By Joshua Glaser and Charlotte Prior-Chappell

SDTM CRT Packages and the Submission Space

Abstract

The main goal of the Submission Space and generating Case Report Tabulation (CRT) Packages is to ensure “Submission Readiness” of a study by assessing the Datasets, Define and Validation Reports. For all current and ongoing studies, the aim should be for a high-quality package to be produced at a study level, with little to no changes required for the CRT Package.

This poster aims to outline what it means for the SDTM side of a CRT package to be “Submission Ready” and how this is achieved, whether we are starting from SDTMs created from the most recent Implementation Guide or from Datasets not in the format of SDTMs yet.

Introduction

A Case Report Tabulation (CRT) Package is submitted with a New Drug Application (NDA) to a Regulatory Agency in charge of Food and Medicine, most of the time being the FDA and PMDA. The complete package will consist of both the SDTMs and ADaMs, but we are going to focus on the SDTMs and how to get them “Submission Ready”.

What is “Submission Ready”?

To determine if an SDTM package is ready to be submitted to a Regulatory Agency, there are three key aspects to consider. Below, in Figure 1, are the three areas we evaluate that determine “Submission Readiness”.

Fortrea

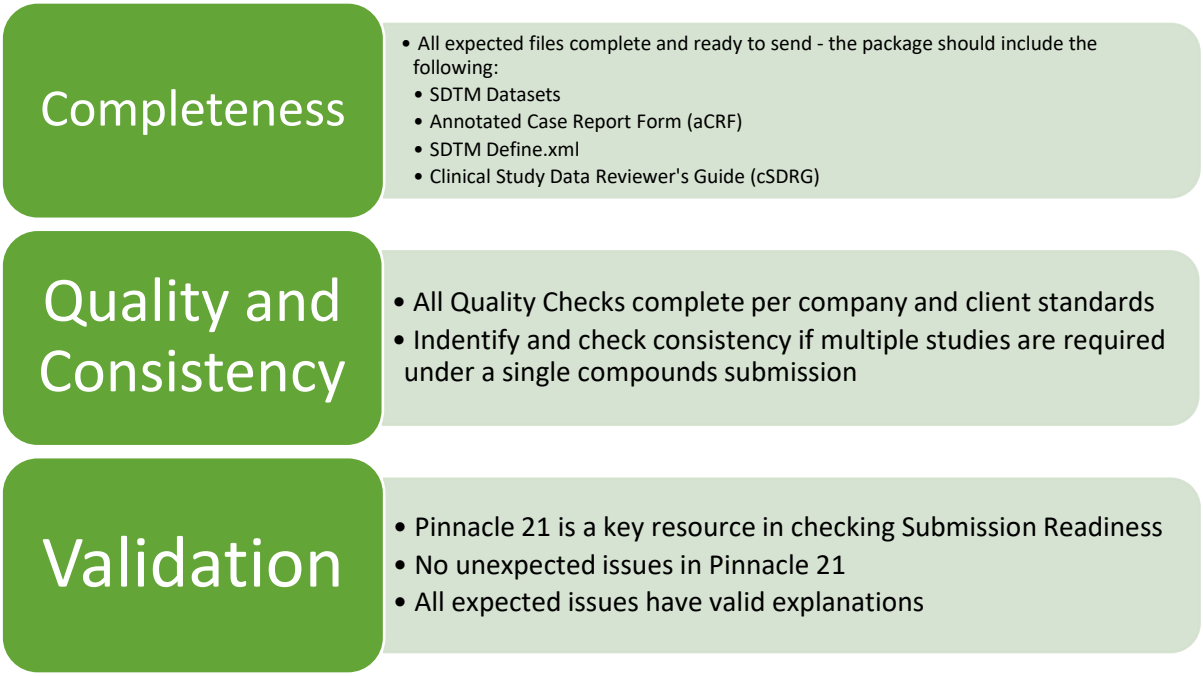

Figure 1: Outline of the three key areas we review prior to sending a SDTM CRT Package

Studies in SDTM format

Single Study

The simplest situation where the Submission Package contains a single study, already in SDTM format. Once all Quality, Consistency and Validation checks are complete, this is good to go!

Multiple Study

It is possible for multiple studies investigating the same compound to be submitted together. In this case, each study will have their own CRT Package, but will have a few unique interactions to consider:

- We aim for consistency across studies where possible, one example being Trial Summary information like TRT and PCLAS being consistent
- The same SDTM Implementation Guide (SDTMIG) version should be used across all studies

What happens when we have differing IG Versions across studies?

There may be a situation where studies under the same compound have been programmed on different SDTMIG versions – in this situation, the outdated studies will need to be up-versioned so all CRT Packages versions within the compound match.

Legacy Conversion

Purpose of a Legacy Conversion

What happens if the datasets required for a submission are not contained in SDTMs? With the current standards/expectations set in place, this is quite rare but you may find yourself in this situation. The Primary goal will be to covert these datasets into SDTM format, where instead of data coming from a Case Report Form database, it would be coming from the provided “Legacy” datasets.

Even though the data is not in the expected format, we would still (hopefully) expect the data to have an intuitive structure. The file received will be case-by-case and non-standard, but the minimum set of documents we would expect are a Protocol, a Case Report Form (or something equivalent) and the Legacy Datasets.

Production of SDTMs

A forethought when producing SDTMs in a Legacy conversion is Traceability – we want to fluidly map and transition data from one source to another. The two key documents that will be required:

- A Mapping Document;
    - Similar to the aCRF, a specification document describing which Legacy Dataset variables are mapped to which SDTM domains/variables.
- An Annotated Case Report Form;
    - Even though the datasets are not in SDTM format, the data should have been collected through a database with an associated Case Report Form (or equivalent). Annotating this will aid with traceability between the Legacy Datasets and the SDTMs, and is a requirement for the Define.xml

Notes, Tips and Tricks

When working in the Submission Space, it is key to understand the difference between the two below spaces/levels:

- **Study Level**: the space in which the programming package is initial created/finalised, during which the study was ongoing/active.
- **Submission Level**: the space in which the Submission CRT Package is updated/finalised.

It is also worth noting that the SDTM CRT Package is synonymous with an Observed CRT Package and the ADaM CRT Package is synonymous with an Analysis CRT Package.

When working with **Older Studies** that are post database lock (DBL):

- it is key to run any Validation Reports on the dictionary versions used at the time of creation of the SDTMs.
- any issues found that require updates to the SDTMs or Define that will make the SDTM CRT Package "Submission Ready" are advised to be made. The SDTMs and Define can then be finalised again under at Submission Level.
- Occasionally, as part of up-versioning of older studies on outdated SDTMIGs, you will be required to produce domains that were not initially created. Take the following into account when up-versioning a study for a Submission Package:
    - If missing SE, but TE is present and EPOCH is found in applicable SDTMs, then SE will need programming.
    - If missing SV, but TV is present and VISIT variables is found in applicable SDTMs, then SV will need programming.
    - If any of the Core Trial Domains are missing, then these will likely be needed for the Submission.

When working with **Ongoing/Active Studies**:

- We aim for "Submission Readiness" at a Study Level, aligning the delivery/finalization of the Study Level SDTM define.xml package with the finalization of the Submission Level CRT Package.
    - Note that this also applies to the ADaM CRT Package as well!

When working with **Multiple Studies**:

- There tends to be two situations when working with multiple studies:
    - The first is that all studies are ongoing/active, with the expectation of systematically working through them in the order the studies are running and preparing them for submission at a Study Level.
    - The second is that one or a couple Studies are active/ongoing, with the majority being Studies post DBL.
- If all studies are ongoing/active that are a part of the Submission, they will likely already be of the same version, but it is worth checking.
- In the case where we have a mixture of older and ongoing studies, it will be important to check what SDTMIG version the old studies are on and identify if any up-versions are needed.
    - There are situations where not all studies need to be the same SDTMIG version, but this will be up to the group Submitting the final Package. In most cases, it is advised that we have Consistency in SDTMIG version, resulting in possible up-versions.

When working with **Legacy Studies**:

- Legacy Conversion can be messy and tricky to navigate – this is very much down to how well the Legacy study was documented and what is available at the time in terms of documentation.
- It is important to keep Study programming areas clean and programs well documented and reviewed. The Mapping Document and aCRF are vital resources to help aid this process.
- Due to the original datasets not being in SDTM format, it is likely they have not been run through Pinnacle 21 before, this may lead to Validation issues that are not possible to resolve and will just have to be explained in the cSDRG as unresolved issues from the Legacy Study

Consolidation for the Process

We have taken into consideration different data sources and how we algin them all and prepare them for submission. Below, in Figure 2, is a consolidation of all these different starting points and how they intertwine.

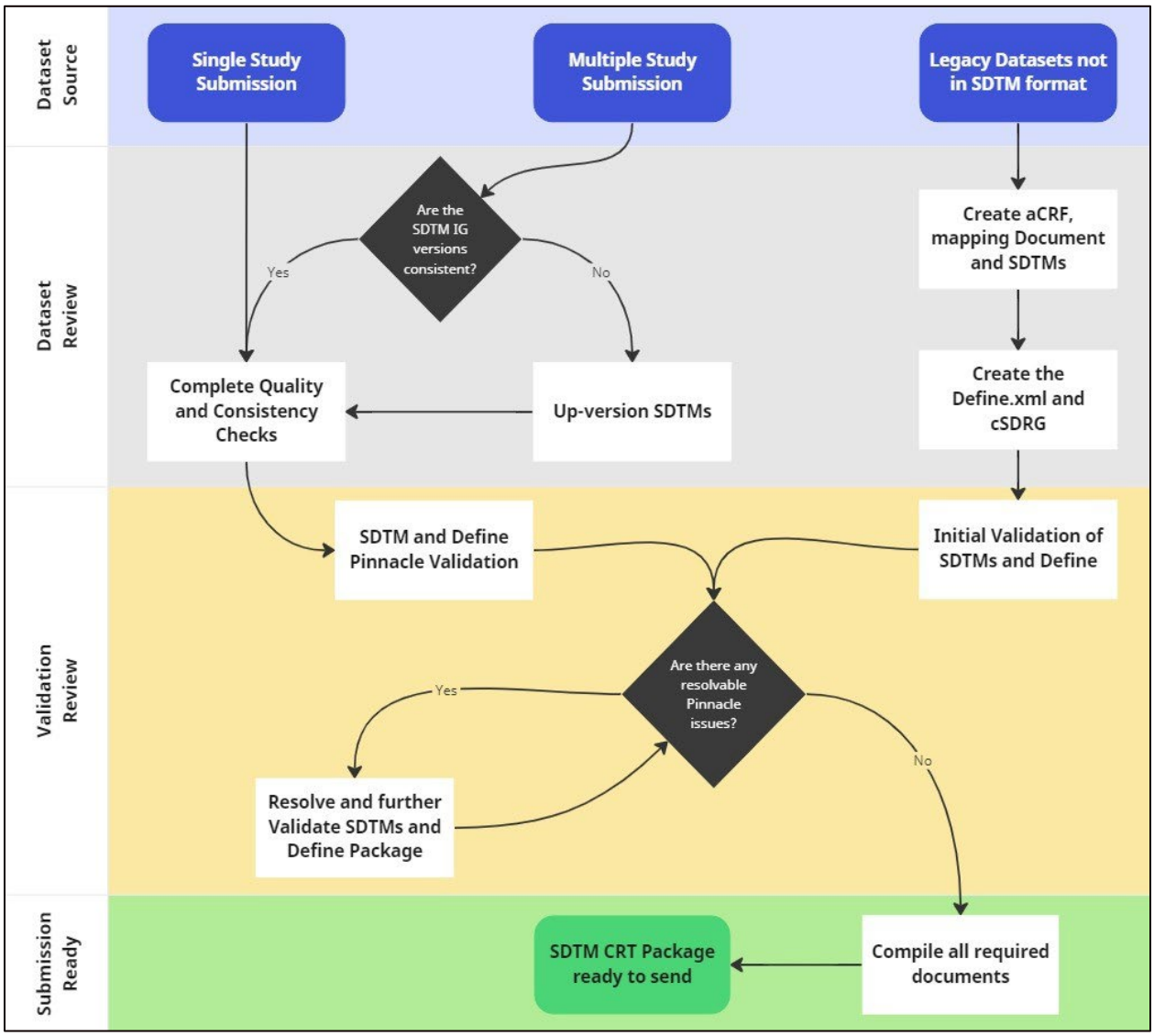

Figure 2: A Flow Diagram outlining the review process and considerations of SDTM CRT Packages

Disclaimer

This paper is an insight into how Fortrea view the Submission CRT Package process based on continued work within this space, it may not align with how other company's processes.

Any difference of opinion or suggestions will hopefully spark a debate or discussion, leading to further development within this area.

Contact Information

Any comments or question are welcome, please find the contact information of the authors below:

Joshua Glaser
Statistical Programmer
Joshua.glaser@fortrea.com

Charlotte Prior-Chappell
Statistical Programmer
charlotte.prior-chappell@fortrea.com

Fortrea Clinical Research Unit Ltd
Drapers Yard
Marshall St, Holbeck, Leeds, LS11 9EH