Report. If, or when, discrepancies are found or suspected, the likely outcome is to ask the sponsor to provide an explanation if one is not already available in the nSDRG. For sponsors this can cause a significant delay cost because while their toxicologists are intimately familiar with their Study Reports they are not used to navigating through the Trial Set data with unfamiliar test names and Trial Arms, nor often able to reconstruct the data into a comparable form to respond to regulatory questions or challenges. Regulatory agencies also assess the review-ability of SEND data prior to making it available to reviewers. Beyond conformance they are looking at consistency, particularly in qualitative domains such as clinical observations. This, and the consistency issues presently seen in SEND data sets is why ensuring consistency before submission is so important.

Improving Consistency

Other than checking the SEND dataset against the corresponding Study Report there is no way to ensure consistency with certainty. It does help if the Study Directors or Investigators are personally involved in the Study process. However, this is not practical for most CROs who need their senior toxicologists to work on other ongoing studies.

That leaves physical comparison of the final SEND data of individual subjects against the reported values, or, reconstructing the SEND Trial sets into the PDF dose groups so their statistics and incidence counts can be compared. Many SEND preparers claim they do "spot checks" of a statistically significant portion of sample data. Even if properly randomized across various findings and visit-days this technique can only pick up bulk dislocation of source data. Manual transcription errors, unit errors, or incidence counts cannot be reliably picked up with spot checks. Nothing short of 100% crosscheck is good enough to check consistency. We have tried this method before and found it to be insufficient. That is why we are sharing our experience.

Quality

Strictly speaking, lack of conformance and consistency is a Quality issue. However – we have parsed the meaning we associate with Quality here more narrowly. In this context we are capturing quality issues that reflect sloppy data transcription, management and shortfalls that do not necessarily prevent the study from being submitted or reviewed. We only include issues that fall in the category of mild, relatively inconsequential conformance issues where there is room for interpretation, to be classified under the "quality" score. Similarly, issues such as TS field values filled in sloppily with generic responses instead of the actual values published in the PDF are also included under quality. Quality issues are expected to reduce or disappear with experience, skills, training and time.

Benchmarking your SEND readiness

Now that it is mandatory to submit SEND data sets for studies started after

December 2017 which are included in IND submissions, it is important that sponsors benchmark the SEND data sets they are getting from their preparers. We are providing tools including the free downloadable MySEND© to help sponsors and SEND data preparers conduct deep and complete checks of the SEND data against their Study Reports. We also plan to provide additional tools such as surveys to help you self-assess your readiness. Consider these 4 simple questions for a start:

- Do your Study Directors or Principal Investigators check the SEND data sets of studies they conducted or reported on through their Study Report? (Score 1 for No, 0 for Yes)
- Does your SEND preparation team have any representatives from the Toxicologists who were part of the study team? (Score 1 for No, 0 for Yes)
- Can you visualize your SEND data using the original terminology used in the Study Report to answer questions? (Score 1 for No, 0 for Yes)
- Do you check the incidence counts from CL, MA, or MI domains in SEND data sets by re-combining them to match the Study Report grouping? (Score 1 for No, 0 for Yes)

If you scored 3 or more on these four questions you should be concerned about your SEND Readiness.

About PointCross Life Sciences:

PointCross Life Sciences has been serving the BioPharma industry for over 10 years with regulatory and research insights solutions for clinical and nonclinical studies. We have led with solutions and services for CDISC SEND preparation, quality and consistency checks, and review tools. We provide cost effective and responsive services for SEND Data Quality Assurance through our SEND-ASSURE services. Our clients include sponsors, CROs and third party standardized data preparers. We also provide SEND Data preparation services through our Data Standardization services.

In January 2018, we released our free, downloadable MySEND tool set including a free SEND validator, a TS.XPT generator for legacy studies, and an advanced SEND data visualizer. Tools for comparing your SEND data sets against a digital file extracted from your Study Report will be included later in Q1-2018.

Contact MySENDteam@pointcross.com or call +1 844 382 7252 to find out how you can check your studies or access all the resources we provide.