SEND Team – Questions for Industry UPDATED Responses

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Agenda

1. Introduction (Disclaimer)
2. Questions & Responses

Introduction

- In preparation for the 2022 Spring (F2F) Event, three questions were posed and the CDISC SEND Team presented their responses; however, those responses were from a small subset of SEND team members and so, considered preliminary.
- While there is value in considering the preliminary responses, the questions were then posed in a broad public setting (via CDISC website, email, and LinkedIn) to give opportunity for a broader industry response.
- The complete set of responses are included in this presentation which is posted on the CDISC SEND public-facing wiki site (here: https://wiki.cdisc.org/pages/viewpage.action?pageId=31313279).

Introduction (cont'd)

- The remaining slides in this presentation show, in this order:
  1. The question
  2. SEND Lead Team response
  3. The aggregated preliminary responses
  4. The additional aggregated responses from the industry survey (in green font)
- Responses are aggregated by type of organization (Software Vendor/Service Provider, CRO, Sponsor). Questions could be skipped, so the number varies across sections. The order of the bullets does not imply the same source of responses.
- Each bullet point is a verbatim response (with minor corrections applied as needed) from one particular industry member. There was no attempt made to summarize responses for all Sponsor's, for example.
- The responses should not be interpreted as the views of any specific organization

Question #1

Since September 15, 2021, there have been some submissions of simplified ts.xpt files where they are not needed (e.g., in eCTD Modules not checked by the Technical Rejection Criteria) or where they use both “NA” (TSVALNF) and a valid study start date (TSVAL). Based on these observations, are there any questions or concerns about how to use the simplified ts.xpt file for nonclinical study report submissions? Are there any specific questions on how to use a simplified ts.xpt depending on study type, study initiation date, scope of SEND, COVID-19 related applications, text-based documents, or the eCTD Module to which the study is submitted?

SEND Lead Team:

- Even though the FDA has provided a significant amount of instruction and communication on this topic, we receive the same questions repeatedly. This is an important topic of interest to organizations at different stages based upon their product development and some organizations are still new to SEND submissions. For these reasons, we find it useful to continue to (repeat) the messages in as many forums as we can (Including: study type, study initiation date, scope of SEND, COVID-19 related applications, text-based documents, or the eCTD Module to which the study is submitted)

Question #1, Aggregated Responses

Feedback from:	Feedback:
Sponsor (includes Academic Institutions)	• No questions, we have only used the simplified TS domain for eCTD categories that currently require SEND datasets • There are some study types that require creation of SEND dataset for submission but do not require simplified ts.xpt. Examples are studies categorized into eCTD section 4.2.1 (in vivo safety pharmacology studies/CV and respiratory) and 4.2.3.7 (other toxicity studies/metabolite toxicity studies etc.). I hope that such gaps can be more clearly explained in the sdTCG or appropriate place. • (2) No • Is it a problem to submit a simplified ts.xpt file when not required? Regardless of the technical rejection criteria, we submit a simplified ts file based on the when the requirement starts and the study starts. For example, we submit a ts file for a Safety Pharmacology Cardiovascular study, IND if it began before March 15, 2020. • As of March 2023 (NDA/BLA) or March 2024 (commercial IND), are simplified ts files expected for DART studies? • No questions, but there are several concerns regarding the provided examples on how to setup the TS • In July 2021, a project group within the PHUSE Nonclinical Working group published a thorough deliverable testing several simplified ts.xpt files. The presented results boosted confidence and left no unclarity.

Question #1, Aggregated Responses (cont'd)

Feedback from:	Feedback:
Software Vendor, Service Provider	• Our software automatically checks that TSVALNF and TSVAL values are mutually exclusive, preventing this issue. We think this issue happens when it is entered manually. The most likely cause for this issue is faulty instructions given in PAGE 7 of 'CREATING SIMPLIFIED TS.XPT FILES' to enter 'NA' contradicts the instructions in the sample code provided in multiple sections. • Safety Pharmacology studies (Cardiovascular and Respiratory) are part of SENDIG v3.1 and I know are not in the automatic rejections criteria checking now. Will they be added to this automatic rejection check at some point in the near future? What would be the notice time for such an addition? • SEND should be used extensively like SDTM for Human Clinical Trials • I think the information from the agency regarding the simplified ts.xpt is really clear.

Question #1, Aggregated Responses (cont'd)

Feedback from:	Feedback:
CRO	• Where a simplified ts.xpt file would be appropriate, we've seen a large number of requests for full ts.xpt files for submission. Is it acceptable to use a full ts.xpt file in place of the simplified? Is there a preference one way or the other? • Some sponsors are being proactive to request simplified TS.xpt files for folder that are currently out of scope, so that when they submit those studies later and the section becomes within scope, they will not have to ask their CRO's after the fact to create the simplified ts.xpt files. Example (safety pharm section) • (6) No

Question #2

Thinking forward to the future CDER requirement of SENDIG DART v1.1 beginning in March 2023 (NDA/BLA) or March 2024 (commercial IND), are there any questions that industry would like the Agency to consider when developing the scope for SENDIG DART v1.1, such as study design or intent of the study?

SEND Lead Team:

- The scope of the SENDIG-DART v1.1 is limited to Embryo Fetal Development (EFD) studies.
- The responses include questions about scope, but the intent of SENDIG-DART v1.1 is limited to EFD studies.
- One of the questions received in the responses was requesting feedback from the SENDIG-DART v1.1 Fit-for-Use (FFU).
  - The learnings are posted on our public-facing wiki page here: https://wiki.cdisc.org/display/NSFFUW/SENDIG-DART+v1.1+Fit+For+Use+Pilot

Question #2, Aggregated Responses

Feedback from:	Feedback:
Sponsor	• When SEND DART becomes an FDA requirement then will a legacy/simplified ts file be expected to be submitted for all DART studies that began before the requirement started? • Perhaps sponsors are interested in whether they are required to create and submit SEND datasets for dose-range finding studies, which are sometimes conducted as non-GLP and using non-pregnant or pregnant animals. If the answer is yes, we will need a clear explanation for which studies we need to create SEND datasets, e.g., studies categorized into eCTD section 4.2.3.5.2. In addition, we would like to know when we should submit such SEND datasets to the regulatory agency. • (3) No • There are no unambiguous rules on how to setup SEND. It has the impression that same mistakes which had been made with respect to SDTM for clinical are made also for SEND • Since I have no experience with DART studies, I cannot answer this question.
Software Vendor, Service Provider	• We do not have any issues with DART 1.1 for EFD studies. For DART studies outside EFD, we use custom domains or draft domains. • Yes • Combination studies such as 'fertility and EFD' are pretty common. Are these studies in scope? Is the whole study in scope, or just the EFD portion? • The scope would hopefully address circumstances of combined studies, for example fertility and EFD combined.

Question #2, Aggregated Responses

Feedback from:	Feedback:
CRO	• The SENDIG DART v1.1 specifically references that it be used in conjunction with SENDIG v3.1. As SENDIG v3.1.1 will become effective on the same day as the SENDIG DART v1.1, should v3.1.1 be used to prepare SEND datasets? • What is the expectation for combo studies, where part of the study has EFD endpoints and part is out-of-scope for SEND reporting? Is a SEND dataset required for the EFD portion of the study? • We should ensure that we all have the same understanding of the scope, which is limited to Embryo-Fetal Development (no other repro study types). • (7) No • A recent full SEND Team discussion did not provide clarity on the "Intent" designation and this needs more discussion/clarity.

Question #3

Would industry like to share any experiences, best practices, or feedback regarding the September 15, 2021, implementation of the Technical Rejection Criteria? For example, if a submission was rejected, did Agency communication and instructions provide sufficient information so that the submission could be resubmitted in a reasonable timeframe? Would industry like to share best practices they have put in place?

SEND Lead Team:

- We suspect that sponsors are still learning the details of TRC and the expectations around study tagging files, ts.xpt/abbreviated ts.xpt, and (though less of a problem) when DM is required. It would be very useful if more detail could be included in the messages of the Rejection Notification (e.g., which step in the process failed, which part/value of the ts.xpt caused the failure). One example is where the study ID is slightly different between the STF versus the ts.xpt study ID, as may be likely when multiple organizations are producing datasets, a standard message stating that the Study ID in STF did not match the Study ID in the data. Today, there is a more general message "No tx.xpt found for this study" that is confusing when a ts.xpt was submitted with no further explanation.

Question #3, Aggregated Responses

Feedback from:	Feedback:
Sponsor	• Had a situation where a study was initially submitted prior to TRC implementation and the study number was provided without dashes which was different from STUDYID or REFID in ts file. Study went through gateway without issue. It was then included in another submission after implementation of TRC where it failed the validation because it did not match the STUDYID or REFID. Example STF study id abc123x456def, ts file STUDYID = 9999999, REFID =ABC-123-X-456-DEF. What does the agency envision sponsors to do in these cases or is there any guidance to direct regulatory publishers to refer when such instances occur. • I think it's a very good idea, but there may be sponsors who are reluctant to share information with their names. I think that the hurdle will be lowered if a system that can support providing information on an anonymous-basis is built for sharing. • Thanks so much for evaluating the test submission coordinated by the PHUSE CSS project. The 6-month period of providing warnings was just enough time to find a consortium willing to start this project, establish the team, and create a test submission. I believe the results of this project helped the industry to be more prepared and helped reduce the number of technical rejections. This was especially helpful for those companies who didn't have a real submission within the warning period and those companies that help prepare submission components for other organizations but don't file submissions themselves. • Best practice - SEND experts contribute towards the review/approval of all the SEND files in the STF/eCTD structure for submissions to ensure TRC is met to avoid a rejection..

Question #3, Aggregated Responses (cont'd)

Feedback from:	
Sponsor (cont'd)	• No • We have had no issues. • As I'm not part of our current submission group I do not have first hand information • Regarding the mentioned publication of the PHUSE project group, our company established measures to ensure simplified ts.xpt files don't get rejected. Regarding full SEND packages we didn't experience any technical rejections from September 15, 2021 until up to now.
Software Vendor, Service Provider	• Yes. I wanted to get more exposure with CDISC SEND • N/A for my organization, though I would say that in my opinion the TRC is very clear and has been very well communicated.
CRO	• (3) No • CRO not involved directly in submissions, so no comment about this; But would be happy to read others' feedback. • Industry could share the info if requested • Yes

Thank you to all our survey respondents!

Thank you to our public audience for attending today!

Thank you to all SEND Team members involved in this week-long event!

Questions or Comments?: www.cdisc.org / contact